NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Antimicrobial health technology evaluation

Ceftazidime with avibactam for treating severe aerobic Gram-negative bacterial infections

**Company evidence submission**

**Document A**

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# List of abbreviations

|  |  |
| --- | --- |
| **Abbreviation** | **Definition** |
| ABSSSI | acute bacterial skin and skin structure infection |
| AE | adverse events |
| AM | antimicrobial |
| AMR | antimicrobial resistance |
| AMS | antimicrobial stewardship |
| APACHE II | acute physiology and chronic health evaluation II |
| BMI | body mass index |
| BSI | bloodstream infection |
| CAP | community-acquired pneumonia |
| CAZ/AVI | ceftazidime with avibactam |
| CE | clinically evaluable |
| cIAI | complicated intraabdominal infection |
| cMITT | clinically modified intention-to-treat |
| CPE | carbapenemase producing *Enterobacteriaceae* |
| CrCl | creatinine clearance |
| CRE | Carbapenem-resistant *Enterobacteriaceae* |
| cSSTI | complicated skin and soft tissue infection |
| cUTI | complicated urinary tract infection |
| diff. | difference |
| ECDC | European Centre for Disease Prevention and Control |
| EEPRU | Policy Research Unit in Economic Evaluation of Health and Care Interventions |
| EMA | European Medicines Association |
| ESBL | Extended Spectrum β-Lactamase |
| ESCMID | European Society of Clinical Microbiology and Infectious Diseases |
| ET/EOT | end of treatment |
| EUCAST | European Committee on Antimicrobial Susceptibility Testing |
| FDA | Food And Drug Agency |
| FDC | fixed drug combination |
| GDP | gross domestic product |
| HAP | hospital-acquired pneumonia |
| HRQoL | health-related quality of life |
| HTA | health technology assessment |
| HVCSs | high-value clinical scenarios |
| IAI | intra-abdominal infection |
| ICU | intensive care unit |
| IMP | Imipenemase metallo-β-lactamase |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| IV | intravenous |
| KPC | *Klebsiella pneumoniae* carbapenemase |
| LFU | last follow-up |
| LOS | length of stay |
| LTO | limited treatment options |
| LY | life year |
| MBL | metallo-β-lactamases |
| MDR | multidrug resistant |
| micro-ITT | microbiological intent-to treat |
| mMITT | microbiologically modified intention-to-treat |
| NMB | net monetary benefit |
| NDM | New Delhi metallo-β-lactamase |
| NHSE | National Health Service England |
| NICE | National Institute for Health and Care Excellence |
| NOS | not otherwise specified |
| PBPs | penicillin binding proteins |
| PHE | Public Health England |
| PIN | Pharmacy Infection Network |
| QALY | quality-adjusted life year |
| RCT | randomised controlled trial |
| RWE | real-world evidence |
| SAE | Serious adverse events |
| SAPS | simplified acute physiology score |
| SD | standard deviation |
| SMDM | Society for Medical Decision Making |
| SmPC | summary of product characteristics |
| *spp.* | species |
| TOC | test of cure |
| UKCPA | UK Clinical Pharmacy association |
| UTI | urinary tract infection |
| VAP | ventilator-associated pneumonia |
| VIM | Verona integron-encoded metallo-β-lactamase |
| WHO | World Health Organization |

# 

# Executive summary

|  |
| --- |
| ***Key messages*** |
| * Antimicrobial resistance (AMR) is a rising global health and economic crisis, highlighting an urgent need to fix the broken market model, rebuild a strong pipeline, and ensure the health of the population. * In the UK, AMR has been estimated to have a substantial impact on the UK economy with real gross domestic product (GDP) losses in the region of £8.7-£34.6 billion per annum, equivalent to 0.4% to 1.6% estimated by Smith et al.1,2 * Ceftazidime with avibactam (CAZ/AVI) has an important place in the market to address high levels of unmet need and demonstrates substantial value to the healthcare system. * Pfizer’s base case economic model, which is based on a published model and aligned to the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) framework, reflects only a portion of the system value, determining significant net monetary benefit (NMB) to England of £599m over a 10-year period. * This base case underestimates the true system value, given the economic model does not fully capture:   (1) Broad range use of CAZ/AVI in practice (2) Total value attributable to antibiotics proposed by EEPRU, e.g. the value of mitigating the impact of probable future events, and the enabling of other procedures (3) Population impact on productivity and fiscal benefit   * To supplement the base case, a separate insurance value analysis is under finalisation and highlights the additional overall significant impact that antibiotics, particularly CAZ/AVI, have on mitigating and protecting against future impacts on costs and usual business via probable events. This will be shared with the project team post completion to inform EEPRU and the committee discussions. * The clinical and economic evidence presented in the company submission aims to inform and complement the analyses performed by EEPRU. * The process outlined by National Institute for Health and Care Excellence (NICE) and National Health Service England (NHSE) has the potential to be truly innovative, and one of the first to offer insights to resolve the increasing silent pandemic on an international scale. |

Project Overview:

The rise in antimicrobial resistance (AMR) is a significant health concern, predicted to cause 90,000 additional deaths in the UK between 2015 and 2050.3 Additionally AMR has been estimated to have a substantial impact on the UK economy with losses in excess of £8.7 - £34.6 billion per annum which is equivalent to 0.4%-1.6% of GDP estimated by Smith et al.1,2 Similar estimates were also reported by O'Neill et al. where the world’s GDP was predicted to be 0.5% smaller in 2020 increasing to 1.4% by 2030 (excluding COVID impact). These economic and population health losses are expected to increase significantly over time as resistance rates continue to rise, equating to 2% to 3.5% by 2050, costing up to $100 trillion globally.4

Despite the threat that AMR poses in the UK and globally, there are few novel antibiotics under development and inappropriate use of existing antibiotics continues in many settings.5 The lack of innovation in the antibiotic field has been driven by scientific difficulties to develop new antibiotics in combination with high financial costs. Alternative strategies need to be explored including novel chemistry, stimulation of innate immunity, and countering resistance mechanisms.5

At present, industry continues to innovate and find ways to stimulate antibiotic development through joint funding such as the AMR Action Fund.6 However, this alone will not drive success; initiatives to develop new economic models and frameworks to assess antibiotic value are urgently required to balance economic risks and returns to a more sustainable level and prevent continued market abandonment as seen through recent years (i.e., Achaogen and Melinta Therepautics),7 that will accelerate the global crisis. This technology appraisal forms a major step in changing the landscape for antibiotic development. The company submission presented in this document aims to optimally inform the novel appraisal process, providing clinical effectiveness evidence as well as analyses from an economic model that describes the value of ceftazidime with avibactam (CAZ/AVI) to the Nation Health Service England (NHSE) for the treatment of severe aerobic Gram-negative bacterial infections.

The field of bacterial infectious disease and AMR is undoubtedly complex, therefore a level of pragmatism and innovative thinking must be taken to continue to drive forwards. The model presented as part of this submission combines this required pragmatism with both traditional and innovative health economic techniques to depict system value across the indications for which CAZ/AVI is licensed. Furthermore, this model can be used for cross-validating the model that is currently being developed by the Department of Health's and Social Care’s Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (EEPRU) and support committee discussions with the aim of capturing indications not covered in detail by the EEPRU model but relevant for the licensed indications of CAZ/AVI and the overall valuation assessment.

Technology being appraised:

CAZ/AVI is a fixed drug combination of the cephalosporin, ceftazidime, and the novel non-β-lactam β-lactamase inhibitor, avibactam. It is indicated for both adult and paediatric patients aged ≥3 months for treatment of the following infections caused by Gram-negative pathogens in the UK:

* Complicated urinary tract infection (cUTI), including pyelonephritis
* Complicated intraabdominal infection (cIAI)
* Hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP)

CAZ/AVI is also indicated for the treatment of adult bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above, as well as for the treatment of infections due to aerobic Gram-negative organisms in adults and paediatric patients aged ≥3 months with limited treatment options (LTO).

CAZ/AVI is also effective against a range of critical priority bacteria defined by the World Health Organization (WHO).

Clinical summary:

Antimicrobial stewardship (AMS) strategies aim to limit the rise of AMR and, at the same time, promote effective treatment of serious infections, which is generally separated into two phases (the “Start Smart – Then Focus” approach8). This consists of an empirical phase (based on prompt risk factor-directed antibiotic prescribing) and a targeted phase (using mechanism / pathogen-directed treatment). CAZ/AVI can be used both as part of risk-based empirical therapy, to accelerate effective treatment and improve patient outcomes, where considered appropriate, and in the setting of pathogen- or resistance mechanism-directed approach, where antimicrobial susceptibility is known when therapy commences.

Whether used as risk-factor based empirical therapy or in patients with confirmed multi-drug resistant (MDR) infections, CAZ/AVI is likely to be employed in settings associated with high unmet need and critical illness, such as the intensive care unit (ICU) and acute medical and surgical wards. The clinical studies of CAZ/AVI included patients from such environments. The efficacy and safety of CAZ/AVI in its licensed indications has been demonstrated across several high-quality pivotal Phase II/III studies and results from a total of 6 trials are presented in the current submission. These trials will be covered in the main body of the submission, however, overall, the clinical efficacy and safety of CAZ/AVI, in addition to being well-established across a number of high-quality trials, is further supported by an extensive wealth of retrospective real-world data.9-15 Many of these studies included severely ill patients infected with difficult-to-treat pathogens, for whom treatment options are limited.

Across both the clinical trials and real-world data, CAZ/AVI was well tolerated, and the safety profile was generally consistent between the adult and paediatric populations.

Several of the CAZ/AVI clinical trials used carbapenems as comparators,16-20 supporting a role for CAZ/AVI as a potential alternative to carbapenems, which are considered the last line of therapy for severe infection management in critically ill patients. This is extremely important from a public health perspective at a time when increased pressures caused by the COVID-19 pandemic have negatively impacted on application of AMS strategies in clinical practice.21 A recent spike in carbapenem prescribing has been observed during the COVID-19 pandemic despite proper training of ICU staff, the high intensity of care for patients in need of re-posturing which required more staff with no ICU experience in a high-risk area, with extended and prolonged patient contact.22 This increase in carbapenem prescribing comes at a time of growing carbapenem resistance, posing a potential risk. While still relatively rare, detection of carbapenem-resistant bacteria has increased by approximately 1,000-fold in England in recent years (2010-2018).23

The rise in AMR in general and carbapenem resistance particularly limits the available treatment options for some patients. Carbapenem-resistant *Enterobacteriaceae* (CRE) infection has been associated with a four-fold increase in inadequate empirical therapy, causing increased morbidity and mortality, length of hospital stay and healthcare costs.24 Time to effective therapy of serious infections, such as CRE infections, is a strong predictor of crucial clinical outcomes (e.g. clearing the infection, length of hospital stay, mortality).25 CAZ/AVI has an important role in addressing this unmet need as it is able to reduce the selection pressure on other antibiotics such as carbapenems. Therefore, for patients in whom CAZ/AVI is deemed appropriate, the time spent on other, ineffective antibiotic therapies could be detrimental to overall patient outcomes.

Economic summary

The primary economic model submitted is based on a recent publication26 and adheres to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) best practice recommendations,27 as well as the National Institute for Health and Care Excellence (NICE) reference case, with adaptations to align to the EEPRU protocol, the Evaluation framework for antimicrobials, and the final NICE scope. The model has been subjected to extensive external validation exercises to demonstrate the scientific rigour, relevance, and value of the model in the context of real-world evidence.

Model inputs were derived from either published sources or based on assumptions verified by external experts, including recent verification by a Delphi panel. The model is capable of reflecting a range of AMS.26 These different treatment lines allow for a simplified treatment pathway to be modelled, capturing key aspects of CAZ/AVI value in an imperfect healthcare setting. This contrasts to the proposed EEPRU model, which predominantly focuses on two high value clinical scenarios (HVCSs) and reflect almost perfect adherence to AMS principles.

The base case analysis encompasses several key indications for CAZ/AVI, i.e. HAP/VAP, cUTI, and cIAI, as well as key settings relevant to the highly heterogenous LTO indication. The aforementioned clinical syndromes are modelled as caused by several pathogens: *Escherichia coli* *(E. coli),* *Klebsiella* species (*spp.*), and *Pseudomonas aeruginosa* (*P. aeruginosa*), which are considered in a weighted manner to maximise the modelled proportion of the population covered by the licensed indications. An all-lines diversity stewardship strategy, was chosen to provide an optimal balance between maximising population health gains and minimising resistance development.26 The diversity strategy aims to reflect real-world practice, where local guidance, resistance levels, and clinician preference may affect treatment choices.

The base-case is in-line with the proposed modelling approaches outlined by EEPRU and demonstrates significant value to the NHS in England. Net monetary benefit (NMB) estimated at a £30,000 per quality-adjusted life year (QALY) is £598,779,222, combined for the three key indications (cUTI, cIAI, and HAP/VAP) over a 10-year time horizon at a national level for England predicting 2,181 deaths avoided and 4,412 infections cleared. The patient numbers in the base case are of circa 3,100 patients per annum, which, accounting also for the below, is expected to be in line with good AMS.

Even with this significant NMB the economic model does not capture the full value of CAZ/AVI in totality. The current model captures only limited indications and pathogens, models a steady state scenario using cautious assumptions, and does not include or explore fully all the additional value elements outlined in the protocol, thus leading to an underestimation of value CAZ/AVI offers to the healthcare system.

Two significant value areas that have not been fully captured in the base case relate to insurance- and enablement- value.

In light of the base case modelling a steady state, assuming a constant number of infections, a supplementary model has been developed to explore separately the value CAZ/AVI may have in mitigating future disruption and probable losses to the healthcare system (one aspect of insurance value). Through this analysis CAZ/AVI is estimated to provide substantial additional system value by mitigating the direct impact specific events have on NHS operations and costs.

Furthermore, the added enablement value associated with the introduction of a new, effective antibiotic such as CAZ/AVI is substantial, and of particular significance when considering the COVID-19 pandemic and the implications associated to foregone, or delayed treatment of various urgent and non-urgent treatments requiring secondary care such as surgery or cancer treatment. As demonstrated by the NICE NG63 resource impact report, preventing 1% of non-elective gastroenteritis and respiratory infection admissions could save around £2.8 million a year in England.28 Pfizer continues to explore the impact antibiotics have the enabling of other procedures with the intention to publish our findings.

It is important to note that neither model submitted accounts for the level of value associated to both productivity and associated cost offsets or relevant ongoing, long term fiscal impacts. While not traditionally included in the NICE reference case, the committee should be aware that antibiotics have a considerable population wide impact, thus their ability to drive productivity and fiscal benefits at a national level could demonstrate substantial wider system value.

Summary

With the current AMR projections, the socioeconomic risks associated with inaction are likely to be significant. This submission highlights a strong call for action with regards to the UK antibiotic treatment landscape and a need for effective antibiotic alternatives. This will (i) alleviate selection pressure with regards to antibiotic prescribing (ii) reduce time to effective therapy – both improving patient outcomes and reducing healthcare resource burden – and (iii) minimise risk of AMR and potential future outbreaks.

The clinical and economic evidence presented in the company submission aims to inform the committee, NICE and the NHS, by identifying the system value in line with the NICE framework for antibiotics and EEPRU approach, whilst complementing and informing the analyses performed by EEPRU.

Despite value being underestimated, the presented core model demonstrates significant value to the NHS and represents an important first step in quantifying the wider value of antibiotics to the population. A crucial part of informing a future value assessment that is aimed to reinvigorate antibiotic development and create a sustainable market model.

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# Background

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| ***Key messages*** |
| * The rise in antimicrobial resistance (AMR) is a significant health concern, predicted to cause 90,000 additional deaths in the UK between 2015 and 2050.3 * Antimicrobial stewardship (AMS) strategies have been developed with the aim of limiting the rise of AMR. * Increased pressures caused by the COVID-19 pandemic have negatively impacted on the application of AMS strategies in clinical practice.21 * It is vital that effective antimicrobial treatment is given as soon as possible, as time to effective treatment is a strong predictor of patient outcomes, including length of hospital stay, morbidity, mortality.25,29-31 * Carbapenems are considered the last line of therapy for severe infection management in critically ill patients. While still relatively rare, detection of carbapenem-resistant bacteria has increased by over 1,000-fold in England.23 The rise in carbapenem resistance limits the available treatment options for some patients. * Carbapenem-resistant *Enterobacteriaceae* (CRE) infection has been associated with a four-fold increase in inadequate empirical therapy, causing increased mortality, length of stay and healthcare costs.24 * Gram-negative pathogens may cause a number of infections in the healthcare setting, including hospital-acquired pneumonia/ ventilator-associated pneumonia (HAP/VAP), complicated intra-abdominal infection (cIAI), and complicated urinary tract infection (cUTI). * There is significant clinical need and societal benefit associated with obtaining a diverse set of novel antibiotics. |

## Antimicrobial resistance burden

Antimicrobial resistance (AMR) occurs where pathogens such as bacteria change over time and no longer respond to medicines making infections harder to treat. AMR is a natural phenomenon caused by selection pressures when pathogens are exposed to antibiotic drugs. Susceptible bacteria are killed by the antibiotic, while bacteria that are resistant (either intrinsically or have acquired antibiotic-resistant traits) are able to survive and multiply.32

AMR is projected to cause 90,000 additional deaths in the UK from 2015-2050 and 10 million worldwide.3,33 Furthermore, between 2013 and 2018[[1]](#footnote-2), significant increases in resistance rates to key antibiotics have been observed among several Gram-negative species, including *Escherichia coli* (*E. coli*)and *Klebsiella pneumoniae* (*K. pneumoniae*) (Figure 1).23 The alarming spread of multidrug resistant (MDR) pathogens worldwide is due to different drivers such as changing patterns of pathogen epidemiology, emergence of drug-resistant genes, the progressive human urbanisation, global travel to the remotest corners of the world, and the ease of movements of products and goods across the globe. This demonstrates that AMR will always be a global issue.

Historically, due to their low cost, very few restrictions were applied to antibiotic use; ultimately leading to the rise of AMR. More recently, the value of antibiotics is slowly becoming recognised and value assessment frameworks for antimicrobials have been proposed.34,35 Still, the number of available treatment options is low at the moment, especially for MDR infections caused by bacteria such as *Pseudomonas* species. With such limited options available any supply interruption of these antibiotic therapies, as was the case for ceftolozane/tazobactam in December 2020, can have considerable operational and health impact, whilst increasing the selection pressure on other critical antibiotics, adding to the already problematic health crisis.

Table

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Figure 1. Estimates of resistance to older key antimicrobials among Gram-negative bacteria; England 2013 to 201823

As a result of increasing AMR, antimicrobial stewardship (AMS) strategies have been developed, with the aim of limiting the spread of resistance. The UK Government has published a five-year action plan5 and a twenty-year vision36 for addressing AMR in the UK. Furthermore, NICE has produced guidelines (NG15) providing recommendations for antimicrobial stewardship.37

## Carbapenem resistance

Although the rise of carbapenem resistance is a well-recognised concern within AMR,38 the use of carbapenems in England remains high and is considered the last line of therapy for severe infection management in critically ill patients.23,39 In addition, the current COVID-19 pandemic has caused a surge of carbapenem prescribing across English acute centres (rising from 65.1 to 94.7 defined daily doses per 1,000 comparing Q3 2019/20 with Q1 2020/21; Figure 2). This, in addition to the observed decline in AMS activities due to COVID-19 has created an opportunity for increased AMR.

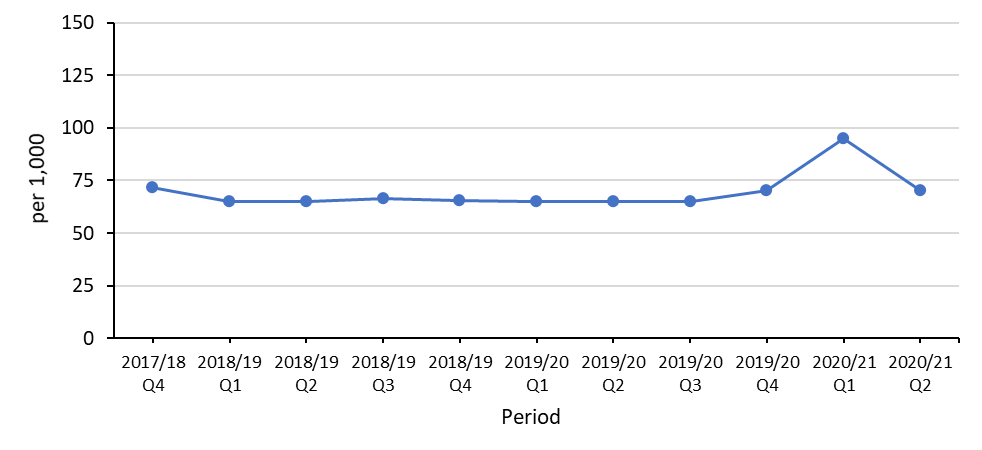


Figure 2. Carbapenem prescribing per 1000 admissions across England acute trusts; by quarter (2017/18 Q4 - 2020/21 Q2)21

While still relatively rare in England, detection of carbapenem-resistant bacteria has increased by approximately 1,000-fold in recent years.23 Resistance is mostly (>99%) attributable to the “big 5” carbapenemase families (*K. pneumoniae* carbapenemase [KPC], OXA-48-like, New Delhi metallo-β-lactamase [NDM], Verona integron-encoded metallo-β-lactamase [VIM] and Imipenemase metallo-β-lactamase [IMP]) and combinations thereof, with the OXA-48 family predominating (52%), followed by NDM (26.5%).23

The rise in carbapenem resistance occurs at a time when the UK is facing unrelenting increases in the incidence of bloodstream infections (up by 21% from 2014 to 2018) and resistant bloodstream infections (32% increase over the same time period). *E. coli* bacteraemia is responsible for much of these, and their prevalence continues to grow year on year.40 Importantly, this rise in bacteraemia is likely to be associated with increases in transmissible β-lactamase resistance41 including Extended Spectrum β-Lactamases (ESBLs), AmpC and carbapenemases. These acquired resistance mechanisms can evolve through selection pressure from antibacterial use or can be transmitted by plasmids from different bacterial species in humans, animals, and in the environment.

Also of concern is the transmission of carbapenem resistance genes together with other resistance genes, resulting in multi-drug resistance.25 Consumption of non-carbapenem antibacterials, such as cephalosporins and fluroquinolones, can also increase the selection pressure on carbapenem-resistant *Enterobacteriaceae* development due to associated resistance gene transmission; this reinforces the essence of an overarching stewardship policy to support the introduction of newer agents especially for hard to treat MDR infections.

Cumulatively, ESBLs and the carbapenemases KPC and OXA-48 account for the majority of MDR Gram negative infections in the UK.23

### The growing burden of carbapenem resistance

Despite the situation in England being relatively favourable compared with a number of other European countries,25 several outbreaks associated with carbapenem resistance have occurred in England in the recent years, posing a threat to patients and incurring substantial costs to the NHS. In 2015, the Central Manchester University Hospital NHS Foundation Trust experienced a major outbreak of KPC-producing *E. coli* (with additional *Enterobacteriaceae* species also becoming involved) that persisted despite infection control measures, resulted in repeated closures of two wards, and was estimated to cost the Trust up to £5.2 million.42 In March 2015, an outbreak of NDM-producing *K. pneumoniae* occurred in a group of 5 West London hospitals and persisted until December 2015. The outbreak required closure of 4 wards and 8 bays and was estimated to cost the NHS £980,000, of which missed revenue from elective procedures (£296,000) was the largest contributor. As many as 840 bed-days were attributable to the outbreak.43,44 A significant outbreak also occurred in University Hospitals of Leicester in 2018 and was caused by OXA-48-producing *K. pneumoniae.* It lasted almost five months, required a total of 10 wards to be decanted and fully cleaned, and is estimated to have cost around £400,000 excluding the impact on delaying or cancelling other procedures.45

Figure 3 illustrates this concerning situation which continues to increase each year. Infections with carbapenem resistant pathogens represent diagnostic complexity, management conundrums and limited effective agents to use. In addition, the recent surge in carbapenem prescribing (Figure 2) may exacerbate the potential of future outbreaks since resistant rates are increasing.21

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Figure 3. Number of confirmed carbapenemase producing *Enterobacteriaceae* (CPEs) referred to Public Health England’s AMRHAI Reference Unit, 2009– 201823

It is important to note that due to an ongoing endemic KPC resistance problem particularly for *E. coli* in Manchester46 this trust developed their own in-house testing and did not submit to PHE in the latter years. The KPC prevalence in Manchester is in fact 10 times the national average.47 Hence, true estimates of KPC may be significantly higher than those presented.

Another important factor to consider is the potential impact of carbapenem resistance outbreaks on availability of effective therapies. A vast number of treatments and procedures rely on the availability of effective antibiotics, therefore there is significant value in enabling these therapies to continue. Additionally, there is value in maintaining an effective therapy for treatment of an escalating health crisis. Analyses to explore the insurance value are currently conducted (see Section 4.9.1 for further details). Carbapenem resistance reduces the available therapies to support these activities and increases the need for the development of novel antibiotics.

### Time to effective treatment

Aligned with the “Start Smart – Then Focus” approach recommended by Public Health England (PHE) effective treatment may be delayed in patients with carbapenem resistant bacteria if infection with a resistant pathogen can be assumed. However, it is vital that effective antimicrobial treatment is given as soon as possible, because time to effective treatment is a strong predictor of patient outcomes, including length of hospital stay, morbidity, mortality.25,29-31 This is particularly true in patients with cIAI; as laparotomy is a common procedure for these patients, timely management of infections is key.

The impact of delay in effective treatment is seen in clinical practice. Carbapenem-resistant *Enterobacteriaceae* (CRE) infection has been associated with a four-fold increase in inadequate empirical therapy, causing increased mortality, length of stay and healthcare costs.24

## The burden of Gram-negative infections

Gram-negative pathogens, such as *Klebsiella* spp.*, Acinetobacter* spp*., Pseudomonas aeruginosa* (*P. aeruginosa*),and *E. coli* cause a number of infections, particularly in the healthcare setting.48 Examples of infections that may be caused by Gram-negative species include:

* Hospital-acquired pneumonia/ ventilator-associated pneumonia (HAP/VAP)49
* Complicated intraabdominal infection (cIAI)50
* Complicated urinary tract infection (cUTI)51
* Bacteraemia
* Infections present in patients with limited treatment options (LTO)9-14, i.e., difficult-to-treat infections for which there are very few treatment options.

These major clinical syndromes are also associated with nosocomial Gram-negative infection and are associated with high mortality rates (Table 1) indicating a high degree of clinical severity. The additional complexity of bacteraemia associated with any of these clinical syndromes greatly increases the severity.

Table 1. Mortality rates associated with cUTI, cIAI, HAP/VAP and bacteraemia

|  |  |
| --- | --- |
| **Disease** | **Mortality rate (%)** |
| cUTI | 20-40%52,53 |
| cIAI | 30%54 |
| HAP/VAP | 38-70%55 |
| Bacteraemia | 12-38% 56-58 |
| cIAI: complicated intraabdominal infection; cUTI: complicated urinary tract infection; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia | |

Across these clinical syndromes, MDR Gram-negative infections are associated with high clinical severity and per pathogen mortality rates are very high (Table 2):

Table 2. Mortality rates for MDR Gram negative resistance mechanisms

|  |  |
| --- | --- |
| **Infecting Pathogen** | **Mortality rate (%)** |
| Carbapenem resistant *Pseudomonas* | 43%59 |
| CRE | 30-75%60 |
| KPC | 34%25 |
| OXA-48 | 50%61 |
| CRE: carbapenem-resistant Enterobacteriaceae; KPC: *K. pneumoniae* carbapenemase | |

#### Hospital-acquired / ventilator-associated pneumonia

NICE defines hospital acquired pneumonia (HAP) as pneumonia that develops 48 hours or more after hospital admission and that was not incubating at hospital admission and ventilator-associated pneumonia (VAP) as pneumonia that occurs in patients who have had intubation with an endotracheal or tracheostomy tube to help or control respiratory function continuously for at least 48 hours before the onset of the pneumonia.62 A 2014 UK survey of 339 intensive care unit (ICU) consultants reported *P. aeruginosa* and *Enterobacteriaceae* as the primary causative pathogens.49 The prevalence of hospital-acquired respiratory infection among inpatients in England is estimated at 1.5%, with HAP not associated with intubation accounting for over half of these.63 HAP requires prompt treatment, and antibiotics should be initiated within 4 hours of diagnosis.62 HAP/VAP has an estimated mortality rate of 30–70% and is estimated to increase hospital stays by approximately 8 days.62

VAP is a condition affecting intubated patients in the ICU. The reported epidemiology varies between studies and precise definitions used. In the UK, prevalence has been estimated at 15–20% and incidence at 32 VAP incidents per 1,000 ventilator days.64 VAP is associated with considerable excess mortality. A meta-analysis of data on 6,284 patients from 24 trials reported the mortality attributable solely to VAP to be 13%, although there was substantial variability between patient groups (trauma, surgical, and medical) and by the acute physiology and chronic health evaluation II (APACHE II) score and the simplified acute physiology score (SAPS).65 In addition, due to the debilitating nature of the disease, HAP/VAP cause significant increases to length of stay and overall healthcare costs.66,67 Therefore, the lack of an effective, timely antibiotic can be detrimental to hospital ICU logistics and with regards to bed and ventilator capacity. This situation is currently further exacerbated due to the COVID-19 pandemic.68

MDR, including carbapenem resistance, is a concern in general but specifically in the treatment of VAP.69 The Faculty of Intensive Care Medicine recommends that ICUs should have standardised systems to monitor VAP rates and antibiotic resistance patterns.70 *P. aeruginosa* possesses intrinsic and acquired resistance mechanisms making it a significant threat for the patient as the treatment choices are limited.71

#### Complicated intra-abdominal infection

Intra-abdominal infections (IAIs) represent a broad spectrum of pathological conditions arising in abdominal organs.72 In cIAIs, the infection progresses from a single organ and affects the peritoneum, causing intra‑abdominal abscesses or diffuse peritonitis. This may be a result of surgery‑associated infection or may arise due to trauma or spontaneous perforation (for example, appendicitis, a perforated ulcer or diverticulitis). Due to the severity of cIAI and the high associated mortality risk in the absence of prompt and appropriate treatment, patients with cIAI are expected to be universally hospitalised. NICE has not published guidelines on the management of cIAI and refers to guidelines from the Surgical Infection Society and the Infectious Diseases Society of America and the World Society of Emergency Surgery.73

In a real-world study of 4,553 patients from 132 hospitals across the globe, 17.4% were admitted to hospital in critical condition with severe sepsis or in septic shock and the overall mortality rate was 9.2%. The most common infection sources included appendicitis (34.2%) and cholecystitis (18.5%).74

Successful treatment for cIAI is dependent on prompt diagnosis, adequate resuscitation, early initiation of appropriate antimicrobial therapy, control of infection source, and reassessment and adjustment of management.75 Drainage of infected foci (percutaneous or surgical, as indicated) is recommended in nearly all patients, with only highly selected patients being candidates for antimicrobial therapy alone.74 Patients who become critically ill can be expected to require intensive care admission, and are at high risk of mortality. A single-centre study from a Belgian university hospital reported 62.5% mortality rate in ICU-admitted patients with bloodstream infection of abdominal origin. The most frequent causative pathogen was *E. coli* and at least one antibiotic-resistant pathogen was implicated in 41% of patients.50

#### Complicated urinary tract infection

Urinary tract infections (UTIs) are one of the most common causes of sepsis presenting to hospitals.76 Specific host factors (e.g. underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding) can result in a UTI which does not conform to the normal clinical trajectory and is considered a cUTI.51,76 Furthermore UTI in males are, by definition, considered a cUTI.76

The potential spectrum of causative pathogens is much larger than in uncomplicated UTIs, and resistance is more likely. The most common species found in cUTI cultures include *E. coli, Proteus spp., Klebsiella spp., Pseudomonas spp., Serratia spp. and Enterococcus spp*., with a predominance of *Enterobacteriaceae* (60–75%), especially *E. coli* (particularly if the cUTI is the initial infection site).51 In catheterised patients, there is a particular risk of the UTI progressing into secondary bacteraemia, as approximately a fifth of all hospital-acquired bacteraemia cases arise from the urinary tract. The associated mortality is approximately 10%.51

In England, NICE Guidelines on antimicrobial prescribing in urinary tract infections recommend that adults with lower UTI, catheter-associated UTI, pyelonephritis, or prostatitis should be referred to hospital if they have any symptoms or signs suggesting a more serious illness or condition.77-80 Patients who do not respond to initial antibiotic therapy, are pregnant, or present with other factors that put them at increased risk of developing complications (e.g. immunosuppression) should also be referred to hospital.77-79

While some patients are likely to be managed on the ward, it should be noted that cUTI may occur in high-risk settings, such as immunosuppressed haematology/oncology or post-transplant patients (up to 25% of renal transplant patients develop a UTI in their first year post-transplant)76 and catheterised patients, including those in an ICU. The daily risk of bacteriuria in patients with indwelling catheters is estimated at 10%, with up to 25% risk of the bacteriuria progressing to a UTI.76

#### Bacteraemia

Bacteraemia (bloodstream infection) is a serious condition with risk of life-threatening sepsis. Sepsis is generally managed in an intensive care hospital setting. The NICE risk stratification tool81 recommends referring patients with a possible infection urgently for emergency care if they show any criteria of high sepsis risk (e.g. heart rate elevated to >130 beats per minute) or if they have moderate-to-high risk criteria and cannot be effectively diagnosed and treated outside of hospital as, according to the Sepsis screening tool acute assessment, IV treatment with antibiotics and fluid support is necessary .82

Bloodstream infections (BSIs) are encountered in the ICUs across the globe. The 2017 EPIC III study was 24-hour point prevalence study conducted at 1150 ICU units in 88 countries. In this large study, 54% of 15,202 patients had suspected or proven infection and as many as 1,239 (15.2%) had a BSI, specifically. Among those patients with at least 1 positive culture (n=5,259), Gram-negative microorganisms were found in 67% overall and were more frequently implicated in hospital- (71%) or ICU-acquired (78%) infections compared with community-acquired infections (57%). The most common Gram-negative microorganisms were *Klebsiella spp*. (27%), *E coli* (25%) and *Pseudomonas spp*. (24%). Furthermore, between 2015 and 2019, the resistance profile of *E. coli* BSI has increased for key antibiotics, including: third-generation cephalosporins (12% to 15%), ciprofloxacin (18% to 20%) and co-amoxiclav (42% to 44%).83 This, alongside increasing infections with vancomycin-resistant *Enterococcus* or *Klebsiella spp*. resistant to third-generation cephalosporins and carbapenems were among those associated with a significantly elevated risk of in-hospital death.84

The burden of bacteraemia and associated sepsis in England is high. A surveillance program of BSIs provided data from 45.5% of all ICUs in England collected over 12 months from May 2016. The rate of BSI was 5.7 per 1,000 patient-days for adult ICUs with high variability between the participating units (range: 0.0–44.0 BSIs per 1000 patient-days). 30-day all-cause fatality rate among adult ICU patients with positive blood cultures was 23.8% (95% CI 21.4–26.4%).85 The high mortality rate could be decreased by shortening the time-to-appropriate therapy.25

## Treatment of Gram-negative infections in England

Treatment of serious infections generally occurs in the hospital setting and can be separated into two phases – the empirical (risk factor-directed) phase and the targeted (mechanism / pathogen-directed) phase, in line with the “Start Smart – Then Focus” approach, advocated by Public Health England.8 The empirical phase, where treatment is given unaware of the causative pathogen and its antimicrobial susceptibility, usually relies on broad-spectrum agents and can ensure that patients are treated promptly and effectively so as to maximise the chances of resolving the infection without sequelae.8 Risk factors, including previous admission to ICU, longer admission times, critical illness, use of invasive devices and prior antibiotic therapy,24,86 should prompt early treatment. The time-to-appropriate therapy is a key factor for a successful treatment of the infection. The sooner an effective treatment is administered the better the outcomes.

Once bacterial culture results are available, a switch to targeted treatment will be made, utilising a targeted, ideally narrower spectrum antimicrobial effective against the infectious pathogen.8 The NICE guideline on antimicrobial prescribing for HAP recommends prompt empirical antibiotic prescribing (within 4 hours of diagnosis) that should be guided by:62

* the severity of signs and symptoms
* length of stay in hospital before onset of symptoms
* the risk of developing complications (e.g. comorbidities, immunosuppression)
* factors that may influence resistance: local hospital and ward-based AMR data, recent antibiotic use, recent microbiological results, and recent contact with a health or social care setting before current admission
* the risk of adverse effects with broad-spectrum antibiotics

Antimicrobial treatment should be reassessed once microbiological results are available and microbiologist’s advice should be sought if the patient’s symptoms are not improving, or if the infection is due to MDR bacteria. Therefore, it is necessary to capture not only highly specific scenarios corresponding to the “ideal” patient pathway, but also account for different therapy options and the potential of treatment failure and resulting treatment switch (for further detail see section 4.1).

### Pathogen-specific treatment approaches

While the licensed indications for antimicrobials often specify the site/type of infections, pathogen-specific treatment approaches may be more appropriate in the targeted treatment phase once the infectious agent and its antimicrobial susceptibility is known. Furthermore, risk factor-based treatment approaches must be adaptable and, due to the aggressive nature of infectious disease, constantly monitored in order to maintain effective treatment. Indeed, this mode of guidance is increasingly being issued by clinical societies, reflecting the challenges associated with treating infections caused by MDR or difficult-to-treat bacteria.

## Value of new antibiotics

As outlined in section 1.1, AMR is a public health priority and there is significant societal benefit and need in obtaining a diverse set of novel antibiotics.

For this reason, the Office of Health Economics has published a briefing outlining 10 elements of value for new antibiotics.34 Of those, four are typically assessed using traditional health technology assessment (HTA) methods (health gain, unmet need, cost offsets and productivity benefits). However, there are six additional benefits not typically included in traditional HTA, outlined in Table 1.

Table 3. Elements of value of relevance to new antibiotics

|  |  |
| --- | --- |
| **Value** | **Description** |
| Transmission value | The population impact and benefits of avoiding the spread of MDR infections |
| Insurance value | The benefits of having a treatment available in case AMR to all other existing antimicrobials rises or as an insurance against future probabilistic events, such as, but not limited tooutbreaks |
| Diversity value | The benefits of having multiple antibiotics available that may be used within treatment strategies aiming to reduce selection pressure and minimise resistance development |
| Spectrum value | the benefits of replacing broad-spectrum antibiotics with narrow-spectrum ones that reduce collateral damage to the microbiome and minimise opportunities for resistant organisms to thrive |
| Novel action value | the benefits associated with a new mechanism of action or structure, which may allow avoiding cross-resistance and boost the development of follow-on drugs, increasing diversity |
| Enablement value | the benefits associated with antibiotic use in the setting of surgical or medical procedures, which could not be safely undertaken were effective antibiotics not available to prevent or treat surgical site or post-procedure infections |

These elements of additional value are directly noted in the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) evaluation framework, the EEPRU protocol and the NICE final scope for this evaluation.

Despite the reference to these additional value elements being particularly pertinent to antibiotics and thus rationalising their inclusion into an HTA framework, these elements still do not fully capture the full societal population benefit. It is important to note that value associated to both productivity and associated cost offsets or relevant ongoing, long term fiscal impacts are not captured. While not traditionally included in the NICE reference case, the committee should be aware that antibiotics have a considerable population wide impact, thus their ability to drive productivity and fiscal benefits at a national level could demonstrate substantial wider system value.

# Decision problem

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| ***Key messages*** |
| * In contrast to conventional HTAs, the aim of the appraisal is to inform a value-based fixed annual payment,87 making it critical that the value of CAZ/AVI is fully captured in this appraisal and that any areas of value not captured are carefully identified and considered by the committee. * CAZ/AVI is a fixed drug combination of the cephalosporin, ceftazidime, and the novel non-β-lactam β-lactamase inhibitor, avibactam. It is indicated in adults and paediatrics for common infections caused by Gram-negative pathogens in the UK – cUTI, cIAI, HAP/VAP, as well as for patients with Gram-negative infections for which LTO exist. It is also indicated for bacteraemia in adults.   + The licensed indication for CAZ/AVI accommodates pathogen-directed therapy as well as syndrome-based/empirical approaches.   + With activity against CRE (including KPC and OXA-48), MDR *Pseudomonas aeruginosa* (*P. aeruginosa*) and ESBL-producing organisms, CAZ-AVI provides an effective and tolerable option for managing some of the most difficult to treat MDR infections faced by patients in the UK.   + CAZ/AVI provides a carbapenem-sparing treatment option, which is an important advantage where carbapenem resistance has been confirmed, or its development is a concern. CAZ/AVI can reduce selection pressure of use of carbapenems and other existing antibiotics. * In line with the stated NICE decision problem and EEPRU protocol,87,88 reflecting the complexity of antimicrobial treatment landscape means that not all possible comparators could be included in the CAZ/AVI trials. For the company economic model, a simplified treatment pathway was designed using expert elicitation. * While the EEPRU protocol has identified specific high-value clinical scenarios (HVCSs), this submission focuses on key indications for CAZ/AVI, i.e. HAP/VAP, cUTI, and cIAI. |

Ceftazidime with avibactam (ZAVICEFTA®, CAZ/AVI) is indicated for patients aged ≥3 months with the following infections:

* cIAI
* cUTI, including pyelonephritis
* HAP, including VAP
* Infections due to aerobic Gram-negative organisms for which LTO exist

AND

* Treatment of adult patients with bacteraemia that occurs in association with or is suspected to be associated with HAP/VAP, cIAI, or cUTI.

This submission covers the full proposed marketing authorisation for CAZ/AVI in these indications and is consistent with the final NICE scope. The decision problem presented in this submission in relation to the final scope published by NICE is outlined in Table 4.

Table 4. The decision problem

|  | **Final scope issued by NICE** | **Decision problem addressed in the company submission** | **Rationale if different from the final NICE scope** | **EEPRU protocol** |
| --- | --- | --- | --- | --- |
| **Population** | Adults or children aged three months or older receiving treatment in secondary or tertiary care settings in whom resistant gram-negative infection is suspected/confirmed, with:   * complicated intra-abdominal infections * complicated urinary tract infections, including pyelonephritis * hospital‑acquired pneumonia, including ventilator‑associated pneumonia * bacteraemia, in adults, that occurs in association with, or is suspected to be associated with, any of the infections listed above. * infections caused by aerobic gram‑negative bacteria with limited treatment options | Adults or children aged three months or older receiving treatment in secondary or tertiary care settings in whom resistant gram-negative infection is suspected/confirmed, with:   * complicated intra-abdominal infections * complicated urinary tract infections, including pyelonephritis * hospital-acquired pneumonia, including ventilator-associated pneumonia * Infections caused by aerobic gram-negative bacteria with limited treatment options   Bacteraemia in adult patients that occurs in association with, or is suspected to be associated with, any of the infections listed above. | As per NICE scope | Focus of the EEPRU model is on two specific HVCS:   * cUTI: patients with suspected or confirmed serine carbapenemase-producing Enterobacterales of the OXA-48 and KPC subtypes (microbiology-directed treatment) * HAP/VAP: infections suspected to be caused by Enterobacterales which are MDR/ carbapenem-resistant / OXA-48 or KPC mechanisms of resistance (risk-based empiric treatment) |
| **Intervention** | Ceftazidime with avibactam | ZAVICEFTA® (ceftazidime with avibactam, CAZ/AVI) | As per NICE scope | Ceftazidime with avibactam alone or in combination |
| **Comparator(s)** | Clinical management without ceftazidime with avibactam | Selection of comparators:   * Comparators included in the economic model:   + Piperacillin with tazobactam   + Colistin   + Meropenem * Comparators used in phase 3 randomised controlled trials of CAZ/AVI:   + Meropenem   + Doripenem   + Best available therapy   + Cefepime | Clinical evidence for CAZ/AVI is available against a range of comparators used in pivotal RCTs and key real-world studies, and this will be presented in the company submission. However, in the company economic model, comparators will be simplified to reflect the most clinically relevant therapies in the empirical and confirmed / suspected resistance settings. This aims to maximise clinical relevance across all of NHS England in a situation where only a finite number of scenarios can be reasonably modelled given the variability of local resistance patterns. The economic model design and inputs (including the comparators included in the model, piperacillin/tazobactam [for cIAI and cUTI] or colistin [for HAP/VAP] and meropenem [all modelled indications]) were validated by a panel of clinical experts, to ensure that the model appropriately captured the dynamics of infection transmission and antimicrobial use. | Microbiology-directed treatment:  Comparators used in clinical practice in England, as defined by susceptibility testing and/or gene testing and considering infection site and infiltration data. Potential comparators include:   * meropenem + colistin * fluoroquinolones (levoflaxin, ciproflaxin) + meropenem * aminoglycosides (gentamicin, amikacin, tobramycin)   If low risk of ESBL and AmpC beta- lactamase suggested by susceptibility testing:   * cephalosporins (ceftriaxone, cefepime, ceftazidime) * astreonam + fosfomycin * astreonam + colistin   For HAP/VAP the following comparators may be included also:   * tigecycline + colistin * tigecycline + meropenem + colistin * aminoglycosides (gentamicin, amikacin, tobramycin) may be used in combination with fosfomycin instead of as monotherapy   Risk-based empiric treatment:  Comparators used in clinical practice in England, as defined by suspected infection, considering knowledge of the local epidemiology where a patient was previously hospitalised, outbreak in the ward where the patient is currently admitted, or previous cultures (taken during previous hospitalisations stays) showing the patient was colonised by an OXA-48 enterobacterales.  Potential comparators in the risk-based empiric HVCS include:   * meropenem + colistin * fluoroquinolones (levoflaxin, ciproflaxin) + meropenem * aminoglycosides (gentamicin, amikacin, tobramycin) + fosfomycin * tigecycline + colistin * tigecycline + meropenem + colistin |
| **Outcomes** | * All-cause mortality * Clinical cure (complete resolution of signs/symptoms of the index infection such that no further antimicrobial therapy was needed) * Microbiologic eradication * Emergence of resistance * Hospital days * ICU days * Readmission rate within 90 days of treatment * Number of treatment days * Health-related quality of life * Adverse events (including those associated with *C. difficile* infection and renal toxicity) | * Clinical cure * Mortality (Note: available data on mortality from clinical trials and key real-world studies will be presented in the company submission. In the economic model, mortality for patients who die from unfavourable response at TOC were applied, while mortality among patients who were treated successfully were captured based on published data sources.) * Microbiologic eradication (available from clinical trials but not captured in the economic model) * Emergence of resistance was not captured as an endpoint in pivotal CAZ/AVI clinical trials; however, resistance development is captured in the economic model and informed by epidemiological and public health sources specific to England. * Hospital days * ICU days (available from clinical trials but ICU days not captured in the company economic model as an outcome). It is crucial that the EEPRU model captures incremental benefits of CAZ/AVI vs comparators in terms of ICU stay, which is particularly critical during COVID-19 and the associated limited ICU capacity. * Number of treatment days * Health-related quality of life data was not collected in the pivotal RCTs of CAZ/AVI, due to the challenges associated with administering questionnaires to acutely ill patients with serious infections. HRQoL was captured in the economic model based on published data sources. * Adverse events (detailed safety data are available from clinical trials, but *C. difficile* infection is the only adverse event captured in the economic model)   While specified in the final scope, readmission rate within 90 days of treatment was not captured in clinical trials of CAZ/AVI or in the economic model, and will not be included in the company submission | | * All-cause mortality * Clinical cure (complete resolution of signs/symptoms of the index infection such that no further antimicrobial therapy was needed) * Microbiologic eradication * Emergence of resistance * Hospital days * ICU days * Readmission rate within 90 days of treatment * Number of treatment days * Health-related quality of life * Adverse events (including those associated with *C. difficile* infection and renal toxicity) |
| **Economic analysis** | The NICE guide to the methods for technology appraisal (2013) will be followed where possible, with the following adaptations.  The aim of the analysis will be to estimate the value of ceftazidime with avibactam to the NHS under the stewardship scenario(s) that is expected to generate the highest net health benefit to the NHS.  Within the timescale and resources assigned, it is unlikely to be possible to undertake detailed economic modelling for all pathogens/clinical syndrome combinations. The evaluation will include one or more high value clinical scenarios for detailed study, together with additional indications that need to be considered but where bespoke economic models will not be developed. For these additional indications a summary of relevant clinical and health economic information will be provided. Estimates of value to the NHS in England need to take account of the high value clinical scenarios and additional indications.  The economic analysis outputs will be, wherever feasible, expressed in population net health benefits as measured in quality-adjusted life years. Population net health benefit should be estimated over the full time horizon of the economic model and options presented for assigning an appropriate proportion of the total value to a potential 10-year contract period.  In the base-case analysis, a threshold of £20,000 per quality-adjusted life year should be used for the calculation of net health benefits.  For antimicrobials, the evaluation will include consideration of additional elements of value as set out in the Evaluation Framework. These include spectrum value, transmission value, enablement value, diversity value, and insurance value.  Depending on available evidence, several stewardship strategies may be modelled and compared (e.g. reserving ceftazidime with avibactam until testing reveals specific resistance patterns, selected empiric use in high-risk settings, rotation of antimicrobials) to identify the optimal usage scenario. | The model which Pfizer used has recently been published26, in a major peer reviewed health economics journal. The model broadly adheres to the NICE reference case with adaptations to align to the EEPRU and Evaluation framework for antimicrobials and final scope, with additional/modified features underlined below:   1. The analysis will explore different stewardship scenarios, identifying those expected to generate the highest health benefits to the NHS while minimising resistance development. 2. Rather than including a single primary indication, the analysis will encompass several key indications for CAZ/AVI, i.e. HAP/VAP, cUTI, and cIAI, as well as key scenarios relevant to the LTO indication, including scenarios exploring pathogen-directed therapy.   The LTO indication introduces the notion that an antibiotic should be reserved for those patients who otherwise have no, or very few, treatment options due to their infections being multidrug- or pan-resistant. This indication is highly heterogeneous due to the variety of clinical syndromes and pathogens that may be encountered, so that economic modelling of LTO has to be necessarily constrained to specific scenarios. As some of these scenarios may be common for CAZ/AVI and cefiderocol, the likely usage of both drugs in relevant clinical scenarios could potentially be assessed.   1. The economic analysis outputs will be expressed in population net health benefits as measured in quality-adjusted life years, estimated both over the full-time horizon of the economic model and the potential 10-year contract period. 2. £20,000 to £30,000 WTP thresholds will be used for the calculation of net health benefit. In line with prior discussions with NICE, the WTP threshold should not be seen as fixed, but rather only as a guidance. 3. The evaluation will include several of the additional elements of value as set out in the Evaluation Framework: diversity value and transmission value are included in the core company model. Both insurance and enablement value are only partially included, with further, more inclusive, modelling to be shared with the project team post submission. Spectrum value is not included. As such there are areas of significant value as outlined in the EEPRU framework that are not captured as part of the proposed model. The committee should take this into account when considering the estimates of value derived from this model and the conservative approach taken. This emphasises point 4 above (and point 3), outlining the strong rationale for the need to apply flexibility in the thresholds.   In addition, it should be noted that:   * In line with the anticipated use of CAZ/AVI, only the healthcare setting is considered within the economic model, and infections treated within the community setting are not modelled. * The company economic model has limited capacity to capture time to effective therapy – the only ways this is accounted for in the model is by:   + Progressing patients by up to 2 lines of ineffective treatment and assessing outcomes vs a scenario where first-line treatment is assumed to be effective   + Within scenarios, varying the percentage of patients receiving pathogen-directed therapy (20% in the base case)   This is an important limitation, underestimating the full value, due to the increased morbidity and mortality associated with inappropriately selected empirical therapy, resulting in a delay to effective treatment.89-96 | | A decision-analytic model will be developed to estimate the population Net Health Effects of the alternative usage scenarios for CAZ/AVI and compactor AMs in the two HVCSs.  The de novo economic model will comprise a patient-level component characterising the likely impact of CAZ-AVI and existing AM usage scenarios on costs, HRQoL and mortality over the lifetime of the patient; and a population-level component that aggregates the patient-level predictions to the population level accounting for the likely trajectory of infections and resistance patterns over time and potentially capturing the effects of usage scenarios on these trajectories.  Where possible the analyses will be consistent with the NICE reference case. The model perspective will be that of the NHS and Personal Social Services. |
| **‘Primary indication(s)’ (high value clinical scenarios) to be considered for detailed modelled** | Not specified in the scope | All licensed indications should be captured within the EEPRU economic model, with the ambition to cover all key indications (cUTI, cIAI, HAP/VAP, LTO, paediatrics and bacteraemia) and pathogen combinations to ensure a more accurate approach can be taken when extrapolating value at a population net health benefit level. An approach to modelling which considers multiple indications and pathogen combinations, including several considerations to EEPRU’s value framework, has been demonstrated through a dynamic disease transmission model in a recent publication26, thereby demonstrating feasibility. A more pragmatic approach to other indications can be taken where there is less available data, whereby Pfizer would like to see a large emphasis on the mitigation of uncertainty through expert elicitation and a practical yet novel approach to the revising of value based on gaps in data for modelling. Where possible without major modifications to the model structure, scenarios related to different indications should be explored to ensure that uncertainty across the full spectrum of CAZ/AVI indications and potential clinical uses is minimised. | | Focus of the EEPRU model is on two specific HVCS:   * cUTI: patients with suspected or confirmed serine carbapenemase-producing Enterobacterales of the OXA-48 and KPC subtypes (microbiology-directed treatment) * HAP/VAP: infections suspected to be caused by Enterobacterales which are MDR/ carbapenem-resistant / OXA-48 or KPC mechanisms of resistance (risk-based empiric treatment) |
| **Other considerations** | Guidance will include consideration of the optimal stewardship scenarios. | In line with the final scope, the analysis will include consideration of the optimal antimicrobial stewardship scenarios. These will include both pathogen- and/or resistance mechanism-specific therapy and risk factor-directed empirical therapy. Within the model’s constraints outlined above, scenarios will be used to explore the best balance between maximising employment of pathogen-directed treatment and ensuring that delays to effective therapy are minimised to avoid the associated adverse outcomes.94-96 | |  |
| AM: antimicrobial; *C.* Difficile: *Clostridium difficile*; CAZ/AVI: ceftazidime with avibactam; cIAI: complicated intra-abdominal infection; COVID-19: Corona Virus Disease 2019; cUTI: complicated urinary tract infection; EEPRU: Policy Research Unit in Economic Evaluation of Health and Care Interventions; HAP: hospital-acquired pneumonia; HRQoL: health-related quality of life; ICU: intensive care unit; LTO: limited treatment options; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; RCT: randomised controlled trial; TOC: test of cure; VAP: ventilator-associated pneumonia; WTP: willingness-to-pay | | | | |

## Description of the technology being evaluated

### CAZ/AVI

The technology being appraised, CAZ/AVI, is a novel, fixed drug combination (FDC) of the cephalosporin, ceftazidime, and the novel non-β-lactam β-lactamase inhibitor, avibactam (Table 5).17,19,97,98

The summary of product characteristics (SmPC) for CAZ/AVI and the European public assessment report are provided in Appendix B.

Table 5. Technology being evaluated

|  |  |
| --- | --- |
| **UK approved name and brand name** | Ceftazidime/avibactam, CAZ/AVI, ZAVICEFTA® |
| **Mechanism of action** | Ceftazidime is a third-generation cephalosporin which, like all β-lactam antibiotics, binds to a variety of bacterial PBPs. The binding of ceftazidime to PBPs inhibits bacterial peptidoglycan cell wall synthesis leading to bacterial cell lysis and death.99  Avibactam is a first-in-class a semi-synthetic, non-β-lactam, β-lactamase inhibitor with a novel [3.2.1]-diazabicyclooctane chemical scaffold. Through covalent acylation of the β-lactamase active-site serine residue,99 avibactam inactivates Ambler class A ESBLs and carbapenemases (e.g. KPC), class C (e.g. AmpC), and some class D oxacillinases and carbapenemases (e.g. OXA-48) β-lactamase.100,101 Avibactam has no inhibitory effect on class B MBLs due to the absence of the active-site serine residue, or against Acinetobacter OXA-type carbapenemases.98  Paired with ceftazidime, avibactam restores the antibacterial activity of ceftazidime against isolates that produce OXA-48-like carbapenamases.102 Although OXA-48-like enzymes only weakly hydrolyse ceftazidime, they generally exist in an environment in which multiple other β-lactamases are present. Furthermore, avibactam reinstates the antibacterial activity of ceftazidime against some strains of Enterobacteriaceae and *Pseudomonas aeruginosa* (*P. aeruginosa*) that express the pre-specified β-lactamases.101 Combination with avibactam does not improve the activity of ceftazidime against carbapenem-resistant *A. baumannii* or *S. maltophilia*102. |
| **Marketing authorisation/CE mark status** | CAZ/AVI received UK marketing authorisation in June 2016. |
| **Indications and any restriction(s) as described in the summary of product characteristics (SmPC)** | CAZ/AVI is indicated in adults and paediatric patients aged 3 months and older for the treatment of the following infections:   * Complicated intra-abdominal infection (cIAI) * Complicated urinary tract infection (cUTI), including pyelonephritis * Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)   Treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.  CAZ/AVI is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults and paediatric patients aged 3 months and older with limited treatment options. |
| **Method of administration and dosage** | The recommended dose of CAZ/AVI in adults is 2g/0.5g administered as an IV infusion over 2 hours given every 8 hours. The recommended treatment duration varies depending on the indication. For paediatric patients, age- and weight-based dosing is recommended. Dose reduction is required in patients with renal impairment. Please consult the SmPC for details. |
| **Additional tests or investigations** | None required |
| **List price and average cost of a course of treatment** | £857.00 per pack of 10 vials containing 2g/0.5g powder for concentrate for solution for infusion. |
| **Patient access scheme (if applicable)** | N/A |
| *A. baumannii*: *Acinetobacter baumannii*; CAZ/AVI: ceftazidime/avibactam; cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection; HAP: hospital-acquired pneumonia; KPC: Klebsiella pneumoniae carbapenemase; MBL: metallo-β-lactamases; PBP: penicillin binding protein; *S. maltophilia*: *Stenotrophomonas maltophilia*; VAP: ventilator-associated pneumonia | |

### Positioning of CAZ/AVI in the treatment landscape

The repertoire of novel antibiotic agents, which are all β-lactam based options, has been enriched over the last few years. Table 6 describes the relative activity of CAZ/AVI and the novel antibiotics now available in the UK against resistant pathogens and key mechanisms of resistance. Importantly, CAZ/AVIprovides a carbapenem treatment option, which is of particular value when selecting empirical treatment in areas where carbapenem resistance is high, in patients with recent carbapenem exposure, or in instances of ongoing or recent outbreaks of CRE.

Table 6. Spectrum of activity of recently marketed antibiotics102,103

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Ambler class and resistance mechanism** | | | | | **Key pathogens** | | | **License** |
| Class A | | Class B | Class C | Class D | *Enterobacteriaceae* | *P. aeruginosa* | *A. Baumannii* | Paediatrics |
| ESBL | KPC | NDM, IMP, VIM | AmpC | OXA-48 |
| Ceftazidime-avibactam |  |  |  |  |  |  |  |  |  |
| Ceftolozane-tazobactam |  |  |  |  |  |  |  |  |  |
| Meropenem-vaborbactam |  |  |  |  |  |  | **\*** |  |  |
| Imipenem-cilastatin-relebactam |  |  |  |  |  |  |  |  |  |
| Cefiderocol |  |  |  |  |  |  |  |  |  |
| \*Clinical efficacy not demonstrated for *Pseudomonas*104  AmpC: ampicillin C β-lactamase enzyme; EMA: European Medicines Agency; ESBL: extended spectrum β-lactamase; IMP: active-on-imipenem; KPC: K. pneumoniae carbapenemase; NDM: New Delhi metallo-β-lactamase; OXA-48: oxacillinase-48; VIM: Verona integron-encoded metallo-β-lactamase. | | | | | | | | | |

The anticipated positioning of CAZ/AVI within the treatment pathway of serious infections managed within the hospital setting is presented in Figure 4. CAZ/AVI can be employed early in the patient journey when there are risk factors for resistance while awaiting full diagnostic results to avoid therapy with an ineffective antibiotic and increase the probability of survival. These risk factors include previous admission to ICU, longer admission times, critical illness, use of invasive devices and prior antibiotic therapy,24,86,105 including cephalosporin, carbapenem or fluoroquinolone use.106 An example of recommended empirical use of CAZ/AVI is presented in the NICE guideline on HAP, which lists CAZ/AVI as a first-choice intravenous antibiotic option in patients with severe symptoms or signs (for example, symptoms or signs of sepsis) or at higher risk of resistance (based on specialist microbiological advice and local resistance data).62 It is vital that effective treatment is given as soon as possible, because time to effective treatment is a strong predictor of outcome related to; length of hospital stay, morbidity, and mortality.25

Within the NHS, CAZ/AVI is also likely to be used as part of a targeted/focused treatment approach (Figure 4). Importantly, CAZ/AVIis effective against several resistant pathogens that are which cause considerable morbidity and mortality, and that feature on the WHO priority list for the development of new antimicrobials (see Table 7).38,103

The positioning of CAZ/AVIpresented in Figure 4 should be interpreted in conjunction with antimicrobial stewardship practices. Previous modelling work has demonstrated that stewardship approaches based on diversified antimicrobial use maximise population and patient-level gains, while avoiding excessive increases in AMR levels26 (see Section 4). Therefore, at population level and over time, CAZ/AVIis likely to be used ***alongside*** other therapy options for early empiric treatment in patients meeting risk factors such as previous ICU admission, longer admission times, critical illness, use of invasive devices or in patients with suspected/confirmed resistance rather than ***instead of*** other antimicrobial therapies if given as monotherapy. Therefore, the treatments used in the economic model should not be considered as comparators but as alternative treatment options.

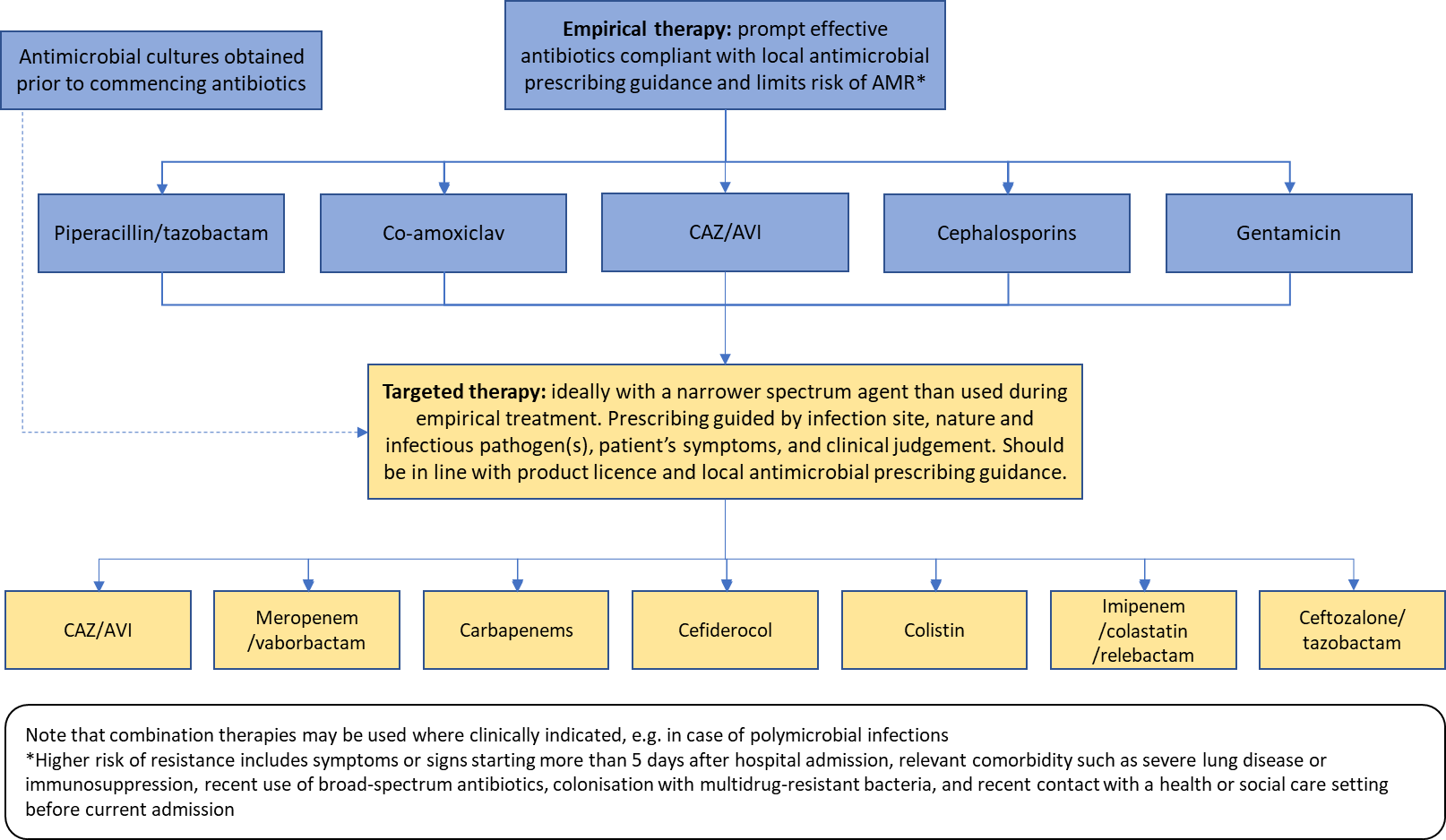


Figure 4. Proposed positioning of CAZ/AVI within the treatment pathway

#### CAZ/AVI-related recommendations in treatment guidelines

CAZ/AVI has recently featured in the following pathogen-specific clinical society guidelines:

* **UK Clinical Pharmacy association (UKCPA) Pharmacy Infection Network (PIN) guidelines on treating infection caused by CPE:**107
  + CAZ/AVI is recommended as a treatment option for invasive CPE infections, and specifically for the treatment of invasive infections caused by KPC- and OXA-48-producing resistant *Enterobacterales*
* **Infectious Diseases Society of America (IDSA) Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections**:108
  + CAZ/AVI is considered a preferred treatment for cUTI, confirmed CRE outside of the urinary tract, and KPC and OXA-48 infections. This guidance also recommends CAZ/AVI as one of the preferred treatments in cUTI and infections outside of the urinary tract caused by difficult-to-treat *Pseudomonas spp.*

CAZ/AVI has demonstrated effectiveness and safety in several serious and potentially life-threatening infections caused by Gram-negative species. This includes infections associated with substantial unmet need, such as HAP/VAP,16 or the treatment of patients with otherwise limited therapeutic options.9-14 Importantly, CAZ/AVI is active against 8 WHO critical priority pathogens (Table 7), which makes it a key component of comprehensive antimicrobial stewardship strategies.

Table 7. Clinical efficacy of CAZ/AVI against specific pathogens38,100

|  |  |
| --- | --- |
| **Pathogen** | **WHO Ranking** |
| *Enterobacteriaceae* (carbapenem-resistant, 3rd generation cephalosporin-resistant):   * *Citrobacter freundii* * *Enterobacter cloacae* * *E. coli* * *Klebsiella oxytoca* * *K. pneumoniae* * *Proteus mirabilis* * *Serratia marcescens* | Critical |
| *P. aeruginosa* (carbapenem-resistant) | Critical |

#### Treatment of Gram-negative infection in adults with limited treatment options

Infections caused by aerobic gram‑negative bacteria with LTO include a wide variety of clinical scenarios in which patients are infected with a difficult-to-treat pathogen susceptible to CAZ/AVI but the infection does not necessarily affect the sites investigated in clinical trials (abdomen, lungs, urinary tract). This indication therefore enables pathogen-directed licensed use of CAZ/AVI where there is a clear clinical need. In this setting, CAZ/AVI has been investigated in patients with bacteraemia, complicated skin and soft tissue infection (cSSTI), bone and joint infections, meningitis due to KPC and OXA-48 resistance mechanisms, and MDR *Pseudomonas spp.*9-14

Carbapenem resistance is particularly relevant to the LTO setting. CRE infection has been associated with a four-fold increase in inadequate empirical therapy. Patients with CRE infections also had an increased mortality, length of stay and healthcare costs.24

Almost all UK acute healthcare institutions have identified new CRE colonisation109 and it is established that colonisation is a risk factor for subsequent invasive infection.12 Outbreaks of CRE have occurred in Manchester, Leicester, London and Swansea with associated significant cost and service disruption (See Section 1.2.1). There is an unmet need for agents like CAZ/AVI that are active against CRE, to counter the risk of CRE outbreaks and to provide carbapenem-sparing treatment options in critically ill populations where treatment options are limited.

#### Paediatric indication

CAZ-AVI is the first novel non-β-lactam, β-lactamase inhibitor to be granted a paediatric indication. The first study of ceftazidime–avibactam in paediatric patients (NCT04040621) was a Phase I, single-dose, pharmacokinetics and safety study in 32 paediatric patients aged from 3 months to <18 years, with suspected or confirmed bacterial infection, for which they were receiving other systemic antibiotic therapy.110

Data from this study were used in pharmacokinetic/pharmacodynamic modelling and simulations to support dose selection for the subsequent Phase II studies, ANDI and KURA,111,112 investigating CAZ-AVI in patients aged 3 months to <18 years with cIAI and cUTI, respectively. The overall safety profile for CAZ–AVI in the paediatric population was consistent with that observed in adults, with no unexpected adverse events occurring in this population. Please refer to sections 3.2.3 and 3.3.3 for more information.

# Clinical effectiveness evidence

|  |
| --- |
| ***Key messages*** |
| * The efficacy and safety of CAZ/AVI in its licensed indications has been demonstrated across several high-quality pivotal Phase II/III studies and is further supported by an extensive wealth of retrospective real-world data. * CAZI/AVI has demonstrated non-inferiority to best available therapies, including meropenem, for key indications, including HAP/VAP, cUTI and cIAI. * CAZ/AVI is well tolerated, with a safety profile typical of injectable cephalosporins.98 * These trials support the positioning of CAZ/AVI as an important alternative to currently available antibiotics aimed to address the high levels of unmet need.   + With activity against CRE (including KPC and OXA-48), MDR *Pseudomonas aeruginosa* (*P. aeruginosa*) and ESBL-producing organisms, CAZ-AVI provides an effective and tolerable option for managing some of the most difficult to treat MDR infections faced by patients in the UK. |

The standard for antimicrobial (AM) trials are non-inferiority randomised controlled trials and only tend to include patients infected with pathogens treatable with both the new AM and a comparator of best available therapy. However, this leads to phase 3 evidence that is not able to demonstrate superiority or all possible diverse treatment approaches. Additionally, there is limited efficacy data for MDR pathogens as it is difficult to enrol patients with a known or suspected resistance.35. Furthermore, it is very difficult to undertake pathogen-directed trials at scale as they are found only retrospectively, and patients have very poor outcomes. Demonstrating pathogen directed value is complex and requires a holistic view of the data which includes an appreciation of time to appropriate therapy. Clinical effectiveness evidence for CAZ/AVI is presented below:

* **HAP/VAP** (Section 3.1):
  + REPROVE (Section 3.1.1): phase 3, international, multicentre, double-blind, double-dummy, pivotal non-inferiority trial comparing CAZ/AVI versus meropenem in adult hospitalised patients with HAP, including VAP.16
* **cIAI** (Section 3.2):
  + RECLAIM 1-3 (Section 3.2.1): three phase 3, randomised, multi-centre, double-dummy, double-blind pivotal studies comparing CAZ/AVI in combination with metronidazole versus meropenem in adult hospitalised patients with cIAI.17,18
  + REPRISE (Section 3.2.2 for cIAI): phase 3, international, randomised, open-label, pivotal trial comparing CAZ/AVI versus best available therapy (including meropenem, imipenem, doripenem, colistin, and [for cIAI] tigecycline) in cUTI and cIAI patients.97 This was study was predominantly focused on patients with cUTI.
  + ANDI (Section 3.2.3): single-blind, randomised, multi-centre, actively controlled trial comparing CAZ/AVI plus metronidazole versus meropenem in paediatric patients (aged from 3 months to <18 years) diagnosed with cIAIs of sufficient severity to require hospitalisation and treatment with IV antibiotics.
* **cUTI** (Section 3.3):
  + RECAPTURE 1 and 2 (Section 3.3.1): phase 3, randomised, multicentre, double-blind, double-dummy, parallel-group pivotal trials comparing the efficacy and safety of CAZ/AVI versus doripenem in treating adult cUTI.19
  + REPRISE (Section 3.3.2): phase 3, international, randomised, open-label, pivotal trial comparing CAZ/AVI versus best available therapy (including meropenem, imipenem, doripenem, colistin, and [for cIAI] tigecycline) in cUTI and cIAI patients.97 This was study was predominantly focused on patients with cUTI.
  + KURA (Section 3.3.3): single blind, randomised, multi-centre, and actively controlled Phase II trial comparing CAZ/AVI versus cefepime in hospitalised paediatric patients (aged from 3 months to <18 years) with cUTI requiring treatment with IV antibiotics.
* **Non-RCT evidence** (Section 3.4): bacteraemia and LTO usage

Although time to effective therapy is key, antimicrobial technologies are assessed in syndrome-based, non-inferiority trials measuring clinical and microbiological response. Non-inferiority trial designs are standard for regulatory assessments of antibiotics, although make treatment comparisons more challenging for HTA purposes.34,87 It is worth noting that trials such as these do not always have a significant number of resistant organisms to be able to capture meaningful resistance data; therefore, other approaches are needed to adapt an economic model based on what information is available (please refer to Section 3.5.3).

## Hospital-acquired / ventilator-associated pneumonia

Evidence to support the effectiveness of CAZ/AVIfor the treatment of adult HAP/VAP is derived primarily from REPROVE (NCT01808092) and is outlined in Table 8.16

Table 8. Summary of clinical effectiveness evidence supporting CAZ/AVI in the treatment of HAP/VAP16

| **Study acronym** | **REPROVE** | | | | |
| --- | --- | --- | --- | --- | --- |
| Population | Adult Hospitalised patients (18-90 years) with diagnosis of either acquired NP or VAP. | | | | |
| Intervention(s) | CAZ/AVI | | | | |
| Comparator(s) | Meropenem | | | | |
| Indicate if trial supports application for marketing authorisation | Yes | ✓ | Indicate if trial used in the economic model | Yes | ✓ |
| No |  | No |  |
| Rationale for use/non-use in the model | Pivotal trial supporting the HAP/VAP indication | | | | |
| Reported outcomes specified in the decision problem | * Clinical cure rates, assessed as:   + The proportion of patients clinically cured at the TOC visit in cMITT and CE populations (primary endpoint)   + Clinical response at the ET visit in cMITT and CE populations (secondary endpoint)   + Clinical response at ET in mMITT and ME populations (secondary endpoint)   + Clinical response at ET and TOC in ceftazidime-non-susceptible pathogens in CE, cMITT and ME populations (secondary endpoint) * Mortality (all cause-mortality at TOC and at day 28 in CE and cMITT and mMITT populations, secondary endpoint) * Microbiologic eradication (Per-patient and per-pathogen microbiological responses at ET and TOC in mMITT, ME, and extended ME, secondary endpoint) populations. While not captured as a defined endpoint, some outcomes related to emergence of resistance (which was included in the scope) were captured as unfavourable microbiological response classified as “persistence with increasing MIC”. * Adverse events * Hospital days * ICU days (assessed as length of stay in the ICU, number of patients transferred to ICU, and days on ventilation)   Two of the outcomes specified in the scope Health-related quality of life data were not collected in REPROVE, due to the challenges associated with administering the questionnaires to acutely ill patients. Readmission within 90 days was also not assessed in REPROVE. | | | | |
| AE: adverse event; CE: clinically evaluable; CrCl: creatinine clearance; ECG: electrocardiogram; ET: end-of-treatment; IV: intravenous; ME: microbiologically evaluable; mMITT: microbiologically modified intention-to-treat; NP: nosocomial pneumonia; TOC: test-of-cure; VAP: ventilator-associated pneumonia | | | | | |

### REPROVE

#### REPROVE trial design and methodology

This phase 3, prospective, international, multicentre, double-blind, double-dummy, non-inferiority trial compared the efficacy and safety of CAZ/AVI with meropenem in adult hospitalised patients with HAP, including VAP.16 The primary endpoint of REPROVE was the proportion of clinically cured patients at the test-of-cure (TOC) visit in the co-primary clinically modified intention-to-treat (cMITT) and clinically evaluable (CE) populations. Secondary endpoints included clinical response; all cause-mortality; clinical response in patients with ceftazidime-non-susceptible pathogens, and per-patient and per-pathogen microbiological responses. Safety analysis included monitoring of adverse events (AEs), clinical laboratory assessments, electrocardiograms, and mortality.

The REPROVE trial design and methodology is outlined in Table 9 and study procedures are summarised Figure 5.

Table 9. REPROVE trial design and methodology16

| **Study acronym** | **REPROVE** |
| --- | --- |
| Study design | Phase III, prospective, international, multicentre, parallel-group, randomised, double-blind, double-dummy, non-inferiority trial |
| Settings/and locations | A large number of study centres in 23 countries participated in the study, including 10 UK patients. |
| Eligibility criteria | Key exclusion criteria: any infections caused by only Gram-positive pathogens or by pathogens not expected to respond to CAZ/AVI, meropenem, or both, and infections expected to require >14 days’ treatment |
| Intervention | CAZ/AVI (2000 mg ceftazidime 500 mg avibactam) administered every eight hours by IV infusion over two hours. Treatment was administered for 7-14 days and dose-adjustment was made for moderate-severe renal impairment (CrCl: 16-50 mL/min) |
| Comparator | Meropenem (1000 mg) administered every eight hours by IV infusion over 30 minutes. Treatment was administered for 7-14 days and dose-adjustment was made for moderate-severe renal impairment (CrCl: 16-50 mL/min) |
| Efficacy outcomes | Primary outcome measure:   * The proportion of patients clinically cured at the TOC visit in cMITT and CE populations   Key secondary outcome measures:   * Clinical response at the ET visit in cMITT and CE populations * Clinical response at ET in mMITT and ME populations * All cause-mortality at TOC and at day 28 in CE and cMITT and mMITT populations * Clinical response at ET and TOC in ceftazidime-non-susceptible pathogens in CE, cMITT and ME populations * Per-patient and per-pathogen microbiological responses at ET and TOC in mMITT, ME, and extended ME populations   Based on clinical outcome, clinical response (at ET or TOC visit) was defined as:   * clinical cure (patient was alive and all signs and symptoms of pneumonia were resolved or improved, such that all antibacterial therapies for HAP/VAP were stopped. No antibacterial therapy other than those outlined by the protocol had been administered for HAP/VAP prior to the visit) * clinical failure (death due to HAP/VAP between day 3 of study treatment and the assessment visit, incomplete resolution or worsening of HAP/VAP that required additional antibiotics before the visit, or development of infectious complications of HAP/VAP after day 2 of study treatment) * indeterminate (loss to follow-up, death on or before the visit that was unrelated to HAP/VAP, death or development of infectious complications of HAP/VAP on day 1 or day 2 of study treatment).   A clinical failure occurring at an earlier time point (e.g., ET visit) was carried forward to the TOC visit. If the clinical response at the TOC visit was missing, it was to be considered as being indeterminate unless there was a previous clinical failure, in which case the clinical response was to be considered as clinical failure at the TOC visit. See Section 5.5.1.2 of the REPROVE CSR for detailed clinical response definition.  Microbiological response at ET or TOC visit was defined as:   * Favourable   + Eradication (absence of the original baseline pathogen\* in the specimen)   + Presumed eradication (specimen not available in a patient assessed as clinical cure) * Unfavourable   + Persistence (continued presence of the original baseline pathogen\* in the specimen)   + Persistence with increasing MIC (continued presence of the original baseline pathogen\* in the specimen obtained during or upon completion of study treatment and displaying a ≥4-fold increase in MIC after treatment)   + Presumed persistence (specimen not available in a patient assessed as clinical failure) * Indeterminate (specimen not available in a patient’s clinical response was assessed as indeterminate)   \*Baseline respiratory cultures were to be obtained within 48 hours prior to randomisation and after development of signs and symptoms of HAP/VAP, ideally before receipt of any systemic antibiotics. |
| Safety outcomes | Safety outcome measures:   * AEs (collected from the time of informed consent to FPFU visit) * Clinical laboratory assessment * 12-lead ECG (read centrally and classified as normal or abnormal) * Mortality |
| Other outcomes used in the economic model/specified in the scope | NA |
| Analysis populations | * MITT: all randomized patients who had the minimum disease criteria and received any amount of study treatment. * mMITT: a subset of the MITT analysis population that included patients who had a properly obtained baseline respiratory culture demonstrating Gram-negative pathogens, excluding patients not expected to respond to either study treatment. * cMITT: a subset of the MITT analysis population that included patients who had properly obtained baseline respiratory or blood cultures demonstrating Gram-negative pathogens, with or without concomitant Gram-positive pathogens, excluding patients with Gram-negative pathogens not expected to respond to either study treatment. The cMITT also included patients in whom no etiologic pathogens were identified from respiratory or blood cultures at baseline * CE: patients who had an adequate course of treatment (defined as those who EITHER received therapy for ≥48 hours, with ≥80% of the scheduled drug administered over the number of days administered OR those who received therapy <48 hours before discontinuing treatment due to an AE) and were found to have clinical response of cure or failure within the protocol-defined visit windows, no major protocol deviations, and did not receive prior antibiotics other than those defined as acceptable by exclusion criterion. * ME: a subset of the CE analysis set including patients who had at least 1 etiologic pathogen from an adequate baseline culture that was susceptible to both study treatments * eME: a subset of the CE analysis set including patients who had at least 1 etiologic pathogen from an adequate baseline culture regardless of susceptibility to the study treatments * Safety: all patients who received any amount of IV study treatment * PK: all patients who had at least 1 plasma concentration data value available for either ceftazidime or avibactam |
| Statistical methods | Sample size:   * Study sample was sized to ensure sufficient power (at least 85%) for the coprimary hypothesis tests against a 12.5% NI margin, assuming evaluability rates of 50% and 85% at TOC in the CE and cMITT populations, respectively. See section 5.7.3 of the REPROVE CSR for further details.   Primary efficacy analysis:   * Statistical analyses and the NI assessment for the primary endpoint were based on the difference in clinical cure rates between treatment groups, assessed in the cMITT and CE populations at TOC (co-primary analysis). The statistical test of NI was performed at the 2.5% 1-sided significance level. NI of CAZ/AVI to meropenem was deemed to be shown if the lower limit of the two-sided 95% CI for the treatment difference (CAZ/AVI minus meropenem) was greater than –12.5%, and the p value was calculated for the corresponding one-sided NI hypothesis test. * Where appropriate, 2-sided 95% CIs for the observed difference were computed using the method of Miettinen and Nurminen for the percentages in the efficacy summaries.   Three sensitivity analyses were done for the primary efficacy variable:   * Adjustment for the effect of prespecified stratification factors, type of infection, and geographical region * Analysis of patients who had received potentially effective concomitant antibiotics as having indeterminate clinical response at TOC * Analysis of patients who died after TOC and up to the final protocol follow-up as clinical failures at TOC   Secondary efficacy variables:   * Analyses of the secondary efficacy variables were considered to be supportive of the primary efficacy results. * No inferential hypothesis was tested and the summary statistics and CIs for these were not adjusted for multiplicity. |
| AE: adverse event; CE: clinically evaluable; CI: confidence interval; cMITT: clinically modified intention-to-treat; CrCl: creatinine clearance; CSR: clinical study report; ECG: electrocardiogram; ET: end-of-treatment; FPFU: final protocol follow up; IV: intravenous; ME: microbiologically evaluable; mMITT: microbiologically modified intention-to-treat; NA: not applicable; NI: non-inferiority; NP: nosocomial pneumonia; PK: pharmacokinetic; TOC: test-of-cure; VAP: ventilator-associated pneumonia | |

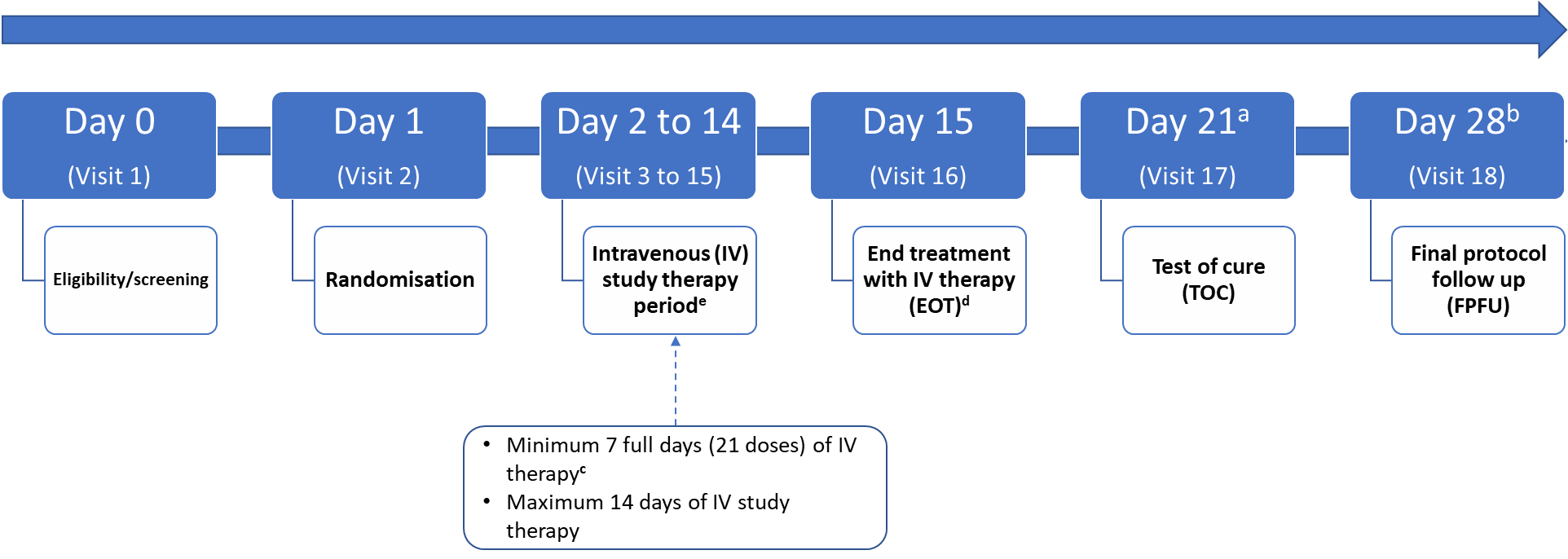


Figure 5. REPROVE study procedure113

a If it was not possible to perform the TOC visit at 21 calendar days from randomisation (baseline), the allowed visit

window was 21 to 25 calendar days from randomisation.

b If it was not possible to perform the final protocol follow up (FPFU) visit at 28 calendar days from randomisation (baseline), the allowed visit

window was 28 to 32 calendar days from randomisation.

c For patients with normal renal function and patients with mild renal impairment.

d The end of treatment (EOT) visit was required within 24 hours after the completion of the last infusion of study treatment.

e Administration of the first dose of IV study treatment marked the beginning of study treatment Day 1. Subsequent study treatment days were based on 24-hour periods from the time of the first infusion.

Please note: this trial design is not reflective of real-world practice as there was a delay in capturing treatment efficacy and risk factor assessments were not undertaken.

#### REPROVE baseline characteristics

Overall, 879 patients were randomly assigned. Across analysis sets, 808 patients included in the safety population, 726 were included in the cMITT population, and 527 were included in the CE population.

* + - * 1. Demographic and baseline clinical characteristics

There were no clinically meaningful differences between the treatment groups for demographic and baseline characteristics in any of the analysis sets. A higher percentage of male patients (74.5%) participated in the study and mean (range) patient age was 62 years (18 to 90 years) with 27.5% of patients aged 75 years of age or older. The majority of patients were Asian (54.8%), reflecting the countries that participated in the study. The mean (range) body mass index (BMI) was 23.9 kg/m2 (11.1 to 60.0 kg/m2) with 10.4% of patients having a BMI ≥30 kg/m2 (Table 10).

Table 10. Demographics and baseline clinical characteristics (REPROVE Safety analysis set)

|  | **CAZ/AVI**  **(n = 405)** | **Meropenem**  **(N = 403)** | **Total**  **(N = 808)** |
| --- | --- | --- | --- |
| Age, Mean (SD) | 61.8 (16.76) | 61.7 (17.57) | 61.7 (17.16) |
| Age group (years), n (%) | | | |
| ≥18-45 | 74 (18.3) | 74 (18.4) | 148 (18.3) |
| 46-64 | 124 (30.6) | 122 (30.3) | 246 (30.4) |
| 64-74 | 97 (24.0) | 95 (23.6) | 192 (23.8) |
| ≥75-≤90 | 110 (27.2) | 112 (27.8) | 222 (27.5) |
| Sex, n (%) | | | |
| Female | 101 (24.9) | 105 (26.1) | 206 (25.5) |
| Male | 304 (75.1) | 298 (73.9) | 602 (74.5) |
| Race, n (%) | | | |
| White | 171 (42.2) | 177 (43.9) | 348 (43.1) |
| Black or African American | 3 (0.7) | 2 (0.5) | 5 (0.6) |
| Asian | 226 (55.8) | 217 (53.8) | 443 (54.8) |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Other | 5 (1.2) | 7 (1.7) | 12 (1.5) |
| BMI (kg/m2), Mean (SD) | 23.92 (6.01) | 23.81 (5.14) | 23.86 (5.59) |
| BMI category, n (%) | | | |
| <18.5 | 56 (13.8) | 54 (13.4) | 110 (13.6) |
| 18.5-<25 | 203 (50.1) | 198 (49.1) | 401 (49.6) |
| 25-<30 | 90 (22.2) | 102 (25.3) | 192 (23.8) |
| ≥30 | 45 (11.1) | 39 (9.7) | 84 (10.4) |
| Percentages are based on the total number of patients in the treatment group.  BMI: body mass index; N: number of patients in treatment group; n: number of patients in category or analysis; SD: standard deviation | | | |

* + - * 1. Disease characteristics at baseline

Baseline disease characteristics were generally similar between analysis sets and treatment groups.

In the safety analysis set, 65.3% of patients had HAP and 34.7% of patients had VAP. Monomicrobial and polymicrobial infection was reported in 31.3% and 18.9% of patients, respectively (49.8% did not have a study-qualifying pathogen identified) and a small proportion (5.0%) of patients were bacteraemic at baseline. As expected for HAP; predominant Gram-negative pathogens isolated from respiratory site or blood were *K. pneumoniae (37%)* and *P. aeruginosa (30%)*. 100 patients (28%) had one or more ceftazidime-non-susceptible Gram-negative pathogen, including 79 with *Enterobacteriaceae* and 25 with *P. aeruginosa*. *Staphylococcus aureus* (*S. aureus*)was the only Gram-positive pathogen isolated in ten or more patients (n = 58; 16%).

Information regarding prior systemic antibiotic use, previous failure of antibiotics, renal function and APACHE II mortality risk scores are described in Table 11.

Table 11. Disease characteristics at baseline (REPROVE Safety analysis set)

|  | **CAZ/AVI**  **(n = 405)** | **Meropenem**  **(N = 403)** | **Total**  **(N = 808)** |
| --- | --- | --- | --- |
| APACHE II score, Mean (SD) | 14.5 (4.06) | 14.9 (4.03) | 14.7 (4.05) |
| APACHE II group, n (%) | | | |
| <10 | 3 (0.7) | 2 (0.5) | 5 (0.6) |
| 10-19 | 350 (86.4) | 345 (85.6) | 695 (86.0) |
| 20-30 | 52 (12.8) | 55 (13.6) | 107 (13.2) |
| Received prior systemic antibiotics in previous 48 hours before randomisation, n (%) | | | |
| Yes | 271 (66.9) | 278 (69.0) | 549 (67.9) |
| No | 134 (33.1) | 125 (31.0) | 259 (32.1) |
| Failure of prior antibiotic use, n (%) | | | |
| Yes | 22 (5.4) | 23 (5.7) | 45 (5.6) |
| No | 351 (86.7) | 356 (88.3) | 707 (87.5) |
| Other | 32 (7.9) | 24 (6.0) | 56 (6.9) |
| Estimated CrCl (mL/min)a, Mean (SD) | 102.4 (67.55) | 100.0 (52.82) | 101.2 (60.63) |
| Ventilation status at baseline, n (%) | | | |
| Ventilated | 184 (45.4) | 175 (43.4) | 359 (44.4) |
| Non-ventilated | 221 (54.6) | 228 (56.6) | 449 (55.6) |
| NP subtype, n (%) | | | |
| VAP | 140 (34.6) | 140 (34.7) | 280 (34.7) |
| Non-VAP | 265 (65.4) | 263 (65.3) | 528 (65.3) |
| Bacteraemia, n (%) | | | |
| Yes | 22 (5.4) | 18 (4.5) | 40 (5.0) |
| No | 383 (94.6) | 385 (95.5) | 768 (95.0) |
| Gram stain, n (%) | | | |
| G+ alone | 72 (17.8) | 82 (20.3) | 154 (19.1) |
| G- alone | 50 (12.3) | 50 (12.4) | 100 (12.4) |
| G-mixed (both + and -) | 243 (60.0) | 248 (61.5) | 491 (60.8) |
| Infection type, n (%) | | | |
| Monomicrobial | 132 (32.6) | 121 (30.0) | 253 (31.3) |
| Polymicrobial | 69 (17.0) | 84 (20.8) | 153 (18.9) |
| a As reported by the site using the Cockcroft Gault method based on local laboratory data.  APACHE II: Acute Physiology and Chronic Health Evaluation II; CrCl: creatinine clearance; N: number of patients in treatment group; n: number of patients in category or analysis; NP: nosocomial pneumonia; SD: standard deviation; VAP: ventilator-associated pneumonia | | | |

#### REPROVE summary of results

A complete summary of results reported are listed in Table 13.

In summary, CAZ/AVI was non-inferior to meropenem in both co-primary populations. In the cMITT population, 245 (68.8%) of 356 patients in the CAZ/AVI group were clinically cured, compared with 270 (73.0%) of 370 patients in the meropenem group (difference –4.2% [95% CI –10.8 to 2.5]). In the CE population, 199 (77.4%) of 257 participants were clinically cured in the CAZ/AVI group, compared with 211 (78.1%) of 270 in the meropenem group (difference –0.7% [95% CI –7.9 to 6.4]) (Figure 6). Per pathogen clinical cure rates and favourable microbiological response rates are described in Table 12.

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Figure 6. Clinical cure rates at test-of-cure visit16  
Data are number of patients with clinical cure (%). Dashed line indicates non-inferiority margin of –12.5%.

Table 12. Per-pathogen clinical cure rates and favourable microbiological response rates16

|  | **Patients with clinical cure (CE)** | | | **Patients with favourable microbiological response\* (eME)** | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | **CAZ/AVI (N=257)** | **Meropenem (N=270)** | **% diff. (95% CI)** | **CAZ/AVI (N=125)** | **Meropenem  (N=131)** | **% diff.  (95% CI)** |
| ***Enterobacteriaceae*** | | | | | | |
| *K. Pneumoniae* | 31/37  (83.8%) | 39/49  (79.6%) | 4.2  (-13.5,20.5) | 29/37  (78.4%) | 39/49  (79.6%) | -1.2  (-19.6,16.0) |
| *E. cloacae* | 20/21  (95.2%) | 7/11  (63.6%) | 31.6  (4.8,61.3) | 18/21  (85.7%) | 7/11 (63.6%) | 22.1  (-8.1,53.7) |
| *E. coli* | 8/11  (72.7%) | 14/18  (77.8%) | -5.1  (-39.3,25.8) | 10/11  (90.9%) | 16/18  (88.9%) | 2.0  (-29.1,26.4) |
| *P. mirabilis* | 11/11  100.0%) | 7/8  (87.5%) | 12.5  (-16.5,48.1) | 9/11  (81.8%) | 6/8  (75.0%) | 6.8  (-30.7,46.5) |
| *S. marcescens* | 10/12  (83.3%) | 8/8  (100.0%) | -16.7  (-45.6,19.5) | 9/12  (75.0%) | 5/8  (62.5%) | 12.5  (-27.5,51.8) |
| *E. aerogenes* | 4/6  (66.7%) | 2/5  (40.0%) | 26.7  (-31.9,70.7) | 5/6  (83.3%) | 3/5  (60.0%) | 23.3  (-31.3,68.3) |
| **Gram-negative pathogens other than *Enterobacteriaceae*** | | | | | | |
| *P. aeruginosa* | 27/42  (64.3%) | 27/35  (77.1%) | -12.8  (-32.3,8.0) | 18/42  (42.9%) | 14/35  (40.0%) | 2.9  (-19.1,24.3) |
| *H. influenzae* | 10/11  (90.9%) | 11/13  (84.6%) | 6.3  (-26.2,36.1) | 11/11  (100.0%) | 12/13  (92.3%) | 7.7  (-20.1,34.0) |
| **Gram-positive aerobes** | | | | | | |
| *S. aureus* | 11/14  (78.6%) | 16/22  (72.7%) | 5.8  (-25.2, 32.8) | 5/14  (35.7%) | 17/22  (77.3%) | -41.6  (-67.0,-8.4) |
| \*Eradication or presumed eradication of the baseline pathogens  CE: clinically evaluable population; CI: confidence interval; diff: difference; eME : extended microbiologically evaluable population | | | | | | |

Adverse events occurred in 302 (75%) patients in the CAZ/AVI group versus 299 (74%) in the meropenem group (safety population) and were mostly mild or moderate in intensity and unrelated to study treatment. Serious adverse events (SAEs) occurred in 75 (19%) patients in the CAZ/AVI group and 54 (13%) patients in the meropenem group. Four SAEs (all in the CAZ/AVI group) were judged to be treatment-related (diarrhoea, n = 1; acute coronary syndrome, n = 1; subacute hepatic failure, n = 1; abnormal liver function test results, n = 1).

Table 13. REPROVE summary of results16

| **Study acronym** | **REPROVE** |
| --- | --- |
| Efficacy results - primary endpoint | * cMITT: 245 (68.8%) patients treated with CAZ/AVI were clinically cured, compared with 270 (73.0%) patients treated with meropenem (diff. -4.2% [95% CI -10.8, 2.5]). * CE: 199 (77.4%) patients treated with CAZ/AVI were clinically cured, compared with 211 (78.1%) patients treated with meropenem (diff. -0.7% [95% CI -7.9, 6.4]) |
| Efficacy results - key secondary endpoint(s) | * Per-pathogen clinical cure rates at TOC among patients with ceftazidime-non-susceptible pathogens in the CE population were similar between CAZ/AVI and meropenem groups (29 [80.6%] vs. 32 [78.0%], respectively; diff. 2.5 [95% CI -16.42, 20.74]) * All-cause mortality was similar between groups at both TOC and day 28. In the cMITT, 29 (8.1%) treated with CAZ/AVI and 25 (6.8%) treated with meropenem died by TOC (diff. 1.4 [95% CI -2.48, 5·35]), whereas 30 (8.4%) and 27 (7.3%), respectively, died by day 28 (diff. 1.1 [95% CI -2.84, 5.18]). In the CE, 11 (4·3%) treated with CAZ/AVI and 8 (3.0%) treated with meropenem died at TOC (diff. 1.3 [95% CI -2.01, 4.89]), whereas 12 (4.7%) and 9 (3.3%), respectively, died by day 28 (diff. 1.3 [95% CI -2.14, 5.04]) * Per-patient favourable microbiological response rates at TOC were generally lower than clinical cure rates, but were similar between CAZ/AVI and meropenem groups and consistent across the mMITT (95 [55.6%] vs. 118 [64.1%]; diff. -8.6 [95% CI -18.65 to 1.64]), extended ME (80 [64.0%] vs. 89 [67.9%]; diff. 3.9 [95% CI -15.49 to 7.66]), and ME (70 [65.4%] vs. 83 [70.3%]; diff. 4.9 [95% CI -17.10 to 7.28]) populations * In patients with ceftazidime-non-susceptible pathogens, per-patient favourable microbiological response rates were similar between groups at ET and TOC in the mMITT, extended ME, and ME populations and were similar to the overall per-patient favourable microbiological response rates * Favourable per-pathogen microbiological response rates at TOC were similar between groups, with numerical differences with wide CIs among individual species. Per-pathogen eradication rates at the TOC in the extended ME population for common *Enterobacteriaceae* ranged from 75.0-90.9% for CAZ/AVI, and from 60.0-88.9% for meropenem; eradication rates for *P. aeruginosa* were 42.9% and 40.0%, respectively. Persistence with increasing MIC, which can be considered a marker for developing resistance, predominantly involved *P. aeruginosa* (10 patients, including 1 [2.4%] patient in the CAZ/AVI group and 9 [25.7%] patients in the meropenem group). It was also observed in 3 patients with *K. pneumoniae* infection (1 [2.7%] patient in the CAZ/AVI group and 2 [4.1%] patients in the meropenem group). |
| Safety results | * AEs occurred in 302 (75%) patients treated with CAZ/AVI vs. 299 (74%) treated with meropenem and were mostly mild or moderate in intensity and unrelated to study treatment. * SAEs occurred in 75 (19%) patients treated with CAZ/AVI and 54 (13%) treated with meropenem. |
| Healthcare resource use | * **Length of hospital stay (cMITT):** Overall, 253/726 (34.8%) patients had a hospital stay of >21 days. A total of 65/124 (52.4%) patients who had a clinical failure (excluding deaths) had a hospital stay of >21 days compared with 179/515 (34.8%) patients who were clinically cured. Results were similar for the CE at TOC analysis * **Length of stay in the intensive care unit (cMITT):** Overall, 115/726 (15.8%) patients had an ICU stay of >21 days; 379/726 (52.2%) patients had an ICU stay of between 0 and 6 days. A total of 32/124 (25.8%) patients who had a clinical failure (excluding deaths) had an ICU stay of >21 days compared with 79/515 (15.3%) patients who were clinically cured. The corresponding number of patients with ICU stays of 15 to 21 days were 24/124 (19.4%) patients and 71/515 (13.8%) patients, respectively (Table 11.2.12.2.1 and Table 11.2.12.1.1). Results were similar for the CE at TOC analysis set * **Number of patients transferred to the intensive care unit (cMITT):** Overall, 26/726 (3.6%) patients were transferred to the ICU (Table 11.2.11.1). A total of 7/124 (5.6%) patients who had a clinical failure (excluding deaths) were transferred to the ICU compared with 14/515 (2.7%) patients who were clinically cured. The results were similar for the CE at TOC analysis set. * **Days on ventilation (cMITT):** Overall, the majority of patients (73.0%) were ventilated for between 0 and 6 days. Of the 124 patients who had a clinical failure (excluding deaths), 18 (14.5%) spent >21 days on ventilation, and 22 (17.7%) were ventilated for 15 to 21 days, compared with 30 (5.8%) and 35 (6.8%), respectively, of the 515 patients who were clinically cured. Results were similar for the CE at TOC analysis set |
| Conclusion(s) | CAZ/AVI was NI to meropenem in the treatment of HAP (including VAP). |
| AE: adverse events; CE: clinically evaluable; CI: confidence interval; cMITT: clinically modified intention-to-treat; diff.: difference; ET: end of treatment; HAP: hospital-acquired pneumonia; ME: microbiologically evaluable population; mMITT: microbiologically modified intention-to-treat population; NI: non-inferiority; SAE: serious adverse events; TOC: test of cure; VAP: ventilator-associated pneumonia | |

## Complicated intra-abdominal infection

Evidence to support the effectiveness of CAZ/AVI for the treatment of cIAI is derived predominantly from RECLAIM 1 (NCT01499290), RECLAIM 2 (NCT01500239),17 RECLAIM 3 (NCT01726023),18 REPRISE (NCT01644643) and ANDI (NCT02475733)111 (Table 14).97

### RECLAIM 1-3

#### RECLAIM trial design and methodology

RECLAIM comprised three identical prospective, randomised, multi-centre, double-dummy, double-blind, comparative, phase 3 studies which compared the efficacy and safety of CAZ/AVI in combination with metronidazole with meropenem in adult hospitalised patients with cIAI. While RECLAIM 1 (NCT01499290) and RECLAIM 2 (NCT01500239)17 were conducted at a global level (136 centres across 30 countries), RECLAIM 3 (NCT01726023) was particularly focused on the Asian population (specifically China, the Republic of Korea and Vietnam).18

The primary endpoint of RECLAIM was the proportion of clinically cured patients at the TOC visit in the microbiologically modified intention-to-treat (mMITT), cMITT, and CE populations (only the CE population was required in RECLAIM 3). Key secondary endpoints were clinical response at end of treatment (ET) and last follow-up (LFU); microbiological response at ET, TOC and LFU; and microbiological response in ceftazidime-resistant pathogens. Safety analysis included monitoring of AEs and SAEs, clinical laboratory assessments and electrocardiograms.

The RECLAIM trial design and methodology is outlined in Table 15 and study procedures are summarised in Figure 7.

Table 14. Summary of clinical effectiveness evidence supporting CAZ/AVI in the treatment of cIAI17,18,97,111

| **Study acronym** | **RECLAIM 1-317,18** | | | | | **REPRISE97** | | | | | **ANDI111** | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Population | Hospitalised patients (18-90 years or 18-65 years in India) with cIAI requiring surgical intervention or percutaneous drainage within 24h before or after randomisation | | | | | Patients (18-90 years) with either cUTI or cIAI caused by ceftazidime-resistant Gram-negative pathogens | | | | | Paediatric patients aged ≥3 months to  <18 years with cIAI. | | | | |
| Intervention(s) | CAZ/AVI with metronidazole | | | | | CAZ/AVI with metronidazole | | | | | CAZ/AVI with metronidazole | | | | |
| Comparator(s) | Meropenem | | | | | BAT | | | | | Meropenem | | | | |
| Indicate if trial supports application for marketing authorisation | Yes | ü | Indicate if trial used in the economic model | Yes | ü | Yes | ü | Indicate if trial used in the economic model | Yes |  | Yes |  | Indicate if trial used in the economic model | Yes |  |
| No |  | No |  | No |  | No | ü | No | ü | No | ü |
| Rationale for use/non-use in the model | Pivotal trial supporting the cIAI indication | | | | | Pivotal trial supporting cIAI and cUTI indications | | | | | Pivotal trial supporting the paediatric cIAI indication | | | | |
| Reported outcomes specified in the decision problem | * Clinical cure rates, assessed as:   + The proportion of patients clinically cured at the TOC visit in the MITT, mMITT, and CE populations (CE population only in RECLAIM 3) (primary endpoint)   + Clinical response in at ET and LFU * Microbiological eradication (per patient and per-pathogen) microbiological response at ET, TOC and LFU (secondary endpoint) * Microbiological response in ceftazidime-resistant pathogens (secondary endpoint) * Adverse events   Analysis of healthcare resource use (i.e. length of hospital stay and ICU admission) was not investigated in RECLAIM. Furthermore, readmission rates, health-related quality-of-life and mortality was not investigated). | | | | | * Clinical cure rates, assessed as:   + Clinical response (cure, failure, or indeterminate) at the TOC visit (primary objective)   + Clinical response at other timepoints (ET, follow-up visit 1, and follow-up visit 2 [cUTI only]) and patient subgroups (entry diagnosis, pathogen, resistance mechanism, and previously failed treatment class) (secondary objective) * Mortality (all-cause mortality at day-28) * Microbiologic eradication (Per-patient and per-pathogen favourable microbiological response at ET, TOC, follow-up visit 1, and follow-up visit 2 (cUTI only), secondary endpoint) * Adverse events * Healthcare resource utilisation   Readmission rates and health-related quality-of-life were not investigated in REPRISE. | | | | | * Adverse events (primary objective) * Clinical cure rates (cure, sustained clinical cure, improvement, relapse, failure, indeterminate) at end of 72 hours, end of IV treatment, end of treatment, test of cure, and late follow-up. * Microbiological response (at EOIV, EOT, TOC, and LFU) * Emergent infections   ANDI was a Phase II study. Therefore, primary endpoints were limited to investigations relating to safety and tolerability as well as pharmacokinetics and pharmacodynamics. Efficacy outcomes were limited to descriptive secondary objectives. | | | | |
| BAT: best available therapy; CAZ/AVI: ceftazidime/avibactam; CE: clinically evaluable; cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection; EOIV: end of intravenous treatment; ET: end of treatment; ICU: intensive care unit; LFU: last follow-up; MITT: modified intent-to-treat; mMITT: microbiologically modified intent-to-treat; TOC: test of cure. | | | | | | | | | | | | | | | |

Table 15. RECLAIM trial design and methodology17,18

| **Study acronym** | **RECLAIM** |
| --- | --- |
| Study design | Identical, Phase III, prospective, randomised, multicentre, double-dummy, double-blind, comparative, global trials |
| Settings and/locations | RECLAIM 1 and 2: 136 centres in 30 countries  RECLAIM 3: China, 26 centres; South Korea, 15 centres; Vietnam, 2 centres. |
| Eligibility criteria | Key exclusion criteria:   * diagnosis of traumatic bowel perforation managed operatively within 12h * perforation of gastroduodenal ulcers managed operatively within 24h * intrabdominal processes in which the primary cause was unlikely to be infectious * abdominal wall abscess, bowel obstruction, or ischemic bowel without perforation * simple cholecystitis or gangrenous cholecystitis without rupture; * simple appendicitis * acute suppurative cholangitis * infected necrotizing pancreatitis or pancreatic abscess |
| Intervention | CAZ/AVI (2000 mg ceftazidime 500 mg avibactam) administered every eight hours by IV infusion over two hours followed by 500 mg metronidazole as a 60-minute IV infusion every 8h. Treatment was administered for 5-14 days and dose-adjustment was made for moderate renal impairment (CrCl: >30 to ≤50 mL/min) |
| Comparator | Meropenem (1000 mg) administered every eight hours by IV infusion over 30 minutes. Treatment was administered for 5-14 days and dose-adjustment was made for moderate renal impairment (CrCl: >30 to ≤50 mL/min) |
| Efficacy outcomes | Primary outcome measure:   * Clinical cure at TOC in mMITT, cMITT, and CE populations * RECLAIM 3 only required the CE population   Key secondary outcome measures:   * Clinical response in at ET and LFU * Microbiological response at ET, TOC and LFU * Microbiological response in ceftazidime-resistant pathogens   Based on clinical outcome, clinical response (at ET, TOC and LFU visits) was defined as:   * Cure – Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary * Failure – Patients who met any one of the criteria below were considered a treatment failure:   + Death related to intra-abdominal infection   + Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively   + Postsurgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that required additional antibiotics and/or nonroutine wound care   + Patients who received treatment with additional antibiotics for ongoing symptoms of intra-abdominal infection (including patients prematurely discontinued from study drug due to an AE who required additional antibiotics for cIAI)   + Patient previously met criteria for failure. * Indeterminate – Study data were not available for evaluation of efficacy for any reason, including:   + Patient lost to follow-up or assessment not undertaken such that a determination of clinical response could not be made   + Death where cIAI was clearly non-contributory   + Circumstances that precluded classification as a cure or failure.   Microbial response at initial/pre-study culture, ET, TOC, and LFU visits were defined as:   * Favourable   + Eradication (absence of causative pathogen from appropriately obtained specimens at the site of infection   + Presumed eradication (Repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure. * Unfavourable   + Persistence (Causative organism still present at or beyond the EOT visit from a culture of intra-abdominal abscess, peritonitis, or surgical wound infection)   + Persistence with increasing MIC (Continued presence of the causative organism in a culture of the intra-abdominal abscess, peritonitis, or surgical wound infection obtained at or after completion of treatment with IV study therapy that displayed a ≥4-fold higher MIC to IV study therapy after treatment with IV study therapy)   + Presumed persistence (Patient was previously assessed as a clinical failure and repeat cultures were not performed/clinically indicated * Indeterminate (specimen not available in a patient’s clinical response was assessed as indeterminate) |
| Safety outcomes | Safety outcome measures:   * Adverse events (including both serious and non-serious adverse events were collected for each patient at time of screening through to LFU visit. * Clinical laboratory assessment * Resting ECG |
| Other outcomes used in the economic model/specified in the scope | Exploratory healthcare utilisation variables including: length of hospital stay, length of ICU stay and/or transfer to the ICU, length of IV therapy, and mortality caused by cIAIs (up to the LFU visit) were collected; however, results were unavailable as these were described outside of the CSR. |
| Analysis populations | * MITT: met the disease definition of cIAI and who received any amount of study drug * mMITT: met the disease definition of cIAI and had at least one etiologic pathogen identified at study entry. Patients with pathogens not typically expected to respond to both study drugs were excluded * CE: Had fulfilled mMITT criteria AND had EITHER received 12-lead ECG (read centrally and classified as normal or abnormal) OR 12-lead ECG (read centrally and classified as normal or abnormal). Included patients also had: clinical response of cure or failure at ET, TOC; no major protocol deviations; no excluded prior antibiotics or concomitant medications; and considered to have adequate initial infection source control * ME: including a subset of CE patients who had at least one Gram-negative aerobic pathogen in the initial/pre-study culture that was susceptible to both treatment arms * eME: including a subset of CE patients who had at least one Gram-negative aerobic pathogen in the initial/pre-study culture regardless of susceptibility * Safety: all patients who received any amount of IV therapy * PK: all patients who had at least 1 plasma concentration data value available for either ceftazidime or avibactam |
| Statistical methods | Sample size:   * Study sample was sized to ensure sufficient power (at least 90%) for the coprimary hypothesis tests against a 10% NI margin, assuming evaluability rates of 90% in the CE and cMITT populations.   Primary efficacy analysis:   * The primary efficacy objective was to assess the noninferiority of CAZ/AVI plus metronidazole compared to meropenem with respect to the percentage of patients with a clinical cure at the TOC visit. * In terms of both US FDA and ROW primary objectives, consistent with the protocol, the sponsor will conclude noninferiority if the lower limit of the 95% CI (corresponding to a 97.5% 1-sided lower bound) is greater than –12.5% for the primary outcome variable.   Where appropriate, statistical analyses as specified for each variable were conducted (all comparisons were between CAZ/AVI plus metronidazole versus meropenem) and 2-sided 95% CIs were produced using the method of Miettinen and Nurminen 1985. Any patients with a missing assessment at the EOT, TOC, or LFU visit were assigned a clinical response of indeterminate, effectively defining any such patients as failure in the statistical analysis for the mMITT set at the relevant timepoint.  Secondary efficacy variables:   * The numbers and percentage in each treatment group for clinical response recorded as cure, failure, and indeterminate are tabulated. Indeterminate or missing assessments are included in the denominator for calculating the percentages for the MITT and mMITT analysis sets, but they are excluded from the denominator for the CE, ME, and extended ME analysis sets. |
| AE: adverse event; CE: clinically evaluable; cMITT: clinically modified intention-to-treat; CrCl: creatinine clearance rate; ET: end of treatment; FDA: Food and Drug Administration; IV: intravenous; LFU: last follow-up; mMITT: microbiologically modified intention-to-treat; ROW: rest of the world TOC: test-of-cure; | |

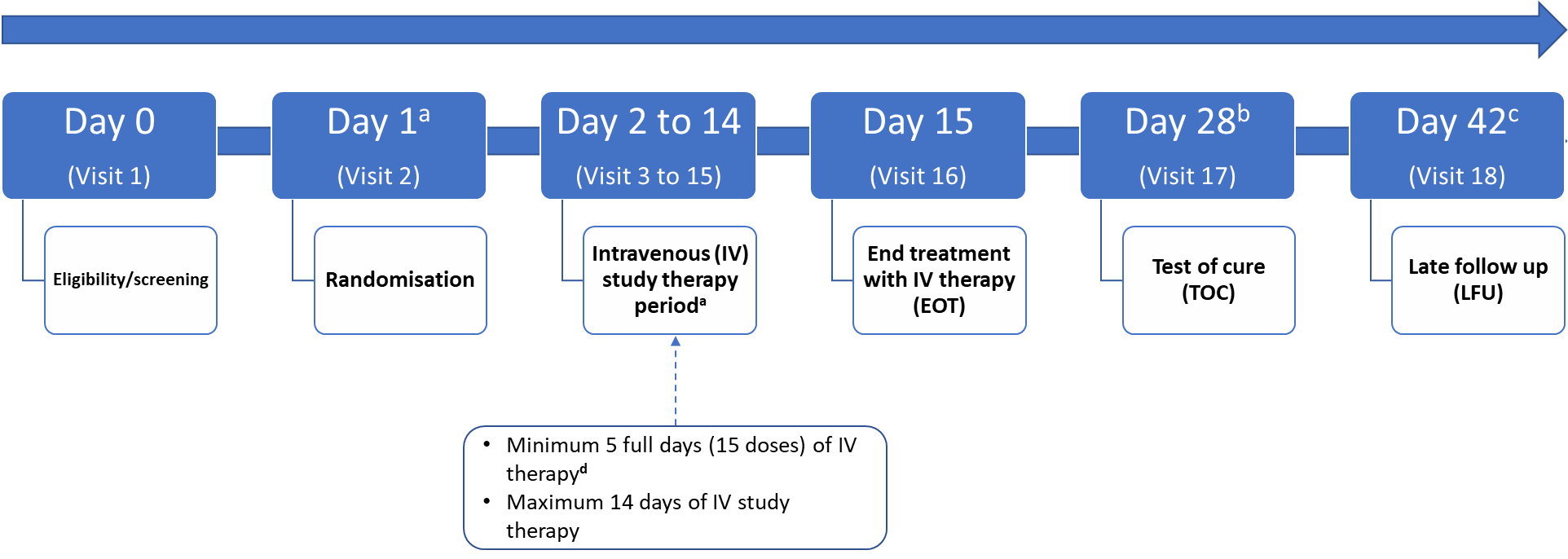


Figure 7. RECLAIM study procedure114

aAdministration of the first dose of IV study therapy marked the beginning of study Day 1. Subsequent

study days were based on 24-hour periods from the start time of the first infusion.

bIf it was not possible to perform the TOC visit 28 calendar days from randomisation (e.g., the patient was on holiday), the allowed visit window was 28 to 35 calendar days from randomisation.

cIf it was not possible to perform the LFU visit 42 calendar days from randomisation (e.g., the patient was on holiday), the allowed visit window was 42 to 49 calendar days from randomisation.

dFor patients with normal renal function and patients with mild renal impairment.

#### RECLAIM 1 and RECLAIM 2

Overall, 1066 out of the 1149 patients enrolled onto this study were randomised. Of these patients, 529 received ≥1 dose of CAZ/AVI plus metronidazole, and 529 ≥1 dose of meropenem.

* + - * 1. **Demographic and baseline clinical characteristics**

There were no clinically meaningful differences between the treatment groups for demographic characteristics in any of the primary analysis sets. In the mMITT analysis set, the majority of patients were white (76.6%) with a higher percentage of male patients (63.1% patients) compared with female patients (36.9% patients). The mean age was 50 years (range: 18 to 90 years) distributed across the age categories and including 10% of patients over 75 years of age. Mean BMI was 26.2 kg/m2 (range 14.2 to 45.0) with 21% of patients having a BMI ≥30 kg/m2 (Table 16).

Table 16. Demographics and baseline clinical characteristics (RECLAIM 1 and 2 mMITT analysis set)

|  | **CAZ/AVI + Metronidazole**  **(n = 520)** | **Meropenem**  **(N = 523)** | **Total**  **(N = 1043)** |
| --- | --- | --- | --- |
| Age, Mean (SD) | 49.8 (17.48) | 50.3 (18.29) | 50.0 (17.88) |
| Age group (years), n (%) | | | |
| ≥18-45 | 224 (43.1) | 218 (41.7) | 442 (42.4) |
| 46-64 | 177 (34.0) | 182 (34.8) | 359 (34.4) |
| 64-74 | 72 (13.8) | 65 (12.4) | 137 (13.1) |
| ≥75-≤90 | 47 (9.0) | 58 (11.1) | 105 (10.1) |
| Sex, n (%) | | | |
| Female | 194 (37.3) | 191 (36.5) | 385 (36.9) |
| Male | 326 (62.7) | 332 (63.5) | 658 (63.1) |
| Race, n (%) | | | |
| White | 403 (77.5) | 396 (75.7) | 799 (76.6) |
| Black or African American | 5 (1.0) | 2 (0.4) | 7 (0.7) |
| Asian | 78 (15.0) | 89 (17.0) | 167 (16.0) |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| American Indian or Alaska Native | 5 (1.0) | 6 (1.1) | 11 (1.1) |
| Other | 27 (5.2) | 30 (5.7) | 57 (5.5) |
| BMI (kg/m2), Mean (SD) | 26.28 (5.10) | 26.20 (5.00) | 26.24 (5.05) |
| BMI category, n (%) | | | |
| <18.5 | 21 (4.0) | 22 (4.2) | 43 (4.1) |
| 18.5-<25 | 221 (42.5) | 214 (40.9) | 435 (41.7) |
| 25-<30 | 170 (32.7) | 167 (31.9) | 337 (32.3) |
| ≥30 | 104 (20.0) | 115 (22.0) | 219 (21.0) |
| Missing | 4 (0.8) | 5 (1.0) | 9 (0.9) |
| Percentages are based on the total number of patients in the treatment group (N).  BMI: body mass index; MITT: modified intent-to-treat; n: number of patients in category or analysis. | | | |

* + - * 1. **Disease characteristics at baseline**

Overall, the types and sites of infection and operative procedures were similar between treatment groups across the 3 primary analysis sets. In the mMITT analysis set, the most common primary diagnoses were appendiceal perforation (41.3%), acute gastric and duodenal perforation (18.7%) and cholecystitis (15.7%). Almost half of the patients in each treatment group were enrolled preoperatively and 76.8% underwent laparotomy (with or without skin closure) as the initial surgical intervention. The proportions of isolated baseline pathogens of the study population were representative of the general cIAI population. Of the mMITT population, 111 patients were infected with ceftazidime-resistant aerobic Gram-negative pathogens, the majority of which were *E. coli* or *K. pneumoniae* (Table 18). Approximately 80% of patients with ceftazidime-resistant pathogens had an ESBL–positive infection, and approximately 3% had an MBL–positive infection. In each treatment group, approximately 40% of patients had a monomicrobial infection, 40% had a polymicrobial infection and the remaining 20% did not have a study qualifying pathogen identified. A small proportion of patients (3.5%) were bacteraemic at baseline.

Information regarding prior systemic antibiotic use, previous failure of antibiotics, renal function and APACHE II mortality risk scores are described in Table 17.

Table 17. Disease characteristics at baseline (RECLAIM 1 and 2 mMITT analysis set)

|  | **CAZ/AVI + Metronidazole**  **(n = 520)** | **Meropenem**  **(N = 523)** | **Total**  **(N = 1043)** |
| --- | --- | --- | --- |
| APACHE II score, Mean (SD) | 6.6 (4.51) | 6.5 (6.5) | 6.6 (4.46) |
| Prior treatment failure, n (%) | | | |
| Yes | 29 (5.6) | 31 (5.9) | 60 (5.8) |
| No | 491 (94.4) | 492 (94.1) | 983 (94.2) |
| Prior systemic antibiotics use in the previous 72 hours before randomisation, n (%) | | | |
| Yes | 324 (62.3) | 325 (62.1) | 649 (62.2) |
| No | 196 (37.7) | 198 (37.9) | 394 (37.8) |
| Complication of a previous abdominal surgerya, n (%) | | | |
| Yes | 32 (6.2) | 20 (3.8) | 52 (5.0) |
| No | 488 (93.8) | 503 (96.2) | 991 (95.0) |
| Estimated CrCl (mL/min)b, Mean (SD) | 101.0 (42.24) | 102.4 (40.85) | 101.7 (41.54) |
| Bacteraemia, n (%) | 22 (4.2) | 14 (2.7) | 36 (3.5) |
| Primary diagnosis, n (%) | | | |
| Cholecystitis | 87 (16.7) | 77 (14.7) | 164 (15.7) |
| Diverticular disease | 35 (6.7) | 52 (9.9) | 87 (8.3) |
| Appendiceal perforation or peri-appendiceal abscess | 218 (41.9) | 213 (40.7) | 431 (41.3) |
| Acute gastric or duodenal perforations | 96 (18.5) | 99 (18.9) | 195 (18.7) |
| Traumatic perforations | 9 (1.7) | 8 (1.5) | 17 (1.6) |
| Secondary peritonitis | 36 (6.9) | 33 (6.3) | 69 (6.6) |
| Intra-abdominal abscesses | 39 (7.5) | 41 (7.8) | 80 (7.7) |
| Single abscesses | 32 (6.2) | 35 (6.7) | 67 (6.4) |
| Multiple abscesses | 7 (1.3) | 6 (1.1) | 13 (1.2) |
| cIAI not confirmed at surgery | 0 | 0 | 0 |
| Infection type, n (%) | | | |
| Monomicrobial | 209 (40.2) | 205 (39.2) | 414 (39.7) |
| Polymicrobial | 208 (40.0) | 209 (40.0) | 417 (40.0) |
| a Qualifying infection was a complication of a previous abdominal surgery  b As reported by the site using the Cockcroft Gault method based on local laboratory data.  APACHE II: Acute Physiology and Chronic Health Evaluation II; CrCl: creatinine clearance; N: number of patients in treatment group; n: number of patients in category or analysis; NP: nosocomial pneumonia; SD: standard deviation; VAP: ventilator-associated pneumonia | | | |

#### RECLAIM 1 and RECLAIM 2 summary of results

The full summary of results reported in RECLAIM 1 and 2 are listed in Table 19.

This study demonstrated non-inferiority of CAZ/AVI plus metronidazole to meropenem across all primary analysis populations. CAZ/AVI plus metronidazole was effective in both ceftazidime-resistant and ceftazidime-susceptible Gram-negative subgroups (83.0% and 82.0%, respectively) with clinical cure rates similar to that of meropenem (85.9% and 87.7% in ceftazidime-resistant and ceftazidime-susceptible Gram-negative subgroups, respectively).

Table 18. Clinical Response at the Test-of-Cure Visit for Patients with Ceftazidime-Resistant and Ceftazidime-Susceptible Gram-Negative Pathogens – RECLAIM 1 and 2 pooled (mMITT Analysis Population)17

| **Pathogen** | **CAZ/AVI**  **(N = 413)** | | **Meropenem**  **(N = 410)** | | **Between-Group difference in clinical cure rates, (95% CI), %a** |
| --- | --- | --- | --- | --- | --- |
| **Pts,**  **n** | **Clinical Cure,**  **n (%)** | **Pts,**  **n** | **Clinical Cure,**  **n (%)** |
| ***All*** | | | | | |
| Ceftazidime-resistant | 47 | 39 (83.0) | 64 | 55 (85.9) | −3.0 (−17.89 to 10.60) |
| Ceftazidime-susceptible | 289 | 237 (82.0) | 292 | 256 (87.7) | −5.7 (−11.57 to 0.17) |
| ***Enterobacteriaceae*** | | | | | |
| Ceftazidime-resistant | 44 | 36 (81.8) | 62 | 53 (85.5) | −3.7 (−19.31 to 10.44) |
| Ceftazidime-susceptible | 279 | 229 (82.1) | 280 | 245 (87.5) | −5.4 (−11.45 to 0.54) |
| ***E. coli*** | | | | | |
| Ceftazidime-resistant | 24 | 19 (79.2) | 37 | 31 (83.8) | −4.6 (−26.77 to 14.86) |
| Ceftazidime-susceptible | 236 | 192 (81.4) | 239 | 210 (87.9) | −6.5 (−13.09 to −0.02) |
| ***K. pneumoniae*** | | | | | |
| Ceftazidime-resistant | 13 | 10 (76.9) | 13 | 9 (69.2) | 7.7 (−27.10 to 40.96) |
| Ceftazidime-susceptible | 34 | 28 (82.4) | 35 | 27 (77.1) | 5.2 (−14.43 to 24.56) |
| ***Non-Enterobacteriaceae*** | | | | | |
| Ceftazidime-resistant | 4 | 4 (100.0) | 4 | 4 (100.0) | 0.0 (−52.33 to 52.33) |
| Ceftazidime-susceptible | 35 | 31 (88.6) | 43 | 41 (95.3) | −6.8 (−22.10 to 5.99) |
| ***P. aeruginosa*** | | | | | |
| Ceftazidime-resistant | 2 | 2 (100.0) | 4 | 4 (100.0) | 0.0 (−69.74 to 53.54) |
| Ceftazidime-susceptible | 30 | 27 (90.0) | 32 | 30 (93.8) | −3.8 (−20.55 to 11.90) |
| CI: confidence interval; mMITT: microbiologically modified intention-to-treat; Pts: patients;. a CIs for group differences were calculated using the unstratified Miettinen and Nurminen method. The analysis includes patients infected by ≥1 ceftazidime-resistant Gram-negative pathogen. | | | | | |

Both interventions shared a similar frequency of AEs with gastrointestinal disorders occurring most frequently. Overall, 21 patients died during the study (CAZ/AVI plus metronidazole, n = 13 (2.5%); meropenem, n = 8 (1.5%)); however, none of the deaths were related to the study drug and no trends in cause of death could be made. Discontinuation was reported in 113 patients (CAZ/AVI plus metronidazole, n = 56; meropenem, n = 57).

Table 19. RECLAIM 1 and RECLAIM 2 summary of results17

| **Study acronym** | **RECLAIM 1 and 2** |
| --- | --- |
| Efficacy results - primary endpoint | * All criteria for the primary end point of NI of CAZ/AVI plus metronidazole compared with meropenem were met across all primary analysis populations. * Clinical cure at TOC was achieved in 337 (81.6%) patients treated with CAZ/AVI plus metronidazole and 349 (85.1%) patients treated with meropenem in the mMITT population (diff. -3.5 [95% CI -8.64, 1.58); 429 (82.5%) and 444 (84.9%), respectively in the cMITT population (diff. -2.4 [95% CI -6.90, 2.10); and 376 (91.7%) and 385 (92.5%), respectively in the CE population (diff. -0.8 [95% CI -4.61, 2.89) |
| Efficacy results - key secondary endpoint(s) | * Clinical cure at ET was achieved in 361 (87.4%) patients treated with CAZ/AVI plus metronidazole and 379 (92.4%) patients treated with meropenem in the mMITT population (diff. -5.0 [95% CI -9.24, -0.93); 459 (88.3%) and 482 (92.2%), respectively in the cMITT population (diff. -0.9 [95% CI -7.57, -0.29); and 381 (92.9%) and 396 (95.2%), respectively in the CE population * Clinical cure at LFU was achieved in 340 (82.3%) patients treated with CAZ/AVI plus metronidazole and 349 (85.1%) patients treated with meropenem in the mMITT population (diff. -3.5 [95% CI -8.64, 1.58); 429 (82.5%) and 436 (83.4%), respectively in the cMITT population (diff. -0.9 [95% CI -5.45, 3.72); and 369 (90.0%) and 376 (90.4%), respectively in the CE population * CAZ/AVI plus metronidazole was effective in patients with ceftazidime-resistant Gram-negative pathogens, with clinical cure rates similar to meropenem (83.0% vs 85.9%, respectively) and to those seen in patients with ceftazidime-susceptible Gram-negative pathogens (82.0% vs 87.7%, respectively) |
| Safety results | * Frequency of AEs were similar in both treatment groups with the most frequent being in the system organ class gastrointestinal disorders. * Deaths occurred in 13 (2.5%) and 8 (1.5%) of the CAZ/AVI plus metronidazole and meropenem groups, respectively. Of these, 4 (0.77%) and 1 (0.19%) of the patients receiving CAZ/AVI plus metronidazole and meropenem, respectively, had moderate renal impairment at baseline and 6 (1.1%) and 3 (0.6%) of the deaths, respectively, were attributed to cIAI progression |
| Conclusion(s) | * CAZ/AVI plus metronidazole was NI to meropenem in the treatment of cIAIs and was effective against ceftazidime-non-susceptible pathogens. |
| AE: adverse event; CE: clinically evaluable; CI: confidence interval; cMITT: clinically modified intention-to-treat; diff: difference; ET: end of treatment; LFU: last follow up; mMITT: microbiologically modified intention-to-treat; NI: non-inferiority; TOC: test-of-cure | |

#### RECLAIM 3

Conducted in Asia, RECLAIM 3 may be seen as less relevant to the decision problem than RECLAIM 1 and 2. Nonetheless, as there is a sizeable Asian minority in England, the results from this trial are briefly summarised for completeness.

Overall, 486 patients we enrolled into the study of which, 441 were randomised. 432 patients received at least ≥1 dose of the study medication (CAZ/AVI plus metronidazole, n = 215; meropenem, n = 217) and 398 completed treatment (CAZ/AVI plus metronidazole, n = 196; meropenem, n = 202).

* + - * 1. RECLAIM 3 demographic and baseline characteristics

Baseline demographics and clinical characteristics in the MITT population were generally balanced between treatment groups (Table 20). The mean (standard deviation [SD]) duration of exposure to study therapy in the safety population was 6.9 (2.9) days in the CAZ/AVI plus metronidazole group and 7.3 (2.8) days in the meropenem group. Across both groups, 21.3% of patients had not received any systemic antimicrobial therapy in the 72 h prior to randomisation. A further 65.4% had received <24 hours of prior systemic antimicrobial therapy. Baseline characteristics in the primary analysis population (the CE population) were generally comparable with those observed in the MITT population.

Table 20. RECLAIM 3 baseline characteristics (MITT analysis set)

|  |  |  |
| --- | --- | --- |
|  | **CAZ/AVI + metronidazole**  **(N = 214)** | **Meropenem**  **(N = 217)** |
| Age (years), Mean (SD) | 48.5 (16.8) | 48.5 (17.4) |
| Sex (male), n (%) | 141 (65.9) | 153 (70.5) |
| Asian, n (%) | 214 (100) | 217 (100) |
| Chinese, n (%) | 127 (59.3) | 135 (62.2) |
| BMI (kg/m2), Mean (SD) | 22.7 (3.5) | 22.4 (3.5) |
| APACHE II score, Mean (SD) | | |
| ≤10 | 201 (93.9) | 201 (92.6) |
| >10-≤30 | 13 (6.1) | 16 (7.4) |
| Primary diagnosis, n (%) | | |
| Appendiceal perforation or periappendiceal abscess | 83 (38.8) | 79 (36.4) |
| Secondary peritonitis | 36 (16.8) | 38 (17.5) |
| Cholecystitis | 33 (15.4) | 27 (12.4) |
| Intra-abdominal abscess | 22 (10.3) | 24 (11.1) |
| Acute gastric and duodenal perforations | 22 (10.3) | 23 (10.6) |
| Traumatic perforations | 13 (6.1) | 17 (7.8) |
| Diverticular disease | 5 (2.3) | 9 (4.1) |
| Prior treatment failure | 26 (12.1) | 27 (12.4) |
| Systemic antimicrobial in the previous 72 h before randomisation | 167 (78.0) | 172 (79.3) |
| Infection type | | |
| Monomicrobial | 84 (39.3) | 101 (46.5) |
| Poly microbial | 58 (27.1) | 52 (24.0) |
| Bacteraemia | 5 (2.3) | 10 (4.6) |
| Renal status, n (%) | | |
| Normal renal function/mild impairment (CrCl>50 mL/min) | 201 (93.9) | 201 (92.6) |
| Moderate impairment (CrCl>30 to≤50 mL/min) | 13 (6.1) | 16 (7.4) |
| S:D: standard deviation; BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation: CrCl, creatinine clearance | | |

* + - * 1. RECLAIM 3 disease characteristics at baseline

In this study, 81% (n = 239) of the mMITT population (n = 295) had one or more *Enterobacteriaceae* isolate with *E. coli* (n = 173; 58.6%) and *K. pneumoniae* (n = 63; 21.4%) most frequently reported. Of the 47 patients (15.9%) with non-*Enterobacteriaceae* Gram-negative pathogens, *P. aeruginosa* was the most frequently reported (n = 37; 12.5%).

Table 21. Clinical Response at the Test-of-Cure Visit for Patients with Ceftazidime-Resistant and Ceftazidime-Susceptible Gram-Negative Pathogens – RECLAIM 3 (extended microbiologically evaluable population)18

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Pathogen** | **CAZ/AVI**  **(N = 100)** | | **Meropenem**  **(N = 119)** | | **Between-Group Differencea in clinical cure rates, (95% CIb), %** |
| **Pts,**  **n** | **Clinical Cure,**  **n (%)** | **Pts,**  **n** | **Clinical Cure,**  **n (%)** |
| ***All*** | | | | | |
| Ceftazidime-resistant | 23 | 22 (95.7) | 26 | 25 (96.2) | −0.5 (−17.93, 15.43) |
| Ceftazidime-susceptible | 76 | 70 (92.1) | 89 | 84 (94.4) | −2.3 (−11.30, 5.82) |
| ***Enterobacteriaceae*** | | | | | |
| Ceftazidime-resistant | 21 | 20 (95.2) | 25 | 24 (96.0) | −0.8 (−19.51, 15.78) |
| Ceftazidime-susceptible | 70 | 64 (91.4) | 81 | 78 (96.3) | −4.9 (−14.28, 3.08) |
| ***E. coli*** | | | | | |
| Ceftazidime-resistant | 14 | 13 (92.9) | 23 | 22 (95.7) | −2.8 (−28.19, 15.54) |
| Ceftazidime-susceptible | 54 | 50 (92.6) | 53 | 51 (96.2) | −3.6 (−14.40, 6.40) |
| ***K. pneumoniae*** | | | | | |
| Ceftazidime-resistant | 3 | 3 (100) | 1 | 1 (100) | 0.0 (−63.06, 83.67) |
| Ceftazidime-susceptible | 16 | 15 (93.8) | 26 | 25 (96.2) | −2.4 (−25.36, 14.04) |
| ***Non-Enterobacteriaceae*** | | | | | |
| Ceftazidime-resistant | 2 | 2 (100) | 1 | 1 (100) | 0.0 (−74.23, 85.21) |
| Ceftazidime-susceptible | 15 | 15 (100) | 15 | 13 (86.7) | 13.3 (−9.08, 38.36) |
| ***P. aeruginosa*** | | | | | |
| Ceftazidime-resistant | 1 | 1 (100) | 0 | 0 | - |
| Ceftazidime-susceptible | 10 | 10 (100) | 14 | 12 (85.7) | 14.3 (-16.23, 40.56) |
| aDifference in clinical cure rates (%).  b95% confidence interval (CI) for group differences was calculated using the unstratified Miettinen & Nurminen method. Clinical cure rate for the eME population was defined as the number of patients with a response of clinical cure at the test-of-cure visit divided by the number of patients with clinical cure + clinical failure. Clinical response was based on surgical review evaluation if it was different from the investigator’s assessment. Ceftazidime resistance includes both the Clinical and Laboratory Standards Institute breakpoint-defined non-susceptible and intermediate categories. Percentages are based on the total number of patients in the subgroup (n). | | | | | |

* + - * 1. RECLAIM 3 summary of results

The full summary of results reported are listed in Table 22.

In the CE population (CAZ/AVI plus metronidazole, n = 177; meropenem, n = 184), non-inferiority of CAZ/AVI plus metronidazole to meropenem was demonstrated, with clinical cure reported for 93.8% (166/177) and 94.0% (173/184) of patients, respectively (between-group difference, −0.2, 95% CI −5.53 to 4.97). The clinical cure rate with CAZ/AVI plus metronidazole was comparable in patients with ceftazidime-non-susceptible and ceftazidime- susceptible isolates (95.7% vs. 92.1%, respectively).

AEs were similar between the study groups with gastrointestinal disorders (including nausea, diarrhoea, constipation, and vomiting) most frequently reported (CAZ/AVI + metronidazole, n = 41 [19.1%]; meropenem, n = 26 [12.0%]).

Table 22. RECLAIM 3 summary of results18

|  |  |
| --- | --- |
| **Study acronym** | **RECLAIM 3** |
| Efficacy results - primary endpoint | * Confirmed NI of CAZ/AVI plus metronidazole vs. meropenem. * Clinical cure at TOC in the CE population was reported in 166 (93.8%) patients treated with CAZ/AVI plus metronidazole and 173 (94.0%) patients treated with meropenem (diff.−0.2 [95% CI −5.53,4.97; P<0.001) |
| Efficacy results - key secondary endpoint(s) | * Clinical cure rate at the ET and LFU visits in the CE population, as well as the EOT, TOC and LFU visits in the ME and extended ME populations, and the EOT visit in the mMITT population were all similar to the primary analysis result, with the lower limit of the 95% CI for the between-group difference numerically above −12.5% * CAZ/AVI was effective in treating infections caused by ceftazidime-non-susceptible Gram-negative pathogens, with clinical cure rates similar to those seen with ceftazidime-susceptible isolates (22/23 [95.7%] vs. 70/76 [92.1%] patients, respectively) |
| Safety results | * 2/215 (38.1%) and 83/217 (38.2%) patients in the CAZ/AVI plus metronidazole and meropenem groups, respectively, experienced at least one AE up to LFU. In both groups, 5 AEs (2.3%) were considered severe in intensity. * There were 9 (4.2%) and 11 (5.1%) serious AEs reported in the CAZ/AVI plus metronidazole and meropenem groups, respectively. None of these were reported in more than one patient in either treatment group. * The most frequently reported AEs were in the system organ class gastrointestinal disorders (CAZ/AVI plus metronidazole, 41 [19.1%]; meropenem, 26 [12.0%]), including nausea, diarrhoea, constipation and vomiting. * Discontinuations due to AEs was low in both treatment groups (CAZ/AVI plus metronidazole, 7 [3.3%]; meropenem, 3 [1.4%]) |
| Conclusion(s) | CAZ/AVI plus metronidazole was NI to meropenem in the treatment of cIAIs and was effective against ceftazidime-non-susceptible pathogens. |
| AE: adverse event; CE: clinically evaluable; CI: confidence interval; cMITT: clinically modified intention-to-treat; diff: difference; ET: end of treatment; LFU: last follow up; mMITT: microbiologically modified intention-to-treat; NI: non-inferiority; TOC: test-of-cure | |

### REPRISE

As the REPRISE trial predominantly focuses on patients with cUTI, the, baseline characteristics, summary of study results and conclusions are described later in Sections 3.3.2.1 and 3.3.2.2.

#### REPRISE trial design and methodology

REPRISE97 was an international, randomised, open-label, phase 3 trial which compared CAZ/AVI with best available therapy (including meropenem, imipenem, doripenem, colistin, and [for cIAI] tigecycline) in cUTI and cIAI patients. The primary endpoint of REPRISE was the proportion of patients with clinical response (cure, failure, or indeterminate) at the TOC visit in the mMITT population. Key secondary endpoints were clinical response at other key study milestones, clinical response at TOC by baseline Gram-negative pathogen isolated and entry diagnosis, per-patient favourable microbiological response at key study milestones, and per-pathogen favourable microbiological response at TOC. Safety analysis included AEs, reasons for treatment change or discontinuation, electrocardiogram, and 28-day all-cause mortality.

The REPRISE trial design and methodology is outlined in Table 23 and study procedures are described in Figure 8.

Table 23. REPRISE trial design and methodology97

| **Study acronym** | **REPRISE** |
| --- | --- |
| Study design | International, randomised, open-label, phase 3 trial |
| Settings/locations | A total of 333 patients were randomised in 53 centres in 16 countries. 306 patients had cUTI and 27 patients had cIAI. |
| Eligibility criteria | Key exclusion criteria:   * CrCl < 6 mL/min, by Cockcroft-Gault formula; * abnormal liver function; * Gram-negative infection unlikely to respond to CAZ/AVItreatment; * and infection considered unlikely to respond to 5–21 days of study treatment.   Patients with cIAI were also excluded from the trial if they had an APACHE II score of > 30 or had previously undergone a liver, pancreas, or small-bowel transplant |
| Intervention(s) | cUTI: CAZ/AVI (2000 mg ceftazidime 500 mg avibactam) administered every eight hours by IV infusion over two hours  cIAI: CAZ/AVI (2000 mg ceftazidime 500 mg avibactam) administered every eight hours by IV infusion over two hours plus IV metronidazole 500 mg, administered as a 60-min infusion every 8 h immediately after CAZ/AVI  Treatment was administered for 5-21 days and dose-adjustment was made for moderate-severe renal impairment (CrCl: 6-50 mL/min) |
| Comparator(s) | Patients received between 5–21 days treatment with best available therapy, including:   * IV Meropenem * Imipenem * Doripenem * Colistin * tigecycline (cIAI only) * Any therapy, including combination treatment, was permitted. |
| Efficacy outcomes | Primary outcome measure:   * Clinical response (cure, failure, or indeterminate) at the TOC (mMITT)   Key secondary outcome measures (mMITT and eME):   * Clinical response at other timepoints (ET, follow-up visit 1, and follow-up visit 2 [cUTI only]); * Clinical response at TOC by baseline Gram-negative pathogen isolated, and entry diagnosis; * Per-patient favourable microbiological response at ET, TOC, follow-up visit 1, and follow-up visit 2 (cUTI only); * Per-pathogen favourable microbiological response at TOC   Other outcome measures:   * Clinical cure at TOC by previously failed antibiotic treatment class * Per-pathogen favourable microbiological response at the other visits (ET follow-up visit 1, and follow-up visit 2), * Per-pathogen favourable microbiological response by CAZ/AVIMIC * Clinical and microbiological response by resistance mechanism   Based on clinical outcome, clinical response (at ET, TOC, FU1 and FU2 visits) was defined as:   * Cure (complete resolution or significant improvement of signs and symptoms such that antibiotic therapy was stopped. In cIAI, no drainage or surgical intervention after 96 hours from randomisation was necessary) * Failure (patients who either: died due to infection; received additional antibiotics outside of those permitted in the protocol or previously met criteria for failure. Patients with cIAI were also considered for failure based on persistent or recurrent infection within the abdomen or post-surgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that required additional antibiotics and/or non-routine wound care * Indeterminate (data were not available for evaluation of efficacy for any reason, including: loss to follow up, death due to non-contributory index infection, or circumstances that precluded classification as a cure or failure)   Microbiological response at ET, TOC, FU1 and FU2 visits was defined as:   * Eradication (absence [or urine quantification <104 CFU/mL for cUTI patients] of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteraemic at Screening, the bacteraemia had also resolved) * Presumed eradication (Repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure ([cIAI only]) * Persistence (pathogen still present at or beyond the EOT visit from a specimen at the site of infection. For cUTI patients, the organism was required to be present at ≥104 CFU/mL) * Persistence with increasing MIC (continued presence of the causative organism to be identical to the originally susceptible to study therapy in a culture taken after at least 2 full days of treatment displays a ≥4-fold higher MIC to study therapy after treatment with study therapy. For cUTI patients, the culture taken after at least 2 full days was required to also demonstrate ≥104 CFU/mL * Presumed persistence (Patient was previously assessed as a clinical failure and repeat cultures were not performed/clinically indicated [cIAI only]) * Indeterminate (data were not available for evaluation of efficacy, for any reason including: patient lost to follow up, death not contributed to infection, or circumstances that precluded classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence |
| Safety outcomes | Safety outcome measures:   * Reasons for treatment change or discontinuation, * 28-day all-cause mortality * Resting ECG * Adverse events |
| Other outcomes used in the economic model/specified in the scope | Health economic variables, including:   * length of hospital stay, * length of ICU stay and/or transfer to the ICU, * length of study therapy, * mortality caused by cIAI and UTI (up to TOC visit). |
| Analysis populations | * mMITT: all patients who had a diagnosis of cIAI or cUTI with a ceftazidime-resistant Gram-negative pathogen on the study-qualifying culture and who received at least 1 dose of study therapy * eME: included all patients who were in the mMITT, received at least 5 days of therapy or received <48 hours of therapy before discontinuing due to an AE, had no major protocol deviations, received no additional systemic, Gram-negative antibiotic therapy for treatment of a non-cIAI/cUTI infection, (cUTI only) had a microbiological assessment from a quantitative urine culture at the EOT, TOC, FU1, and FU2 (cUTI only) visits, respectively, with a microbiological response other than indeterminate, (cIAI only) had a microbiological response at the EOT, TOC, and FU1 visits other than indeterminate * Safety: all patients who received any amount of study therapy * PK: all patients who had at least 1 plasma concentration data value available for either ceftazidime or avibactam |
| Statistical methods | Sample size:   * Due to the unfeasibility of recruiting large numbers of patients infected with resistant Gram-negative pathogens, no formal power calculations were performed and no formal statistical comparisons between treatment groups were undertaken. Sample size was based on practical considerations only. * Approximately 200 patients per treatment group were planned to be recruited for this study. This was expected to provide sufficient data that the 95% CI for the cure rate within each treatment group would extend at most approximately 7% on either side of the observed proportion in the overall summary, or at most 17% on either side for each separate pathogen infecting at least 30 patients, or 13% on either side for pathogens infecting at least 60 patients.   Primary efficacy analysis:   * For the primary outcome variable, 2-sided 95% CI for the proportion of clinical cure at the TOC visit for CAZ/AVI and BAT were computed using the Jeffreys method * Forest plots were used to present the point estimate and the associated 2-sided 95% CI using the Jeffreys method for the clinical cure rate within each treatment group and entry diagnosis.   Secondary efficacy analysis:   * Analyses of the secondary efficacy variables were considered to be supportive of the primary efficacy results. * The 2-sided 95% CIs were calculated using the Jeffreys method |
| APACHE: Acute Physiology and Chronic Health Evaluation; BAT: best available therapy; CI: confidence interval; cIAI: complicated intra-abdominal infection; CrCl: creatinine clearance; cUTI: complicated urinary tract infection; eME: extended microbiologically evaluable population; ET: end-of-treatment; ICU: intensive care unit; IV: intravenous; MIC: minimum inhibitory concentration; mMITT: microbiologically modified intention-to-treat; PK: pharmacokinetic; TOC: test-of-cure | |

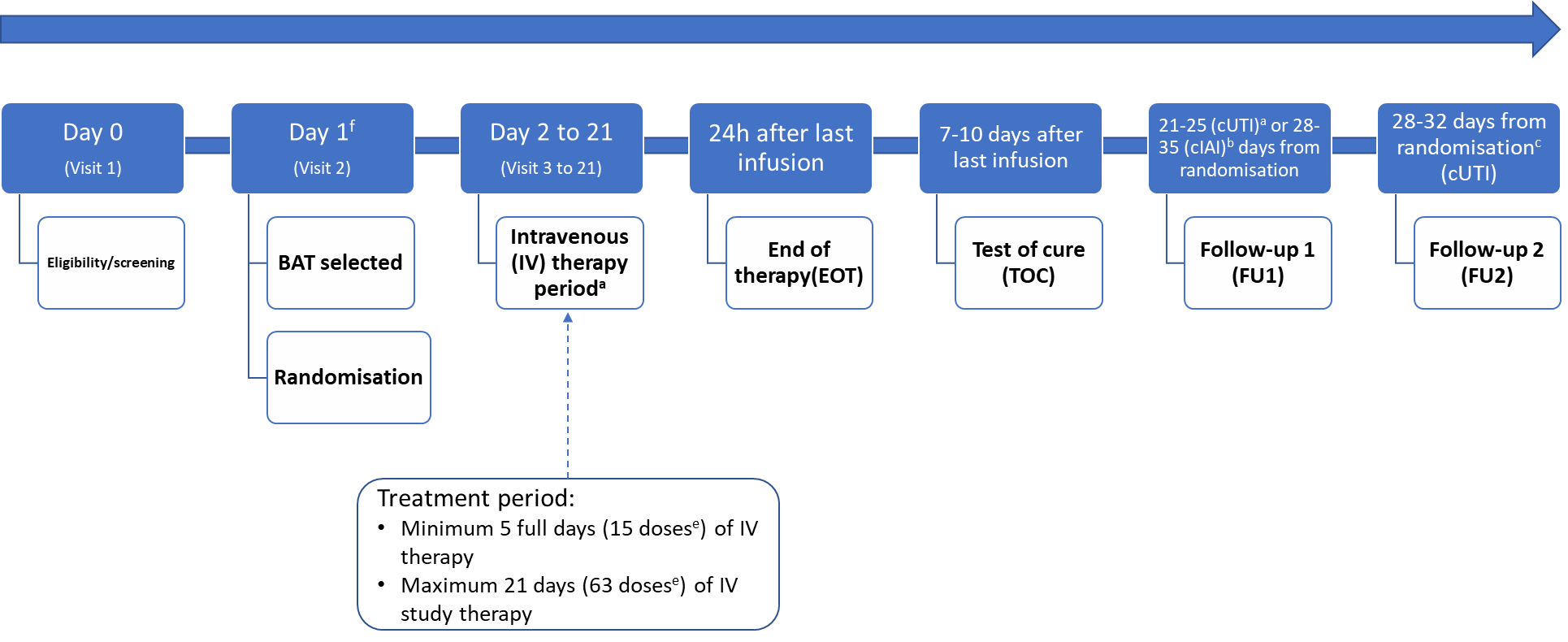


Figure 8. REPRISE study procedure115

a/bTOC and FU1 visits may have overlapped depending upon the number of days the cUTI/cIAI patient received study therapy. In those instances, the TOC and FU1 visits were combined on the same day. Depending on the duration of study therapy and the timing of the TOC and FU1 visits, it was possible that the FU1 visit could have occurred prior to the TOC visit.

cTOC and FU2 visits may have overlapped depending upon the number of days the cUTI patient received study therapy. In those instances, the TOC and FU2 visits were combined on the same day.

d Treatment doses were only for patients randomized to CAZ/AVI. Dosing for BAT were per the local standard of care.

eFor patients with creatinine clearance >50 mL/min.

fAdministration of the first dose of IV study therapy marked the beginning of study Day 1.

BAT: best available therapy; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection;

### ANDI20

#### ANDI trial design and methodology

ANDI was a single-blind, randomised, multi-centre, and actively controlled trial conducted in paediatric patients (aged from 3 months to <18 years) diagnosed with cIAIs of sufficient severity to require hospitalisation and treatment with intravenous (IV) antibiotics (specifically CAZ/AVI plus metronidazole or meropenem). Key primary outcome measures included the onset of AEs and SAEs (including cephalosporin class effects and additional AEs of special interest), vital signs, renal functions, electrocardiogram, laboratory assessments. Other outcome measures included clinical cure rates, microbiological response and reporting of emergent infections.

The ANDI trial design and methodology is outlined in Table 24 and study procedures are outlined in Figure 9.

Table 24. ANDI trial design and methodology

| **Study acronym** | **ANDI** |
| --- | --- |
| Study design | Single-blind, randomised, multi-centre, actively controlled Phase II trial |
| Settings / locations | 29 centres across 10 countries participated in this study. A total of 86 patients were screened with 83 randomly assigned (3:1) to CAZ/AVI + metronidazole or meropenem. |
| Eligibility criteria | Key exclusion criteria: History of hypersensitivity reactions to carbapenems, cephalosporins, penicillin, other β-lactam antibiotics, metronidazole, or to nitroimidazole derivatives; concurrent infection that may have interfered with the evaluation of response to the study antibiotics at the time of randomisation; need for effective concomitant systemic antibacterials alongside the study medication; poor survival/response expectation. |
| Intervention | IV treatment by infusion, with CAZ/AVI (2000mg) plus metronidazole (500 mg) for a minimum of 72 hours. Doses were based on the age and weight of the patient with adjustment according to renal function.  IV study drug was administered every 8 hours for 3 days for a total of 9 doses. On Day 4, there was an option to switch to oral therapy at the Investigator’s discretion, if the patient had good or sufficient clinical response, and the patient was tolerating oral fluids or food. Alternatively, patients could continue to take IV CAZ/AVI plus metronidazole from Day 4 up to Day 15. |
| Comparator | IV treatment by infusion, with meropenem (1000 g) for a minimum of 72 hours. Doses were based on the age and weight of the patient with adjustment according to renal function.  IV study drug was administered every 8 hours for 3 days for a total of 9 doses. On Day 4, there was an option to switch to oral therapy at the Investigator’s discretion, if the patient had good or sufficient clinical response, and the patient was tolerating oral fluids or food. Alternatively, patients could continue to take IV meropenem from Day 4 up to Day 15. |
| Efficacy outcomes | Secondary outcome measures:   * Clinical cure rates (cure, sustained clinical cure, improvement, relapse, failure, indeterminate) at end of 72 hours, end of IV treatment, end of treatment, test of cure, and late follow-up. * Microbiological response (at end of IV treatment, EOIV, EOT, TOC, and LFU) * Emergent infections   Clinical response varies dependent at time of measurement. Response definitions were categorised at:   * Clinical cure: Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required * Sustained clinical cure: continued favourable response as defined by clinical cure (LFU only) * Improvement: Improvement, but not enough to switch therapy (end of 72 hours only) and absence of new signs and symptoms, and improvement in at least 1 symptom or sign from Baseline, and with no worsening of any symptom or sign * Relapse: reappearance or worsening of signs and symptoms of cIAI that requires further antimicrobial therapy and/or surgery or death at TOC attributable to cIAI (LFU only) * Failure: Discontinuation due to AEs or lack of efficacy, death due to cIAI, or incomplete resolution or worsening of cIAI. * Indeterminate: Data are not available for evaluation of efficacy for any reason   Microbial response at end of IV treatment, EOIV, EOT, TOC, and LFU defined as:   * Eradication: source specimen demonstrated absence of the original baseline pathogen * Presumed eradication: source specimen was not available to culture, and the patient was assessed as a clinical cure or sustained clinical cure or (for EOIV only) clinical improvement * Persistence: source specimen demonstrates continued presence of the original baseline pathogen * Persistence with increasing MIC: source specimen demonstrates continued presence of the original baseline pathogen with an MIC value ≥4-fold larger than that observed for the baseline pathogen * Presumed persistence: Source specimen was not available to culture and the patient was assessed as a clinical failure or clinical relapse * Indeterminate: Source specimen was not available to culture and the patient’s clinical outcome was assessed as indeterminate |
| Safety outcomes | Primary outcome measure:   * Onset of adverse events and serious adverse events * Cephalosporin class effects and additional AEs of special interest * Vital signs * Physical examination * Laboratory parameters * CrCl * ECG |
| Other outcomes used in the economic model/specified in the scope | None specified |
| Analysis populations | * Safety: all randomised patients who received any amount of IV study therapy * Safety evaluable: a subset of the patients in the Safety analysis set who received at least 9 doses of study treatment * PK: a subset of the patients in the Safety analysis set who had at least 1 ceftazidime and/or avibactam plasma measurement available * ITT: All patients who were assigned a randomised treatment * MITT: all randomised patients who had a baseline pathogen known to cause cIAI. * CE: included all randomised patients who received any amount of IV study drug that had a confirmed diagnosis of cIAI and patients must have also met the following specific conditions:   + Received at least 48 hours of IV study drug, defined as 6 doses, in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE;   + Received at least 72 hours of IV study drug, defined as 9 doses, in order to be considered an evaluable clinical cure;   + Had a clinical response other than indeterminate at the associated study visit;   + Had no important protocol deviations that would affect assessment of efficacy based on ECMA review;   + Did not receive concomitant antibiotics which would impact assessment of efficacy based on ECMA review. * ME: all randomised patients that had a confirmed diagnosis of cIAI and who met the following criteria:   + Received at least 48 hours of IV study drug, defined as 6 doses, in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE;   + Received at least 72 hours of IV study drug, defined as 9 doses, in order to be considered an evaluable clinical cure;   + At the specific visit had a microbiological response other than indeterminate;   + Had no important protocol deviations that would affect assessment of efficacy based on ECMA review.   + Did not receive concomitant antibiotics which would impact assessment of efficacy based on ECMA review.   + Had at least 1 typical IAI bacterial pathogen (based on ECMA review) which had been isolated from an adequate microbiological specimen at Baseline that was susceptible to both study agents (CAZ/AVI and meropenem). |
| Statistical methods | Sample size:   * The proposed sample size for this study was 80 evaluable patients comprised of a minimum of 60 and 20 patients, respectively, from the CAZ/AVI plus metronidazole and meropenem groups. * The sample size was based on the probability of observing a ‘rare’ safety event. The ‘rare’ term used in this section is not based on the regulatory definition but is instead intended to reflect uncommon events.   Efficacy analysis:   * Descriptive statistics (number, mean, SD, median, minimum, and maximum) were provided for continuous variables, and counts and percentages were presented for categorical variables. The study was not powered for inferential testing and based on the 3:1 randomisation, direct comparisons of safety and efficacy data between treatment groups must be interpreted with caution.   Safety analysis:   * No inferential statistical tests were performed for any safety parameters as the study was not powered for inferential testing. In addition to the limited sample size, the 3:1 randomisation ratio would also warrant caution in the interpretation of direct comparisons of safety data between treatment groups. All data were presented by treatment group, cohort, and overall for each treatment.   Sensitivity analysis:   * A sensitivity analysis was conducted to assess the impact of the method originally planned for the derivation of the analysis window for the End of 72 hours assessment visit |
| AE: adverse event; CE: clinically evaluable; cIAI: complicated intra-abdominal infection; CrCl: creatinine clearance; ECG: echocardiogram; EMCA: Evaluability and Clinical/Microbiological Assessment; EOIV: end of IV treatment; EOT: end of treatment; ITT: intent to treat; IV: intravenously LFU: last follow-up; ME: microbiologically evaluable; MIC: minimum inhibitory concentration; MITT: microbiological intent to treat; PK: pharmacokinetic; SD: standard deviation; TOC: test of cure | |

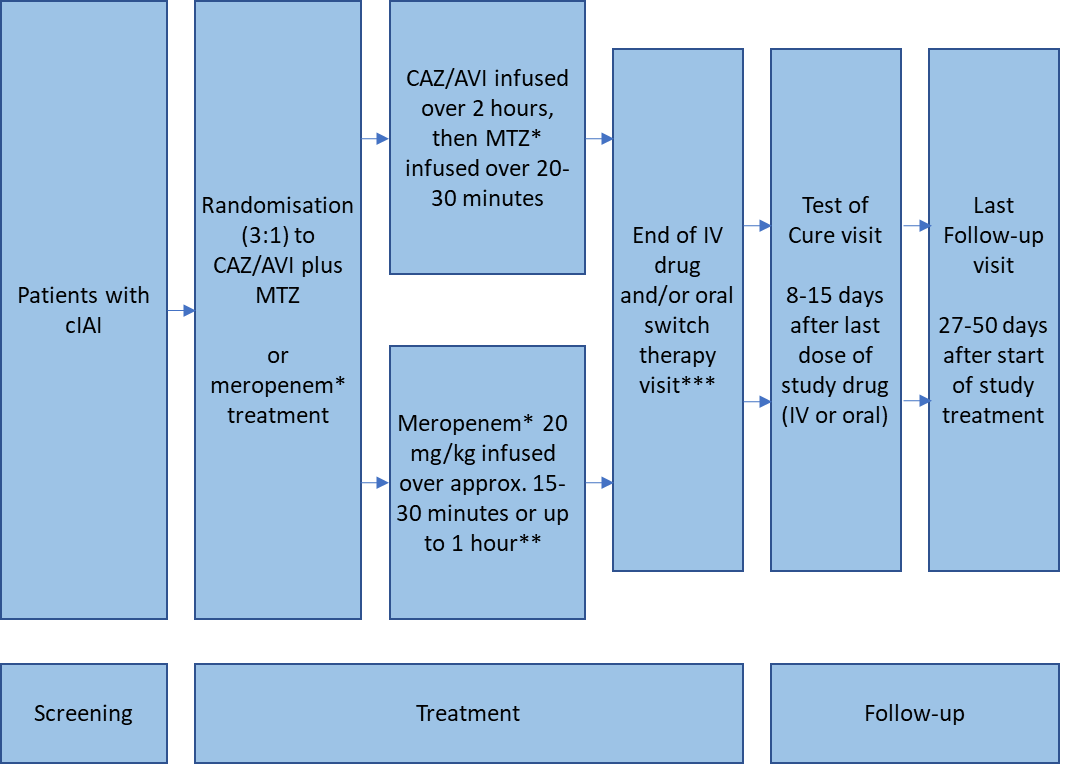


Figure 9. ANDI study procedure20

\*Optional switch to oral therapy permitted on or after Study Day 4 (i.e., after 72 hours [3 full days, i.e., 9 doses] of IV study drug. Assessment should be performed no later than 8 hours after the 72-hour time point. The decision to switch to oral therapy was at the Investigator’s discretion.

\*\* Or infusion duration as per local guidelines. For patients weighing over 50 kg, the maximum dose of meropenem should not exceed 1 g every 8 hours.

\*\*\* Visit performed within 24 hours of completion of last infusion or within 48 hours after the last dose of oral switch therapy.

CAZ/AVI: ceftazidime avibactam plus metronidazole; cIAI: complicated intra-abdominal infection; IV: intravenous; MTZ: metronidazole.

#### ANDI baseline characteristics

* + - * 1. ANDI baseline demographics and clinical characteristics

The majority (63.9%) of patients were male and the proportion of males was larger in the CAZ/AVI plus metronidazole group (72.1%) than in the meropenem group (40.9%). The mean (SD) BMI for all patients was 18.2 (3.63) kg/m2 (the CAZ/AVI plus metronidazole group was: 18.1 [3.35] kg/m2 [range: 13 to 26 kg/m2] and for the meropenem: group 18.4 [4.40] kg/m2 [range: 12 to 28 kg/m2]). At baseline, the majority of patients (85.5%) had creatinine clearance (CrCl) values in the normal range of >80 mL/min for both treatment groups. Eleven (13.3%) patients overall had mild renal insufficiency with CrCl values >50 to <80 mL/min. No patient had a CrCl value <50 mL/min.

A total of 75 patients (90.4%) had a diagnosis of appendicitis at Screening. The most commonly reported operative procedures in each treatment group were reflective of this diagnosis. The types of operative procedures performed were similar across cohorts for CAZ/AVI plus metronidazole and meropenem treated patients. The most common interventional procedures performed were appendectomy not otherwise specified (NOS) for both treatment groups (n = 45 [54.2%] overall; n = 36 [59.0%] for the CAZ/AVI plus metronidazole group and n = 9 [40.9%] for the meropenem group).

Table 25. ANDI baseline demographic and clinical characteristics (Safety analysis set)

|  | **CAZ/AVI + Metronidazole**  **(N = 61)** | **Meropenem**  **(N = 22)** | **Total**  **(N = 83)** |
| --- | --- | --- | --- |
| Age (years), Mean (SD) | 10.4 (3.64) | 10.1 (3.63) | 10.3 (3.62) |
| Age (months), Mean (SD) | - | 21.0 (-) | 21.0 (-) |
| Sex (male), n (%) | 44 (72.1) | 9 (40.9) | 53 (63.9) |
| Race, n (%) | | | |
| Black or African American | 0 | 0 | 0 |
| White | 53 (86.9) | 16 (72.7) | 69 (83.1) |
| Asian | 7 (11.5) | 4 (18.2) | 11 (13.3) |
| Native Hawaiian or Pacific Islander | 0 | 0 | 0 |
| American Indian or Alaska Native | 1 (1.6) | 0 | 1 (1.2) |
| Other | 0 | 2 (9.1) | 2 (2.4) |
| BMI, Mean (SD) | 18.1 (3.35) | 18.4 (4.40) | 18.2 (3.63) |
| CrCl category, n (%) | | | |
| <30mL/min | 0 | 0 | 0 |
| ≥30 to <50 mL/min | 0 | 0 | 0 |
| ≥50 to <80 mL/min | 9 (14.8) | 2 (9.1) | 11 (13.3) |
| ≥80 mL/min | 51 (83.6) | 20 (90.9) | 71 (85.5) |
| Type of procedure, n (%) | | | |
| Laparoscopy | 14 (23.0) | 9 (40.9) | 23 (27.7) |
| Laparotomy | 8 (13.1) | 2 (9.1) | 10 (12.0) |
| Percutaneous Drainage | 3 (4.9) | 2 (9.1) | 5 (6.0) |
| Appendectomy NOS | 36 (59.0) | 9 (40.9) | 45 (54.2) |
| Confirmed appendicitis at screening, n (%) | 55 (90.2) | 20 (90.9) | 75 (90.4) |
| Diagnosis of IAI, n (%) | | | |
| Appendiceal perforation or peri-appendiceal abscess | 52 (85.2) | 20 (90.9) | 72 (86.7) |
| Secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites) | 8 (13.1) | 1 (4.5) | 9 (10.8) |
| Traumatic perforation of the intestines, only if operated on >12 hours after perforation occurs | 1 (1.6) | 1 (4.5) | 2 (2.4) |
| BMI: body mass index; CrCl: creatinine clearance; IAI: intra-abdominal infection; NOS: not otherwise specified; SD: standard deviation | | | |

* + - * 1. ANDI baseline pathogens

In the mMITT analysis set, the most frequently reported *Enterobacteriaceae* pathogen reported at baseline was *E. coli* (79.7%). The most frequently reported Gram-negative pathogen other than *Enterobacteriaceae* was *P. aeruginosa* (33.3%). *K. pneumoniae* was reported in 3 (4.3%) patients overall. No other Gram-negative aerobic pathogens were identified in more than 2 patients in any treatment group. A total of 37 patients (53.6%) had Gram-positive pathogens identified at baseline, the most frequently reported was *Streptococcus anginosus* (47.8%). The most frequently reported anaerobe was *B. fragilis* (30.4%). Two patients in the CAZ/AVI plus metronidazole group and none in the meropenem group had Gram-negative pathogens identified in the blood at baseline.

Table 26. ANDI summary of baseline pathogens (mITT analysis set)

|  |  |  |  |
| --- | --- | --- | --- |
| **Pathogen group**  *Pathogen* | **CAZ/AVI + Metronidazole**  **(N = 61)** | **Meropenem**  **(N = 22)** | **Total**  **(N = 83)** |
| ***Enterobacteriaceae*** | 42 (84.0) | 14 (73.7) | 56 (81.2) |
| *E. coli* | 42 (84.0) | 13 (68.4) | 55 (79.7) |
| *K. pneumoniae* | 2 (4.0) | 1 (5.3) | 3 (4.3) |
| **non-***E****nterobacteriaceae* Gram-negatives** | 16 (32.0) | 10 (52.6) | 26 (37.7) |
| *P. aeruginosa* | 14 (28.0) | 9 (47.4) | 23 (33.3) |
| **Gram-positive** | 26 (52.0) | 11 (57.9) | 37 (53.6) |
| *Enterococcus avium* | 4 (8.0) | 1 (5.3) | 5 (7.2) |
| *Enterococcus faecium* | 2 (4.0) | 0 | 2 (2.9) |
| *Streptococcus anginosus group* | 23 (46.0) | 10 (52.6) | 33 (47.8) |
| **Anerobes** | 24 (48.0) | 12 (63.2) | 36 (52.2) |
| *Bacteroides caccae* | 3 (6.0) | 0 | 3 (4.3) |
| *Bacteroides fragilis* | 14 (28.0) | 7 (36.8) | 21 (30.4) |
| *Bacteroides fragilis group* | 2 (4.0) | 2 (10.5) | 4 (5.8) |
| *Bacteroides ovatus* | 2 (4.0) | 0 | 2 (2.9) |
| *Bacteroides thetaiotaomicron* | 3 (6.0) | 3 (15.8) | 6 (8.7 |
| *Bacteroides vulgatus* | 2 (4.0) | 0 | 2 (2.9) |
| *Clostridium perfringens* | 0 | 2 (10.5) | 2 (2.9) |
| *Clostridium ramosum* | 2 (4.0) | 0 | 2 (2.9) |
| *Eggerthella lenta* | 2 (4.0) | 0 | 2 (2.9) |
| *Parabacteroides distasonis* | 2 (4.0) | 0 | 2 (2.9) |
| *Parvimonas micra* | 4 (8.0) | 5 (26.3) | 9 (13.0) |
| *Prevotella buccae* | 2 (4.0) | 0 | 2 (2.9) |

#### ANDI summary of results

In general, across all analysis sets, favourable clinical response rates of ≥90% were observed at the End of 72 hour visit and were sustained through the LFU visit for both treatment groups. At TOC, 56 patients (91.8%) in the CAZ/AVI plus metronidazole group and 21 patients (95.5%) in the meropenem group had a favourable clinical response for the ITT analysis set. In the ME analysis set, the majority of patients had favourable clinical responses at every visit. At TOC, 36 patients (90.0%) in the CAZ/AVI plus metronidazole group and 14 patients (93.3%) in the meropenem group had a favourable clinical response (Table 27).

Table 27. Favourable Clinical Response by Visit, Treatment Group and Cohort (ITT, Micro-ITT, CE, and ME analysis sets by visit)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | **Analysis set** | **CAZ/AVI + metronidazole** | | | **Meropenem** | | |
| **N** | **n** | **Favourable Response Rate (95% CIa)** | **N** | **n** | **Favourable Response Rate (95% CIa)** |
| End of 72 Hours | ITT | 61 | 57 | 93.4 (85.2, 97.7) | 22 | 20 | 90.9 (73.9, 98.1) |
| MITT | 50 | 47 | 94.0 (84.8, 98.3) | 19 | 18 | 94.7 (77.9, 99.4) |
| CE | 49 | 48 | 98.0 (90.9, 99.8) | 20 | 19 | 95.0 (78.9, 99.5) |
| ME | 33 | 32 | 97.0 (86.7, 99.7) | 15 | 15 | 100.0 (84.8, 100.0) |
| End of IV Treatment | ITT | 61 | 59 | 96.7 (89.9, 99.3) | 22 | 22 | 100.0 (84.8, 100.0) |
| MITT | 50 | 48 | 96.0 (87.8, 99.2) | 19 | 19 | 100.0 (84.8, 100.0) |
| CE | 54 | 53 | 98.1 (91.7, 99.8) | 20 | 20 | 100.0 (84.8, 100.0) |
| ME | 40 | 39 | 97.5 (88.9, 99.7) | 15 | 15 | 100.0 (84.8, 100.0) |
| End of Treatment | ITT | 61 | 56 | 91.8 (83.0, 96.8) | 22 | 22 | 100.0 (84.8, 100.0) |
| MITT | 50 | 45 | 90.0 (79.5, 96.1) | 19 | 19 | 100.0 (84.8, 100.0) |
| CE | 52 | 59 | 94.2 (85.4, 98.3) | 20 | 20 | 100.0 (84.8, 100.0) |
| ME | 36 | 33 | 91.7 (79.4, 97.6) | 15 | 15 | 100.0 (84.8, 100.0) |
| Test of Cure | ITT | 61 | 56 | 91.8 (83.0, 96.8) | 22 | 21 | 95.5 (80.7, 99.5) |
| MITT | 50 | 45 | 90.0 (79.5, 96.1) | 19 | 18 | 94.7 (77.9, 99.4) |
| CE | 56 | 52 | 92.9 (83.9, 97.5) | 20 | 19 | 95.0 (78.9, 99.5) |
| ME | 40 | 36 | 90.0 (78.0, 96.5) | 15 | 14 | 93.3 (72.8, 99.3) |
| Late Follow-up | ITT | 61 | 56 | 91.8 (83.0, 96.8) | 22 | 21 | 95.5 (80.7, 99.5) |
| MITT | 50 | 45 | 90.0 (79.5, 96.1) | 19 | 18 | 94.7 (77.9, 99.4) |
| CE | 48 | 48 | 100.0 (94.9, 100.0) | 18 | 18 | 100.0 (87.1, 100.0) |
| ME | 33 | 33 | 89.2 (76.3, 96.2) | 14 | 13 | 92.9 (71.2, 99.2) |
| CE: clinically evaluable; CI: confidence interval; ITT: intent-to-treat; IV: intravenous; ME: microbiologically evaluable. MITT: microbiological intent-to treat  a. Jeffrey’s method was used to calculate the two-sided 95% confidence intervals. | | | | | | | |

Across both treatment groups, favourable microbiological response rates were high for the aerobic Gram-negative pathogens (≥ 90.5% for the *Enterobacteriaceae* and ≥ 85.7% for *P. aeruginosa*.

The results for the microbiologically evaluable (ME) analysis set were similar to the results observed for the microbiological intent-to treat (micro-ITT) analysis set. At all visits, the majority of patients with *E. coli* and *P. aeruginosa* infections showed favourable microbiological responses in both treatment groups.

Table 28. Per-Pathogen Favourable Microbiological Response Rate in ≥2 Patients in Either Treatment Group at TOC by Pathogen and Treatment Group (Micro-ITT Analysis Set)

|  |  |  |
| --- | --- | --- |
| **Pathogen group**  *Pathogen* | **CAZ/AVI + Metronidazole**  **(N = 50)** | **Meropenem**  **(N = 19)** |
| ***Enterobacteriaceae*** | 38/42 (90.5) | 13/14 (92.9) |
| *E. coli* | 38/42 (90.5) | 12/13 (92.3) |
| *K. pneumoniae* | 2/2 (100) | 1/1 (100) |
| **non-***E****nterobacteriaceae* Gram-negatives** | 14/16 (87.5) | 9/10 (90.0) |
| *P. aeruginosa* | 12/14 (85.7) | 8/9 (88.9) |
| **Gram-positive** | 24/26 (92.3) | 11/11 (100) |
| *Enterococcus avium* | 4/4 (100) | 1/1 (100) |
| *Enterococcus faecium* | 2/2 (100) | 0 |
| *Streptococcus anginosus group* | 21/23 (91.3) | 10/10 (100) |
| **Anaerobes** | 22/24 (91.7) | 11/12 (91.7) |
| *Bacteroides fragilis* | 13/14 (92.9) | 7/7 (100) |
| *Bacteroides fragilis group* | 2/2 (100) | 2/2 (100) |
| *Bacteroides ovatus* | 2/2 (100) | 0 |
| *Bacteroides thetaiotaomicron* | 3/3 (100) | 3/3 (100) |
| *Bacteroides vulgatus* | 2/2 (100) | 0 |
| *Clostridium perfringens* | 0 | 2/2 (100) |
| *Parabacteroides distasonis* | 2/2 (100) | 0 |
| *Parvimonas micra* | 4/4 (100) | 5/5 (100) |
| *Prevotella buccae* | 2/2 (100) | 0 |

Overall, 52.5% and 59.1% of patients in the study experienced an AE in the combined CAZ/AVI plus metronidazole and meropenem groups, respectively. A total of 6 patients experienced SAEs (CAZ/AVI plus metronidazole: n = 5 [8.2%] and meropenem: n = 1 [4.5%]), and none of the SAEs were considered to be related to study treatment. There were no discontinuations from study drug due to AEs. There were 4 (6.6%) and 1 (4.5%) patients who experienced severe AEs in the CAZ/AVI plus metronidazole and meropenem groups, respectively. The majority of AEs reported were not related to study treatment, as assessed by the Blinded Observer, with 1 patient (1.6%) in the CAZ/AVI plus metronidazole group and 2 patients (9.1%) in the meropenem group experiencing AEs that were assessed as related to study treatment.

There were no deaths among patients who participated in this study.

## Complicated urinary tract infection

Evidence to support the effectiveness of CAZ/AVI for the treatment of cUTI is derived from RECAPTURE 1 (NCT01595438), RECAPTURE 2 (NCT01599806)19, REPRISE (NCT01644643)97 andKURA (NCT02497781)112 (Table 29).

Table 29. Summary of clinical effectiveness evidence supporting CAZ/AVI in the treatment of adult cUTI

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study acronym** | **RECAPTURE 1 and 219** | | | | | **REPRISE97** | | | | | **KURA112** | | | | |
| Population | Patients (18-90 years) with cUTI or acute pyelonephritis considered serious and requiring hospitalisation for IV antibiotic therapy | | | | | Patients (18-90 years) with either cUTI or cIAI caused by ceftazidime-resistant Gram-negative pathogens | | | | | Hospitalised children ≥3 months to <18 years diagnosed with cUTI, including acute pyelonephritis, that required IV antibiotics | | | | |
| Intervention(s) | CAZ/AVI | | | | | CAZ/AVI with metronidazole | | | | | CAZ/AVI | | | | |
| Comparator(s) | Doripenem | | | | | BAT | | | | | Cefepime | | | | |
| Indicate if trial supports application for marketing authorisation | Yes | ✓ | Indicate if trial used in the economic model | Yes | ✓ | Yes | ✓ | Indicate if trial used in the economic model | Yes |  | Yes |  | Indicate if trial used in the economic model | Yes |  |
| No |  | No |  | No |  | No | ✓ | No | ✓ | No | ✓ |
| Rationale for use/non-use in the model | Pivotal trial supporting cUTI indication | | | | | Pivotal trial supporting cIAI and cUTI indications | | | | | Pivotal trial supporting the paediatric cUTI indication | | | | |
| Reported outcomes specified in the decision problem | * Clinical cure rates, assessed as:   + Clinical response (cure at EOT, TOC and LFU [secondary objective]; sustained cure at LFU [secondary objective]; symptomatic resolution of UTI-specific symptoms at day 5 visit [primary objective]) * Microbiologic eradication   + Per-patient microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms at TOC (primary objective)   + Per-patient microbiological response at TOC, ET and LFU (secondary objective)   + Per-patient and per-pathogen microbiological response at TOC and LFU in patients with ceftazidime-nonsusceptible or only ceftazidime-susceptible pathogens (secondary objective)   + Per-patient and per-pathogen microbiological response using a cut-off of 103 CFU/mL * Adverse events * Healthcare resource utilisation   Readmission rates and health-related quality-of-life were not investigated in RECAPTURE. | | | | | * Clinical cure rates, assessed as:   + Clinical response (cure, failure, or indeterminate) at the TOC visit (primary objective)   + Clinical response at other timepoints (ET, follow-up visit 1, and follow-up visit 2 [cUTI only]) and patient subgroups (entry diagnosis, pathogen, resistance mechanism, and previously failed treatment class) (secondary objective) * Mortality (all-cause mortality at day-28) * Microbiologic eradication (Per-patient and per-pathogen favourable microbiological response at ET, TOC, follow-up visit 1, and follow-up visit 2 (cUTI only), secondary endpoint) * Adverse events * Healthcare resource utilisation   Readmission rates and health-related quality-of-life were not investigated in REPRISE. | | | | | * Clinical cure rates, assessed as:   + Clinical response (cure, relapse (LFU only), failure, or indeterminate) at the End of 72 hours treatment, EOIV, EOT, and TOC visit (secondary objective) * Microbiological response (at end of IV treatment, EOIV, EOT, TOC, and LFU) * Emergent infections   KURA was a Phase II study. Therefore, primary endpoints were limited to investigations relating to safety and tolerability as well as pharmacokinetics and pharmacodynamics. Efficacy outcomes were limited to descriptive secondary objectives. | | | | |
| BAT: best available therapy; CAZ/AVI: ceftazidime/avibactam; CFU: colony-forming units; cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection; EOIV: end of intravenous treatment; ET/EOT: end of treatment; LFU: last follow-up; TOC: test of cure; UTI: urinary tract infection. | | | | | | | | | | | | | | | |

### RECAPTURE 1 and 219

#### RECAPTURE trial design and methodology

RECAPTURE comprised 2 identical phase 3, randomised, multicentre, double-blind, double-dummy, parallel-group trials comparing the efficacy and safety of CAZ/AVI with doripenem in treating adult cUTI according to Food and Drug Agency (FDA) and European Medicines Association (EMA) guidance.

The primary endpoint of RECAPTURE was agency-dependent and included the proportion of patients with symptomatic resolution of UTI-specific symptoms (FDA cohort) and both microbiological eradication and symptomatic resolution of UTI-specific symptoms at TOC in the microbiologically modified intention-to-treat (mMITT) population (both FDA and EMA cohorts). Key secondary outcomes included per-patient microbiological response, per-patient and per-pathogen microbiological response in patients with ≥1 ceftazidime-non-susceptible or only ceftazidime-susceptible pathogens isolated at baseline, investigator-determined clinical cure, and sustained clinical cure. Safety analysis included incidence and severity of AEs and SAEs, mortality, vital signs, electrocardiogram, and reasons for discontinuation of both study therapy and the study.

The RECAPTURE trial design and methodology is outlined in Table 30 and study procedures are described in Figure 10.

Table 30. RECAPTURE trial design and methodology19

| **Study acronym** | **RECAPTURE** |
| --- | --- |
| Study design | Identical phase III, randomised, multicentre, double-blind, double-dummy, parallel-group trials |
| Settings/locations | Randomised patients from 160 centres in 25 countries participated in the study |
| Eligibility criteria | Key exclusion criteria:   * complete obstruction of any portion of the urinary tract, perinephric or intrarenal abscess, or prostatitis; * UTI symptoms potentially attributable to another process; * urinary diversion or vesicoureteral reflux; * CrCl: ≤30 mL/minute (including patients on dialysis) |
| Intervention | CAZ/AVI (2000 mg ceftazidime 500 mg avibactam) administered every eight hours by IV infusion over two hours  Patients meeting prespecified clinical improvement criteria after ≥5 days of IV therapy could be switched to oral ciprofloxacin (500 mg every 12 hours) or sulfamethoxazole-trimethoprim (800 mg/160 mg every 12 hours) for those with a fluoroquinolone-resistant pathogen, administered approximately 8 hours after the last dose of IV treatment.  Total study treatment duration (IV plus optional oral therapy) was 10 days, or up to 14 days for patients with bacteraemia at baseline |
| Comparator | 500 mg doripenem every 8h  Patients meeting prespecified clinical improvement criteria after ≥5 days of IV therapy could be switched to oral ciprofloxacin (500 mg every 12 hours) or sulfamethoxazole-trimethoprim (800 mg/160 mg every 12 hours) for those with a fluoroquinolone-resistant pathogen, administered approximately 8 hours after the last dose of IV treatment.  Total study treatment duration (IV plus optional oral therapy) was 10 days, or up to 14 days for patients with bacteraemia at baseline |
| Efficacy outcomes | Primary outcome measures were defined based on FDA and EMA guidance   * FDA: the proportion of patients with symptomatic resolution (or return to premorbid state) of UTI-specific symptoms, except flank pain, with resolution or improvement in flank pain from baseline at the day 5 visit; the proportion of patients with both microbiological eradication and symptomatic resolution (or return to premorbid state) of all UTI-specific symptoms at TOC in the mMITT population * EMA: the proportion of patients with a favourable per-patient microbiological response (i.e. eradication) at TOC in the mMITT population.   Secondary outcome measures:   * Per-patient microbiological response at ET and LFU * Per-patient and per-pathogen microbiological response at TOC and LFU in patients with ≥1 ceftazidime-non-susceptible or only ceftazidime-susceptible pathogens isolated at baseline; * Investigator-determined clinical cure at ET, TOC, and LFU * Sustained clinical cure at LFU   Exploratory outcome measures:   * Per-patient and per-pathogen microbiological response using a cut-off of 103 CFU/mL   Symptomatic response at Day 5, TOC and LFU was defined as:   * Resolution: sufficient data was available to confirm symptomatic resolution based on all of the following baseline cUTI-specific symptoms having resolved or returned to premorbid state (frequency, urgency, dysuria, and suprapubic pain) and having resolution or improvement in flank pain * Persistence: Confirmed persistence of at least 1 symptom of frequency, urgency, dysuria, and suprapubic pain and there was worsening or lack of improvement in flank pain; or death related to cUTI on or before Day 5, TOC and LFU. * Indeterminate: Circumstances that precluded assessment of symptom persistence or symptomatic resolution; or Day 5/TOC/LFU PSAQ was not administered for reason other than death related to cUTI.   Investigator-determined clinical response at the EOT (IV), TOC, and LFU visits were defined as:   * Cure: All or most pretherapy signs and symptoms of the index infection had improved or resolved such that no additional antibiotics were required * Failure: Death related to cUTI, lack of treatment response, persistence or progression of infection, or patient previously mat failure criteria (not applicable at EOT visit) * Indeterminate: loss to follow-up, death not related to cUTI, circumstances that precluded classification as a cure or failure   Microbiological response at initial/pre-study culture, EOT (IV), TOC, and LFU were defined as:   * Eradication: urine culture obtained at the relevant visit demonstrated <104 CFU/mL of the original uropathogen, and the patient was not bacteraemic * Persistence: uropathogen present at screening grew at ≥104 CFU/mL at EOT (IV), TOC, or LFU or death related to cUTI prior to each visit * Persistence with increasing MIC: A urine culture taken after at least 2 full days of treatment grew ≥104 CFU/mL of an original uropathogen species and displayed ≥4-fold higher MIC to study therapy after treatment with IV study therapy at EOT (IV), TOC, or LFU, respectively. * Indeterminate: loss to follow-up, death not contributed to cUTI, no baseline culture, or circumstances that precluded classification as an eradication, persistence, or persistence with increasing MIC |
| Safety outcomes | Safety assessments included:   * incidence and severity of AEs and SAEs * exposure * mortality * reasons for discontinuation of study therapy and the study, * vital sign measurements * physical examination findings and UTI-focused physical examination findings * 12-lead ECG (resting only)   clinically important changes in clinical chemistry, haematology, coagulation and urinalysis laboratory values |
| Other outcomes used in the economic model/specified in the scope | Exploratory health utilization variables (reported outside this CSR), include the following:   * Length of hospital stay * Length of intensive care unit (ICU) stay and/or transfer to the ICU * Length of IV therapy * Mortality caused by cUTI (up to the LFU visit or Day 45) |
| Analysis populations | * mMITT: all patients with a confirmed cUTI diagnosis and a positive study entry urine culture defined as ≥105 CFU/mL of a Gram-negative pathogen and no more than 2 species of microorganisms identified in the study entry urine culture, regardless of colony count. Any patient with a Gram-positive pathogen, or a bacterial species typically not expected to respond to both study drugs ≥105 CFU/mL was excluded. * ME (at TOC and EOT): those of the mMITT analysis set who either received therapy for ≥48 hours, with ≥80% of the scheduled IV drug administered over the number of days administered or received therapy <48 hours before discontinuing treatment due to an AE. Patients also had no major protocol deviations, had microbiological responses other than indeterminate at EOT or TOC, did not receive prior antibiotics before initiation of study therapy, had a study entry urine culture obtained ≤48 hours before randomisation or had 1 or, at most 2 baseline Gram-negative aerobic uropathogens susceptible to both IV study therapies * ME (at LFU): included in ME set at TOC, had an assessment at LFU and did not receive any antibiotic therapy with potential activity against any of the baseline uropathogens. * eME: included patients who met ME criteria with the exception that baseline pathogens did not need to be susceptible to either study therapy * CE (at EOT or TOC): included all mMITT patients who either received therapy for ≥48 hours, with ≥80% of the scheduled IV drug administered over the number of days administered or received therapy <48 hours before discontinuing treatment due to an AE. Patients also had no major protocol deviations, had microbiological responses other than indeterminate at EOT or TOC, did not receive prior antibiotics before initiation of study therapy, had a study entry urine culture obtained ≤48 hours before randomisation or had 1 or, at most 2 baseline Gram-negative aerobic uropathogens susceptible to both IV study therapies * CE (at LFU): included in CE set at TOC, had an assessment at LFU, had no important protocol deviations and did not receive any antibiotic therapy with potential activity against any of the baseline uropathogens. * Safety: all patients who received any amount of IV study therapy * PK: all patients who had at least 1 plasma concentration data value available for either ceftazidime or avibactam |
| Statistical methods | Sample size:   * The sample size across the combined study database ensured 90% power for a 10.0% NI margin and 95% power for a 12.5% NI margin.   Primary endpoint:   * For each primary endpoint, noninferiority of CAZ/AVI vs. doripenem was considered demonstrated if the lower limit of the 2-sided 95% CI around the treatment difference was > −12.5% (EMA) or > −10.0% (FDA). * A combined total of approximately 964 patients were planned to be randomized to provide 90% power for a 10% noninferiority margin using the lower limit of a 2-sided 95% CI for each of the 2 US FDA coprimary endpoints in the mMITT analysis set, assuming that the underlying true response rate for was >73.5% for each coprimary endpoint and that 85% of patients were included in the mMITT analysis set. In terms of the ROW requirements for the primary endpoint, assuming the underlying true per-patient microbiologic response at TOC in the mMITT analysis set was >73.5%, this sample size provided 90% power for a 10% NI margin.   Sensitivity analyses:  Sensitivity analyses for the primary efficacy variables included: adjusting for prespecified stratification factors (type of infection, region, and protocol) using the Miettinen and Nurminen stratified method with Cochran-Mantel-Haenszel weights for the stratum weights; treating indeterminate response as favourable response; and considering symptomatic response at day 5 using a last postbaseline completed questionnaire carried-forward approach |
| CFU: colony-forming units; CI: confidence interval; CrCl: creatinine clearance rate; EMA: European Medicines Agency; ET: end of treatment; FDA: Federal Drug Association; IV: intravenous; LFU: last follow-up; mMITT: microbiologically modified intention-to-treat; NI: non-inferiority; TOC: test-of-cure; UTI: urinary tract infection | |

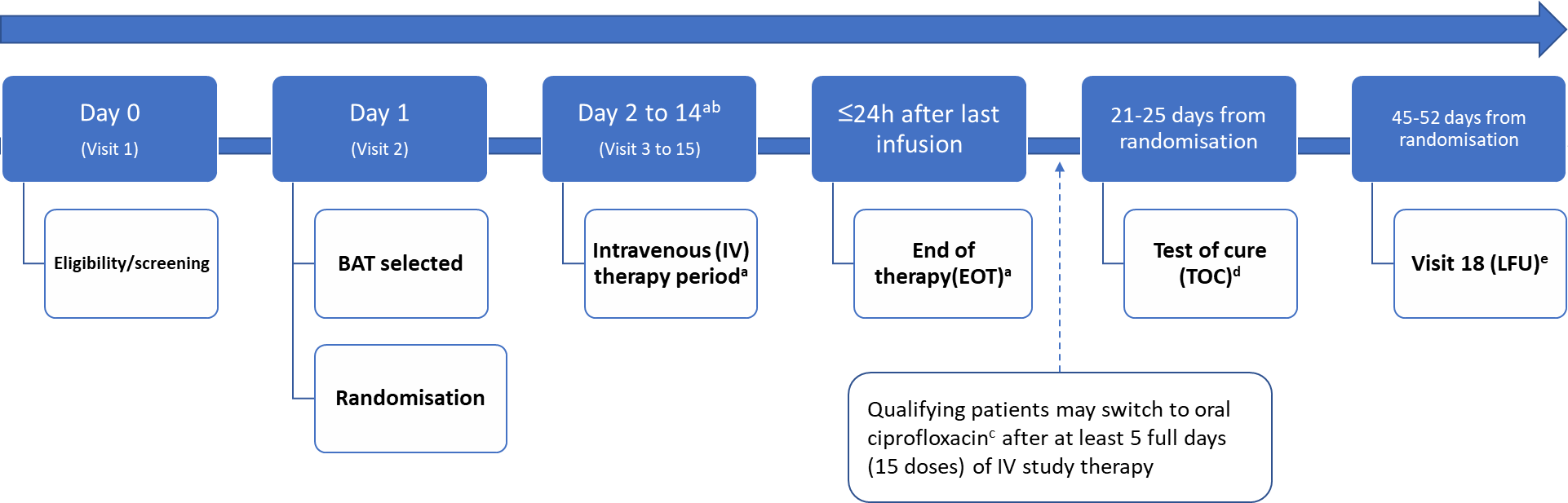


Figure 10. RECAPTURE study procedure116

a Study treatment was started as soon as a patient’s eligibility was confirmed and the patient had been randomized. Consequently, Day –1 and Day 0 could have been the same calendar day as Day 1. Administration of the first dose of IV study therapy marked the beginning of study Day 1. Subsequent study days were based on 24-hour periods from the time of the first infusion. The Treatment Period included the baseline visit (Day 1), Visits 3 to 15 (Days 2 to 14), and the EOT (IV) visit. Visit 16 (EOT [IV]) needed to occur and urine specimen for culture needed to be obtained before the patient started oral therapy.

b The duration of treatment with study therapy (IV plus optional oral therapy) was to be 10 days. If the patient was bacteraemic at study entry, then the duration of treatment was 14 days.

c If the patient had a fluoroquinolone-resistant pathogen, sulfamethoxazole/trimethoprim was an alternative oral option.

d If it was not possible to perform the TOC visit 21 calendar days from randomisation (e.g., the patient was on holiday), the allowed visit window was 21 to 25 days from randomisation.

e If it was not possible to perform the LFU visit 45 calendar days from randomisation (e.g., the patient was on holiday), the allowed visit window was 45 to 52 calendar days from randomisation.

EOT (IV): End of Intravenous Therapy: IV, intravenous; LFU: Late Follow-Up; TOC: Test of cure.

#### RECAPTURE baseline characteristics

* + - * 1. RECAPTURE demographics and baseline clinical characteristics

There were no clinically meaningful differences between the treatment groups for demographic characteristics in the mMITT and safety analysis sets. In the mMITT analysis set, the majority of patients were White (83.0%) with a higher percentage of female patients (69.8%). The mean (range) age of patients was 52 years (18 to 89 years) with 14.4% of patients over 75 years of age. The number of patients >65 years of age was balanced between treatment groups (31.6% in the CAZ/AVI group and 32.6% in the doripenem group). Mean (range) BMI was 26.268 kg/m2 (15.06 kg/m2 to 48.33 kg/m2) with 22.6% of patients having a BMI ≥30 kg/m2 (Table 31).

Table 31. RECAPTURE baseline demographic and clinical characteristics (mMITT analysis set)

|  | **CAZ/AVI**  **(n = 393)** | **Doripenem**  **(N = 417)** | **Total**  **(N = 810)** |
| --- | --- | --- | --- |
| Age, Mean (SD) | 51.4 (20.22) | 53.3 (18.62) | 52.4 (19.43 |
| Age group (years), n (%) | | | |
| ≥18-45 | 153 (38.9) | 131 (31.4) | 284 (35.1) |
| 46-64 | 116 (29.5) | 150 (36.0) | 266 (32.8) |
| 64-74 | 61 (15.5) | 82 (19.7) | 143 (17.7) |
| ≥75-≤90 | 63 (16.0) | 54 (12.9) | 117 (14.4) |
| Sex, n (%) | | | |
| Female | 272 (69.2) | 293 (70.3) | 565 (69.8) |
| Male | 121 (30.8) | 124 (29.7) | 245 (30.2) |
| Race, n (%) | | | |
| White | 321 (81.7) | 351 (84.2) | 672 (83.0) |
| Black or African American | 1 (0.3) | 4 (1.0) | 5 (0.6) |
| Asian | 35 (8.9) | 28 (6.7) | 63 (7.8) |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| American Indian or Alaska Native | 1 (0.3) | 3 (0.7) | 4 (0.5) |
| Other | 35 (8.9) | 31 (7.4) | 66 (8.1) |
| BMI (kg/m2), Mean (SD) | 26.22 (5.87) | 26.31 (5.58) | 26.27 (5.72) |
| BMI category, n (%) | | | |
| <18.5 | 19 (4.8) | 24 (5.8) | 43 (5.3) |
| 18.5-<25 | 155 (39.4) | 167 (40.0) | 322 (39.8) |
| 25-<30 | 123 (31.3) | 129 (30.9) | 252 (31.1) |
| ≥30 | 90 (22.9) | 93 (22.3) | 183 (22.6) |
| Missing | 6 (1.5) | 4 (1.0) | 10 (1.2) |
| Percentages are based on the total number of patients in the treatment group.  BMI: body mass index; N: number of patients in treatment group; n: number of patients in category or analysis; SD: standard deviation | | | |

* + - * 1. RECAPTURE disease characteristics at baseline

In the mMITT analysis set, 227 (28.0%) patients were enrolled with cUTI without pyelonephritis while 583 (72.0%) patients were enrolled with acute pyelonephritis, of which 503 patients had no complicating factors. Of the 80 (9.9%) patients with acute pyelonephritis and at least one complicating factor, 64 patients met the qualifying symptom criteria for cUTI. Therefore 291 (35.9%) patients (with or without pyelonephritis) in the mMITT analysis set met the qualifying symptom criteria for cUTI.

At baseline, most patients (98.9%) had a single uropathogen; 9 patients each had 2 pathogens. *E. coli* was most frequently isolated from the study group. In the mMITT population, ceftazidime-non-susceptible pathogens were identified in 159 (19.6%) patients; most from *E. coli* or *K. pneumoniae* isolates.

Approximately 90% of patients in each treatment group entered the study with normal renal status or mild renal impairment (CrCl >50mL/min) (Table 20). Of the remaining patients, 9.5% had moderate renal impairment (CrCl ≥31 to ≤50 mL/min) (42 [10.7%] in the CAZ/AVI group, 35 [8.4%] in the doripenem group) and 0.5% had severe renal impairment (CrCl <31 mL/min) (1 [0.3%] in the CAZ/AVI group, 3 [0.7%] in the doripenem group).

Table 32. RECAPTURE baseline disease characteristics (mMITT analysis set)

|  | **CAZ/AVI**  **(n = 393)** | **Doripenem**  **(N = 417)** | **Total**  **(N = 810)** |
| --- | --- | --- | --- |
| Type of infection, n (%) | | | |
| cUTI without pyelonephritis | 106 (27.0) | 121 (29.0) | 227 (28.0) |
| Acute pyelonephritis | 287 (73.0) | 296 (71.0) | 583 (72.0) |
| No complicating factors present | 246 (62.6) | 257 (61.6) | 503 (62.1) |
| With at least 1 complicating factor | 41 (10.4) | 39 (9.4) | 80 (9.9) |
| Meeting criteria for cUTI | 33 (8.4) | 31 (7.4) | 64 (7.9) |
| Not meeting criteria for cUTI | 8 (2.0) | 8 (1.9) | 16 (2.0) |
| CrCl (mL/min), Mean (SD) | 87.62 (34.48) | 85.90 (34.47) | 86.73 (34.47) |
| Renal status, n (%) | | | |
| Normal/mild | 350 (89.1) | 379 (90.9) | 729 (90.0) |
| Moderate | 42 (10.7) | 35 (8.4) | 77 (9.5) |
| Severe | 1 (0.3) | 3 (0.7) | 4 (0.5) |
| Complicating factors, n (%) | | | |
| Male urinary retention | 47 (12.0) | 54 (12.9) | 101 (12.5) |
| Partial obstructive uropathy | 63 (16.0) | 75 (18.0) | 138 (17.0) |
| Functional or anatomical abnormality of urogenital tract | 70 (17.8) | 77 (18.5) | 147 (18.1) |
| Use of intermittent catheterization or use of an indwelling urinary catheter | 21 (5.3) | 23 (5.5) | 44 (5.4) |
| Urogenital procedure within 7 days prior to study entry | 17 (4.3) | 18 (4.3) | 35 (4.3) |
| Bacteraemic, n (%)a | 38 (9.7) | 33 (7.9) | 71 (8.8) |
| Prior systemic antibiotics, n (%)b | 28 (7.1) | 27 (6.5) | 55 (6.8) |
| a Includes only patients with blood pathogens that were also identified as uropathogens.  b Per Protocol Amendment 3, patients were allowed to receive single dose of antibiotics with activity against pathogens under study.  CrCl, creatinine clearance; cUTI, complicated urinary tract infection | | | |

#### RECAPTURE summary of results

The full summary of results reported in RECAPTURE 1 and 2 are listed in Table 34.

At test-of-cure, per-pathogen eradication rates were numerically higher for CAZ/AVI compared to doripenem for all baseline pathogens, including ceftazidime-non-susceptible and ceftazidime-susceptible Enterobacteriaceae (Table 33), and for *E. coli, K. pneumoniae, and Proteus mirabilis (P. mirabilis)*, specifically, across all analysis populations.

Table 33. Per-Pathogen Favourable Microbiological Response Rates at Test of Cure (mMITT Population)19

| **Favourable Response Rate, no./No. (%)** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Pathogen** | **CAZ/AVI**  **(N = 393)** | **Doripenem**  **(N = 417)** | | **Difference, % (95% CI)** | |
| ***All baseline pathogens*** | | | | | |
| Overall | 311/400 (77.8) | 297/419 (70.9) | | 6.9 (0.88,12.81) | |
| Enterobacteriaceae | 299/382 (78.3) | 281/398 (70.6) | | 7.7 (1.54, 13.75) | |
| *Citrobacter freundii* complex | 4/4 (100.0) | 1/2 (50.0) | | 50.0 (23.13, 91.76) | |
| *Citrobacter koseri* | 0/1 (0.0) | 1/1 (100.0) | | −100.0 (−100.00, 58.69) | |
| *Enterobacter aerogenes* | 1/1 (100.0) | 1/1 (100.0) | | 0.0 (−88.48, 88.48) | |
| *Enterobacter cloacae* | 6/11 (54.5) | 9/13 (69.2) | | −14.7 (−50.01, 23.88) | |
| *Escherichia coli* | 229/292 (78.4) | 220/306 (71.9) | | 6.5 (−0.41, 13.41) | |
| *Klebsiella oxytoca* | 5/6 (83.3) | 1/1 (100.0) | | −16.7 (−59.15, 71.03) | |
| *Klebsiella pneumoniae* | 33/44 (75.0) | 35/56 (62.5) | | 12.5 (−6.15, 29.84) | |
| *Morganella morganii* | 4/4 (100.0) | 0/0 | | - | |
| *Proteus mirabilis* | 16/17 (94.1) | 9/13 (69.2) | | 24.9 (−2.79, 53.59) | |
| *Proteus vulgaris* group | 0/0 | 2/2 (100.0) | | - | |
| *Providencia rettgeri* | 0/1 (0.0) | 0/1 (0.0) | | 0.0 (−88.48, 88.48) | |
| *Serratia marcescens* | 1/1 (100.0) | 2/2 (100.0) | | 0.0 (−85.21, 74.23) | |
| Other gram-negative pathogens | 12/18 (66.7) | 16/21 (76.2) | | −9.5 (−37.59, 18.91) | |
| *Burkholderia cepacia* complex | 0/0 | 1/1 (100.0) | | - | |
| *Pseudomonas aeruginosa* | 12/18 (66.7) | 15/20 (75.0) | | −8.3 (−36.77, 20.66) | |
| ***Ceftazidime-non-susceptible pathogensa*** | | | | | |
| Overall | 48/75 (64.0) | 51/85 (60.0)b | | 4.0 (−11.11, 18.81) | |
| Enterobacteriaceae | 43/68 (63.2) | 46/79 (58.2) | | 5.0 (−10.87, 20.50) | |
| *Citrobacter freundii* complex | 3/3 (100.0) | 0/0 | | - | |
| *Enterobacter cloacae* | 3/7 (42.9) | 5/6 (83.3) | | −40.5 (−76.04, 14.76) | |
| *Escherichia coli* | 22/36 (61.1) | 20/37 (54.1) | | 7.1 (−15.54, 28.93) | |
| *Klebsiella pneumoniae* | 13/18 (72.2) | 17/30 (56.7) | | 15.6 (−13.30, 40.34) | |
| *Morganella morganii* | 1/1 (100.0) | 0/0 | | - | |
| *Proteus mirabilis* | 1/2 (50.0) | 4/5 (80.0) | | −30.0 (−82.00, 39.20) | |
| *Providencia rettgeri* | 0/1 (0.0) | 0/1 (0.0) | | 0.0 (−88.48, 88.48) | |
| Other gram-negative pathogens | 5/7 (71.4) | 5/6 (83.3) | | −11.9 (−54.78, 37.60) | |
| *Pseudomonas aeruginosa* | 5/7 (71.4) | 5/6 (83.3) | | −11.9 (−54.78, 37.60) | |
| ***Ceftazidime-susceptible pathogensa*** | | | | | |
| Overall | 254/311 (81.7) | | 228/312 (73.1) | | 8.6 (2.03, 15.14) |
| Enterobacteriaceae | 247/301 (82.1) | | 217/297 (73.1) | | 9.0 (2.32, 15.66) |
| *Citrobacter freundii* complex | 1/1 (100.0) | | 1/2 (50.0) | | 50.0 (−64.16, 93.08) |
| *Citrobacter koseri* | 0/1 (0.0) | | 1/1 (100.0) | | −100.0 (−100.00, 58.69) |
| *Enterobacter aerogenes* | 1/1 (100.0) | | 1/1 (100.0) | | 0.0 (−88.48, 88.48) |
| *Enterobacter cloacae* | 3/4 (75.0) | | 4/7 (57.1) | | 17.9 (−41.27, 62.79) |
| *Escherichia coli* | 206/254 (81.1) | | 193/262 (73.7) | | 7.4 (.21, 14.63) |
| *Klebsiella oxytoca* | 5/6 (83.3) | | 1/1 (100.0) | | −16.7 (−59.15, 71.03) |
| *Klebsiella pneumoniae* | 20/26 (76.9) | | 18/26 (69.2) | | 7.7 (−16.81, 31.50) |
| *Morganella morganii* | 2/2 (100.0) | | 0/0 | | - |
| *Proteus mirabilis* | 15/15 (100.0) | | 5/8 (62.5) | | 37.5 (11.44, 69.98) |
| *Proteus vulgaris group* | 0/0 | | 2/2 (100.0) | | - |
| *Serratia marcescens* | 1/1 (100.0) | | 2/2 (100.0) | | 0.0 (−85.21, 74.23) |
| Other gram-negative pathogens | 7/10 (70.0) | | 11/15 (73.3) | | −3.3 (−40.10, 30.94) |
| *Burkholderia cepacia* complex | 0/0 | | 1/1 (100.0) | | - |
| *Pseudomonas aeruginosa* | 7/10 (70.0) | | 10/14 (71.4) | | −1.4 (−38.84, 33.69) |
| CI: confidence interval.  Patients could have >1 pathogen. Multiple isolates of the same species in the same patient are counted only once.  a Ceftazidime-non-susceptible was defined as a central microbiology reference laboratory minimum inhibitory concentration ≥8 µg/mL for *Enterobacteriaceae* or ≥16 µg/mL for *P. aeruginosa*, or local laboratory disk diffusion diameter (from a 30-μg ceftazidime disk) of ≤20 mm for Enterobacteriaceae and ≤17 mm for *P. aeruginosa*.  Nine patients were not included in either subset (ceftazidime-non-susceptible or ceftazidime-susceptible) because no susceptibility tests were performed (6 patients) or baseline blood or urine susceptibility results were missing (3 bacteraemic patients). b One patient in the doripenem group had 2 ceftazidime-non-susceptible pathogens isolated at baseline. | | | | | |

AEs were predominantly mild or moderate in intensity, and generally balanced across groups. Twenty-one (4.1%) and 12 (2.4%) patients treated with CAZ/AVI and doripenem, respectively, had ≥1 serious AE, of which most occurred after the last dose of IV treatment. Few AEs led to study drug discontinuation and no deaths occurred. AEs reported in ≥2% of patients comprised headache, nausea, diarrhoea, and constipation.

Table 34. RECAPTURE summary of results19

| **Study acronym** | **RECAPTURE** |
| --- | --- |
| Efficacy results- primary endpoint | NI of CAZ/AVI vs doripenem was demonstrated for the FDA co-primary endpoints, as well for the EMA primary endpoint.  FDA:   * Patient-assessed symptomatic resolution at day 5: CAZ/AVI, 276 (70.2%); doripenem, 276 (66.2); Diff. 4.0 (95% CI −2.39, 10.42) * Proportion of patients with both microbiological eradication and symptomatic resolution at TOC: CAZ/AVI, 280 (71.2%); doripenem, 269 (64.5); Diff. 6.7 (95% CI 0.30, 13.32) * Per-patient favourable microbiological response at TOC: CAZ/AVI, 304 (77.4%); doripenem, 296 (71.0); Diff. 6.4 (95% CI 0.33, 12.36) * Patient-reported symptomatic resolution at TOC: CAZ/AVI, 332 (84.5%); doripenem, 360 (86.3); Diff. -1.9 (95% CI 6.78, 3.02)   EMA:   * Per-patient favourable microbiological response at TOC: CAZ/AVI, 304 (77.4%); doripenem, 296 (71.0); Diff. 6.4 (95% CI 0.33, 12.36) |
| Efficacy results - key secondary endpoint(s) | Microbiological:   * Per-patient favourable microbiological response at ET (IV): CAZ/AVI, 374 (95.2%); doripenem, 395 (94.7%); diff: 0.4 (95% CI−2.7, 3.56) * Per-patient favourable microbiological response at LFU: CAZ/AVI, 268 (68.2%); doripenem, 254 (60.9%); diff. 7.3 (95% CI 0.68, 13.81) * Per-patient favourable microbiological response at TOC in patients with a ceftazidime-non-susceptible pathogen: CAZ/AVI, 47 (62.7%); doripenem, 51 (60.7%); diff. 2.0 (95% CI -13.18, 16.89) * Per-patient favourable microbiological response at LFU in patients with a ceftazidime-non-susceptible pathogen: CAZ/AVI, 46 (61.3%), doripenem, 38 (45.2%); diff 16.1 (95% CI 0.50 to 30.89) * Per-patient favourable microbiological response at TOC in patients with a ceftazidime-susceptible pathogen: CAZ/AVI, 256 (81.0%); doripenem, 238 (73.0%); diff. 8.0 (95% CI 1.50, 14.48) * Per-patient favourable microbiological response at LFU in patients with a ceftazidime-susceptible pathogen: CAZ/AVI, 221 (69.9%), doripenem, 209 (64.1%); diff. 5.8 (95% CI −1.46 to 13.05)   Clinical:   * Investigator-determined clinical cure:   + ET: CAZ/AVI, 378 (96.2%), doripenem 407 (97.6%); diff. −1.4 (95% CI −4.07, 1.02)   + TOC: CAZ/AVI, 355 (90.3%), doripenem, 377 (90.4%); diff. −0.1 (95% CI −4.23, 4.03)   + LFU: CAZ/AVI, 335 (85.2%); doripenem, 350 (83.9%); diff. 1.3 (95% CI −3.71 to 6.30)   + Sustained clinical cure at LFU in patients who were cured at TOC: CAZ/AVI, 330 (93.0%); doripenem, 345 (91.5%); diff −0.6 (95% CI −3.5 to 2.3) * Investigator-determined clinical cure at TOC in patients with a ceftazidime-susceptible pathogen: CAZ/AVI, 287 (90.8%); doripenem, 295 (90.5%); diff. 0.3 (95% CI −4.3 to 4.9) * Investigator-determined clinical cure at TOC in patients with a ceftazidime-non-susceptible pathogen: CAZ/AVI, 67 (89.3%), doripenem, 75 (89.3%); diff. 0.0 (95% CI −10.4 to 10.1) |
| Safety results | * 1 AE occurred in 185 (36.2%) and 158 (31.0%) CAZ/AVIand doripenem patients, respectively * 21 (4.1%) and 12 (2.4%) patients treated with CAZ/AVIand doripenem, respectively, had ≥1 serious AE, of which most occurred after the last dose of IV treatment |
| Conclusion(s) | CAZ/AVIwas NI vs doripenem for the treatment of hospitalised patients with cUTI or acute pyelonephritis based on FDA and EMA-defined endpoints |
| AE: adverse event; CE: clinically evaluable; CI: confidence interval; cMITT: clinically modified intention-to-treat; cUTI: complicated urinary tract infection; diff: difference; EMA: European Medicines Agency; ET: end of treatment; FDA: Food and Drug Association; LFU: last follow up; NI: non-inferiority; TOC: test-of-cure | |

### REPRISE

#### REPRISE baseline characteristics

* + - * 1. RERPISE patient baseline demographics and clinical characteristics

Demographic characteristics were generally well balanced between treatment groups for cUTI patients, and also broadly in cIAI patients, although patient numbers were small.

In the mMITT analysis set, the majority of cUTI patients were white. The mean (SD) age of cUTI patients in the CAZ/AVI group was 64.3 (14.64) years and 61.3 (15.33) years in the BAT group. The majority of cIAI patients were also White. The mean (SD) age of cIAI patients was 49.9 (16.14) years in the CAZ/AVI plus metronidazole group and 68.4 (11.12) years in the BAT group. There was a similar number of male and female cUTI patients within treatment groups; 55.6% compared with 44.4% in the CAZ/AVI group and 54.0% compared with 46.0% in the BAT treatment group. Mean (SD) BMI in cUTI patients was similar between treatment groups; 28.1 (5.47) kg/m2 and 28.0 (5.78) kg/m2 in the CAZ/AVI and BAT groups, respectively.

Table 35. REPRISE baseline demographic and clinical characteristics (mMITT analysis set)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **cIAI** | | **cUTI** | | **cIAI + cUTI** | | |
|  | **CAZ/AVI + metronidazole**  **(n = 10)** | **BAT**  **(n = 11)** | **CAZ/AVI + metronidazole**  **(n = 144)** | **BAT**  **(n = 137)** | **CAZ/AVI + metronidazole**  **(n = 154)** | **Meropenem**  **(n = 148)** | **Total**  **(n = 302)** |
| Age, Mean (SD) | 49.9 (16.14) | 68.4 (11.12) | 64.3 (14.64) | 61.3 (15.33) | 63.4 (15.11) | 61.9 (15.15) | 62.6 (15.12) |
| Age group (years), n (%) | | | | | | | |
| ≥18-45 | 3 (30.0) | 0 | 19 (13.2) | 21 (15.3) | 22 (14.3) | 21 (14.2) | 43 (14.2) |
| 46-64 | 5 (50.0) | 3 (27.3) | 41 (28.5) | 49 (35.8) | 46 (29.9) | 52 (35.1) | 98 (32.5) |
| 64-74 | 2 (20.0) | 4 (36.4) | 46 (31.9) | 40 (29.2) | 48 (31.2) | 44 (29.7) | 92 (30.5) |
| ≥75-≤90 | 0 | 4 (36.4) | 38 (26.4) | 27 (19.7) | 38 (24.7) | 31 (20.9) | 69 (22.8) |
| Sex, n (%) | | | | | | | |
| Female | 6 (60.0) | 4 (36.4) | 64 (44.4) | 63 (46.0) | 70 (45.5) | 67 (45.3) | 137 (45.4) |
| Race, n (%) | | | | | | | |
| White | 9 (90.0) | 11 (100) | 136 (94.4) | 131 (95.6) | 145 (94.2) | 142 (95.9) | 287 (95.0) |
| Black or African American | 1 (10.0) | 0 | 2 (1.4) | 1 (0.7) | 3 (1.9) | 1 (0.7) | 4 (1.3) |
| Asian | 0 | 0 | 2 (1.4) | 1 (0.7) | 2 (1.3) | 1 (0.7) | 3 (1.0) |
| Other | 0 | 0 | 4 (2.8) | 4 (2.9) | 4 (2.6) | 4 (2.7) | 8 (2.6) |
| BMI (kg/m2), Mean (SD) | 25.2 (6.30) | 28.6 (4.58) | 28.1 (5.47) | 28.0 (5.78) | 27.9 (5.55) | 28.1 (5.69) | 28.0 (5.61) |
| BMI category, n (%) | | | | | | | |
| <18.5 | 2 (20.0) | 0 | 3 (2.1) | 3 (2.2) | 5 (3.2) | 3 (2.0) | 8 (2.6) |
| 18.5-<25 | 3 (30.0) | 3 (27.3) | 41 (28.5) | 44 (32.1) | 44 (28.6) | 47 (31.8) | 91 (30.1) |
| 25-<30 | 2 (20.0) | 4 (36.4) | 51 (35.4) | 38 (27.7) | 53 (34.4) | 42 (28.4) | 95 (31.5) |
| ≥30 | 3 (30.0) | 4 (36.4) | 48 (33.3) | 51 (37.2) | 51 (33.1) | 55 (37.2) | 106 (35.1) |
| Missing | 0 | 0 | 1 (0.7) | 1 (0.7) | 1 (0.6) | 1 (0.7) | 2 (0.7) |
| Percentages are based on the total number of patients in the treatment group.  BMI: body mass index; N: number of patients in treatment group; n: number of patients in category or analysis; SD: standard deviation | | | | | | | |

* + - * 1. REPRISE disease characteristics

Disease characteristics for cUTI and cIAI in the mMITT analysis set were generally balanced between treatment groups and were representative of both indications. Overall, there was a slightly higher proportion of patients without acute pyelonephritis compared to patients with acute pyelonephritis (54.8% and 45.2%, respectively). Complicated urinary tract infection without pyelonephritis was more common in the CAZ/AVI group than the BAT group (60.4% and 48.9%, respectively). Among cIAI patients, the most common primary diagnoses were cholecystitis and intra-abdominal abscess (each in 6 patients). The majority of cIAI patients (66.7%) had APACHE II scores of ≤10.

Most patients with cUTI, were infected with *Enterobacteriaceae* (commonly *E. coli* and *K. pneumoniae*). Ten (4%) of 281 patients with cUTI also had bacteraemia; in nine of these patients, the isolates were *E. coli* or *K. pneumoniae*. Of the study isolates, 132 (99%) of all 133 *Enterobacteriaceae* isolated from urine in the CAZ/AVI group and 132 (96%) of 138 isolated in the best available therapy group were ceftazidime resistant (Table 36). In the cIAI cohort, polymicrobial infections were more common than monomicrobial infections (13 patients and 8 patients, respectively) and none of the patients experienced bacteraemia.

Table 36. REPRISE baseline disease characteristics (cUTI - mMITT analysis set)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CAZ/AVI**  **(n = 144)** | **Meropenem**  **(N = 137)** | **Total**  **(N = 281)** |
| Type of infection, n (%) | | | |
| Acute pyelonephritis | 57 (39.6) | 70 (51.1) | 127 (45.2) |
| cUTI without pyelonephritis | 87 (60.4) | 67 (48.9) | 154 (54.8) |
| CrCl (mL/min), Mean (SD) | 79.0 (39.00) | 81.1 (36.85) | 80.1(37.91) |
| Renal status, n (%)a | | | |
| CrCl >50 mL/min | 118 (81.9) | 113 (82.5) | 231 (82.2) |
| CrCl 31 to 50 mL/min | 19 (13.2) | 18 (13.1) | 37 (13.2) |
| CrCl 16 to 30 mL/min | 4 (2.8) | 5 (3.6) | 9 (3.2) |
| CrCl 6 to 15 mL/min | 3 (2.1) | 1 (0.7) | 4 (1.4) |
| CrCl <6 mL/min | 0 | 0 | 0 |
| Bacteraemic, n (%)a | 4 (2.8) | 6 (4.4) | 10 (3.6) |
| Complicating factors, n (%) | | | |
| Male urinary retention | 33 (22.9) | 24 (17.5) | 57 (20.3) |
| Partial uropathy | 45 (31.3) | 21 (15.3) | 66 (23.5) |
| Functional or anatomical abnormality of urogenital tract | 39 (27.1) | 38 (27.7) | 77 (27.4) |
| Use of intermittent catheterisation or use of an indwelling urinary catheter | 30 (20.8) | 25 (18.2) | 55 (19.6) |
| Urogenital procedure within 7 days prior to study entry | 27 (18.8) | 21 (15.3) | 48 (17.1) |
| Infection type, n (%) | | | |
| Monomicrobial | 139 (96.5) | 131 (95.6) | 270 (96.1) |
| Polymicrobial | 5 (3.5) | 6 (4.4) | 11 (3.9) |
| 2 pathogens | 4 (2.8) | 6 (4.4) | 10 (3.6) |
| 3 pathogensb | 1 (0.7) | 0 | 1 (0.4) |
| a Estimated CrCl (mL/min) is calculated by Cockcroft Gault method (Cockcroft and Gault 1976) based on local laboratory data.  b Note, a maximum of 2 uropathogens was allowed for study entry, however 1 patient (Patient E1801002) in the CAZ/AVI group presented with 3 pathogens, *Proteus mirabilis* in the urine culture and 2 anaerobes in the blood culture  CrCl: creatinine clearance; n: number of patients in category or analysis | | | |

#### REPRISE summary of results

The full summary of results reported in REPRISE is listed in Table 37.

The overall proportions of patients with a clinical cure at the test-of-cure visit (7–10 days after last infusion of study therapy) in the cUTI group were similar between treatment groups (132/144 [92%; 95% CI 86.3–95.4] in the CAZ/AVI group versus 129/137 [94%; 89.3–97.2] of 137 in the best available therapy group).

AEs were reported in 51 (31%) of 164 patients in the CAZ/AVI group and 66 (39%) of 168 in the best available therapy group, most of which were mild or moderate in intensity (**Error! Reference source not found.**). The most frequently reported AEs were gastrointestinal disorders for both CAZ/AVI (n = 21, 13%) and best available therapy (n = 30, 18%).

Table 37. REPRISE summary of results97

|  |  |
| --- | --- |
| **Study acronym** | **REPRISE** |
| Efficacy results- primary endpoint | * The overall proportions of mMITT patients with a clinical cure at the TOC were similar with CAZ/AVI (140 [91%; 95% CI 85·6–94·7] of 154 patients) and BAT (135 [91%; 85·9–95·0] of 148 patients) * cUTI: clinical cure at TOC were similar between treatment groups (132 [92%; 95% CI 86·3–95·4] of 144 patients in the CAZ/AVI group vs 129 [94%; 89·3–97·2] of 137 in the BAT group) * cIAI: clinical cure at TOC was eight (80% [95% CI 47·9–95·6]) of ten in the CAZ/AVI plus metronidazole group, and six (55% [27·0–80·0]) of 11 in the BAT group The CIs were very wide due to the small number of patients with cIAI |
| Efficacy results - key secondary endpoint(s) | * The proportion of patients with a favourable microbiological response at TOC in cUTI were higher in the CAZ/AVI group (118 [82%, 95% CI 75·1–87·6] of 144 patients) than with BAT (88 [64%; 56·0–71·9] of 137 patients; * Per-pathogen favourable microbiological response for E. coli and K. pneumoniae isolated from urine in patients with cUTI was higher in the CAZ/AVI group than the BAT group (52 [88%; 95% CI 78·1–94·5] of 59 vs 38 [67%; 53·8–77·8] of 57, respectively, for E coli, and 46 [84%; 72·3–91·6] of 55 vs 43 [66%; 54·1–76·8] of 65, respectively, for *K. pneumoniae* |
| Safety results | * By the last follow-up, 51 (31%) of 164 patients in the CAZ/AVI group and 66 (39%) of 168 in the BAT group had reported an AE most of which were mild or moderate in intensity * Gastrointestinal disorders were the most frequently reported treatment-emergent adverse events with both CAZ/AVI (21 [13%] of 164 patients) and BAT (30 [18%] of 168 patients * Three adverse events led to discontinuation of study drug: one patient (1%) in the CAZ/AVI group and two (1%) in the BAT |
| Conclusion(s) | CAZ/AVIand BAT led to the same proportion of patients achieving an overall clinical cure at the test-of-cure visit in the mMITT population (91% in both groups).  These results provide evidence of the efficacy of ceftazidime-avibactam as a potential alternative to carbapenems in patients with ceftazidime-resistant *Enterobacteriaceae* and *P. aeruginosa* |
| BAT: best available therapy; CI: confidence interval; cUTI: complicated urinary tract infection; mMITT: microbiologically modified intention-to-treat population; TOC: test-of-cure | |

### KURA

#### KURA trial design and methodology

KURA was a single blind, randomised, multi-centre, and actively controlled Phase II trial conducted in hospitalised paediatric patients (aged from 3 months to <18 years) with cUTI requiring treatment with IV antibiotics, in which CAZ/AVI was compared with cefepime). Key primary outcome measures included the onset of AEs and SAEs (including cephalosporin class effects and additional AEs of special interest), vital signs, renal function, electrocardiogram, laboratory assessments. Other outcome measures included clinical cure rates, microbiological response and reporting of emergent infections.

The KURA trial design and methodology is outlined in Table 38 and the study procedures are illustrated in Figure 11.

Table 38. KURA trial design and methodology19

| **Study acronym** | **KURA** |
| --- | --- |
| Study design | Single-blind, randomised, multicentre, active-controlled, Phase 2 study |
| Settings / locations | A total 25 sites from 9 countries participated in this study. The Czech Republic (32.0%) and Greece (22.7%) contributed the most patients. |
| Eligibility criteria | Key exclusion criteria: History of hypersensitivity reactions to carbapenems, cephalosporins, penicillin, other β-lactam antibiotics, concurrent infection that may have interfered with the evaluation of response to the study antibiotics at the time of randomisation; need for effective concomitant systemic antibacterials alongside the study medication; poor survival/response expectation, genitourinary-specific restrictions (i.e. pelvic trauma, prior renal transplant, etc.) |
| Intervention | IV CAZ/AVI (2000 mg) for a minimum of 72 hours. Doses were based on the age and weight of the patient with adjustment according to renal function. IV study drug was to have been administered every 8 hours for 3 days for a total of 9 doses if given 3 times daily. Beginning on Day 4, there was an option to switch to oral therapy at the Investigator’s discretion, if the patient had good or sufficient clinical response, and the patient was tolerating oral fluids or food. Alternatively, patients could continue to take IV CAZ/AVI from Day 4 up to Day 14. |
| Comparator | IV Cefepime (1-2g) for a minimum of 72 hours. Doses were based on the age and weight of the patient with adjustment according to renal function. IV study drug was to have been administered every 8 hours for 3 days for a total of 9 doses if given 3 times daily, or 6 doses if given twice daily. Beginning on Day 4, there was an option to switch to oral therapy at the Investigator’s discretion, if the patient had good or sufficient clinical response, and the patient was tolerating oral fluids or food. Alternatively, patients could continue to take IV cefepime from Day 4 up to Day 14. |
| Efficacy outcomes | Secondary outcome measures:   * Clinical cure rates (cure, sustained clinical cure, improvement, relapse, failure, indeterminate) at end of 72 hours, end of IV treatment, end of treatment, test of cure, and late follow-up. * Microbiological response (at end of IV treatment, EOIV, EOT, TOC, and LFU) * Emergent infections * Combined response   Clinical response varies dependent at time of measurement. Response definitions were categorised at:   * Clinical cure: Resolution of all acute signs and symptoms of cUTI or improvement to such an extent that no further antimicrobial therapy is required * Sustained clinical cure: continued favourable response as defined by clinical cure (LFU only) * Improvement: Improvement, but not enough to switch therapy (end of 72 hours only) and absence of new signs and symptoms, and improvement in at least 1 symptom or sign from Baseline, and with no worsening of any symptom or sign * Relapse: reappearance or worsening of signs and symptoms of cUTI that requires further antimicrobial therapy and/or surgery or death at TOC attributable to cUTI (LFU only) * Failure: Discontinuation due to AEs or lack of efficacy, death due to cUTI, or incomplete resolution or worsening of cUTI. * Indeterminate: Data are not available for evaluation of efficacy for any reason   Microbial response at end of IV treatment, EOIV, EOT, TOC, and LFU defined as:   * Eradication: source specimen demonstrated absence of the original baseline pathogen * Presumed eradication: source specimen was not available to culture, and the patient was assessed as a clinical cure or sustained clinical cure or (for EOIV only) clinical improvement * Persistence: source specimen demonstrates continued presence of the original baseline pathogen * Persistence with increasing MIC: source specimen demonstrates continued presence of the original baseline pathogen with an MIC value ≥4-fold larger than that observed for the baseline pathogen * Presumed persistence: Source specimen was not available to culture and the patient was assessed as a clinical failure or clinical relapse * Indeterminate: Source specimen was not available to culture and the patient’s clinical outcome was assessed as indeterminate |
| Safety outcomes | Primary outcome measure:   * Onset of adverse events and serious adverse events * Cephalosporin class effects and additional AEs of special interest * Vital signs * Physical examination * Laboratory parameters * CrCl * ECG |
| Other outcomes used in the economic model/specified in the scope | None specified |
| Analysis populations | * Safety: all randomised patients who received any amount of IV study therapy * Safety evaluable: a subset of the patients in the Safety analysis set who received at least 9 doses of study treatment * PK: a subset of the patients in the Safety analysis set who had at least 1 ceftazidime and/or avibactam plasma measurement available * ITT: All patients who were assigned a randomised treatment * MITT: all randomised patients who had a baseline pathogen known to cause cIAI. * CE: included all randomised patients who received any amount of IV study drug that had a confirmed diagnosis of cUTI and patients must have also met the following specific conditions:   + Received at least 48 hours of IV study drug, defined as 6 doses, in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE;   + At the specific visit had a clinical response of cure, improvement or failure (or have been assessed as a clinical failure before the planned assessment visit);     - or for LFU, were evaluated with a clinical response of sustained cure or relapse.   + Had no important protocol deviations that would affect assessment of efficacy;   + Did not receive concomitant antibiotics which would impact assessment of efficacy. This did not include antibiotic therapy taken for the treatment of cUTI by patients who were considered clinical failures. * ME: all randomised patients that had a confirmed diagnosis of cUTI and who met the following criteria:   + Received at least 48 hours of IV study drug, defined as 6 doses, in order to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE;   + At the specific visit had a microbiological response other than indeterminate;   + Had no important protocol deviations that would affect assessment of efficacy based on ECMA review.   + Did not receive concomitant antibiotics which would impact assessment of efficacy based on ECMA review. * Had at least 1 Gram-negative typical UTI bacterial pathogen which had been isolated from an adequate microbiological specimen (in the urine) at Baseline that was susceptible to both study agents |
| Statistical methods | Sample size:   * The proposed sample size for this study was 80 evaluable patients comprised of a minimum of 60 and 20 patients, respectively, from the CAZ/AVI plus metronidazole and meropenem groups. * The sample size was based on the probability of observing a ‘rare’ safety event. The ‘rare’ term used in this section is not based on the regulatory definition but is instead intended to reflect uncommon events.   Efficacy analysis:   * Descriptive statistics (number, mean, SD, median, minimum, and maximum) were provided for continuous variables, and counts and percentages were presented for categorical variables. The study was not powered for inferential testing and based on the 3:1 randomisation, direct comparisons of safety and efficacy data between treatment groups must be interpreted with caution.   Safety analysis:   * No inferential statistical tests were performed for any safety parameters as the study was not powered for inferential testing. In addition to the limited sample size, the 3:1 randomisation ratio would also warrant caution in the interpretation of direct comparisons of safety data between treatment groups. All data were presented by treatment group, cohort, and overall for each treatment.   Sensitivity analysis:  A sensitivity analysis was conducted to assess the impact of the method originally planned for the derivation of the analysis window for the End of 72 hours assessment visit |
| AE: adverse event; CE: clinically evaluable; cUTI: complicated urinary tract infection; CrCl: creatinine clearance; ECG: echocardiogram; EOIV: end of IV treatment; EOT: end of treatment; ITT: intent to treat; IV: intravenous; LFU: last follow-up; ME: microbiologically evaluable; MIC: minimum inhibitory concentration; MITT: microbiological intent to treat; PK: pharmacokinetic; SD: standard deviation; TOC: test of cure | |

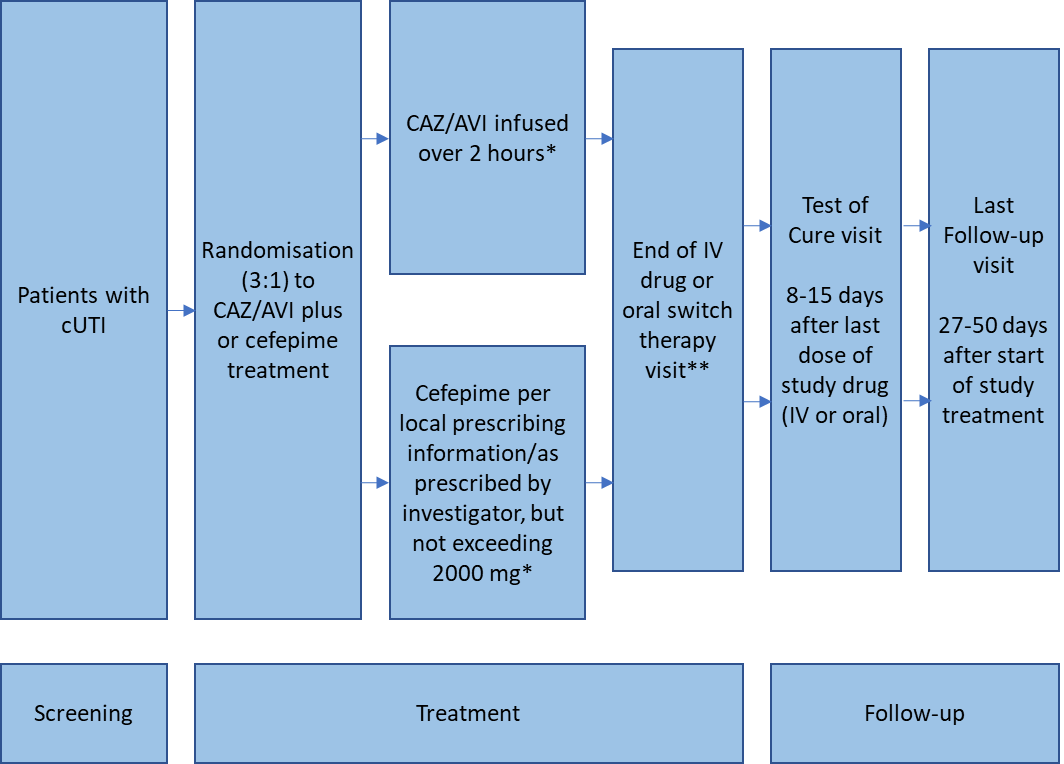


Figure 11. KURA study procedure117

\*Optional switch to oral therapy was permitted on or after Study Day 4. Assessment should be performed no later than 8 hours after the 72-hour time point. The patient may continue on IV study drug for the entire duration of the study therapy (7 to 14 days), at the discretion of the Investigator.

\*\*Visit performed within 24 hours of completion of last infusion or within 48 hours after the last dose of oral switch therapy.

\*\*\*And 20 to 36 days from the last dose of study drug.

#### KURA baseline characteristics

* + - * 1. KURA patient baseline demographics and clinical characteristics

The median (range) age was 4.2 years (0.3 to 17.7 years) in the CAZ/AVI group and 3.2 years (0.3 to 17.9 years) in the cefepime group. The majority of patients in the study were female in both groups (83.6% in the CAZ/AVI group and 75.0% in the cefepime group). The mean (SD) BMI for patients in Cohorts 1 to 3 was 18.6 (4.46) kg/m2.

The majority of patients (66.3%) had CrCl values in the normal for both treatment groups. Thirty (31.6%) patients had mild renal insufficiency and 2 (2.1%) had CrCl values ≥30 to <50 mL/min/1.73 m2. No patients had a CrCl value <30 mL/min/1.73 m2. A total of 79 patients (83.2%) had a diagnosis of acute pyelonephritis at Screening. The majority of patients (77.9%) had no complicating factors. Of those patients that did have at least 1 complicating factor at Screening (22.1%), the most frequently occurring complicating factor was a functional or anatomical abnormality of the urogenital tract (11.6%). A total of 15 (15.8%) patients had urological abnormalities recorded at Screening.

Table 39. KURA baseline demographics and clinical characteristics (Safety analysis set)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CAZ/AVI**  **(N = 67)** | **Cefepime**  **(N = 28)** | **Total**  **(N = 95)** |
| Age (years), Mean (SD) | 6.08 (5.65) | 6.19 (6.07) | 6.12 (5.74) |
| Sex (male), n (%) | 11 (16.4) | 7 (25.0) | 18 (18.9) |
| Race, n (%) | | | |
| White | 49 (73.1) | 23 (82.1) | 72 (75.8) |
| Asian | 12 (17.9) | 5 (17.9) | 17 (17.9) |
| American Indian or Alaska Native | 1 (1.5) | 0 | 1 (1.1) |
| Other | 5 (7.5) | 0 | 5 (5.3) |
| BMI, Mean (SD) | 18.6 (4.47) | 18.5 (4.56) | 18.6 (4.46) |
| CrCl category, n (%) | | | |
| ≥30 to <50 mL/min | 1 (1.5) | 1 (3.6) | 2 (2.1) |
| ≥50 to <80 mL/min | 23 (34.3) | 7 (25.0) | 30 (31.6) |
| ≥80 mL/min | 43 (64.2) | 20 (71.4) | 63 (66.3) |
| Diagnosis, n (%) | | | |
| cUTI without pyelonephritis | 12 (17.9) | 4 (14.3) | 16 (16.8) |
| Acute pyelonephritis | 55 (82.1) | 24 (85.7) | 79 (83.2) |
| No complicating factors present | 53 (79.1) | 21 (75.0) | 74 (77.9) |
| With at least 1 complicating factor | 2 (3.0) | 3 (10.7) | 5 (5.3) |
| Complicating Factors, n (%) | | | |
| No complicating factors present | 53 (79.1) | 21 (75.0) | 74 (77.9) |
| With at least 1 complicating factor | 14 (20.9) | 7 (25.0) | 21 (22.1) |
| Recurrent UTI | 7 (10.4) | 1 (3.6) | 8 (8.4) |
| Functional or anatomical abnormality of the urogenital tract | 6 (9.0) | 5 (17.9) | 11 (11.6) |
| Vesicoureteral reflux | 5 (7.5) | 4 (14.3) | 9 (9.5) |
| Intermittent bladder catheterisation | 0 | 1 (3.6) | 1 (1.1) |
| Urological Abnormalities, n (%) | | | |
| No | 58 (86.6) | 22 (78.6) | 80 (84.2) |
| Yes | 9 (13.4) | 6 (21.4) | 15 (15.8) |
| BMI: body mass index; CrCl: creatinine clearance; NOS: not otherwise specified; SD: standard deviation | | | |

* + - * 1. KURA disease characteristics

All patients in the mITT analysis set had *Enterobacteriaceae* reported at baseline (Table 40). The most frequently reported pathogen in this group was *E. coli* (92.2%)

No patients in the mITT analysis set had Gram-negative other than *Enterobacteriaceae* reported at baseline. Furthermore, no uropathogens were identified in the blood in the mITT and ME at TOC analysis sets.

Table 40. KURA summary of baseline pathogens (mITT analysis set)

|  |  |  |  |
| --- | --- | --- | --- |
| **Pathogen group**  *Pathogen* | **CAZ/AVI**  **(N = 54)** | **Cefepime**  **(N = 23)** | **Total**  **(N = 77)** |
| ***Enterobacteriaceae*** | 54 (100) | 23 (100) | 77 (100) |
| *Citrobacter freundii complex* | 0 | 1 (4.3) | 1 (1.3) |
| *Enterobacter cloacae* | 1 (1.9) | 0 | 1 (1.3) |
| *E. coli* | 49 (90.7) | 22 (95.7) | 71 (92.2) |
| *K. pneumoniae* | 2 (3.7) | 0 | 2 (2.6) |
| *P. mirabilis* | 2 (3.7) | 0 | 2 (2.6) |
| **non-*Enterobacteriaceae* Gram-negatives** | 0 | 0 | 0 |

#### KURA summary of results

A summary of favourable per-patient clinical response rates by visit for patients is presented in Table 25. In general, across all analysis sets, favourable clinical response rates of ≥86% were observed at the End of 72 hour visit and were sustained through to the EOT visit, with responses remaining ≥80% at LFU for both treatment groups for the intention-to-treat (ITT), micro-ITT, and CE analysis sets. At TOC, 59/68 patients (86.8%) in the CAZ/AVI group and 24/29 patients (82.8%) in the cefepime group had a favourable clinical response (corresponding to clinical cure) for the ITT analysis set.

A clinical failure at EOIV was carried forward to the EOT and TOC visits, and a clinical failure at EOT was carried forward to the TOC visit. Three patients in the CAZ/AVI treatment group had clinical failure reported before the LFU due to a treatment-limiting AE. One patient in the cefepime group with clinical failure at the end of IV treatment (EOIV) visit had *E. coli* at baseline that was found to be non-susceptible to cefepime, and study medication was discontinued at the EOIV visit.

Table 41. Favourable Clinical Response by Visit, Treatment Group and Cohort (ITT, Micro-ITT, CE, and ME analysis sets by visit)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | **Analysis set** | **CAZ/AVI** | | | **Cefepime** | | |
| **N** | **n** | **Favourable Response Rate (95% CIa)** | **N** | **n** | **Favourable Response Rate (95% CIa)** |
| End of 72 Hours | ITT | 68 | 60 | 88.2 (79.0, 94.3) | 29 | 25 | 86.2 (70.5, 95.2) |
| MITT | 54 | 49 | 90.7 (80.9, 96.4) | 23 | 22 | 95.7 (81.4, 99.5) |
| CE | 47 | 47 | 100 (94.8, 100) | 21 | 20 | 95.2 (79.8, 99.5) |
| End of IV Treatment | ITT | 68 | 62 | 91.2 (82.7, 96.2) | 29 | 26 | 89.7 (74.9, 97.0) |
| MITT | 54 | 52 | 96.3 (88.6, 99.2) | 23 | 22 | 95.7 (81.4, 99.5) |
| CE | 52 | 51 | 98.1 (91.4, 99.8) | 22 | 21 | 95.5 (80.7, 99.5) |
| ME | 35 | 35 | 100 (93.1, 100) | 16 | 16 | 100 (85.7, 100) |
| End of Treatment | ITT | 68 | 60 | 88.2 (79.0, 94.3) | 29 | 26 | 89.7 (74.9, 97.0) |
| MITT | 54 | 49 | 90.7 (80.9, 96.4) | 23 | 22 | 95.7 (81.4, 99.5) |
| CE | 49 | 48 | 98.0 (90.9, 99.8) | 19 | 18 | 94.7 (77.9, 99.4) |
| ME | 39 | 39 | 100 (93.8, 100) | 14 | 14 | 100 (83.8, 100) |
| Test of Cure | ITT | 68 | 59 | 86.8 (77.2, 93.2) | 29 | 24 | 82.8 (66.3, 93.1) |
| MITT | 54 | 48 | 88.9 (78.5, 95.2) | 23 | 19 | 82.6 (63.8, 93.8) |
| CE | 49 | 46 | 93.9 (84.6, 98.2) | 20 | 17 | 85.0 (65.1, 95.6) |
| ME | 41 | 38 | 92.7 (81.7, 97.9) | 16 | 14 | 87.5 (65.6, 97.3) |
| Late Follow-up | ITT | 68 | 55 | 80.9 (70.4, 88.8) | 29 | 24 | 82.8 (66.3, 93.1) |
| MITT | 54 | 44 | 81.5 (69.6, 90.1) | 23 | 19 | 82.6 (63.8, 93.8) |
| CE | 44 | 41 | 93.2 (82.9, 98.0) | 15 | 15 | 100 (84.8, 100) |
| ME | 16 | 12 | 75.0 (50.9, 90.9) | 9 | 6 | 66.7 (34.8, 89.6) |
| CE: clinically evaluable; CI: confidence interval; ITT: intent-to-treat; IV: intravenous; ME: Microbiologically Evaluable. MITT: microbiological intent-to treat  a. Jeffrey’s method was used to calculate the two-sided 95% confidence intervals. | | | | | | | |

Across both treatment groups, favourable microbiological response rates for the CAZ/AVI and cefepime groups for *E. coli* at TOC were: 79.6% and 59.1% respectively in the micro-ITT analysis set and 86.5% and 66.7%, respectively in the ME analysis set.

Table 42. Per-Pathogen Favourable Microbiological Response Rate in >2 Isolates in Either Treatment Group at TOC by Pathogen and Treatment Group (micro-ITT and ME analysis sets)

|  |  |  |
| --- | --- | --- |
| **Pathogen group**  *Pathogen* | **Number (%) of patients** | |
| **CAZ/AVI** | **Cefepime** |
| MITT Analysis Set | N = 54 | N = 23 |
| ***Enterobacteriaceae*** | 43/54 (79.6) | 14/23 (60.9) |
| *E. coli* | 39/49 (79.6) | 13/22 (59.1) |
| ME Analysis Set | N = 41 | N = 16 |
| ***Enterobacteriaceae*** | 36/41 (87.8) | 11/16 (68.8) |
| *E. coli* | 32/37 (86.5) | 10/15 (66.7) |
| A patient could have more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for that pathogen. Likewise, patients with multiple isolates within the same pathogen group were counted only once for that pathogen group.  ME: microbiologically evaluable; micro-ITT: microbiological intent-to-treat; | | |

Overall, 36 (53.7%) patients in the CAZ/AVI group and 15 (53.6%) patients in the cefepime group experienced an AE. Overall, a total of 10 patients experienced SAEs (CAZ/AVI: n = 8 [11.9%] and cefepime: n = 2 [7.1%]), and only 1 of these SAEs, experienced by a patient in the CAZ/AVI group, was considered to be related to study treatment. There were 3 (4.5%) patients, all in the CAZ/AVI group, with AEs leading to discontinuation of study treatment. There were 6 (9.0%) and 2 (7.1%) patients who experienced severe AEs in the CAZ/AVI and cefepime groups, respectively. The majority of AEs reported were not related to study treatment, with 7 (10.4%) patients in the CAZ/AVI group and 1 (3.6%) patient in the cefepime group experiencing AEs that were assessed as related to study treatment. A total of 10 (14.9%) patients in the CAZ/AVI group and 4 (14.3%) patients in the cefepime group had AE severe intensity. There were no AEs with an outcome of death.

## Non-RCTs

### Non-RCTs supporting the bacteraemia and LTO indications

By definition, patients falling under this are critically ill and have exhausted most treatment options. It is therefore essential that prompt and effective treatment is provided to reduce the risk of mortality and maximise the chance of recovery. Table 43 describes a wealth of real-world evidence (RWE) studies describing the efficacy and safety of CAZ/AVI in patients with LTO.

Table 43. Summary of real-world studies supporting CAZ/AVI use in bacteraemia and LTO indications9-14

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Tumbarello et al.14** | **Sousa et al.13** | **Temkin et al.12** | **van Duin et al.11** | **Castón et al.10** | **Shields et al.9** |
| Study design | * Retrospective * Observational | * Retrospective * Observational | * Retrospective * Observational | * Prospective * Observational | * Multicentre, * Retrospective, * Observational | * Single centre * Retrospective cohort |
| Population | Adult patients (N = 138) treated with CAZ/AVI (≥ 72 h) for culture-confirmed KPC-Kp infection | Patients (N = 57) with CPE infections treated with CAZ/AVI (≥ 48 h) for any OXA-48-producing CPE infection | Patients (N = 38) with infection caused by CRE or CRPa that was sensitive to CAZ/AVI and received CAZ/AVI for compassionate use | Patients (N = 137) with carbapenem-resistant K. pneumoniae and CRE | Patients (N = 31) aged >18 years; initiation of empirical treatment within the first 24 h after blood culture collection; and initiation of targeted treatment within the first 7 days after blood culture collection | Patients (N = 109) with carbapenem-resistant K. Pneumoniae bacteraemia, who received ≥3 days of treatment between January 2009 and February 2017 |
| Intervention(s) | CAZ/AVI (IV) at 2.5 g every 8 h, with dosage adjustments for renal impairment  CAZ/AVI may be received with or without other antimicrobials | CAZ/AVI either as monotherapy or in combination treatment | CAZ/AVI | CAZ/AVI | CAZ/AVI | CAZ/AVI |
| Comparator(s) | NA | NA | NA | Colistin | Other active agents | Carbapenem plus aminoglycoside (CB + AG)  Carbapenem plus colistin (CB + COL)  Other |
| Reported outcomes specified in the decision problem | * Describe characteristics (demographic, clinical, and epidemiological) of the infections, their treatment, and their outcomes (i.e., 30-day mortality) * Assess the efficacy of CAZ/AVI specifically in patients with KPC-Kp bacteraemia | * 14 day all-cause mortality * 30 day all-cause mortality, clinical cure and microbiological cure | * Clinical response at ET, * Microbiological response at the ET, * All-cause in-hospital mortality | * Efficacy:   + Hospital death   + Alive in hospital or discharged not to home   + Discharged home * Safety:   + Hospital death   + Not observed to die, with incident renal failure   + Not observed to die, without incident renal failure | * Clinical features, treatment and outcomes * Crude mortality at 30 days from the day the blood cultures were taken * Clinical cure at 14 days after the onset of antibiotic treatment | * Survival within 30 and 90 days * Clinical success at 30 days, defined as survival, resolution of signs and symptoms of infection, sterilization of blood cultures within 7 days of treatment initiation, and absence of recurrent infections |
| All other reported outcomes | * NR | * AEs and/or development of resistance during or after treatment | * NR | * Benefit-risk * Hospital death * Alive in hospital or discharged not to home, incident renal failure * Discharged home | * NR | * Reasons for treatment failure * Infection recurrence |
| Efficacy results | * The overall 30-day mortality rate was 34.1% (47/138). The highest rate (36.5% [38/104]) was recorded in the patients with bacteraemic KPC-Kp infections; the lowest (16.7% [1/6]) was observed in those with UTIs * Three (2.2%) of the patients who died (2, bacteraemia, 1 pneumonia) had persistently positive cultures after starting CAZ/AVI treatment, and their isolates eventually developed *in vitro* resistance to the drug. Two of the 3 were treated with CAZ/AVI monotherapy, and 1 of the 2 received chronic renal replacement therapy * During the index hospitalisation, 12 (8.7%) patients (10 bacteraemia, 1 UTI, 1 pneumonia) experienced KPC-Kp infection relapses after CAZ/AVI was discontinued. In all 12 cases, the KPC-Kp isolates remained susceptible to CAZ/AVI, and clinical and/or microbiological cures were achieved after retreatment with CAZ/AVI + gentamicin 30-day mortality rate among KPC-Kp bacteraemia patients who received CAZ-AVI was significantly lower than that of controls (36.5% vs 55.8%, P = .005) * Among patients managed with single-drug salvage treatment regimens, those who received CAZ/AVI displayed significantly lower 30-day mortality than those treated with alternative single-drug regimens (9/22 [40.9%] vs 21/27 [77.8%], P = .008). * A similar difference was observed in patients managed with combination regimens (29/82 [35.4%], in those who received CAZ/AVI vs 37/77 [48.1%], in the control group), although it was not statistically significant (P = .10). | * Clinical and microbiological cure were achieved in 77% and 65% of patients, respectively and microbiological failure was observed in10% of cases * All-cause mortality rates assessed at 14 and 30 days were 14% and 22%, respectively * Infection-attributed 30 day mortality was 14% (n" 8), comprising three cases with pulmonary infection, two cases with urinary and intra-abdominal infection and one patient with a complicated SSTI * The only factor related to 14 day mortality was an INCREMENT-CPE score .7 (HR 11.7, 95% CI 4.2–20.6, P" 0.001). * Recurrence of infection (evaluated at day 90) was observed in six patients (10%) with a median time of 41 days (IQR 9–71) from the end of treatment | * Twenty-eight patients (73.7%; 95% confidence interval [CI], 56.9 to 86.6%) experienced clinical and/or documented microbiological cure at ET * All-cause in-hospital mortality was 39.5% (95% CI, 24.0 to 56.6%). * Ten patients died during their hospitalisation due to treatment failure, such that infection-related mortality was 26.3% (95% CI,13.4 to 43.1%). | * All-cause in-hospital mortality 30 days after the start of treatment was 3 (8%) in the CAZ/AVI group vs 33 (33%) in the colistin group. After IPTW adjustment, the estimated adjusted percentages were 9% and 32%, respectively, resulting in a difference of 23% (95% CI, 9%–35%; P = 0.001; * Patients treated with CAZ/AVI were less likely to die and more likely to be discharged home during the first 30 days after starting treatment IPTW-adjusted probability of a better outcome on CAZ/AVI compared with colistin is 64% (95% CI, 57%–71 | * Eight patients (25.8%) received treatment with CAZ/AVI. In all cases, this antibiotic was used as a targeted treatment and in combination with other antimicrobials at a median of 2 days from the blood cultures were taken. * Overall mortality at 30 days was 45.2%. * Crude mortality at30 days was 25% (n = 2) in the patients of the study group and 52.2%(n = 12) in the comparator group. No significant differences were found between the two groups (p = 0.19) * Patients who received CAZ/AVI had higher clinical cure rates than the patients in the comparator group within14 days of initiating treatment (75% vs. 34.8%, respectively, p = 0.031). | * Survival rates at 30 days were not significantly different between the regimens (92% with CAZ/AVI vs 68%, 70%, and 68% with CB + AG, CB + COL and Other, respectively, p=0.37) * Survival rates at 90 days were 92% with CAZ-AVI vs 56%, 63%, and 49% with CB + AG, CB + COL and Other, respectively, p=0.04). * Patients treated with CAZ/AVI had higher rates of 90-day survival than those treated with CB + AG (p=0.03) or other regimens (p=0.008); there was a non-significant trend towards higher 90-day survival for C-A compared with CB+COL (p=0.07). * The 90-day survival rates were higher among patients treated with C-A than in those treated with all other regimens (p=0.01) * Clinical success rate at 30 days was 85% with CAZ/AVI vs 48%, 40% and 37% with CB + AG, CB + COL and Other, respectively, p=0.02. * Patients treated with CAZ/AVI had higher rates of clinical success than those treated with CB+AG (p=0.04), CB+COL (p=0.009), or other regimens (p=0.004). * Clinical success rates were higher among patients treated with CAZ/AVI than in those treated with all other regimens (p=0.006) |
| Safety | * NR | * Two patients developed acute kidney injury during ceftazidime/avibactam treatment (one of them on concomitant IV colistin) but discontinuation owing to side effects was required in no patient | * Six patients (15.8%) developed adverse events that were attributed to CAZ-AVI. Blood alkaline phosphatase increased in two patients; nausea/vomiting, Clostridium difficile-associated diarrhoea, convulsions, and disorientation progressing to stupor occurred in one patient each | * The IPTW-adjusted estimates for hospital death, not observed to die with incident renal failure, and not observed to die without incident renal failure were 9%, 5%, and 86% for CAZ/AVI, respectively, and 25%, 13%, and 62% for colistin | * In no case was CAZ/AVI discontinued due to AEs. * In two patients (25%) who developed renal failure during treatment, the dosing was adjusted. | * 2 patients (18%) receiving CAZ/AVI developed acute kidney injury at the end of treatment |
| Other key results | * NR | * NR | * NR | * The IPTW-adjusted estimates for hospital death, alive in the hospital or discharged not to home with incident renal failure, alive in the hospital or discharged not to home without incident renal failure, and discharged home were 9%, 5%, 65%, and 20% for CAZ/AVI * respectively, and 25%, 11%, 56%, and 8% for colistin | * NA | * NA |
| Conclusion | CAZ-AVI is likely to be an important option for treating serious KPC-Kp infections, particularly those involving bacteraemia | CAZ/AVI shows promising results, even in monotherapy, for the treatment of patients with severe infections due to OXA-48-producing *Enterobacteriaceae* and limited therapeutic options. The emergence of resistance to CAZ/AVI was not observed. | Three-quarters of the patients experienced clinical and/or microbiological cure following CAZ/AVI treatment.  CAZ/AVI shows promising clinical results for infections for which treatment options are extremely limited | The use of CAZ/AVI was associated with  improved clinical outcomes, especially decreased all-cause hospital mortality rate and improved benefit-risk outcomes | CPE bacteraemia is associated with high mortality in patients with hematologic malignancies.  CAZ/AVI may be an effective alternative for treating these patients | The study provides evidence to support CAZ/AVI as the first-line treatment for CR-Kp bacteraemia |
| CPE: carbapenemase-producing *Enterobacteriaceae;* IPTW: inverse probability of treatment weighting; UTI: urinary tract infection | | | | | | |

### Real-world use of CAZ/AVI in the UK

Real-world use of CAZ/AVI has been recently reported in a UK-based multicentre study from 2 tertiary cardiopulmonary centres. The study design and results are described in Table 44 below. Additional reference to real-world use of CAZ/AVI may also be found in Lim *et al.*45

Table 44. Summary of UK real-world evidence supporting CAZ/AVI

| **Study** | **Nwankwo et al.15** |
| --- | --- |
| Study design | Retrospective, observational study |
| Population | Patients (N = 28; 16 female, 12 male) who received CAZ/AVI within a specialist cardio-thoracic centre. The patient groups were patients with respiratory diseases including cystic fibrosis (n = 7), post-lung transplantation (n = 14), patients in the intensive care units (n = 4) and paediatric patients (n = 3, ages 10,15 and 16 years). The age range was 10 to 71 years (mean age of 40.5 years; SD 18.9). |
| Intervention(s) | CAZ/AVI   * For patients 18 years and over: 2 g/0.5 g three times a day by IV infusion over 2 h * Doses were reduced according to the manufacturers’ instructions in patients with mild to severe renal impairment, or in patients on hemofiltration (CrCl: 31–50 ml/min: 1 g/0.25 g Q8H; CrCl 16–30 ml/min: 0.75 g/0.1875 g Q12H; CrCl 6–15 ml/min: 0.75 g/0.1875 g Q24H and haemodialysis: 0.75 g/ 0.1875 g Q48 H). * Weight and age-based doses were applied for paediatric patients aged <18 years |
| Comparator(s) | NA |
| Reported outcomes specified in the decision problem | * Patient outcome was assessed by reviewing infection markers (CRP and WCC) * Development of AMR in any further clinical samples cultured within 6 months of follow-up * A crude mortality assessment was done, wherein in any cases of death, the cause was assessed to see if it was due to the infection. |
| All other reported outcomes | * Tolerability * Cost-utility analysis |
| Efficacy results | * In assessing the effect of the addition/switch/escalation with CAZ/AVI on inflammatory markers within 48 h of treatment initiation, a decrease in CRP in 69% (18/26) of patients, and a normalisation of previously raised WCC in 63% (15/24) of patients was observed. * CRP data were missing in two patients and four patients had normal WCC before and after treatment. * In the 15 patients with pathogens sensitive to CAZ/AVI who received treatment, at 3 months follow up, two patients did not re-culture the organism, in six patients there was no testing for sensitivities, and in the remaining seven patients that persistently regrew the organism, there was no evidence of emerging CAZ/AVI resistance. * 8/28 (29%) deaths occurred during the course of the study; 11% of the deaths (3/28) were due to the patient succumbing to overwhelming infection and the others were unrelated to the infection. * CAZ/AVI was used in four CF patients to treat NTM pulmonary disease. Treatment duration was 28 days, 21 days and 14 days respectively, for patients two to four. All (patients two to four) had good clinical response at the end of the prescribed course. Of the four patients, all were alive and clinically well at one-year post use, and one achieved eradication of organism |
| Safety | * 7% (2/28) of patients experienced adverse events – one developed a rash and raised eosinophils after 3 days. The other developed deranged liver function tests after 9 days of treatment. * In both cases, full resolution of AEs was observed after CAZ/AVI was discontinued. |
| Other key results | * The cost utility for the use of CAZ/AVI was £187,580 for 31 prescriptions issued to 28 patients during the course of the study. However, the methodology of this analysis was not reported and the way that results are reported suggest this was not, in fact, a cost-utility analysis but rather a simple calculation of drug acquisition costs. |
| Conclusion | CAZ/AVI remains an option in the treatment of MDR bacterial infections with limited treatment options. |
| AMR: antimicrobial resistance; CrCl: creatinine clearance; CRP: C-Reactive Protein; h: hour(s); IV: intravenous; WCC: white cell count | |

## Conclusions on clinical evidence and the role of CAZ/AVI in the treatment landscape

### CAZ/AVI in the treatment of Gram-negative infections

CAZ/AVI is indicated in HAP (including VAP), cUTI, cIAI, bacteraemia (associated with the above indications), and in patients with aerobic Gram-negative infections with LTO. In all these indications except for bacteraemia (adult patients only), CAZ/AVI is licensed for the treatment of both adults and paediatric patients aged 3 months and older.

Amongst the causative pathogens in these indications, there are a number of critical priority bacteria (as defined by the World Health Organization) against which CAZ/AVI is effective (see Table 7).

While clinical efficacy has not yet been established, *in vitro* studies suggest the following pathogens relevant to the approved CAZ/AVI indications would be susceptible to ceftazidime/avibactam in the absence of acquired mechanisms of resistance, making CAZ/AVI a valid treatment option to be considered where these pathogens are implicated:

* Critical pathogens – carbapenem-resistant, 3rd generation cephalosporin-resistant *Enterobacteriaceae*:
  + *Enterobacter aerogenes* (*E. aerogenes*)
  + *Morganella morganii* (*M. morganii*)
  + *Proteus vulgaris* (*P. vulgaris*)
  + *Providencia rettgeri* (*P. rettgeri*)
* *Citrobacter koseri* (*C. koseri*; a member of the *Enterobacteriaceae* family not listed on the WHO priority pathogens list)100

The European Committee on Antimicrobial Susceptibility Testing (EUCAST), a standing committee jointly organised by European Society of Clinical Microbiology and Infectious Diseases (ESCMID), European Centre for Disease Prevention and Control (ECDC) and European national breakpoint committees define *Enterobacteriaceae* and *P. aeruginosa* susceptible to treatment with CAZ/AVI at a minimum inhibitory concentration (MIC) breakpoint of ≤8 mg/L. A breakpoint is a chosen concentration of an antibiotic that defines whether a species of bacteria is susceptible or resistant to the antibiotic; breakpoints >8 mg/L define resistant pathogens.100 As the MIC for CAZ/AVI is less than or equal to the susceptibility breakpoint, the bacteria can be considered susceptible to CAZ/AVI.

### Clinical efficacy of CAZ/AVI

The efficacy and safety of CAZ/AVI in its licensed indications has been demonstrated across several high-quality pivotal Phase II/III studies (Table 45) and is further supported by an extensive wealth of retrospective real-world data (Table 46). Overall, CAZ/AVI is safe and has demonstrated non-inferiority to best available therapies, including meropenem, for key indications.

Table 45. RCTs supporting CAZ/AVI

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Trial no. (acronym)** | **Intervention** | **Comparator** | **Population** | **Conclusion** | **Section ref.** |
| REPROVE | CAZ/AVI | meropenem | Adult HAP/VAP | CAZ/AVI has demonstrated non-inferiority to meropenem for the treatment of HAP/VAP and offers coverage against key relevant pathogens, including *Enterobacteriaceae* and *P. aeruginosa.* | 3.1.1 |
| RECAPTURE | CAZ/AVI | doripenem | Adult cUTI, (including pyelonephritis) | CAZ/AVI demonstrated noninferiority to doripenem for the treatment of hospitalised patients with cUTI or acute pyelonephritis based on FDA and EMA-defined endpoints. | 3.3.1 |
| RECLAIM 1 and 2 (Global trial) | CAZ/AVI + metronidazole | meropenem | Adult cIAI. | CAZ/AVI + metronidazole demonstrated non-inferiority to meropenem across all primary analysis populations. CAZ/AVI + metronidazole was effective in both ceftazidime-resistant and ceftazidime-susceptible Gram-negative subgroups (83.0% and 82.0%, respectively) with clinical cure rates similar to that of meropenem (85.9% and 87.7% in ceftazidime-resistant and ceftazidime-susceptible Gram-negative subgroups, respectively). | 3.2.1.2 |
| RECLAIM 3 (Asian population) | CAZ/AVI + metronidazole | meropenem | Adult cIAI | CAZ/AVI + metronidazole was non-inferior to meropenem in the treatment of patients with cIAI in China, the Republic of Korea and Vietnam, with a safety profile reflective of ceftazidime alone. In addition, CAZ/AVI + metronidazole was effective against ceftazidime-non-susceptible Enterobacteriaceae. | 3.2.1.4 |
| REPRISE | CAZ/AVI | best available therapy | Adult cUTI or cIAI | Serious ceftazidime-resistant Gram-negative cUTI with CAZ/AVI results in similar clinical cure rates to treatment with best available therapy and a numerically higher per-patient favourable microbiological response rate. In cUTI, although the study population was small, the proportion of patients with a clinical and microbiological response was also high for CAZ/AVI and in-line with that observed with best available therapy. | 3.3.2 |
| ANDI | CAZ/AVI + metronidazole | meropenem | Paediatric cIAI (3 months to <18 years) | CAZ/AVI + metronidazole was well tolerated in children with cIAI; safety observations were consistent with the established safety profiles of ceftazidime monotherapy and/or metronidazole in children as well as CAZ/AVI in adults. Likewise, ceftazidime-avibactam plus metronidazole appeared effective in the treatment of paediatric cIAI caused by the predominant aerobic and anaerobic pathogens, including ceftazidime-non-susceptible Gram-negative pathogens. | 3.2.3 |
| KURA | CAZ/AVI | cefepime | Paediatric cUTI (3 months to <18 years) | CAZ/AVI was well tolerated in children with cUTI, with a safety profile consistent with that of adults with cUTI and of ceftazidime alone and appeared effective in children with cUTI due to Gram-negative pathogens. | 3.3.3 |
| CAZ/AVI: ceftazidime/avibactam; cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia. | | | | | |

Table 46. Non-RCTs supporting CAZ/AVI

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ref.** | **Intervention** | **Population** | **Objectives** | **Summary** |
| Tumbarello et al. (2019)14 | CAZ/AVI as salvage therapy | Patients with documented KPC-producing *K. pneumoniae* (KPC-Kp) infections | * Document the clinical features and outcomes of patients with documented KPC-Kp infections receiving CAZ/AVI as salvage therapy. * Explore outcomes and predictors of mortality in patients with KPC-Kp bacteraemia | Of the included patients, 75% experienced bacteraemic infections and 25% experienced non-bacteraemic infections involving (in order of decreasing frequency) the lower respiratory tract, intra-abdominal structures, the urinary tract, or other sites. The overall 30-day mortality rate was 34.1%. The highest rate (36.5%) was among patients with bacteraemic KPC-Kp infections; the lowest (16.7%) was observed in those with UTIs. The 30-day mortality rate among patients with KPC-Kp bacteraemia showed a significantly lower trend with CAZ/AVI than that of a matched cohort treated with other second-line regimens (controls) (36.5% versus 55.8%, respectively, p=0.005). |
| Sousa et al. (2018)13 | CAZ/AVI (as monotherapy or in combination with other treatments) as salvage therapy | Hospital patients with carbapenem-resistant infections caused by OXA-48-producing *Enterobacteriaceae* | Analyse the effectiveness and safety of CAZ/AVI for the treatment of infections due to carbapenemase-producing *Enterobacteriaceae* (CPE) in a cohort of patients treated in the centre during an epidemic outbreak of OXA-48-producing *K. pneumoniae*. | The most frequent sources of infection were intra-abdominal (28%), HAP/VAP (26%), and urinary source (25%); bacteraemia was confirmed in 46% of patients. CAZ/AVI showed a trend of promising results against OXA-48-producing *Enterobacteriaceae* for which treatment options are limited. In the patient cohort, all-cause mortality was 14% at 14 days, rising to 22% at 30 days, and the recurrence rate of infection was 10% at 90 days. Moreover, resistance to CAZ/AVI was not detected in any case and only two patients experienced treatment-related AEs (TRAEs). |
| Temkin et al. (2017)12 | CAZ/AVI as salvage therapy | Patients with infections caused by either carbapenem-resistant *Enterobacteriaceae* or *P. aeruginosa* | * Evaluate clinical cure at the end of treatment, microbiological cure at the end of treatment, and all-cause in-hospital mortality. * Identify predictors of cure and of survival. | CAZ/AVI showed a trend towards promising clinical results for infections for which treatment options are limited. Twenty-eight patients (73.7%) experienced a trend towards clinical and/or microbiological cure at end of treatment. Furthermore, microbiological cure suggested a trend towards improved survival as 79% of patients with negative cultures at the end of treatment survived until discharge. |
| van Duin et al. (2018)11 | CAZ/AVI or colistin | Patients with carbapenem-resistant *Enterobacteriaceae* infections | “Evaluated combined benefits and risks to estimate patient-level differences between ceftazidime-avibactam and colistin.” | In patients treated with CAZ/AVI versus colistin, inverse probability of treatment weighting (IPTW)-adjusted all-cause hospital mortality 30 days after starting treatment was 9% versus 32%, respectively (p = 0.001). In an analysis of disposition at 30 days, patients treated with CAZ/AVI, compared with those treated within colistin, had an IPTW-adjusted probability of a better outcome of 64%. |
| Castón et al (2017)10 | CAZ/AVI or other treatments | Patients with carbapenemase-producing *Enterobacteriaceae* bacteraemia, including high-risk patients with haematologic malignancies | * Describe clinical features, treatment, and outcomes in patients with carbapenemase-producing *Enterobacteriaceae* (CPE) bacteraemia. * Compare patients treated with CAZ/AVI to remaining patients to determine the influence of the treatment on crude mortality and clinical cure. | A total of 31 patients were included. Bacteraemia was considered primary in 14 (45%) patients. Overall crude mortality at 30 days was 45.2% (n = 14). Eight patients (25.8%) received treatment with CAZ/AVI. No significant differences in crude mortality were found between study and comparator groups (p = 0.19). In contrast, patients in the CAZ/AVI group showed promising results, with higher clinical cure rates than the comparator group within 14 days of initiating treatment (85.7% vs. 34.8%, respectively, p = 0.031).  CAZ/AVI may be an effective alternative for treating patients with CPE bacteraemia, which is associated with high mortality in high-risk patients with haematologic malignancies. |
| Shields et al. (2017)9 | CAZ/AVI or other treatments | Patients with carbapenem-resistant *K. Pneumoniae* bacteraemia | Compare the outcomes of patients with carbapenem-resistant *K. pneumoniae* bacteraemia who received definitive treatment with a regimen containing CAZ/AVI or alternative regimens | CAZ/AVI treatment of carbapenem-resistant *K. pneumoniae* bacteraemia was associated with higher rates of clinical success (P = 0.006) and survival (P = 0.01) than other regimens. |
| Nwankwo et al. (2021)15 | CAZ/AVI | Patients who received CAZ/AVI in the hospital setting | Assess the use of CAZ/AVI and evaluate prescribing against relevant standards. | Prescribing according to the approved indications was observed for 68% of prescriptions (p < 0.0001). Duration of therapy was often prolonged but improved with antimicrobial stewardship interventions. We observed 56% susceptibility (15/27 isolates) of MDR organisms (*Pseudomonas, Klebsiella, Burkholderia, Enterobacter aerogenes, Achromobacter*). CAZ/AVI was well tolerated, with no evidence of development of resistance at 6-months follow-up.  Antimicrobial stewardship interventions led to a more appropriate use of Ceftazidime/avibactam (as measured by duration of therapy), preserving it as a treatment option for MDR infections. |
| AE: adverse events; CAZ/AVI: ceftazidime/avibactam; CPE: carbapenemase-producing Enterobacteriaceae; HAP: hospital-acquired pneumonia; IPTW: inverse probability of treatment weighting; KPC: Klebsiella pneumoniae carbapenemase; TRAE: treatment-related adverse events; VAP: ventilator-associated pneumonia. | | | | |

### Limitations of clinical evidence

Despite the wealth of clinical trial and real-world evidence supporting the use of CAZ/AVI in patients with infections caused by Gram-negative pathogens, trials were not conducted specifically in the LTO indication. Due to the ethical and logistical challenges associated with conducting a trial in patients with LTO, the evidence supporting this indication is derived from real-world data, rather than RCTs. Data exists to support the use of CAZ/AVI in cSSTI, bone and joint infections and meningitis due to KPC and OXA-48 or MDR *Pseudomonas*.9-14 CAZ/AVI was the first antibacterial in history to be granted an LTO licence, allowing its use in areas of extremely high unmet need, i.e., in patients for whom other treatment options have been exhausted or are limited.

The pivotal RCTs of CAZ/AVI were predominantly non-inferiority trials. While uncommon in many therapy areas, non-inferiority trials are, in fact, standard when assessing antibiotics, due to the challenges associated with demonstrating superiority. These have been comprehensively discussed in a 2017 report from the Office of Health Economics34 and, briefly, include:

* the ethical obligation to test a new antibiotic against an active comparator considered best available therapy,
* the overall goal to provide evidence that the proposed antibiotic is effective and facilitates the availability of alternative treatment options that may have the potential to reduce selection pressure on other agents,
* high bacterial clearance rates for the comparator (particularly for susceptible pathogens), leaving little room to demonstrate superiority,
* the challenges of recruiting very severely ill patients (in whom a new antibiotic is likely to be most valuable) into a clinical trial,
* time and cost pressure to recruit patients for a sample size sufficient for superiority investigation.

Furthermore, EMA guidance now stipulates that non-inferiority trials are appropriate for five major indications:118

* acute bacterial skin and skin structure infection (ABSSSI)
* community-acquired pneumonia (CAP)
* HAP/VAP
* IAI
* UTI

A non-inferiority trial design demonstrates clinical efficacy and safety versus current standard of care, which CAZ/AVI has demonstrated in the licensed indications HAP/VAP, cIAI, and cUTI. By design, the non-inferiority trials did not capture utilisation and impact of antimicrobials on resistance development within a population over time, where antibiotic effectiveness, and patient and population outcomes are reduced with increasing levels of resistance.119,120

### CAZ/AVI in the English treatment landscape

Whether used as targeted empirical therapy or in patients with confirmed MDR infections, CAZ/AVI is likely to be employed in settings associated with high unmet need, such as the ICU and acute medical and surgical wards.

The burden of bacteraemia and associated sepsis in England is high. A surveillance program of BSIs provided data from 45.5% of all ICUs in England collected over 12 months from May 2016. The rate of BSI was 5.7 per 1,000 patient-days for adult ICUs with high variability between the participating units (range: 0.0–44.0 BSIs per 1000 patient-days). 30-day all-cause fatality rate among adult ICU patients with positive blood cultures was 23.8% (95% CI 21.4–26.4%).85

CAZ/AVI is a valuable treatment option for infections with a broad spectrum of Gram-negative pathogens, including those resistant to a number of “last resort” antibiotics and associated with high mortality and otherwise limited treatment options. While infections due to CRE may be often treated with colistin, resistance to colistin in this setting has been reported to develop rapidly, raising concerns of emerging pan-drug resistant infections.25,121 Against this backdrop, CAZ/AVI was approved in 2016 for the treatment of Gram-negative infections that can be associated with very high mortality rates, including cUTI (6-60% mortality rate),122,123 cIAI (30%),54 HAP/VAP (38– >70%),55 bacteraemia that occurs in association with, or is suspected to be associated with any of the aforementioned infections (45%),10,91 and infections due to aerobic Gram-negative organisms in adult patients with limited treatment options. CAZ/AVI was approved for paediatric use in cUTI, cIAI, and HAP/VAP, subsequently. Specifically, outside of cUTI, cIAI and HAP/VAP, data support the use of CAZ/AVI in bacteraemia, cSSTI, bone and joint infections, meningitis due to KPC and OXA-48 resistance mechanisms, and MDR *Pseudomonas* infections.9-14,106 Given the severity, poor prognosis, and limited treatment options associated with these infections, it is clear that CAZ/AVI fills a substantial unmet need, providing a carbapenem- and colistin-sparing option in light of increasing resistance concerns.

### Benefits to the NHS realised through the use of CAZ/AVI

Delays to appropriate therapy for serious infections with Gram-negative species have been reported to associate with approximately 70% increase in length of hospital stay, 65% increase in total in-hospital costs and 20% increase in the risk of in-hospital mortality or discharge to hospice.124 A UK hospital-based budget impact model for CAZ/AVI use in complex healthcare-associated infections (cIAI, cUTI, and HAP/VAP) estimated increases in the proportion of cured patients and reductions in hospital stay for all indications with the use of CAZ/AVI as opposed to a carbapenem125 (Figure 12).

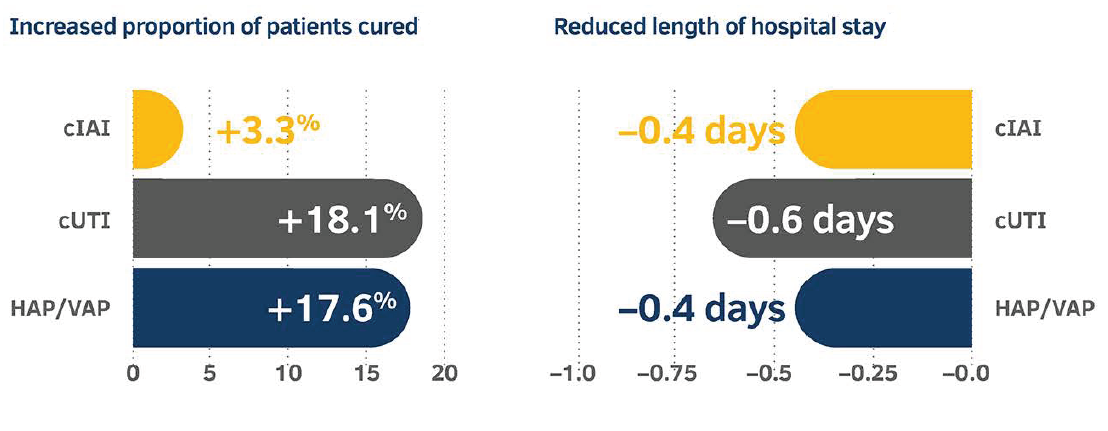


Figure 12. Estimates of the benefits associated with CAZ/AVI use instead of a carbapenem from the UK hospital perspective125

Clinical efficacy data are based on RECAPTURE/RECLAIM/REPROVE trials. Cost per bed day is derived from 2017–2018 NHS Reference Costs, and drug acquisition costs from October 2019 BNF. Resistance rates reflect the Italian setting.

CAZ/AVI is a valuable asset to the NHS and strategies should be put in place to maximise its potential benefits. To this end, Pfizer had commissioned and published a novel, well-validated, non-product specific model to investigate the impact of different antimicrobial treatment strategies on the development of AMR, and clinical and economic outcomes at patient and population level26. This published model was used as the basis for the economic model provided as part of this submission, updated with CAZ/AVI-specific data, and is further described in Section 4.

# Cost-effectiveness

|  |
| --- |
| ***Key messages*** |
| * Pfizer’s has a long-standing commitment to actively participate in finding a solution to the global AMR problem and hopes the economic modelling included below informs both the committee and EEPRU of the value CAZ/AVI brings to the population. * The company economic model was based off a recent publication26 and subjected to extensive external validation exercises to demonstrate the scientific rigour, relevance and the generalisability to the real-world setting. In addition, model inputs were taken from published sources or based on assumptions verified by external experts via Delphi panel. * The model adheres to the NICE reference case, with adaptations to align to the EEPRU protocol, framework for antimicrobials, and the final NICE scope. * Critically the model takes a pragmatic approach to modelling a treatment pathway across the indications / pathogens most relevant to CAZ/AVI licensed indications to more fully explore the value of CAZ/AVI. * In the base case analysis, the 10-year population-level NMB for CAZ/AVI was £598,779,222 (£30,000/QALY) and it predicted an incremental gain of 25,768 discounted life-years and 20,487 discounted QALYs. * The base-analysis encompasses several key indications for CAZ/AVI (HAP/VAP, cUTI, and cIAI), as well as key settings relevant to the LTO indication caused by different pathogens, i.e. *E. coli, Klebsiella spp*., and *P. aeruginosa* in a weighted manner to maximise the modelled proportion of the population covered by the licensed indications and reflect the real-world scenario as well as possible. * This base case underestimates the true system value, given the economic model does not fully capture:   (1) Broad range use of CAZ/AVI in practice (2) Total value attributable to antibiotics proposed by EEPRU, e.g. the value of mitigating the impact of probable future events, and the enabling of other procedures (3) Population impact on productivity and fiscal benefit   * To supplement the base case, a separate insurance value model is under finalisation and highlights additional significant system impact antibiotics have on mitigating and protecting against future probable events. This will be shared with the project team post completion to inform both the EEPRU and the committee discussions. |

## Economic analysis

### Overview of approach

The economic evidence provided with this submission is based on a published dynamic, disease transmission and cost-effectiveness model26, which has been validated by rigorous peer review (described in Section 4.1.3). The model is fully compliant with best practice recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)27. Additionally, the economic analysis approach broadly adheres to the NICE reference case, EEPRU protocol and Evaluation framework for antimicrobials and final NICE scope (as described in Section 4.1.1.2).35,87,126

Aligned with the final NICE scope, the analysis aims to estimate the value of CAZ/AVI under stewardship scenarios, likely to be applied in clinical practice, that are expected to generate the greatest value to the NHS while maximising population health. The analysis encompasses several key indications for CAZ/AVI (described in Section 4.1.2.1). The economic analysis outputs are expressed as population net health benefits as measured in quality-adjusted life years.

#### Approach to model development and population

The economic model was informed by a systematic review by Drake et al and ISPOR best practice recommendations.127,128 Further, expert advice was elicited to inform model development and population. This was initially conducted as expert consultations further validated via a recently conducted Delphi panel.

**Expert consultation**

Clinical and methodological experts selected by Pfizer were involved in the design of the model to ensure that it captured the relevant dynamics of infection transmission and antimicrobial use, and that model inputs and data sources were appropriate. During consultation, the experts were requested to comment on the appropriateness of model conceptualisation and completeness of the captured infection transmission/AMR components, assess model inputs and their application and guide research questions. Recommendations were incorporated within the model, and the changes were subsequently reviewed by the experts. This process was repeated until the experts concluded that the final model captured the desired components appropriately and robustly, and that model output had clinical validity.

**Delphi panel process**

The Delphi panel method is an accepted, robust approach for obtaining formal consensus from a group of experts and is recommended by NICE and EEPRU.35 It is a highly structured group interaction, wherein expert opinion is elicited through a multistage self-completed questionnaire with individual and group feedback. Further details can be found in the Delphi panel report.129

Participants were identified and recruited based on the experience and expertise of the following: the AMR healthcare landscape, the antibiotic in question (CAZ/AVI), the overall treatment pathways in AMR, and where possible an understanding of economic modelling concepts.

As outlined modelling an antibiotic treatment pathway can be complex, therefore statements were developed to explore assumptions made, comparators modelled, and scenarios investigated within the economic model for relevancy and appropriateness. Those statements were collated into an online questionnaire format and circulated to the participants, with the availability to include written comments providing context for each rating. Responses were summarised using descriptive statistics and thematic analysis was performed to identify common issues, themes, and suggestions from participants to inform round 2 statement development. Round 2 questionnaires were individualised to each participant. Each survey contained the redrafted statements, original round 1 statements, individual respondent rating from round 1, collated round 1 rating from the entire panel and a selection of anonymised comments. Round 2 scoring and analyses were structured the same as in the first round.

The model inputs are summarised in Table 60 and the model inputs required for model calibration are the ones listed in Table 49, Table 51 to Table 53, and Table 55.

#### Alignment with recommended approach

The economic model broadly adheres to the NICE reference case with adaptations to align to the EEPRU protocol and Evaluation framework for antimicrobials and final NICE scope,35 with additional/modified features outlined below:

1. The analysis explored different stewardship scenarios, aligned to the objective of identifying those expected to generate the highest health benefits to the NHS while minimising resistance development.
2. Rather than including a single primary indication, or focusing specifically on the HVCS, the analysis encompassed several key indications for CAZ/AVI, i.e. HAP/VAP, cUTI, and cIAI.
3. The economic analysis outputs were expressed in population NMB as measured in QALYs to inform the potential annual value, estimated both over the full-time horizon of the economic model and the potential 10-year contract period.
4. The evaluation included several of the additional elements of value as set out in the Evaluation Framework. Diversity value and transmission value are included in the modelled analysis. Both insurance and enablement value are only reflected in the modelled analysis to a very limited capacity (see Section 4.1.3.1 for further details) but additionally analysis on the insurance value is ongoing (see Section 4.9.1 for further details). However, spectrum value is not reflected. As such, there are aspects of significant value, outlined in the EEPRU evaluation framework, that are not captured within the provided analysis. Hence, this approach should be considered an underestimation of the true value and conclusions on the value of CAZ/AVI should consider the potential for the value elements not captured or captured completely in the economic model.
5. The cost per QALY threshold of £30,000 was used for the calculation of the NMB.

Development of a model that looks at exploring the enablement value attributable to antibiotics further is ongoing, with a publication plan in place. In addition, specifically for this submission an economic model that describes insurance value through the modelling of a number of future probabilistic events using a Monte Carlo approach is being undertaken with a full report analysis to be shared once complete.

In addition, it should be noted that, in line with the anticipated use of CAZ/AVI, only the hospital setting is considered within the economic model; infections treated within the community setting are not modelled.

Overall, the economic model aims to reflect real-world practice, focusing on a treatment pathway and assuming a steady state, that accounts for time to effective therapy via a risk factor approach in order to identify and treat those with MDR Gram-negative infection. This is in-line with PHE standards.

### Patient population

#### Indications of interest

The economic model considers infections across three key indications in which CAZ/AVI is licensed, and which also represent the most common healthcare-associated infections in the UK130, including:

* cIAI
* cUTI
* HAP/VAP

By contrast, the EEPRU protocol is focusing on only two HVCSs, which are as follows:

* **Microbiology-directed treatment:** patients with cUTI infection, limited to suspected or confirmed serine carbapenemase-producing *Enterobacterales* of the OXA-48 and KPC subtypes
* **Risk-based empiric treatment**: HAP/VAP infections suspected to be caused by *Enterobacterales* which are MDR /carbapenem-resistant /OXA-48 or KPC mechanisms of resistance

EEPRU will then take a more descriptive effort to extrapolate this value across the broader indication coverage; however, these indications may not demonstrate the highest value to the NHS. In comparison, the submitted analyses capture the broader indication and therefore can more comprehensively assess the value of CAZ/AVI across its licensed indications. Therefore, these analyses will allow a more informed extrapolation to the population health level.

#### Pathogens

The economic analysis considers mechanisms of infection with three Gram-negative bacterial species across each indication, including:

* *E. coli*
* *K. pneumoniae*
* *P. aeruginosa*

For the base case analysis and relevant scenarios, a weighted analysis was performed, combining results from all pathogens for each indication so that the numbers of infections, costs incurred and QALYs lost as a result of infection were summed across causal pathogens.

### Model structure

#### Overview

The structure of the published dynamic disease transmission and cost-effectiveness model26 is presented in Figure 13. The model combines a multi-state disease transmission component (Figure 13A; described further in Section 4.1.3.2) and a decision-tree treatment pathway component (Figure 13B; described further in Section 4.1.3.3).

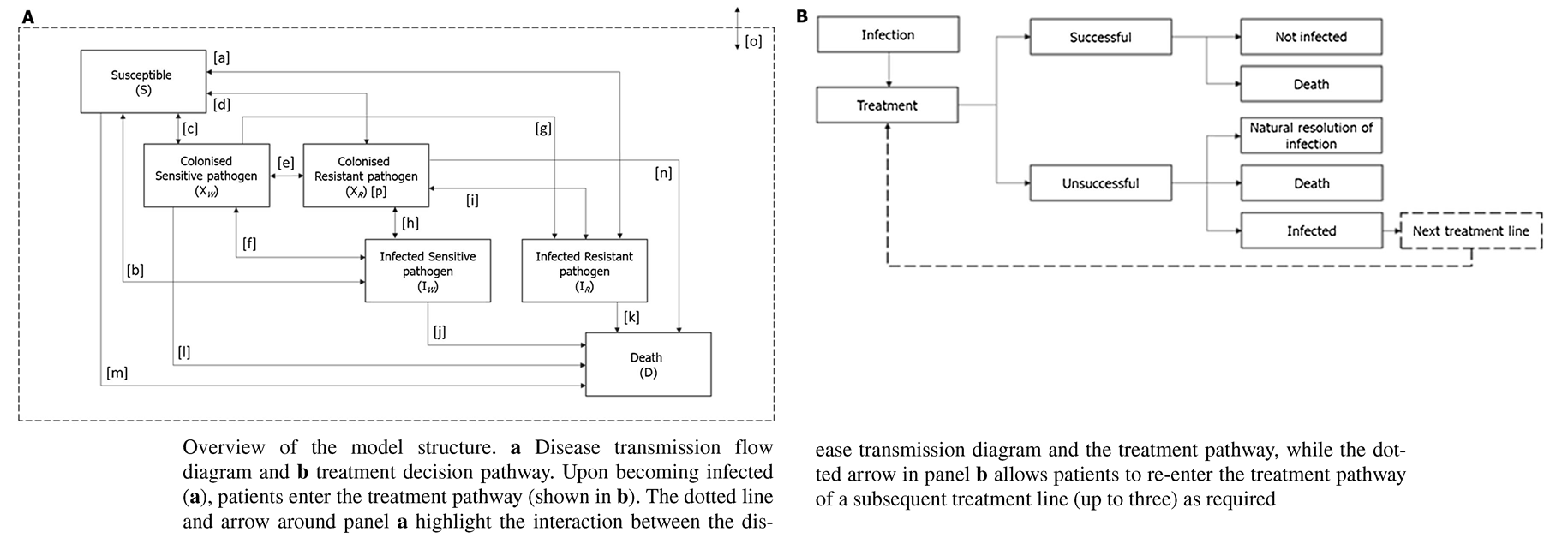


Figure 13. Structure of the economic model.

Source: Gordon et al.26

The model design was predominantly based on the findings of a systematic review by Drake et al.127 and recommendations from ISPOR and the Society for Medical Decision Making (SMDM) related to good research practices in dynamic transmission modelling128. Further, the modelling approach was designed in consultation with experts in microbiology, infection control and economic modelling, as outlined in Section 4.1.1.1.

While no specific economic model is outlined in the EEPRU protocol, it is suggested that the de novo economic model will comprise: a patient-level component characterising the likely impact of CAZ-AVI and existing AM usage scenarios on costs, HRQoL and mortality over the lifetime of the patient; and a population-level component that aggregates the patient-level predictions to the population level accounting for the likely trajectory of infections and resistance patterns over time and potentially capturing the effects of usage scenarios on these trajectories (e.g. by reflecting effects on transmission). This can be considered broadly aligned to the approach suggested within the submitted economic model.

As previously described, the economic analysis reflects the diversity value (benefits of reducing selection pressure and preserving the efficacy of existing antibiotics) and transmission value (benefits of avoiding the spread of infection to the wider population) of new antimicrobials. Additionally, insurance value (value of having a treatment available in case of future outbreaks) and enablement value (value associated with enabling other treatments or procedures) are partially reflected. Currently, analyses on the insurance value are conducted (see Section 4.9.1 for further details). Spectrum value (value associated with narrow spectrum antibiotics) is not currently reflected. The economic model is able to explore scenarios associated with withholding an antimicrobial for the treatment of resistant infections but is unable to explore insurance value associated with avoiding outbreaks and other major catastrophic health consequences. Outcomes specifically relevant to enablement value were not explored, such as prophylaxis use, gains in hospital capacity and the enablement of procedures that would otherwise be foregone. However, some of its elements are included implicitly, as patients infected after surgical and medical procedures fell within the modelled population. Given the absence of fully capturing these areas of value this approach should be considered as an underestimation of the population wide value of CAZ/AVI availability.

#### Disease transmission module

The compartmental multi-state disease transmission module (Figure 13A) estimates the incidence and prevalence of bacterial infections within a hospital environment, based on patient interactions and exposure to antimicrobials over a time horizon of 10 years. During each model cycle patients may move between discrete health states representing:

* **Colonised [X]:** Patients colonised with the pathogen of interest.
  + **XW** represents colonisation with a sensitive pathogen (i.e., no resistance to modelled treatments)
  + **XR**represents colonisation with a resistant pathogen (i.e., resistance to either one, two, or all three modelled treatments)
* **Infected [I]:** Patients infected with pathogen of interest.
  + **IW** represents infection with a sensitive pathogen (i.e., no resistance to modelled treatments)
  + **IR**represents infection with a resistant pathogen (i.e., resistance to either one, two or all three modelled treatments)
* **Susceptible [S]:** Patients not colonised or infected with a pathogen of interest.
* **Death [D]** (absorbing state)

During each monthly model cycle, patients may move between colonised, infected, or susceptible health states, or death. Colonised and infected states contain sub-states split by pathogen type (sensitive or resistant), allowing differential probabilities of successfully treating resistant pathogens, and enabling resistance development to be retained and propagated as treated individuals in the infected state move to the colonised state.

The economic model considers a single hospital with a constant infectious environment of 1,000 patients. As a simplifying assumption, health states are assumed to be homogeneous; consequently, each infection is independent and once a patient is discharged from the infectious environment they are not readmitted. It was assumed that the number of admissions and discharges are equal in each cycle (i.e., the total number of patients modelled in the infectious environment is constant between cycles) and that newly admitted patients have the same resistance profiles as discharged patients. Model outcomes were scaled to reflect the population level in England based on 2019 overnight hospital bed occupancy where it was assumed 93,432 beds in England are constantly occupied in the general and acute wards. 131 The NMB was calculated by multiplying the incremental gain in QALYs with the cost per QALY threshold subtracting the incremental costs. Additionally, the number of deaths avoided and infections cleared were calculated.

Transitions between health states are controlled by the incidence and prevalence of bacterial infection and colonisation within the modelled environment and were derived from data reported by PHE132 and the Health Protection Agency130 (see Section 4.2.3).

Where evidence was unavailable, model inputs describing infection transmission dynamics and resistance development were derived empirically through calibration, such that the model reproduced observed data from PHE describing infection incidence and resistance development over time. Further information is provided in Section 4.2.4.

#### Treatment pathway component

The multi-state disease transmission module described in Section 4.1.3.2 is linked to a treatment pathway component determining the health economic impact of a specified treatment strategy in the context of the modelled infectious environment. Individuals with new infections enter the treatment pathway (Figure 13B) and are treated according to pre-determined antibiotic regimens, until they are either cured (successful treatment or infection resolves spontaneously) or die from infection.

The model assumes that patients may receive up to three treatment lines as a simplifying assumption. This reflects strong clinical evidence (RCTs and real-world data) and the numerous plausible antimicrobial treatments that may be used in clinical practice, depending on clinician choice and local resistance rates. Subsequent lines of treatment are received only if the prior treatment is unsuccessful, so that patients’ progression through the treatment pathway is dependent on treatment efficacy and the prevalence of AMR in the infected population. The design of this economic model therefore allows it to be used as a proxy to assess time to effective treatment, e.g. for patients in whom CAZ/AVI is identified as appropriate, the time spent on other treatments could be considered “inappropriate”. This also approximates to some real-life practice in the age before very rapid diagnostic role out.

After a patient is successfully treated, they may return to the susceptible or colonised health states. Patients may return to the colonised health state with a pathogen resistant to an antibiotic treatment they received during the course of treatment for their infection. Patients infected with treatment-resistant pathogens have different probabilities of successful treatment when compared with those infected with pathogens sensitive to antibiotic treatment. Model inputs describing efficacy for the treatment pathway component are provided in Section 4.3.1.

**Stewardship approach applied in the economic model**

The treatment pathway component can assess the efficacy of CAZ/AVI as part of several different treatment strategies that may reflect varying antimicrobial stewardship approaches. To accommodate different stewardship strategies, the order in which treatments are received and/or the number of lines of treatment available can be modified. Furthermore, the order in which treatments are received can be altered on a time-dependent basis, reflecting a treatment cycling stewardship strategy.

While the model is capable of reflecting a range of antimicrobial stewardship scenarios26, the base case analysis uses an all-lines diversity stewardship strategy which, provides an optimal balance between maximising population health gains and minimising resistance development26 and is also likely to reflect real-world practice, where local guidance, resistance levels, and clinician preference are likely to affect treatment choices. Most crucially, this diversity approach provides a pragmatic modelling proxy whereby CAZ/AVI may be given to patients meeting risk factors for early empiric therapy such as previous ICU admission, longer admission times, critical illness, use of invasive devices, or prior antibiotic therapy as first treatment option. This is a crucial element of value for CAZ/AVI given improved outcomes can be associated with appropriate early effective treatment.

This contrasts in some way with the approach proposed for the EEPRU model, which is focusing on specific HVCSs that almost reflect the perfect stewardship scenario but clinical evidence for those is scarce. Using the diversity approach will be able to provide a more realistic value of CAZ/AVI given it represents the best estimation of effective treatment strategies and is able to capture the simplified treatment pathways of the majority of the patients eligible for antimicrobial therapy in this complex disease area

#### Model settings

The disease transmission model utilises a ten-year time horizon with a monthly cycle to evaluate model outputs. The model cycle length and time horizon were informed by Jansen et al., a previously published antimicrobial cost-effectiveness evaluation.133 Additionally, expert opinion elicited during model development and the recent Delphi panel supported the cycle length and time horizon.

Since the value of a new antimicrobial becomes more apparent as the time horizon is extended, a 10-year horizon was selected to balance the inherent uncertainty associated with long-term extrapolation and the underestimation of value that would arise from a short time horizon. This is aligned with the EEPRU protocol which states that the time horizon should be sufficiently long to reflect all important differences in costs and effects between the alternative comparators.35

All infections are assumed to be resolved within the incident cycle, aligned to clinical expert opinion from the Delphi panel. Patients who die due to infection incur a loss of life expectancy and quality-adjusted life expectancy corresponding to that of the general population. Capturing life years and QALYs lost due to unsuccessful treatment allows the model to quantify the impact of infections avoided in addition to the benefits of successful treatment.

An annual discount rate of 3.5% was applied to costs and benefits. A half cycle correction was not required as the decision tree outcomes were derived on a daily basis.

### Intervention technology and comparators

Clinical evidence for CAZ/AVI is available against a range of comparators used in pivotal RCTs and key real-world studies, as outlined in Section 3. However, comparators were simplified to reflect the most clinically relevant therapies in the empirical and confirmed / suspected resistance settings. This aimed to maximise clinical relevance across all of NHS England in a situation where only a finite number of scenarios can be reasonably modelled given the variability of local resistance patterns.

The most appropriate comparators included in the economic model, determined during expert elicitation were as follows: piperacillin/tazobactam (cIAI and cUTI) or colistin (HAP/VAP) and meropenem (all modelled indications), as described in Table 47.

Table 47. Summary of intervention technology and comparators across indications

|  |  |  |  |
| --- | --- | --- | --- |
| **Intervention** | **Indication** | | |
| **cIAI** | **cUTI** | **HAP/VAP** |
| Piperacillin/tazobactam (Pip/Taz) | 🗸 | 🗸 | 🗴 |
| Colistin | 🗴 | 🗴 | 🗸 |
| Meropenem | 🗸 | 🗸 | 🗸 |
| CAZ/AVI | 🗸\* | 🗸 | 🗸 |
| cIAI: complicated intra-abdominal infections; cUTI: complicated urinary tract infection; HAP/VAP: hospital acquired pneumonia or ventilator-associated pneumonia  CAZ/AVI plus metronidazole for the cIAI indication | | | |

## Epidemiological parameters

In clinical practice, increased prevalence of AMR reduces antibiotic efficacy, described as the likelihood of successfully treating bacterial infections with an antibiotic agent. This results in increased treatment cost and health resource utilisation, along with reduced QoL in infected patients and increased mortality. Increased resistance also produces a negative downstream effect on the outcomes of future infections as a result of suboptimal antibiotic treatment strategies. On the other hand, increased antibiotic efficacy due to lower resistance results in higher rates of successful treatment and a reduced exposure to subsequent treatment lines, reducing the probability of resistance to subsequent treatments developing.

The economic model has been parameterised to replicate these clinical outcomes, using UK-relevant sources. Additionally, model outputs have been validated against real world evidence, to ensure predictive accuracy.

### Development of antibiotic resistance

Both *de novo* resistance development and transmission of resistance are captured in the model. Resistance acquired through either mechanism can be propagated throughout the infectious environment in the disease transmission component of the model.

*De novo* development of resistance is primarily a function of treatment exposure. Each day a patient receives a given antibiotic the exposed pathogen has a probability of developing resistance to that treatment. The development of resistance is therefore time-updated as a function of the number of patients requiring treatment, the antimicrobials used, and treatment efficacy. Pathogens may develop resistance to multiple treatments, resulting in infections that are more difficult to treat, or infections that cannot be treated with available antibiotic agents.

Treatment resistant infection or colonisation may also arise through transmission, i.e., as a result of patients becoming infected with an already resistant pathogen. These patients receive the same outcomes as patients whose infection became resistant *de novo* because of treatment exposure.

#### Baseline resistance levels

Due to the comprehensiveness and quality of data collected, baseline pathogen resistance levels were sourced primarily from the 2019 ESPAUR report134; where required data were not available, the 2018 report135 was used as supplementary evidence.

The ESPAUR 2020 report39 was not used to parametrise the model for two reasons. Firstly, the rules for reporting of carbapenem resistance have changed in 2020, so that resistance levels in the latest ESPAUR report appear substantially lower than for the previous years; for example, areas such as Manchester with a high incidence rate have historically not submitted previous CRE data as testing is performed in house.39 Considerations will need to be made to how this data collection may impact the ability to utilise the ESPAUR report for future modelling purposes. Secondly, the COVID-19 pandemic means that 2020 data is likely to be an outlier, both due to limited healthcare capacity potentially affecting the reporting to PHE, and due to social distancing measures instituted at NHS hospitals potentially reducing the spread of bacterial, as well as viral infections.

The ATLAS surveillance data was used for the CAZ/AVI baseline resistance in the UK specifically.136 It was decided to use the 2018 UK values as those were in line with the 2018 EU values and the 2019 UK values were deemed to be unrealistically low.

Key model inputs related to baseline resistance are provided in Table 48. The model calculated the mean weighted resistance associated with each indication based on the baseline resistance for each pathogen provided in Table 49. Resistance was assumed not to differ by infection site.

Table 48. Baseline resistance to modelled treatments for each pathogen

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment (applicable indication)a** | **Pathogen** | | | **Source** |
| ***E. coli*** | ***Klebsiella spp.*** | ***P. aeruginosa*** |
| Piperacillin/tazobactam (cIAI & cUTI) | 8.89% | 14.62% | 6.57% | ESPAUR 2018-2019134 |
| Meropenem (cIAI, cUTI, HAP/VAP) | 0.09% | 0.87% | 6.87% | ESPAUR 2018-2019134 |
| Colistin (HAP/VAP) | 1.06% | 3.15% | 1.22% | ESPAUR 2018135 |
| CAZ/AVI (all indications) | 0.57% | 5.31% | 3.79% | ATLAS surveillance data 2018136 |
| cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP/VAP: hospital acquired pneumonia or ventilator-associated pneumonia  aPHE does not stratify by indication so baseline resistance assumed equal across indications | | | | |

### Loss of resistance

Following discussion with clinical and microbiology experts, the economic model includes two mechanisms included by which resistance to antimicrobials is lost: following successful treatment and due to selection pressure.

#### Loss of resistance following successful treatment

Following successful treatment, a proportion of patients can enter the susceptible health state, at which point they are no longer colonised or infected with the pathogen of interest, including resistant pathogens. The probability of successful treatment is determined by the efficacy of the antibiotic treatment received and the sensitivity of the pathogen. The economic model assumes that patients who are successfully treated receive a full course of treatment (see Table 53 in Section 4.3.1 for treatment durations) and then exit the treatment component of the model. All cost and QALY consequences occurring prior to cure because of infection are recorded.

The duration of unsuccessful treatment is assumed to be two days in all pathogens and indications where patients would move onto the next available treatment option. After this time, it is likely that the efficacy of a treatment in an individual patient will be known, and patients not responding to treatment would discontinue to a subsequent treatment line, if one is available. If no subsequent treatments are available, then patients have a probability of natural resolution of infection. As a simplifying assumption, the economic model assumes that patients who have exhausted all available antibiotic treatment options and fail to clear the infection naturally die three days after their last available treatment, in line with the published literature. During the Delphi panel, several clinicians stated that the assumption is reasonable and is observed in clinical practice; however, others noted that outcomes depend on several factors and may vary widely.129

#### Loss of resistance due to “fitness cost”

The second mechanism of resistance loss is as consequence of the microbiological concept termed “fitness cost”. Informed by expert opinion, mutations conferring antibiotic resistance can make the physiological processes in bacterial cells less effective, impacting the “fitness” of the microorganism, i.e., its ability to survive and replicate in a given environment. While in the presence of an antibiotic resistant strains have a clear competitive advantage over susceptible strains, when selection pressure from the antibiotic is removed (e.g., antibiotics are switched as part of a cycling treatment strategy), resistant pathogens lose their competitive advantage and, as potentially less “fit”, may be outcompeted by susceptible organisms. Consequently, resistant pathogens in colonised patients are assumed to gradually lose resistance at a fixed rate over time, with the rate of resistance loss proportional to the fitness cost.

### Baseline infection incidence

Table 49 presents the baseline distribution of patients across the susceptible, colonised and infected health states by pathogen and indication. These parameters were calculated based on published infection incidence data (Table 48). All infected patients were further stratified into infected with a resistant pathogen or infected with a susceptible pathogen, as described by baseline resistance values in Table 49.

It is assumed that no patients with HAP/VAP or cIAI are susceptible; instead, all patients are either colonised or infected. Per definition, HAP/VAP develops in a hospital and cIAI patients in need of antibiotic therapy were exposed to and likely colonised with pathogens during surgery.

Table 49. Baseline distribution of patients across susceptible, colonised, and infected health states

|  |  |  |  |
| --- | --- | --- | --- |
| **Indication/population** | **Pathogen** | | |
| ***E. coli*** | ***Klebsiella spp.*** | ***P. aeruginosa*** |
| **cUTI, %** | | | |
| Susceptible\* | 95.79% | 99.27% | 99.72% |
| Colonised | 4.09% | 0.68% | 0.26% |
| Infected | 0.118% | 0.049% | 0.024% |
| **cIAI, %** | | | |
| Susceptible\* | 0.00% | 0.00% | 0.00% |
| Colonised | 99.94% | 99.98% | 99.99% |
| Infected | 0.060% | 0.025% | 0.012% |
| **HAP/VAP, %** |  |  |  |
| Susceptible\* | 0.00% | 0.00% | 0.00% |
| Colonised | 99.84% | 99.94% | 99.97% |
| Infected | 0.157% | 0.064% | 0.031% |
| cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP/VAP: hospital acquired pneumonia or ventilator-associated pneumonia  \*Susceptible includes patients with no infection, or infected or colonised by pathogens not of interest  Note: The values were calculated from the model calibration. | | | |

### Transition parameters

The parameters governing transitions between the states of the disease transmission module were derived empirically through calibration to observed infection incidence and resistance data to ensure the model aligns to real-world resistance development and infection incidence. To this end, the model was fitted to published figures of infection prevalence, as reported by PHE132 and the Health Protection Agency130 (Table 50), and resistance development, as reported in the 2018135 and 2019134 ESPAUR reports (Table 51). Goodness of fit was assessed though minimising the sum of the mean absolute percentage errors for both resistance to piperacillin/tazobactam at first-line and infection prevalence simultaneously. For further details of the calibration process, see Section 5 of the Model Technical Report.137

Table 50. Infection incidence used to derive transition parameters

|  |  |  |
| --- | --- | --- |
| **Description** | **Value** | **Source** |
| ***E. coli*** | | |
| 12 month rolling rate of hospital-acquired E. coli bacteraemia (cases/100,000 bed days) | 22.57 | PHE (Fingertips)132 |
| New cases per day in a 500-bed hospital (cases/500 bed days) | 0.11 | Calculateda |
| New cases per model cycle (one month, multiply by 365.25/12) | 3.43 | Calculatedb |
| Of which, cUTI (17.2%) | 0.59 | Health Protection Agency130 |
| Of which, cIAI (8.8%) | 0.30 | Health Protection Agency130 |
| Of which, HAP/VAP (22.8%) | 0.78 | Health Protection Agency130 |
| ***Klebsiella spp.*** | | |
| 12 month rolling rate of hospital-acquired Klebsiella spp. bacteraemia (cases/100,000 bed days) | 9.29 | PHE (Fingertips)132 |
| New cases per day in a 500-bed hospital (cases/500 bed days) | 0.05 | Calculateda |
| New cases per model cycle (one month) | 1.41 | Calculatedb |
| Of which, cUTI (17.2%) | 0.24 | Health Protection Agency130130130 |
| Of which, cIAI (8.8%) | 0.12 | Health Protection Agency130 |
| Of which, HAP/VAP (22.8%) | 0.32 | Health Protection Agency130 |
| ***P. aeruginosa*** | | |
| 12 month rolling rate of hospital-acquired P. aeruginosa bacteraemia (cases/100,000 bed days) | 4.53 | PHE (Fingertips)132 |
| New cases per day in a 500-bed hospital (cases/500 bed days) | 0.02 | Calculateda |
| New cases per model cycle (one month) | 0.69 | Calculatedb |
| Of which, cUTI (17.2%) | 0.12 | Health Protection Agency130 |
| Of which, cIAI (8.8%) | 0.06 | Health Protection Agency130 |
| Of which, HAP/VAP (22.8%) | 0.16 | Health Protection Agency130 |
| cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP/VAP: hospital acquired pneumonia or ventilator-associated pneumonia  a 12-month rolling rate divided by 200 (100,000/500)  b new cases per day in 500-bed hospital\*365.25/12 | | |

Table 51. Resistance time series reported by ESPAUR134, used to derive transition parameters

|  |  |  |  |
| --- | --- | --- | --- |
| **Year** | ***E. coli*** | ***K. pneumoniae*** | ***Pseudomonas spp.*** |
| **Piperacillin/tazobactam** | | | |
| 2013 | 8.65% | 13.08% | 6.03% |
| 2014 | 8.97% | 13.55% | 6.88% |
| 2015 | 9.14% | 14.57% | 6.25% |
| 2016 | 8.94% | 13.35% | 6.54% |
| 2017 | 9.19% | 13.64% | 6.15% |
| 2018 | 8.89% | 14.62% | 6.57% |
| **Carbapenems** | | | |
| 2013 | 0.04% | 0.65% | 7.20% |

Clinical parameters impacting the treatment pathway component

### Treatment efficacy

In line with the ““Start Smart – Then Focus” approach8, patients in clinical practice are typically treated empirically with broad-spectrum antibiotics recommended in the local formulary. Treatment is reviewed once the causative pathogen and its antibiotic susceptibility are known, and may be switched, for example in cases of resistance to empirical treatment or where a narrower spectrum agent is preferable.

In the base case analysis, it was assumed that 80% of modelled patients initially receive empirical treatment. Patients who prove to be infected with a pathogen resistant to the empirical therapy move to a subsequent line of treatment (if one is available) that is effective against the infectious pathogen. The duration of unsuccessful treatment in the model is assumed to be 2 days for all pathogens and indications.26 Although in clinical practice ineffective treatment may be switched sooner, this simplifying assumption was validated by a panel of clinical and microbiology experts during model development and was confirmed as appropriate by the Delphi panel.129

The efficacy of modelled therapies against susceptible pathogens is listed in Table 52. The efficacy of treatment against resistant pathogens was assumed to be zero, and a 3% probability of the infection resolving naturally was assumed in this setting.

It is assumed that the remaining 20% of modelled patients are infected with a pathogen where susceptibility is known and receive directed treatment, meaning that they cannot receive an antibiotic to which the infectious pathogen is resistant. The main advantage of pathogen-directed treatment is the careful use of antibiotics, which limits the spread of AMR. In response to the growing recognition of the importance of pathogen-directed antimicrobial therapy, the proportion of patients receiving targeted treatment was varied in scenario analysis (see Section 4.8).

#### Treatment duration

The treatment of the infection is dependent on a number of patient-specific clinical markers, including general health, inflammatory markers, microbiological data and site of infection. Therefore, duration of treatment is strongly influenced by these factors. Hence, the duration of drug usage from the clinical trials is a better approximation of the real-world practice than what is described in the Summary of Product Characteristics. Indication-specific treatment durations associated with successful treatment were derived from clinical trials for CAZ/AVI and comparators, as presented in Table 53. The duration of treatment informs time spent in infected health states and bed occupancy. The duration of treatment was assumed not to vary by infectious pathogen. The model does not specifically account for time to appropriate therapy but the chosen treatment strategy can be considered a good approximation.

Table 52. Treatment efficacy

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indication/treatment** | **Treatment efficacy** | | | **Source** |
| ***E. coli*** | ***Klebsiella spp.*** | ***P. aeruginosa*** |
| **cUTI** | | | | |
| Piperacillin/tazobactam | 91.6% | 91.6% | 91.6% | Kaye et al.138 |
| Meropenem | 71.9% | 62.5% | 75.0% | RECAPTURE Clinical Study Report139 |
| CAZ/AVI | 78.4% | 75.0% | 66.7% | RECAPTURE Clinical Study Report139 |
| **cIAI** | | | | |
| Piperacillin/tazobactam | 82.4% | 82.4% | 82.4% | Tellado et al.140 |
| Meropenem | 87.4% | 75.5% | 94.4% | RECLAIM Clinical Study Report114 |
| CAZ/AVI | 80.4% | 78.4% | 85.7% | RECLAIM Clinical Study Report114 |
| **HAP/VAP** | | | | |
| Colistin | 75.0% | 75.0% | 75.0% | Kallel et al.141 |
| Meropenem | 80.0% | 74.6% | 38.3% | REPROVE Clinical Study Report113 |
| CAZ/AVI | 76.5% | 62.7% | 37.9% | REPROVE Clinical Study Report113 |
| cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP/VAP: hospital acquired pneumonia or ventilator-associated pneumonia | | | | |

Table 53. Treatment duration for successful treatment

|  |  |  |
| --- | --- | --- |
| **Indication/treatment** | **Treatment duration** | **Source** |
| **cUTI** | | |
| Piperacillin/tazobactam | 7.3 days | Harris et al.142 |
| Meropenem | 7.8 days | RECAPTURE Clinical Study Report139 |
| CAZ/AVI | 7.6 days | RECAPTURE Clinical Study Report139 |
| **cIAI** | | |
| Piperacillin/tazobactam | 7.3 days | Harris et al.142 |
| Meropenem | 8.3 days | RECLAIM Clinical Study Report114 |
| CAZ/AVI | 8.0 days | RECLAIM Clinical Study Report114 |
| **HAP/VAP** | | |
| Colistin | 9.5 days | Kallel et al.141 |
| Meropenem | 9.7 days | REPROVE Clinical Study Report113 |
| CAZ/AVI | 9.6 days | REPROVE Clinical Study Report113 |
| cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP/VAP: hospital acquired pneumonia or ventilator-associated pneumonia | | |

### Treatment-related adverse events: Clostridium difficile infection

As a simplifying assumption, the only adverse event included in the model was *Clostridium difficile* (*C. diff.)* infection, an opportunistic infection that may be associated with antimicrobial treatment. The probability of developing *C. diff* infection (Table 54) was applied in the model only whilst patients were receiving treatment and was assumed to be equivalent across treatments.

Patients with a *C. diff* infection incur additional treatment- and length of stay-related costs, as well as a utility decrement representing the reduction in quality of life due to this opportunistic infection (Table 58). All *C. diff* infections are assumed to be treated successfully and incur no additional risk of mortality.

Table 54. Incidence of *C. diff* infection

|  |  |  |
| --- | --- | --- |
| **Indication/treatment** | **Incidence (%)** | **Source** |
| **cUTI** | | |
| Piperacillin/tazobactam | 0.10% | RECAPTURE Clinical Study Report139 |
| Meropenem | 0.10% |
| CAZ/AVI | 0.10% |
| **cIAI** | | |
| Piperacillin/tazobactam | 0.19% | RECLAIM Clinical Study Report114 |
| Meropenem | 0.19% |
| CAZ/AVI | 0.19% |
| **HAP/VAP** | | |
| Colistin | 0.12% | REPROVE Clinical Study Report113 |
| Meropenem | 0.12% |
| CAZ/AVI | 0.12% |
| cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP/VAP: hospital acquired pneumonia or ventilator-associated pneumonia | | |

### Mortality

Patients in the infected health state experience a risk of death associated with bacterial infection, described using a daily probability of mortality that differs by infection site (Table 55). Patients whose treatment is unsuccessful have a higher daily probability of death compared with successfully treated patients. The on-treatment risk of mortality is therefore influenced by the efficacy of a patient’s current treatment regimen (i.e., treatment success or treatment failure) and treatment duration.

As mentioned in Section 4.2.1.1, patients who are unsuccessfully treated, have exhausted all available antibiotic treatment options, and fail to clear the infection naturally are assumed to die three days after their last available treatment as a result of their infection. Patients who die incur additional bed days and costs associated with death. Mortality also results in a QALY loss corresponding to the discounted life expectancy of a successfully treated patient.143-145 Additionally, the economic model is able to assess the number of deaths avoided as well as infections cleared.

Patients who are successfully treated are subject to a daily mortality rate, derived from ONS144,145, associated with the average age of a patient for each indication from NHS hospital activity data146 (cUTI: mean age 73 years; cIAI: mean age 53 years; HAP/VAP: mean age 66 years). The mortality rate is consistent with the general population.

Table 55. Daily mortality rates

|  |  |  |
| --- | --- | --- |
| **Indication/treatment** | **Daily death rate** | **Source** |
| **cUTI** | | |
| Successful treatment | 0.0059% | ONS statistics144,145  NHS hospital activity^146 |
| Unsuccessful treatment | 0.30% | REPRISE Clinical Study Report\*113 |
| **cIAI** | | |
| Successful treatment | 0.0009% | ONS statistics144,145  NHS hospital activity^146 |
| Unsuccessful treatment | 0.33% | RECLAIM Clinical Study Report\*114 |
| **HAP/VAP** | | |
| Successful treatment | 0.0030% | ONS statistics144,145  NHS hospital activity^146 |
| Unsuccessful treatment | 1.40% | REPROVE Clinical Study Report\*113 |
| cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP/VAP: hospital acquired pneumonia or ventilator-associated pneumonia  \* Calculated based on data available in the source  ^ Used to inform the average age of a patient for each indication where cUTI is based on the definition "Urinary tract infection, site not specified", cIAI is based on a weighted average of "Other specified bacterial intestinal infections" and "Bacterial intestinal infection, unspecified" and HAP/VAP is based on a weighted average of "Pneumonia due to *K. pneumoniae*", "Pneumonia due to *Pseudomonas*" and "Pneumonia due to *E. coli*" | | |

## Measurement and valuation of health effects

As mentioned in Section 3.5.3, no HRQoL data was collected in the CAZ/AVI clinical trials, largely due to the challenges associated with administering HRQoL questionnaires to acutely ill patients. Therefore, published utility values were used in the model; these were specific to each infection site. For non-infected patients, age-matched general population utility was used, with the average age of patients experiencing cUTI, cIAI, and HAP/VAP based on NHS hospital activity data146. Patients who die due to infection were assumed to lose QALYs corresponding with the quality-adjusted life expectancy of the general population.

As mentioned in Section 4.3.2, the only adverse event included in the model was opportunistic *C. diff.* infection. Since a specific disutility associated with *C. diff.* infection was not identified, the disutility for diarrhoea was used as a proxy, calculated as the average disability weight across European countries for which data was reported in Mathers et al.147 This decrement is applied for any additional length of stay associated with *C. diff.* infection.

All utility and disutility values used within the economic model are summarised in Table 56.

Table 56. Utility values used in the economic model

|  |  |  |
| --- | --- | --- |
| **Indication** | **Utility value** | **Source** |
| cUTI – not infected (mean age 73 years146) | 0.78 | York CHE143 |
| cUTI – infected | 0.68 | Ernst et al.148 |
| cIAI – not infected (mean age 53 years146) | 0.85 | York CHE143 |
| cIAI – infected | 0.60 | Brasel et al.149 |
| HAP/VAP – not infected (mean age 66 years146) | 0.78 | York CHE143 |
| HAP/VAP – infected | 0.58 | Beusterien et al.150 |
| Disutility associated with *C. difficile* infection\* | 0.106 | Mathers et al.151 |
| CHE: centre for health economics; cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP/VAP: hospital acquired pneumonia or ventilator-associated pneumonia | | |

## Cost and healthcare resource use identification, measurement and valuation

Within the model, costs and resource use are only applied to patients in the infected health state. Three categories of costs are considered: costs associated with antibiotic treatment, hospitalisation costs, and costs associated with *C. diff* infection. All costs are accrued over the modelled time horizon (10 years in the base case) and are discounted at a 3.5% annual rate.

### Antibiotic treatment costs

Daily antibiotic treatment costs (Table 57) are applied for the duration of treatment specified in Table 53 in Section 4.3.1. Patients may incur costs associated with multiple treatments, dependent on whether empirical treatment is successful. In contrast, administration costs were not included since the patients were treated for the underlying disease with non-antimicrobial therapies already.87

Table 57. Daily antibiotic treatment costs

|  |  |  |
| --- | --- | --- |
| **Indication/treatment** | **Treatment cost (daily)** | **Source** |
| Piperacillin/tazobactam | £7.73 | eMIT\*152 |
| Meropenem | £5.60 | eMIT\*152 |
| Colistin | £16.20 | BNF\*153 |
| Metronidazole | £0.78 | eMIT\*152 |
| \*Calculated based on information available in the BNF and eMIT (March 2021) | | |

The EEPRU protocol specifies that the drug acquisition cost for CAZ/AVI is excluded from the calculation of population Net Health Effects, as the purpose of the evaluation work is to inform a value-based payment for CAZ/AVI. Therefore, we did not include the costs for CAZ/AVI in the NMB calculation.

### Clostridium difficile infection

The cost associated with *C. diff.* infection included the cost of treating the infection with vancomycin (Table 58) and additional length of stay (LOS). It was assumed that patients with *C. diff.* infection receive a 10-day course of oral vancomycin, at 125 mg administered every 6 hours, and remain on the ward for the duration of this treatment. The cost of treatment and additional LOS associated with *C. diff.* infection is applied as a one-off cost.

Table 58. Cost of *C. diff.* infection

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Input** | **Source** |
| Treatment duration | 10 days | Median duration from the BNF153 |
| Vancomycin treatment cost (per 10-day course of treatment) | £55.14 | eMIT\*152 |
| Additional LOS - cUTI | £4,513.40 | National Schedule of NHS costs 2018-2019154 |
| Additional LOS - cIAI | £4,326.20 | National Schedule of NHS costs 2018-2019154 |
| Additional LOS – HAP/VAP | £5,091.60 | National Schedule of NHS costs 2018-2019154 |
| \*Calculated based on information available in eMIT (March 2021)  For the National Schedule of NHS codes used to calculate additional LOS please see the technical report137 | | |

### Length of stay

Costs from the National Cost Collection were used to calculate the daily costs of hospital stay on a general ward.154 The per-day cost of cUTI was assumed to be equivalent to the weighted average NHS reference cost of non-elective short stay associated with kidney or urinary tract infections with/without interventions (LA04H to LA04S). The per-day cost of cIAI was assumed equivalent to the weighted average NHS reference cost of non-elective short stay associated with gastrointestinal infections with/without interventions (FD01A to FD01J). This conservative approach likely leads to an underestimation of the cost impact on the system, as experts highlight that these patients will likely require surgical drainage often involving an emergency laparotomy; however, this is independent of type of antimicrobial therapy applied so the incremental effect is expected to be very minor. The per-day cost of HAP/VAP was assumed equivalent to the weighted average NHS reference cost of non-elective short stay associated with bronchopneumonia with/without interventions (DZ23H to DZ23N).

It was assumed that patients with cUTI and cIAI receive treatment on a general ward. Expert opinion stated that critical patients are transferred to the ICU. For HAP/VAP, the patients with VAP are treated in the ICU while patients with HAP are treated on a general ward, and the model calculates a weighted average cost based on the proportions of patients with VAP and HAP. Again, this is a potential underestimation of the costs incurred, as experts verified that a proportion of patients with HAP is treated in the ICU setting. Of note, patients were assumed to be treated in either the general ward or ICU; interim settings between general ward and ICU, such as high dependency units, were not considered in the model. The proportion of HAP/VAP patients with VAP (as opposed to pneumonia not associated with mechanical ventilation) was 35.5%, based on an US survey of healthcare-associated infections including 12,299 patients in 199 hospitals155. The daily cost of stay in an ICU was calculated based on the weighted average NHS reference cost of non-specific, general adult critical care patient, 0-2 organs supported (XC05Z-XC07Z).

Daily costs of hospital stay are summarised in Table 59.

Table 59. Daily cost for additional length of stay

|  |  |  |
| --- | --- | --- |
| **Indication** | **Cost (£ per day)** | **Source** |
| cUTI | £451.34 | National Schedule of NHS costs 2018-2019154 |
| cIAI | £432.62 | National Schedule of NHS costs 2018-2019154 |
| HAP | £509.16 | National Schedule of NHS costs 2018-2019154 |
| Percentage of HAP/VAP patients with VAP | 35.5% | Magil, et al. 2018155 |
| VAP (ICU stay) | £1,315.26 | National Schedule of NHS costs 2018-2019154 |
| cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP: hospital acquired pneumonia; ICU: intensive care unit; VAP: ventilator-associated pneumonia | | |

### Cost of death

As mentioned in Sections 4.2.1.1 and 4.3.3, patients who have exhausted all available antibiotic treatment options and fail to clear the infection naturally are assumed to die from infection 3 days after their last available treatment. cUTI and cIAI patients incur the daily general ward cost (Table 59) for the relevant indication for 3 days of hospital stay, while the costs of HAP/VAP is the weighted average cost of general ward and ICU stay, with VAP patients (35.5% as per Table 59) assumed to incur ICU stay costs.

## Summary of base-case analysis inputs and assumptions

Key model inputs used in the base case analysis are summarised in Table 60 and the key assumptions are summarised in Table 61.

The assumptions were validated by external experts previously when the model was developed initially.26 A Delphi panel was conducted to verify or update the model assumptions with a focus on specific assumptions that have the most impact in the model.129

Table 60. Summary of model inputs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | | | **Value** | **Section** |
| **Model settings** | Annual cost discount rate | | 3.5% | 4.1.3 |
| Annual benefit discount rate | | 3.5% |
| Disease transmission horizon | | 10 years |
| **Baseline parameters** | Life expectancy post treatment success - cUTI | | 13.8 years | 4.3.3 |
| Life expectancy post treatment success - cIAI | | 30.3 years |
| Life expectancy post treatment success – HAP/VAP | | 19.2 years |
| QALY expectancy post treatment success - cUTI | | 10.76 QALYs |
| QALY expectancy post treatment success - cIAI | | 25.75 QALYs |
| QALY expectancy post treatment success – HAP/VAP | | 14.95 QALYs |
| Baseline incidence of E. coli infection - cUTI | | 0.118% | 4.2.3 |
| Baseline incidence of E. coli infection - cIAI | | 0.060% |
| Baseline incidence of E. coli infection – HAP/VAP | | 0.157% |
| Baseline incidence of K. pneumoniae infection – cUTI | | 0.049% |
| Baseline incidence of K. pneumoniae infection – cIAI | | 0.025% |
| Baseline incidence of K. pneumoniae infection –HAP/VAP | | 0.064% |
| Baseline incidence of P. aeruginosa infection – cUTI | | 0.024% |
| Baseline incidence of P. aeruginosa infection – cIAI | | 0.012% |
| Baseline incidence of P. aeruginosa infection – HAP/VAP | | 0.031% |
| Baseline resistance for piperacillin/tazobactam – E.coli | | 8.89% | 4.2.1.1161 |
| Baseline resistance for piperacillin/tazobactam – K. pneumoniae | | 14.62% |
| Baseline resistance for piperacillin/tazobactam – P. aeruginosa | | 6.57% |
| Baseline resistance for meropenem – E.coli | | 0.09% |
| Baseline resistance for meropenem – K. pneumoniae | | 0.87% |
| Baseline resistance for meropenem – P. aeruginosa | | 6.87% |
| Baseline resistance for colistin – E.coli | | 1.06% |
| Baseline resistance for colistin – K. pneumoniae | | 3.15% |
| Baseline resistance for colistin – P. aeruginosa | | 1.22% |
| Baseline resistance for CAZ/AVI – E.coli | | 0.57% |
| Baseline resistance for CAZ/AVI – K. pneumoniae | | 5.31% |
| Baseline resistance for CAZ/AVI – P. aeruginosa | | 3.79% |
| **Efficacy** | Percentage of patients with known resistance status | | 20% | 4.3.1 |
| Efficacy of piperacillin/tazobactam in cUTI – all pathogens | | 91.6% |
| Efficacy of piperacillin/tazobactam in cIAI – all pathogens | | 82.4% |
| Efficacy of colistin in HAP/VAP – all pathogens | | 75.0% |
| Efficacy of meropenem in cUTI ­­– E coli. | | 71.9% |
| Efficacy of meropenem in cUTI ­­– K. pneumoniae | | 62.5% |
| Efficacy of meropenem in cUTI ­­– P. aeruginosa | | 75.0% |
| Efficacy of meropenem in cIAI ­­– E coli. | | 87.4% |
| Efficacy of meropenem in cIAI ­­– K. pneumoniae | | 75.5% |
| Efficacy of meropenem in cIAI ­­– P. aeruginosa | | 94.4% |
| Efficacy of meropenem in HAP/VAP ­­– E coli. | | 80.0% |
| Efficacy of meropenem in HAP/VAP ­­– K. pneumoniae | | 74.6% |
| Efficacy of meropenem in HAP/VAP ­­– P. aeruginosa | | 38.3% |
| Efficacy of CAZ/AVI in cUTI ­­– E coli. | | 78.4% |
| Efficacy of CAZ/AVI in cUTI ­­– K. pneumoniae | | 75.0% |
| Efficacy of CAZ/AVI in cUTI ­­– P. aeruginosa | | 66.7% |
| Efficacy of CAZ/AVI in cIAI ­­– E coli. | | 80.4% |
| Efficacy of CAZ/AVI in cIAI ­­– K. pneumoniae | | 78.4% |
| Efficacy of CAZ/AVI in cIAI ­­– P. aeruginosa | | 85.7% |
| Efficacy of CAZ/AVI in HAP/VAP ­­– E coli. | | 76.5% |
| Efficacy of CAZ/AVI in HAP/VAP ­­– K. pneumoniae | | 62.7% |
| Efficacy of CAZ/AVI in HAP/VAP ­­– P. aeruginosa | | 37.9% |
| Duration of successful therapy- piperacillin/tazobactam -cUTI | | 7.3 days |
| Duration of successful therapy- piperacillin/tazobactam cIAI | | 7.3 days |
| Duration of successful therapy - colistin – HAP/VAP | | 9.5 days |
| Duration of successful therapy - meropenem - cUTI | | 7.8 days |
| Duration of successful therapy - meropenem – cIAI | | 8.3 days |
| Duration of successful therapy - meropenem – HAP/VAP | | 9.7 days |
| Duration of successful therapy – CAZ/AVI - cUTI | | 7.6 days |
| Duration of successful therapy – CAZ/AVI – cIAI | | 8.0 days |
| Duration of successful therapy – CAZ/AVI – HAP/VAP | | 9.6 days |
| Duration of unsuccessful therapy ­– all treatments and indications | | 2 days |
| Patients starting empirical therapy | | 95% |
| Patients starting targeted therapy | | 5% |
| Probability of clearing infection naturally - all indications | | 3% |
| Daily mortality rate – successful treatment - cUTI | | 0.0059% | 4.3.3 |
| Daily mortality rate – successful treatment - cIAI | | 0.0009% |
| Daily mortality rate – successful treatment – HAP/VAP | | 0.0030% |
| Daily mortality rate – unsuccessful treatment - cUTI | | 0.30% |
| Daily mortality rate – unsuccessful treatment - cIAI | | 0.33% |
| Daily mortality rate – unsuccessful treatment – HAP/VAP | | 1.40% |
| Adverse event rates | C diff. infection | | 4.3.2 |
| cUTI – all treatments | 0.10% |
| cIAI – all treatments | 0.19% |
| HAP/VAP – all treatments | 0.12% |
| **Utilities** | Not infected | cUTI | 0.78 | 4.4 |
| cIAI | 0.85 |
| HAP/VAP | 0.78 |
| Infected | cUTI | 0.68 |
| cIAI | 0.60 |
| HAP/VAP | 0.58 |
| Disutility associated with C diff. infection | 0.106 |  |  |
| **Costs** | Daily antibiotic treatment costs | Piperacillin/tazobactam | £7.73 | 4.5.1 |
| Meropenem | £5.60 |
| Colistin | £16.20 |
| Metronidazole (for cIAI: in combination with CAZ/AVI) | £0.78 |
| Hospital stay costs per day | cUTI (general ward) | £451.34 | 4.5.3 |
| cIAI (general ward) | £432.62 |
| HAP (general ward) | £509.16 |
| VAP (ICU) | £1,315.26 |
| Proportion of HAP/VAP patients with VAP | 35.5% |
| Adverse event costs associated with C diff. infection | Vancomycin treatment (10 days) | £55.14 | 4.5.2 |
| Additional LOS - cUTI | £4,513.40 |
| Additional LOS - cIAI | £4,326.20 |
| Additional LOS – HAP/VAP | £5,091.60 |
| Costs of death | cUTI | £3,945.78 | 4.5.4 |
| cIAI | £3,945.78 |
| HAP/VAP | £3,945.78 |

Table 61. Key model assumptions

|  |  |  |  |
| --- | --- | --- | --- |
| **Assumption** | **Justification** | **Validated by Delphi panel (Y/N)\*** | **Conclusion from Delphi panel** |
| **General** | | | |
| Homogeneous health states meaning that the patient is in one specific health state at any given time | Model simplification | N |  |
| **Colonisation/Infection** | | | |
| Deaths from the susceptible and colonised health states are not explicitly captured by the model and it is assumed that these are incorporated through patient discharges | Incidence and prevalence of infections and their impact on costs, benefits and mortality are the primary outcome assessed by the model | N |  |
| Patients who are discharged from the infectious environment are not re-admitted | Model simplification required due to assumption of homogeneous health states | Y | No consensus was reached but the split opinions support an underestimation of the assumption. |
| Patients who die as a result of infection are able to cause infection in other patients for one additional cycle | Pathogens may still be present in the environment after death; assumption made to prevent underestimation of resistance development in patients who died as a result of infection | Y | Verbal consensus that this is a possibility but that the probability is relatively low. |
| The number of admission and discharges are equal resulting in constant occupancy | Model simplification | N |  |
| All patients are colonised or infected with a pathogen associated with cIAI and HAP/VAP. | Informed by Tlaskalová-Hogenová et al.156 | Y | Consensus reached verifying this assumption |
| cUTI patients lose colonisation following successful treatment | Informed by Tlaskalová-Hogenová et al.156 | Y | Consensus was not reached with the comment from some panellist that this would depend on whether the patient has a device or not. The model assumptions are an underestimation. |
| Only infections and colonisations associated with pathogen and indication of interest are considered | Model simplification | N |  |
| All infections are considered to be resolved within one model cycle, i.e. all patients are either cured of their infection or have died within one month of initial infection | Model simplification | Y | Consensus reached that monthly cycle length is appropriate. |
| Infected patients resistant to their current antibiotic treatment regimen or having exhausted all treatment options have a probability of naturally clearing their infection while on treatment; sensitive pathogens are subject only to the efficacy of the treatment. | Treatment efficacy is derived from trial data and likely to include natural clearances, adding probabilities of cure due to treatment and natural clearance would potentially result in double counting in pathogens sensitive to the current treatment regimen. | Y | Verbal consensus that this is a possibility but that the probability is relatively low. |
| Transmission between the colonised and susceptible health states has been restricted when the number of individuals in the colonised health state exceeds the number of individuals in the susceptible health state | Model requirement to ensure inappropriate inputs do not produce nonsensical results (e.g. negative patient prevalence) | N |  |
| Patients may not move directly between different colonised health states (e.g. Xw -> XR1) | Model simplification | N |  |
| Patients may not move directly between different infected health states (e.g. Iw -> IR1) | Model simplification | N |  |
| Patients colonised with a resistant pathogen (e.g. R1) may become infected through contact with a patient infected with a pathogen with a different resistance status (e.g. R2); in this case, the newly infected patient becomes infected with the pathogen acquired through contact with the infected patient (R2). | Model simplification | N |  |
| **Resistance** | | | |
| Patients colonised and not infected with resistant pathogen may lose resistance | Exposure to treatment puts selection pressure benefitting resistance-giving mutations; removing this selection pressure promotes non-resistant pathogens outcompeting resistant pathogen strains | N |  |
| Rate of resistance loss is less in patients with MDR | The potential presence of multiple resistance-giving mutations makes it less likely that all resistance giving mutations are lost in a given model cycle | N |  |
| **Treatment** | | | |
| Duration for successful treatment involves a full course of antibiotic treatment | Validated by experts | N |  |
| Duration for unsuccessful treatment is less than a full course of antibiotic treatment; assumed to be two days before treatment is switched | Unsuccessful treatment will become apparent before the full course of antibiotic treatment is complete | Y | Consensus reached that treatment is switched or escalated two days after unsuccessful antibiotic therapy. |
| Patients are hospitalised for the entire duration of treatment | Majority of treatments of interest are given by IV infusion and was validated by experts | N |  |
| Patients who have exhausted all their antibiotic treatment options and fail to clear the infection naturally are assumed to die 3 days after their last treatment dose | The prognosis of patients who have no available treatment options is very poor. This assumption as validated by experts. | Y | No consensus was reached but the split opinions support an underestimation of the assumption. |
| Different dosing regimens of the same antibiotic are not considered with respect to cost, treatment duration of efficacy | Model simplification | N |  |
| Treatment of *C. diff*. infection is assumed to be effective in all cases and there is no associated risk of mortality as a result of C. diff infection. | Model simplification | N |  |
| 80% of patients receive empirical therapy, while in 20% antimicrobial susceptibility is known and the treatment is targeted | Prompt empirical therapy is aligned with PHE guidance; however, the importance of pathogen-directed treatment is increasingly recognised, 135and it was considered important to include it in the model | Y | The Delphi panel statement included a value of 5% in the first and 15% in the second round with the majority of the panellists stating that was still too low and that it would be in the range of 20% or 25%. |
| **Costs and utilities** | | | |
| Costs and health benefits are only recorded for patients who have acquired an infection | Incidence and prevalence of infections and their impact on costs, benefits and mortality are the primary outcome assessed by the model | N |  |
| No general cost for IV infusion | Model simplification | N |  |
| General ward costs for *C. diff.* is the same as the indication of which *C. diff*. was acquired | Assumption | N |  |
| Patients with cUTI, cIAI and HAP are assumed to be hospitalised on a general ward, while patients with VAP are assumed to be hospitalised in an ICU. | Model simplification | Y | No consensus was reached for cUTI, cIAI, and HAP patients but the split opinions support an underestimation of the assumptions since a portion of patients are treated in an ICU.  A consensus was reached for the VAP patients being treated in an ICU. |
| Cost of hospital bed days for HAP/VAP calculated as a weighted average of reference costs for intensive care and general wards; this assumption applies only to costs and has no impact on patient quality of life or length of stay | Model simplification | N |  |
| cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection; HAP/VAP: hospital-acquired pneumonia or ventilator-associated pneumonia; ICU: intensive care unit; IV: intravenous.  \* Note: The Delphi panel was conducted to verify/update the assumptions made earlier but allowed only a limited number of questions. The results are presented in a report.129 | | | |

## Base-case results

The resulting base-case NMB estimate a cost per QALY threshold of £30,000 was £598,779,222 combined for the three indications cUTI, cIAI, and HAP/VAP combined for the 10-year time horizon at a national level for England.

Base-case results are summarised in Table 62 for cUTI, cIAI, and HAP/VAP. This includes life years and QALYs lost due to infection as well as the NMB when evaluating the diversity approach using CAZ/AVI compared with the setting without CAZ/AVI. Additionally, the predicted number of patients eligible for treatment to CAZ/AVI, deaths, and number of infections cleared are displayed.

Without CAZ/AVI, the model predicted a loss of 11,426 discounted life years due to cUTI, corresponding to a loss of 8,921 discounted QALYs over the 10-year horizon when scaled to the national population level of England. The use of CAZ/AVI within the all-lines diversity antimicrobial stewardship strategy used in this economic model predicted a gain of 7,090 life-years and 5,529 QALYs, where the total number of life-years lost due to infection in a scenario with CAZ/AVI was 4,337, corresponding to 3,392 QALYs.

For cIAI, the model predicted an infection-associated discounted loss of 7,561 life-years and 6,434 QALYs, respectively, in a scenario without CAZ/AVI. Introducing CAZ/AVI within a diversity strategy predicted a gain of 5,585 discounted life-years, corresponding to 4,747 discounted QALYs.

The greatest clinical benefits of CAZ/AVI were realised in HAP/VAP. Without CAZ/AVI, discounted life-year loss due to infection was estimated at 25,992 life years, equivalent to 20,302 discounted QALYs. Introducing CAZ/AVI within a diversity strategy predicted a gain of 13,093 discounted life-years (10,211 discounted QALYs), where the total loss of life due to infection was 12,899 discounted years (10,090 discounted QALYs) with CAZ/AVI.

In total, the model predicts that 2,181 deaths can potentially be avoided within 10 years when using CAZ/AVI in the modelled diversity setting with 30,689 patients being eligible for the treatment. Furthermore, an additional 4,412 infections can be cleared if CAZ/AVI is used. These numbers are expected to be an underestimate of the true benefit, given that the focus of the economic model was on specific indications and pathogens.

Table 62 provides clinical and economic results and Table 63 provides a detailed cost breakdown of results for each indication.

Table 62. Base case analysis results from a single hospital with a constant infectious environment of 1,000 patients scaled to 93,432 beds occupied over a 10-year horizon by indication

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LYs lost due to infection** | **QALYS lost due to infection** | **Incremental costs (£)^** | **Incremental LYs lost due to infection** | **Incremental QALYS lost due to infection** | **NMB\*** | **Patients eligible for CAZ/AVI** | **Deaths** | **Infections cleared** |
| **cUTI** | | | | | | | | | |
| CAZ/AVI | 4,337 | 3,392 | 9,034,972 | -7,090 | -5,529 | £156,835,028 | 11,417 | 456 | 23,049 |
| No CAZ/AVI | 11,426 | 8,921 | 0 | 1,192 | 20,083 |
| **cIAI** | | | | | | | | | |
| CAZ/AVI | 1,975 | 1,687 | 827,252 | -5,585 | -4,747 | £141,582,748 | 5,086 | 121 | 10,809 |
| No CAZ/AVI | 7,561 | 6,434 | 0 | 471 | 10,459 |
| **HAP/VAP** | | | | | | | | | |
| CAZ/AVI | 12,899 | 10,090 | 5,968,554 | -13,093 | -10,211 | £300,361,446 | 14,185 | 1,069 | 27,249 |
| No CAZ/AVI | 25,992 | 20,302 | 0 | 2,164 | 26,153 |
| **All indications above combined** | | | | | | | | | |
| CAZ/AVI | 19,211 | 15,169 | 15,830,778 | -25,768 | -20,487 | £598,779,222 | 30,689 | 1,645 | 61,107 |
| No CAZ/AVI | 44,979 | 35,657 | 0 | 3,826 | 56,695 |
| ^Please note that the acquisition costs for CAZ/AVI are not included.  \*at cost per QALY threshold of £30,000  AMS: antimicrobial stewardship; cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP: hospital acquired pneumonia; NMB: net monetary benefit; QALY: quality-adjusted life year; VAP: ventilator-associated pneumonia | | | | | | | | | |

Table 63. Base case analysis cost breakdown from a single hospital with a constant infectious environment of 1,000 patients scaled to 93,432 beds occupied over a 10-year horizon

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **No CAZ/AVI** | | | **CAZ/AVI within a diversity AMS strategy** | | |
| **cUTI** | **cIAI** | **HAP/VAP** | **cUTI** | **cIAI** | **HAP/VAP** |
| **Treatment cost** | | | | | | |
| Piperacillin/tazobactam (Colistin for HAP/VAP) | £880,772 | £419,740 | £2,901,737 | £442,982 | £174,802 | £1,383,418 |
| Meropenem | £103,126 | £97,225 | £264,942 | £238,002 | £139,529 | £393,948 |
| CAZ/AVI\* | £0 | £0 | £0 | £0 | £22,765\* | £0 |
| **Hospitalisation costs** | | | | | | |
| Cost of hospitalisation | £59,814,061 | £31,075,460 | £180,304,629 | £71,634,057 | £33,264,119 | £191,352,608 |
| **Death** | | | | | | |
| Cost of death | £4,004,984 | £1,579,766 | £7,262,779 | £1,509,543 | £404,355 | £3,584,496 |
| \* For cIAI used in combination with metronidazole  AMS: antimicrobial stewardship; cIAI: complicated intraabdominal infections; cUTI: complicated urinary tract infection; HAP: hospital acquired pneumonia; QALY: quality-adjusted life year; VAP: ventilator-associated pneumonia | | | | | | |

## Scenario analyses

As discussed in Section 4.2.4, model inputs describing infection transmission dynamics and resistance development were derived empirically through calibration, in line with recommendations from the EEPRU evaluation framework. As a result of this approach, no estimates of uncertainty or covariance are produced that would enable robust sensitivity analyses, preventing probabilistic sensitivity analyses. Therefore, scenario analyses were conducted to analyse the impact of specific parameters upon variation. The following scenarios were explored where key parameters of the base case analysis were varied:

* scenarios using different literature-derived values of baseline CAZ/AVI resistance (varying the baseline resistance from Table 48 by ± 20%)
* scenarios varying the percentage of patients receiving targeted treatment (15% and 25%, respectively)
* 3-year time horizon

The annual NMB and annual clinical outcomes related to additional infections cleared, deaths avoided and patients eligible for CAZ/AVI therapy based on the uncertainty analysis shows minor variation across the majority of scenarios where the largest variation comes from the 3-year time horizon scenario. Results are displayed in Figure 14, Figure 15 and Figure 16.

Chart, bar chart

Description automatically generated

Figure 14.Annual NMB outcomes based on the uncertainty analysis on key model parameters; cost per QALY threshold of £30,000.

Chart, bar chart

Description automatically generated with medium confidence

Figure 15. Clinical outcomes based on the uncertainty analysis on key model parameters; proportional increase in infections cleared and proportional reduction in deaths.

**Chart, bar chart

Description automatically generated**

Figure 16. Clinical outcomes based on the uncertainty analysis on key model parameters; patients eligible for CAZ/AVI therapy

To further analyse the impact of variation of model parameters, scenarios were explored where the following parameters in the base case scenario were varied by +/- 10%:

* Baseline resistance
* Infection incidence
* Treatment efficacy
* Treatment/hospital duration
* Rate of death
* Costs
* Utilities
* Inputs related to *C.diff* infections
* Inputs related to disease transmission parameters
* Patients with known resistance status

A scenario was also included to explore the impact of varying the discount rate on costs and benefits at 1.5% and 5%.

The majority of scenarios demonstrated a small influence on the base case NMB, suggesting the base case results are relatively stable as shown in the tornado diagrams in Figure 17 for a cost per QALY threshold of £30,000, respectively. Key drivers within the model giving the biggest influence on NMB is the treatment efficacy as expected but additionally discounting, utility, life expectancy and various inputs related to the disease transmission parameters. The baseline resistance when varied by 10% is not having a big influence on NMB though it needs to be noted that the baseline resistance of the various treatment including for CAZ/AVI are not high. If the baseline resistance of the antimicrobials increases in the future the impact on NMB will be higher.

Diagram

Description automatically generated with medium confidence

Figure . Tornado diagram based on uncertainty analysis – NMB at a £30,000 cost per QALY threshold

## Validation

The model has been subjected to extensive external validation exercises to demonstrate the scientific rigour, relevance and value of the model in the context of real-world evidence. External validation exercises compared outputs from the model to publicly available data not used to construct the disease transmission component, to verify the accuracy of projections for resistance. This validation has been extensively described in the supplementary material to the previous publication using this model26, which is provided as an appendix to this submission.

Recognising that epidemiological data used in the model have been updated since the previous validation, we have conducted additional validation exercises for the purpose of this submission.129

## Interpretation and conclusions of economic evidence

### Conclusion on economic evidence

The analyses presented in this submission are based on a validated, published, population-based disease transmission and cost-effectiveness model26. The model captures the key broad indications of CAZ/AVI, complementing the analyses proposed in the EEPRU protocol for this technology appraisal87. Briefly, EEPRU suggests focusing on two key HVCSs, due to limited time and resources available for the appraisal. These scenarios are very specific, with one scenario focused on empirical therapy in clinically urgent HAP/VAP with a high risk of infection with a resistant pathogen, and the other scenario on cUTI caused by CPE susceptible to CAZ/AVI. These scenarios pose areas where CAZ/AVI may be used in the immediate future, or is currently used within NHSE, but do not capture the full range of current, or potential, use of CAZ/AVI being available to NHSE patients. The analyses presented in this submission are therefore complimentary to those expected to be performed by EEPRU, demonstrating the value of CAZ/AVI in a much broader population of patients, aligned with good stewardship practice, that encompasses the three largest approved indications, cUTI, cIAI, and HAP/VAP. It must however be recognised that there may also be other areas where CAZ/AVI may have a significant impact, including the LTO indication, where the greatest value is expected. This has not been explicitly or fully captured in the base case.

Following the submission, the company will also finalise further analyses with a focus on insurance value of CAZ/AVI and aim to make these available during the appraisal process.

Insurance value of antibiotics has been described in a number of ways.4,35,87 However, largely two common themes occur; (1) The value of a new antibiotic in mitigating the rise of resistance, and (2) the impact of potentially catastrophic situation(s), but having antibiotics available to limit or mitigate this impact, the “fire-engine” analogy. The Pfizer base case economic model captures, in part, the first of these two definitions as outlined in Section 4.6. However, with a lack of literature and modelling to estimate the impact of antibiotics to the healthcare system in preventing or mitigating other probable events, Pfizer is conducting an additional analysis to help quantify the additional insurance value by modelling a number of future probabilistic events through a Monte Carlo analysis. Actuarial approaches consistent with how these risks would be analysed in an insurance context157 were applied, although possibly novel to the healthcare system with respects to medicinal value, these are well founded approaches when considering insurance in other contexts or industries158 and directly transferable in this context. This includes, identifying relevant risk events and their range of quantifiable impacts and direct costs to the NHS. Model parameters and assumptions are being identified by both literature reviews and expert elicitation, including relevant key opinion leaders across the NHS (clinical and operational) and health economic fields. This enables the modelling of the frequency of occurrence and the severity of the impact of each risk event, using distributions commonly used for extreme events.159

Initial early analysis, which focuses exclusively on the direct costs to the healthcare providers, already demonstrates significant value to NHSE, both in being able to understand the overall costs of each event to the NHSE, and the level of mitigation attributable to CAZ/AVI for each scenario. Once finalised a report will be shared with NICE and EEPRU to help inform future modelling considerations and support the committee in determining the overall expected value of CAZ/AVI to NHS England.

The company would also like to highlight the impact of enablement value not captured within the economic model. Pfizer continues to explore the impact antibiotics have in the enabling of other settings (i.e., enabling surgical procedures and chemotherapy). This analysis was not discussed within this submission; however, Pfizer expects additional value to be quantifiable and intends to publish any findings.

Combined, the company and EEPRU analyses should aim to capture the value of CAZ/AVI to NHSE as comprehensively as possible.

### Strengths of the modelling approach

The strengths of the modelling approach include capturing several novel value aspects, aligned to those outlined in the EEPRU protocol, including:

* Extensive assessment of diversity value through capturing different antimicrobial stewardship approaches
* Transmission value, i.e. population benefits obtained due to reduced infection spread

The model has been published and underwent rigorous scrutiny of peer review. It has also been extensively validated, increasing the confidence in model predictions. Initial model development was guided by close cooperation with a panel of clinical, microbiology, and health economics experts, who validated all modelling assumptions and were consulted throughout the development process to validate that the model indeed behaves as expected. When updating and adapting the model for the present submission, the company conducted a Delphi panel to re-validate the model against a broader expert group and the current AMR and infection treatment landscape. Undoubtedly, such thorough validation should reduce the uncertainty associated with model outputs and is in line with the NICE and EEPRU requirement to conduct expert elicitation. Additionally, the model not only uses strong trial data but includes UK-specific costs and epidemiological information.

The majority of scenarios demonstrated a small influence on the base case NMB, suggesting the base case results are relatively stable as shown in the tornado diagrams with the key driver being treatment efficacy, in line with expectations.

### Imperfection of the modelling approach

EEPRU and the committee should be aware that the although the company model is relatively comprehensive, still it significantly underestimates the full value of CAZ/AVI, in that it does not capture all indications / usage for CAZ/AVI nor all the value elements outlined by EEPRU:

* It has particularly limited ability to explore the highly heterogenous LTO indication, in which highest QALY gains may be expected.
* While the increased costs associated with VAP are captured, the outcomes of HAP/VAP are analysed together and the model does not permit the two indications to be explored separately. This is an important limitation because, while VAP prevention remains an important goal in NHS hospitals, the burden of non-VAP HAP is also substantial67.
* Furthermore, the model includes only a handful of the pathogens against which CAZ/AVI is effective and does not capture spectrum value. The current model assumes a constant size of the infectious environment and is not suitable to assess the insurance value of CAZ/AVI in a setting of preventing or managing outbreaks. Relevant analyses on insurance value are currently being conducted by the company, with an aim to provide these later in the appraisal process.
* Enablement value is only partially captured within the model. Outcomes such as prophylactic antimicrobial use, gains in hospital capacity and the enablement of procedures that would otherwise be foregone were not explored in the current model. However, some of its elements were included implicitly, as patients infected after surgical and medical procedures fell within the modelled population.

The model approximates the patient’s treatment journey which involves providing the most appropriate antibiotic therapy as soon as the cause of the severe infection is identified. In reality, it is known that treating patients for CRE with piperacillin/ tazobactam would be inappropriate, but this has been used to simulate the time to appropriate and effective therapy where, in clinical practice, a number of other antimicrobials may be used to poor effect while susceptibility results are pending.

The treatment pathway incorporated in the model is restricted to a maximum of three antimicrobials, whereas in clinical practice many more antimicrobial agents could be in use within a hospital. There is an inherent difficulty in determining which comparator antimicrobials should be modelled, because antimicrobial use is heterogenous, depending on local stewardship guidelines, risk factors for resistance (empirical treatment), and known susceptibility results (pathogen-directed therapy). The modelled comparator selection was based on clinical expert opinion and captures only part of the antimicrobial treatment landscape within NHSE. This simplified landscape reflects the pragmatism required to develop a robust model including the most clinically relevant therapies in the empirical and confirmed/suspected resistance settings.

As transmission parameters could not be directly sourced due to lack of available data and were instead derived based on expert opinion, probabilistic sensitivity analysis would not be appropriate to measure uncertainty associated with these parameters. Although considered a technical limitation, the model instead allows uncertainty to be explored deterministically through scenario analyses.

Despite value being underestimated, the presented core model demonstrates significant value to the NHS and represents an important first step in quantifying the wider value of antibiotics to the population, A crucial part of informing a future value assessment that is aimed to reinvigorate antibiotic development and create a sustainable market model.

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# List of appendices

In line with the user guide for company evidence submission template, appendices start at B, because document A is the main submission.

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| --- | --- | --- |
| **Appendix number** | **Appendix Title** | **Location** |
| B | B1 SmPC  B2 EPAR | Provided as a separate document |
| C | Identification, selection and synthesis of clinical evidence | No clinical SLR was conducted |
| D | Subgroup analysis | Provided in the main body of the report |
| E | Adverse reactions | Provided in the main body of the report |
| F | Published cost-effectiveness studies: systematic literature review | No CE SLR was conducted |
| G | Health-related quality-of-life studies: systematic literature review | No HRQoL SLR was conducted |
| H | Cost and healthcare resource identification: | No cost and healthcare use SLR was conducted |
| I | Clinical outcomes and disaggregated results from the model | Provided in the main body of the report |
| J | Checklist of confidential information | Not required |
| K | Cost-effectiveness model technical report | Provided as a separate document |
| L | Delphi panel report | Provided as a separate document |
| M | Economic model | Provided as a separate document |

1. **Note**: Due to COVID-19, data reported in the ESPAUR 2019-20 report will not be referenced in both clinical and economic summaries as well as the economic model. [↑](#footnote-ref-2)