Relebactam in combination with imipenem and cilastatin for the treatment of drug resistant Gram-negative infections

LAY SUMMARY

Hospital acquired infections: including hospital acquired pneumonia, ventilator associated pneumonia, complicated urinary tract infections and complicated intra-abdominal infections are serious infections and a huge problem for the NHS. They prolong patients’ stay in hospital and increase health costs. These infections are frequently caused by Gram negative bacteria that are becoming increasingly resistant to commonly prescribed antibiotics and are a serious global concern.

If licensed, relebactam in combination with imipenem/cilastatin will offer a treatment option for those patients who have acquired a serious infection caused by multi-drug resistant and carbapenem resistant Gram-negative bacteria.

NIHR HSRIC ID: 8075
TARGET GROUP

Multi-drug resistant and carbapenem resistant Gram-negative bacteria: including hospital acquired pneumonia (HAP), ventilator associated pneumonia (VAP), complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI), documented imipenem-resistant infections and empirical therapy where drug resistance is suspected - first or second line.

DESCRIPTION

Relebactam (MK-7655) is a beta-lactamase inhibitor active against class A and C beta-lactamases, which are a family of enzymes produced by some bacteria that can cause resistance to several widely used beta-lactam antibiotics, such as penicillins, cephalosporins and carbapenems. The combination of a beta-lactamase inhibitor with a beta-lactam antibiotic may help to overcome the problem of antibiotic resistance. A high proportion of hospital acquired infections are caused by antibiotic resistant bacteria such as multi-drug resistant Gram-negative bacteria. Gram negative bacteria are becoming increasingly resistant to existing antimicrobials. Most concerning is the evolution of extended-spectrum beta-lactamase producing Enterobacteriaceae, as well as multi-drug resistant *Pseudomonas aeruginosa*.

Relebactam is administered in a fixed dose combination (MK-7655A) with the carbapenem antibiotic imipenem, a beta-lactam bacterial cell wall inhibitor, and cilastatin, a cyclopropane that inhibits the human enzyme dehydropeptidase, thereby prolonging the antibacterial effect of imipenem. In preclinical studies, relebactam in combination with imipenem/cilastatin demonstrated antibacterial activity against a broad range of Gram-negative and beta-lactamase producing pathogens. The addition of relebactam may restore the clinical activity of imipenem against certain multi-drug resistant strains of Gram-negative bacteria, including *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae carbapenemase* (KPC) producing *Enterobacteriaceae*.

In phase III clinical trials, participants were treated with 500mg imipenem/cilastatin in combination with 250mg relebactam administered intravenously (IV) as a fixed dose combination every 6 hours for a minimum of 5 days, and up to 14 days.

Relebactam is not currently licensed in the EU for any indication. Imipenem/cilastatin is licensed in the EU for the treatment of the following infections in adults and children 1 year of age and above: cIAI, severe pneumonia including HAP and VAP, intra- and post-partum infections, cUTI, complicated skin and soft-tissue infection, neutropenic fever, and bacteraemia associated with any of the infections listed above. Common adverse effects include: eosinophilia, thrombophlebitis, diarrhoea, vomiting, nausea, rash (e.g. exanthematous), increases in serum transaminases and increases in serum alkaline phosphatase.

INNOVATION and/or ADVANTAGES

If licensed, relebactam in combination with imipenem/cilastatin will offer a treatment option for those patients who have acquired a serious infection caused by multi-drug resistant and carbapenem resistant Gram-negative bacteria. For many patients with these infections, current treatment options are severely limited and represent salvage therapy.

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* Company provided information.
DEVELOPER

Merck Sharp & Dohme (MSD).

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Hospital acquired infections (HAI) are frequently caused by highly resistant pathogens and need to be treated with broad-spectrum antibiotics. HAI are defined by the World Health Organization as infections developing after 48 hours of hospitalisation or stay at a healthcare facility, which were not present at the time of admission. HAI are serious infections and a major problem for the NHS. They prolong patients’ stays in hospital and increase mortality, morbidity, and cost. In adults urinary tract infections are the most common healthcare-associated infections; whereas in children, bloodstream infections, pneumonia and urinary tract infections are the most common healthcare-associated infection.

Hospital acquired pneumonia (HAP) occurs after a hospital stay of at least 48 hours. This form of pneumonia can be very severe and life-threatening due to the patients’ underlying illness and frailty, and the resistant nature of the pathogens.

Ventilator associated pneumonia (VAP) is a hospital associated pneumonia that occurs 48 hours or more after tracheal intubation. Early onset VAP occurs within 4 days of intubation and mechanical ventilation, and is often caused by bacteria that remain sensitive to first line antibiotic therapy, whereas late onset VAP develops after 4 days and is often caused by multi-drug resistant pathogens.

Complicated intra-abdominal infections (cIAI) are commonly encountered in general surgery. In cIAI, the infection progresses from the organ and affects the peritoneum, causing intra-abdominal abscesses. CIAI can also result from surgery-associated infection, trauma or spontaneous perforation. The pathogens most frequently encountered in cIAI are the Gram-negative bacteria Escherichia coli, other common Enterobacteriaceae (i.e. Proteus spp. or Klebsiella spp.), Pseudomonas aeruginosa and Bacteroides fragilis. Second or third generation cephalosporins in combination with metronidazole, beta-lactam antibiotics (such as penicillins) in combination with beta-lactamase inhibitors and carbapenems are commonly used for treating cIAI. However, increasing resistance to commonly prescribed antimicrobial agents is a serious global concern.

Complicated urinary tract infections (cUTI) are a frequent cause of hospital admissions and healthcare associated complications. The most common pathogen encountered in cUTI are the Gram-negative bacteria Escherichia coli, other common Enterobacteriaceae (i.e. Klebsiella spp. or Citrobacter spp.) and Pseudomonas spp. Successful treatment remains a challenge due to the majority of pathogens in cUTI showing multi-drug resistance.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to the following Department of Health policy area:
CLINICAL NEED and BURDEN OF DISEASE

Around one in eleven patients admitted to hospital acquires a HAI. There are at least 100,000 hospital infections a year, which cost the NHS hundreds of millions of pounds annually. The English National Point Prevalence Survey 2011 reported that 6.4% of inpatients in acute care hospitals had a healthcare-associated infection. More than 80% of all healthcare-associated infections were pneumonia and other respiratory infections (23%). Other commonly reported infections were urinary tract infections (17%), surgical site infections (16%), clinical sepsis (11%), gastrointestinal infections (9%), and bloodstream infections (7%).

Approximately 1.5% of hospital inpatients in England have a hospital-acquired respiratory infections, and more than half of these (at least 7,000 people) have HAP (excluding infection associated with intubation). HAP is estimated to increase hospital stays by 8 days and has a mortality of between 30 and 70%. VAP is the most common and fatal infection in the intensive care unit. Approximately 10-28% of critical care patients will develop VAP and around 86% of HAP is linked with mechanical ventilation. VAP occurs in 9-27% of mechanically ventilated patients with approximately 5 cases per 1,000 ventilator days. This results in increasing patient length of stay by 28% and increasing health costs by £6,000 to £22,000 for each incidence of VAP. Infection with Pseudomonas aeruginosa accounts for 12% of all reported cases of VAP, and is reported to have imipenem resistance rates of around 20%, a drug considered to be first-line therapy for this indication.

Complicated intra-abdominal infections have reported mortality rates as high as 25%. The 2015 English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report found that overall, antibiotic resistant organisms continue to increase.

The population likely to be eligible to receive relebactam in combination with imipenem/cilastatin could not easily be estimated from available routine published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

Horizon Scanning Research & Intelligence Centre

- NICE advice. Three-day courses of antibiotics for uncomplicated urinary tract infection (KTT10) January 2015.

Other Guidance


CURRENT TREATMENT OPTIONS

HAI are frequently caused by highly resistant pathogens that need treatment with broad-spectrum antibiotics (such as: extended-spectrum penicillins, third-generation cephalosporins, aminoglycosides, carbapenems, linezolid, vancomycin, teicoplanin, or colistin), as recommended by British Society of Antimicrobial Chemotherapy guidance.

It is very important to initiate antibiotics as soon as possible after diagnosis, and the choice should be guided by careful consideration of patient specific factors, such as severity of illness, duration of hospital stay, and previous antibiotic exposure. In addition, local epidemiology should be considered in line with good antimicrobial surveillance.

Current treatment options for HAP or VAP may include antibiotic therapy, oxygen, and ventilator support. The choice of agent for initial antibiotic therapy will depend on the likelihood of infection with multi-drug resistant pathogens. Late onset pneumonia (>5 days stay in hospital) has a significantly greater risk for being caused by multi-drug resistant bacteria and therefore requires combination antibiotic therapy. This may include an anti-pseudomonal cephalosporin, carbapenem or penicillin administered in combination with an anti-pseudomonal fluoroquinolone, aminoglycoside, or a beta-lactamase inhibitor. In contrast, for early onset pneumonia (<5 days stay in hospital), antibiotic monotherapy may be adequate using an appropriate cephalosporin, quinolone, or extended-spectrum penicillin. Generally, with effective treatment, improvements will be seen within 42 to 72 hours. Antibiotics can be safely discontinued after 7 days if signs and symptoms improve (such as a reduction in C reactive protein, white cell count and temperature alongside a clinical improvement and an improvement in oxygenation).

The major goals of VAP management are early, appropriate antibiotics in adequate doses followed by de-escalation based on microbiological culture results and the clinical response of the patient. There is no clear consensus, but many experts will continue antibiotic treatment for 14-21 days, although 7 days of antibiotic therapy may be adequate in many cases.

The management of cUTIs includes the removal of indwelling catheters, if possible, and antibiotic therapy. These infections (including acute pyelonephritis) are frequently caused by Gram-negative bacteria and according to European Association of Urology Guidelines, second or third generation cephalosporins, beta-lactam antibiotics (e.g. penicillins) in...
combination with beta-lactamase inhibitors and quinolones are often used for treating cUTIs\textsuperscript{12}.

Effective management of cIAIs requires early diagnosis, appropriate surgical intervention and broad-spectrum antimicrobial treatment. Empirical antibiotic treatment with single or combination agent is recommended after considering the severity of infection, taking into account whether the infection is community or healthcare-associated, and local antibiotic resistance patterns. Guidelines state that bacteriological cultures often have little impact on the course of treatment and are not necessary for all patients\textsuperscript{10}.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>RESTORE-IMI 2, NCT02493764, MK-7655A-014, EudraCT2015-000246-34; imipenem/cilastatin in combination with relebactam vs piperacillin and tazobactam; phase III.</th>
<th>RESTORE-IMI 1, NCT02452047, MK-7655A-013, EudraCT2015-000066-62; imipenem/cilastatin/relebactam vs colistimethate sodium (colistin) + imipenem/cilastatin; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Merck Sharp &amp; Dohme Corp.</td>
<td>Merck Sharp &amp; Dohme Corp.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{4}.</td>
<td>Trial registry\textsuperscript{21}.</td>
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<tr>
<td>Location</td>
<td>EU (not UK), USA and other countries.</td>
<td>EU (not UK), and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=536 (planned); age ≥18 years old; treatment with IV antibiotic therapy for hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP); fulfills clinical and radiographic criteria, with onset of criteria occurring after &gt;48 hrs of hospitalisation or within 7 days after discharge from a hospital (for HABP), or at least 48 hrs after mechanical ventilation (for VABP); adequate baseline lower respiratory tract specimen obtained for Gram stain and culture; infection known or thought to be caused by microorganisms susceptible to the IV study therapy; no baseline lower respiratory tract specimen Gram stain that shows the presence of Gram-positive cocci only; no confirmed or suspected community-acquired bacterial pneumonia (CABP); no confirmed or suspected pneumonia of viral, fungal or parasitic origin; no HABP/VABP caused by an obstructive process, including lung cancer or other known obstruction; no carcinoid tumor or carcinoid syndrome; no active immunosuppression defined as either receiving immunomodulatory medications or having a medical condition associated with immunodeficiency; no concurrent condition or infection that would preclude evaluation of therapeutic response; no effective antibacterial drug therapy for the</td>
<td>n=64 (planned); age ≥18 years old; hospitalisation that requires treatment with IV antibiotic therapy for a new, persistent or progressing bacterial infection involving at least 1 of 3 primary infection types (HABP/VABP, cIAI, or cUTI); positive culture data from the primary infection-site specimen collected within 1 week of study entry. At least one of the suspected causative pathogens from the specimen meets all of the following: identified as a Gram-negative bacterium, culture-confirmed imipenem resistance (and colistin resistance for group 3 only), culture-confirmed susceptibility to imipenem/relebactam and to colistin (for groups 1 and 2 only); no concurrent infection that would interfere with evaluation of the response to the study antibiotics; no treatment with any form of systemic colistin for &gt;24 hrs within 72 hrs before initiation of study drug (for groups 1 and 2 only); no HABP or VABP caused by an obstructive process; no cUTI which meets: complete obstruction of any portion of the urinary tract, known ileal loop, intractable vesico-ureteral reflux, presence of an indwelling urinary catheter which cannot be removed at study entry; no allergy, hypersensitivity, or any serious reaction to listed antibiotics (per-protocol); no concurrent endocarditis, osteomyelitis, meningitis,</td>
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</table>
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<table>
<thead>
<tr>
<th>Index infection of HABP/VABP for more than 24 hrs continuously, during the previous 72 hrs; no serious allergy, hypersensitivity or a serious reaction to any penicillin or beta-lactamase; no seizure disorder requiring ongoing prior treatment with anti-convulsive therapy within the last 3 yrs.</th>
<th>Prosthetic joint infection, disseminated fungal infection, or active pulmonary tuberculosis; not currently undergoing hemodialysis; no seizure disorder requiring ongoing prior treatment with anti-convulsive therapy within the last 3 yrs.</th>
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<tbody>
<tr>
<td><strong>Schedule</strong></td>
<td>Randomised to Group 1: imipenem+cilastatin/relebactam; participants will be stratified by infection type (HABP/VABP, cIAI, and cUTI) and will receive imipenem and cilastatin/relebactam at (200mg/100mg to 500mg/250mg depending on renal function) IV once every 6 hrs and placebo for colistimethate sodium IV infusion once every 12 hrs for 5 to 21 days for cIAI and cUTI or for 7 to 21 days for HABP or VABP. Group 2: colistimethate sodium + imipenem+cilastatin; participants will be stratified by infection type (HABP/VABP, cIAI, and cUTI) and will receive colistimethate sodium (CMS) (colistimethate base activity 300mg (~720mg CMS)) IV loading dose, followed by colistimethate base activity 75mg to 150mg (~180 to 360mg CMS) depending on renal function IV infusion once every 12 hrs and imipenem+cilastatin (200mg to 500mg depending on renal function) IV infusion once every 6 hrs for 5 to 21 days for cIAI and cUTI or for 7 to 21 days for HABP or VABP. Group 3: Imipenem+cilastatin/relebactam; participants with documented imipenem-resistant and colistin-resistant bacterial infections will receive open-label imipenem and cilastatin/relebactam (200mg/100mg to 500mg/250mg depending on renal function) IV infusion once every 6 hrs for 5 to 21 days for cIAI and cUTI or for 7 to 21 days for HABP or VABP.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment 7 to 14 days and follow-up to day 28.</td>
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<tr>
<td>Primary outcome/s</td>
<td>% surviving at day 28.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Favourable clinical response at early follow up visit (up to 16 days after end of therapy).</td>
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<table>
<thead>
<tr>
<th>Expected reporting date</th>
<th>March 2018 (final data collection date for primary outcome measure).</th>
<th>April 2017 (final data collection date for primary outcome measure).</th>
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<tbody>
<tr>
<td><strong>Trial</strong></td>
<td>NCT01506271, MK-7655-004, EudraCT2011-005686-20; MK-7655 vs placebo, both with imipenem/cilastatin; phase II.</td>
<td>NCT01505634, MK-7655-003, EudraCT2011-005707-32; MK-7655 vs placebo, both with imipenem/cilastatin; phase II.</td>
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<td><strong>Status</strong></td>
<td>Completed.</td>
<td>Completed</td>
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<td><strong>Design</strong></td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td><strong>Participants</strong></td>
<td>n=351; age ≥18 years old; clinically suspected and/or bacteriologically documented cIAI requiring hospitalisation and treatment with IV antibiotic therapy. Enrolled intraoperatively or postoperatively on the basis of operative findings or enrolled preoperatively on the basis of compelling preoperative clinical findings; no infection which should be managed by staged abdominal repair (STAR) or open abdomen technique; no APACHE II score &gt;30; no effective antibiotic therapy after obtaining the culture for admission to this study and prior to the administration of the first dose of IV study therapy; no infection treated with &gt;24 hrs with systemic antibiotic; no serious allergy, hypersensitivity (e.g. anaphylaxis), or any serious reaction to carbapenem antibiotics, any cephalosporins, penicillins, or other β-lactam agents; no seizure disorder requiring ongoing treatment with anticonvulsive therapy or prior treatment with anti-convulsive therapy in the last 3 yrs; not currently receiving immunosuppressive therapy, including use of high-dose; no estimated or actual creatinine clearance of &lt;50 mL/minute.</td>
<td>n=302; age ≥18 years old; clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis judged by the investigator to be serious (requiring hospitalisation and treatment with IV antibiotic therapy); pyuria, determined by a midstream clean-catch (MSCC) or catheterised urine specimen with ≥10 white blood cells (WBCs) per high-power field on standard examination of urine sediment or ≥10 WBCs/mm³ in unspun urine; 1 positive urine culture within 48 hrs of enrollment; no complete obstruction of any portion of the urinary tract; no temporary indwelling urinary catheter that cannot be removed at study entry; no uncomplicated UTI; no history of recent accidental trauma to the pelvis or urinary tract; no infection treated with &gt;24 hrs with systemic antibiotic therapy known to be effective against the presumed or documented pathogen(s) within the 72 hr period immediately prior to consideration for the study; no serious allergy, hypersensitivity (e.g. anaphylaxis), or any serious reaction to other beta-lactam inhibitors (e.g. tazobactam, sulbactam, clavulanic acid); not currently being treated with valproic acid or has received treatment with valproic acid in the 2 wks prior to screening.</td>
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<tr>
<td>Schedule</td>
<td>Randomized to MK-7655, 250mg or 125mg; or placebo. All given IV in combination with imipenem/cilastatin 500mg every 6 hrs for 5 to 14 days.</td>
<td>Randomised to MK-7655 250mg with imipenem/cilastatin 500mg, MK-7655 125mg with imipenem/cilastatin 500mg or placebo to MK-7655 (normal saline 0.9%) with imipenem/cilastatin 500mg; all given IV every 6 hrs for a minimum of 96 hrs. After at least 96 hrs of IV treatment, participants may be switched, at the discretion of the investigator, to 500mg ciprofloxacin, administered orally, twice daily.</td>
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<tr>
<td>Follow-up</td>
<td>4 to 14 days post initiation of IV drug with early follow-up to day 9 following end of treatment; late follow-up to day 42 following end of treatment.</td>
<td>42 days follow-up.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Favourable clinical response at completion of study therapy; % elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory values that are greater than or equal to 5x the upper limit of normal ULN (up to 14 days following completion of study therapy); % elevated AST or ALT laboratory values that are greater than or equal to 3x the ULN, as well as elevated total bilirubin greater than or equal to 2x the ULN, and alkaline phosphatase values that are less than 2x the ULN (up to 14 days following completion of study therapy); % with any AE (up to 14 days following completion of study therapy); % with any serious adverse event (SAE) (up to 42 days following completion of all study therapy); % with any drug-related AE (up to 14 days following completion of all study therapy); % with any SAE and drug-related AE (up to 42 days following completion of all study therapy); % who discontinued IV study therapy due to an AE (up to 14 days post initiation of IV study therapy); discontinued IV study therapy due to a drug-related AE (up to 14 days post initiation of IV study therapy); specific AEs, system organ class or pre-defined limit of change with incidence of ≥4 participants in one treatment group (up to 14 days following completion of all study therapy).</td>
<td>Favourable microbiological response at completion of study therapy (up to post randomisation day 14); % elevated AST or ALT laboratory value ≥5x the upper limit of normal (ULN) (up to 14 days following completion of all study therapy); % elevated AST or ALT laboratory values ≥3x the ULN, as well as elevated total bilirubin ≥2x the ULN, and alkaline phosphatase values ≤2x the ULN (up to 14 days following completion of all study therapy); % any adverse event (AE); any SAE (up to 42 days following completion of all study therapy); any drug-related AE (up to 14 days following completion of all study therapy); any SAE and drug-related AE (up to 42 days following completion of study therapy); discontinued IV study therapy due to an AE (up to 14 days post initiation of IV study therapy); discontinued IV study therapy due to a drug-related AE (up to 14 days post initiation of IV study therapy); specific AEs, system organ class or pre-defined limit of change with incidence of ≥4 participants in one treatment group (up to 14 days following completion of all study therapy).</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Favourable clinical response at completion of study therapy in participants who have imipenem-resistant, Gram-negative cIAI infections; favourable clinical response at early follow-up; favourable microbiological response at completion of study therapy; favourable microbiological response at early follow-up; favourable clinical response at late follow-up; favourable microbiological response at late follow-up.</td>
<td>Favourable microbiological response at completion of study therapy who have imipenem-resistant, Gram-negative cUTIs (up to post-randomisation day 14); favourable microbiological response at early follow-up (up to 9 days following completion of all study IV and oral therapy); favourable clinical response at completion of study therapy (up to post-randomisation day 14); favourable clinical response at early</td>
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follow-up (up to 9 days following completion of all study IV and oral therapy); favourable clinical response at late follow-up (up to 42 days following completion of all study IV and oral therapy); favourable microbiological response at late follow-up (up to 42 days following completion of all study IV and oral therapy).

**Key results**

Favourable clinical response at the end of therapy was similar across treatment groups: relebactam 250mg (96.3%) (n=83), relebactam 125mg (98.8%) (n=87) and placebo (95.2%) (n=85).

**Adverse effects (AEs)**

The most common AEs (nausea, diarrhea and vomiting) occurred at similar rates across treatment groups: relebactam 250mg (6.8%, 6.0%, 6.0%), relebactam 125mg (7.8%, 6.0%, 7.8%) and placebo (7.0%, 4.4%, 2.6%).

**Expected reporting date**

August 2014 (final data collection date for primary outcome measure). July 2015 (final data collection date for primary outcome measure).

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**ESTIMATED COST and IMPACT**

**COST**

The cost of relebactam is not yet known. However, imipenem/cilastatin is already licensed and marketed in the UK; a single vial of 500mg/500mg powder for reconstitution costs £12.0024.

**IMPACT - SPECULATIVE**

- **Impact on Patients and Carers**
  - ☑ Reduced mortality/increased length of survival
  - ☑ Reduced symptoms or disability
  - ☐ Other:
    - ☐ No impact identified

- **Impact on Health and Social Care Services**
  - □ Increased use of existing services
  - □ Decreased use of existing services
  - □ Need for new services
  - ☑ None identified
  - □ Re-organisation of existing services
  - □ Other

- **Impact on Costs and Other Resource Use**
  - ☑ Increased drug treatment costs
  - ☑ Reduced drug treatment costs
  - □ Other increase in costs
  - ☑ Other reduction in costs: company believes there is the potential to reduce costs associated with patient monitoring and the treatment of adverse events (when compared to colistin)\(^b\).
  - □ Other:
    - □ None identified

\(^b\) Company provided information.
Other: expert opinion states it is very hard to know how to advise clinicians on when to suspect that patients may be suffering from infections with relevant resistant pathogens. In addition, when there is a microbiological diagnosis of a carbapenem resistant bacterium, it takes time to find out what the exact mechanism may be, and if this agent is used empirically then it may actually not be necessary and would incur unnecessary additional costs.

Clinical uncertainty or other research question identified: expert opinion states there are a number of competitor agents either available or in development which work on the same principle and it will be difficult for clinicians to decide which one to use. Another issue is that many clinicians moved away from using imipenem/cilastatin to other carbapenems (mainly meropenem) because of perceptions that the side effect profile of imipenem/cilastatin was not as good (mainly because it is a combination of agents).

REFERENCES