20 September 2018
EMA/CHMP/700663/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vabomere

International non-proprietary name: meropenem / vaborbactam

Procedure No. EMEA/H/C/004669/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AM	Alveolar Macrophages
AmpC hyper	AmpC hyperproducer
ANOVA	Analysis of variance
AP	Acute Pyelonephritis
AST	Antimicrobial susceptibility testing
AUC0-inf	Area under the plasma concentration-time curve from time zero to infinity
AUC0-8	Area under the plasma concentration-time curve from 0 to 8 hours
AUC0-24	Area under the concentration-time curve from 0 to 24 hours
AUC0-t	Area under the plasma concentration-time curve time zero to the last measurable concentration
AUC:MIC	Area under the concentration-time curve (AUC) to MIC
AVI	Avibactam
AZT	Aztreonam
BAL	Bronchoalveolar Lavage
BAT	Best Available Therapy
BLI	Beta-lactamase inhibitor
BSA	Body surface area
CAMHB	Cation-adjusted Mueller-Hinton broth
CAZ	Ceftazidime
CEP	Certificate of Suitability of the European Pharmacopoeia
CDC	Center for Disease Control and Prevention
CFU	Colony forming units
CI	Confidence Interval
cIAI	Complicated intra-abdominal infections
CLcr	Creatinine clearance
CLd	Distributional clearance
CLnr	Non-renal clearance
CLR	Renal clearance
CLSI	Clinical and Laboratory Standards Institute
CLt	Plasma clearance
Cmax	Maximum drug concentration
CRE	Carbapenem-Resistant Enterobacteriaceae
cUTI	Complicated Urinary Tract Infection
CV%	Percent coefficient of variation
CYP450	Cytochrome P450
DSC	Differential Scanning Calorimetry
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration
ELF	Epithelial Lining Fluid
Emax	Sigmoid maximum reduction
EOIVT	End of intravenous treatment
EOT	End of treatment
ESBLs	Extended-spectrum beta-lactamases
ESRD	End-stage renal disease
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
fe0-8	Percentage of dose excreted in the urine over 8 hours
FL	Full-length
FME	Frequencies of mutant emergence
g	Grams
GC-FID	Gas Chromatography- Flame Ionization Detector

GENT	Gentamicin
HABP/HAP	Hospital Acquired (Bacterial) Pneumonia
HDPE	high density polyethylene
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation
ICP-OES	Inductively coupled plasma - optical emission spectrometry
IIV	Inter-individual variability
IMI	Imipenem
IPCs	in-process controls
IR	InfraRed spectroscopy
IV	Intravenous
Ki	Inhibition constant
KPC	Klebsiella pneumoniae carbapenemase
LDPE	low-density polyethylene
LFU	Late follow-up
LS	Least squares
MAD	Multiple-ascending dose
MBL	Metallo-β-lactamase
MDRD	Modification of diet in renal disease
ME	Microbiologically Evaluable
MER	Meropenem
MER-VAB	Meropenem-vaborbactam
MIC	Minimum inhibitory concentrations
MIC50	Lowest concentration of the antibiotic at which 50% of the isolates were inhibited
MIC90	Lowest concentration of the antibiotic at which 90% of the isolates were inhibited
MINO	Minocycline
m-MITT	Microbiological modified intent-to-treat
n	Number of observations
N/A	Not available
NMT	not more than
OAT	Organic anion transport
PAE	Post-antibiotic effect
PBPs	Penicillin-binding proteins
PD	Pharmacodynamic
PDE	permitted daily exposure
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PK-PD	Pharmacokinetic-pharmacodynamic
PLIE	Post-β-lactamase-inhibitor effect
P. mirabilis	Proteus mirabilis
PSD	Particle size distribution
P/T	Piperacillin/tazobactam
q8h	Every 8 hours
QC	Quality control
ΔΔQTcF	Placebo-corrected, change-from-baseline QTcF
RH	relative humidity
RV	Residual variability
SAD	Single ascending dose
SD	Standard Deviation
%SEM	Standard error of the mean (percent standard error of the mean)
Ser130	Serine 130
SLC	Solute Carrier
SmPC	Summary of Product Characteristics

%T>MIC	Percent of dosing interval that free plasma drug [meropenem] concentrations exceed the indicated meropenem-vaborbactam MIC
T1/2	Half-life
TGA	Thermogravimetric Analysis
TOC	Test of cure
UTI	Urinary tract infection
UV	Ultra Violet spectrometry
USP	United States Pharmacopoeia
VAB	Vaborbactam
VABP/VAP	Ventilator Acquired (Bacterial) Pneumonia
Vc	Volume of distribution of the central compartment
Vp	Volume of distribution of the peripheral compartment
Vd	Volume of distribution
WFI`	Water for injections
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Rempex London Ltd submitted on 21 April 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Vabomere, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2016.

The applicant applied for the following indication: Vabomere is indicated for the treatment of the following infections in adults:

- Complicated urinary tract infection (cUTI), including pyelonephritis
- Complicated intra-abdominal infection (cIAI)
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Vabomere is also indicated for the treatment of infections due to bacterial organisms in adult patients with limited treatment options.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0229/2015 and P/0230/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0229/2015 and P/0230/2015 were not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance vaborbactam contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	date	Area
EMA/H/SA/2485/2/2013/SME/II	3 April 2013	the scientific advice pertained to clinical aspects
EMA/H/SA/2485/3/2014/SME/III	25 April 2014	the scientific advice pertained to pharmaceutical, nonclinical and clinical aspects

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: Filip Josephson

The application was received by the EMA on	21 April 2017
The procedure started on	13 July 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 September 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	29 September 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	11 October 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 March 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	30 April 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	31 May 2018

The applicant submitted the responses to the CHMP List of Outstanding Issues on	31 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	30 August 2018
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 September 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vabomere on	20 September 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Vabomere is proposed by the applicant to be indicated for the treatment of the following infections in adults:

- Complicated urinary tract infection (cUTI), including pyelonephritis
- Complicated intra-abdominal infection (cIAI)
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Vabomere is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

2.1.2. Epidemiology

The types of infections to be treated are commonplace, except for those due to organisms that are resistant to multiple classes of antibacterial agents, which are discussed below. Acute pyelonephritis may result from an ascending uncontrolled bladder infection or may be haematogenous, while complicated UTIs are usually associated with anatomical abnormalities or foreign bodies placed in the tract, such as catheters and renal stents. Complicated IAIs are common infections encountered in general surgery and have been estimated to be responsible for 20% of all severe sepsis episodes in the intensive care unit. Overall mortality rates in cIAIs remain as high as 25%, with subjects who develop tertiary peritonitis experiencing even higher rates. HAP/VAP is a major resource-consuming problem especially associated with patients who have had a complication of an underlying illness or medical intervention. Mortality rates are commonly at least 20%. In each case the severity of the underlying disease and inappropriate antimicrobial therapy, due in part to increased antimicrobial resistance, significantly contribute to the mortality rates.

2.1.3. Aetiology and pathogenesis

Complicated urinary tract infections (cUTI) constitutes a heterogeneous clinical entity that includes UTI in the presence of factors that predispose to persistent or relapsing infection, such as indwelling catheters, urinary obstruction, instrumentation of the urinary tract, or other functional or anatomical abnormalities of the urogenital tract, and may occur in the lower or upper urinary tract. Pyelonephritis, a subset of cUTI, is an infection of one or both kidneys that can occur in patients with or without functional or anatomic abnormalities of the urinary tract. Complicated UTIs are a frequent cause of hospitalisation and a common health-care associated complication. Gram-negative organisms account for approximately 60% to 80% of complicated and nosocomial UTIs. The most common uropathogens are *E. coli*, *Klebsiella* spp., *Pseudomonas* spp., *Proteus* spp., *Enterobacter* spp. and *Citrobacter* spp.

Intra-abdominal infections include a wide spectrum of pathological conditions, ranging from uncomplicated appendicitis to faecal peritonitis. In complicated IAI (cIAI) the infection progresses beyond a singularly affected organ and causes either localised peritonitis (intra-abdominal abscesses) or diffuse peritonitis. This peritoneal contamination may result from spontaneous perforation (e.g. appendicitis, perforated ulcer or diverticulitis), surgical intervention or trauma. Pathogens most

commonly encountered in cIAI are *Escherichia coli*, other common *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Bacteroides fragilis*.

HAP and VAP occur in hospitalised patients. A hospital stay of 48 hours or more will place patients at risk for colonisation and potential infection of the respiratory tract with a variety of Gram-positive and Gram-negative bacteria. Examples of pathogens of hospital acquired bacterial pneumonia/ventilator acquired bacterial pneumonia include Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus*, Gram-negative *Enterobacteriaceae* such as *Klebsiella pneumoniae* and Gram-negative aerobic non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter* spp.

2.1.4. Clinical presentation, diagnosis

The types of infections listed in the proposed indications are diagnosed based on clinical presentations, which are described in CHMP guidance on the development of antibacterial medicinal products, and on microbiological investigations to isolate and characterise ± quantify (in case of UTI) the pathogens.

2.1.5. Management

There are many guidelines available regarding recommendations for the treatment of the types of infections listed in the proposed indications. The selection of antibacterial agent(s) for the individual patient is also guided by the results of pathogen identification and susceptibility testing.

Successful treatment of cUTIs has become increasingly more challenging because of rising rates of antimicrobial resistance among these pathogens. Indeed, the majority of pathogens responsible for healthcare-associated cUTIs, including catheter-related infections, are now commonly resistant to multiple antimicrobial agents. Effective management of these infections requires a combination of early diagnosis, appropriate surgical intervention and empiric, broad-spectrum antimicrobial therapy.

Second or third generation cephalosporins in combination with metronidazole, extended-spectrum penicillin/beta (β)-lactamase inhibitors (BLIs) and carbapenems are commonly used for the treatment of cIAI. However, increasing resistance to commonly prescribed antimicrobial agents remains a serious global problem. Indeed, susceptibility data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) indicate that 18% of *E. coli* collected worldwide were extended spectrum beta-lactamase (ESBL)-positive from 2005 to 2007, while the number of ESBL-positive *Klebsiella pneumoniae* significantly increased from 13.3% in 2002 to 30.9% in 2007. In addition, *P. aeruginosa* resistance in cIAI remains a problem.

Treatment of HAP/VAP commonly involves multiple agents to cover all possibilities, at least until culture results are available. However, results are often uninformative even in the cases with very clear radiological pneumonias and other signs of active infection. Due to the types of patients in which these infections occur and their underlying conditions, as well as the typically multi-resistant nature of their pathogens, it is common that at least two antibacterial agents are used unless the susceptibility of the organism(s) has been clarified.

Beta-lactam antibacterial agents are very commonly used to manage the above types of infections when they involve Gram-negative pathogens. Increasing resistance to beta-lactams, including the carbapenems, has led to some organisms being effectively untreatable or treatable only with resource to colistin with or without other agents to which they remain at least partly susceptible. Although carbapenem resistance remains at relatively low levels for most EU countries, increasing trends for the period 2011 to 2014 were observed for seven EU Member States: Bulgaria, Croatia, France, Germany, Italy, Portugal and Spain. As of March 2013, *K. pneumoniae* carbapenemase was the most widely disseminated carbapenemase across the EU. OXA-48 was the most frequently detected carbapenemase in Belgium, France and Malta. New Delhi metallo-beta-lactamases were responsible for occasional

hospital outbreaks in a few countries, but were not widely disseminated in European countries. In the medical literature, mortality rates attributable to CRE infections range from 20% to 54.3%. Thus, there is a high unmet medical need for patients with CRE.

In 2016 Zavicefta (ceftazidime-avibactam), which has activity against some CRE, was approved in several countries, including the EU. While laboratory studies showed *in vitro* activity of Zavicefta against many clinical isolates, they also showed selection of mutations in the genes encoding *K. pneumoniae* carbapenemase (KPC) resulting in resistance. Recent experience published from a single-centre study demonstrated that these resistance mutations could occur during treatment of patients, such that KPC-mediated resistance was detected in 3/10 microbiologic failures.

About the product

Vabomere consists of a known beta-lactam agent (the carbapenem meropenem) and a new beta-lactamase inhibitor (vaborbactam; formerly RPX7009). Meropenem has been licensed and used in the EU since the 1990s. It has a spectrum that includes Gram-positive, Gram-negative and anaerobic bacteria. It is given intravenously at doses up to 2 g q8h. Vaborbactam is a new active substance, being a beta-lactamase inhibitor of a new class (cyclic boronates).

The clinical programme was conducted using individual vials of meropenem (commercially available Meropenem for Injection - 1000 mg/vial) and vaborbactam (Vaborbactam for Injection - 500 and 1000 mg/vial). Two vaborbactam drug product formulations were used - a sterile frozen solution formulation and a sterile lyophilised formulation. Meropenem and vaborbactam vials were reconstituted with 0.9% saline and were immediately further diluted to a final concentration of 8 mg/ml each in 0.9% saline. The product for the market is provided as a sterile powder blend of crystalline meropenem trihydrate, crystalline vaborbactam and lyophilised sodium carbonate to assure solubility. It is presented as a powder for concentrate for solution for infusion in vials containing 1 g of each active substance.

2.2. Quality aspects

2.2.1. Introduction

The finished product is a powder for concentrate for solution for infusion containing 1 g meropenem (as trihydrate) and 1 g vaborbactam as the active substances. After reconstitution, 1 ml of the solution contains 50 mg meropenem and 50 mg vaborbactam.

The only other ingredient is sodium carbonate as described in section 6.1 of the SmPC.

The product is available in a 50 ml clear glass vial (Type 1) closed with a rubber (bromobutyl) stopper and aluminium overseal with flip-off cap, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Meropenem

General information

The chemical name of meropenem is (4R,5S,6S)-3-[[(3S,5S)-5-[(Dimethylamino)carbonyl] pyrrolidin-3-yl]sulfanyl]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate corresponding to the molecular formula $C_{17}H_{25}N_3O_5S\ 3H_2O$. It has a relative molecular mass 437.5 g/mol and has the following structure (*Figure 1*):

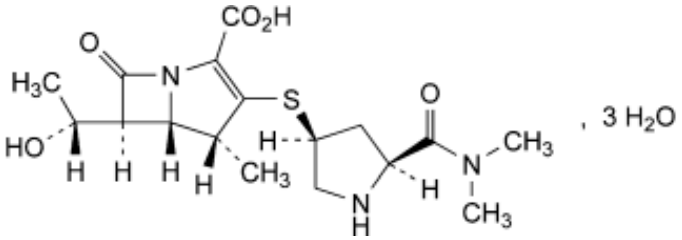


Figure 1. Chemical structure of meropenem.

Meropenem appears as white or light yellow, crystalline powder. It is non hygroscopic and is sparingly soluble in water.

Meropenem is a well-known active substance and it is monographed in the European Pharmacopoeia (monograph number 2234). As there is a monograph of meropenem in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for meropenem which has been provided within the current Marketing Authorisation Application. With regard to meropenem characterisation reference is made to the Certificate of Suitability R0-CEP 2011-238-Rev 02. The molecule has 6 asymmetric carbon atoms. Only one crystal form of meropenem trihydrate is manufactured by the active substance manufacturer.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability (R0-CEP 2011-238-Rev 02). No information is provided on the elucidation of the structure, which is acceptable in view of the CEP. The absence of materials of animal/human origin is declared. Water for injections (WFI) is used in the last synthesis step.

Meropenem is provided as sterile material and the sterility of the finished product relies upon meropenem sterility, as no further sterilisation steps are introduced in the finished product manufacture. The sterilisation process and validation of meropenem is identical to that provided to the EDQM to support the current CEP. The relevant CEP sections that describe the sterilization process and validation, including media fills and acceptable bioburden limits for meropenem trihydrate solution before the sterilizing filtration have been provided.

Specification

Reference is made to the Certificate of Suitability R0-CEP 2011-238-Rev 02 with regard to specification and analytical methods. The specifications are according to the Ph. Eur. monograph with additional tests for acetone, palladium and sterility. The control of sterile meropenem trihydrate has been evaluated by the EDQM in relation to the Certificate of Suitability for meropenem trihydrate R0-CEP 2011-238-Rev 02; this is acknowledged and accepted.

Stability

Reference is made to the CEP according to which the re-test period is 2 years if stored in a sterile bottle-shape polyethylene bag in a sterile PE bag within a four-layer bag.

Vaborbactam

General information

The chemical name of vaborbactam is (*3R,6S*)-2-hydroxy-3-[[2-(2-thienyl)acetyl]amino]-1,2-oxaborinane-6-acetic acid corresponding to the molecular formula $C_{12}H_{16}BNO_5S$. It has a relative molecular mass 297.14 g/mol and has the structure shown in

Figure 2.

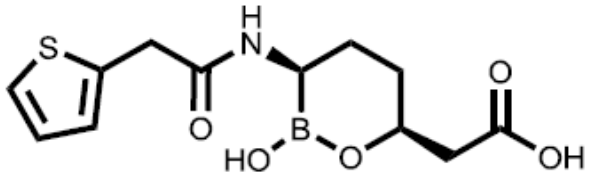


Figure 2. Chemical structure of vaborbactam.

Vaborbactam appears as white to off-white, non-hygroscopic crystalline powder. It is slightly soluble in water and has two ionisable functional groups: a carboxylic acid with pKa=1.9 and a boronic acid with pKa=8.2.

The structure of the active substance was elucidated by a combination of spectroscopic methods (UV, IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry), elemental analysis, DSC and TGA. Vaborbactam is sufficiently characterised and its structure is adequately elucidated.

Vaborbactam has two asymmetric carbon atoms (3R, 6S). One stereocenter is determined by the starting material (REBO-01) in the first step of the synthesis, the second is introduced in step 2 (REBO-04 intermediate synthesis). The desired and undesired isomers are formed in a ratio of 97:3. The controls of the stereocenter in starting material (REBO-01) and in the intermediate (REBO-04) minimize stereoisomers.

It exists in three crystalline forms (polymorphs A, B and C) as well as amorphous material. Form A is the anhydrous non-solvated crystalline form that is obtained by the proposed synthesis process and Forms B and C are solvates. Powder XRD spectra of several batches have been submitted (comparative between previous and current synthesis process) and these indicate that Form A is consistently produced.

Manufacture, characterisation and process controls

Vaborbactam is manufactured in five converging main stages. Two starting materials are defined which are acceptable and controlled by suitable specifications. The manufacturing process includes 4 isolated intermediates resulting in non-sterile vaborbactam. A sixth step is also described where sterile substance is obtained by sterile filtration, crystallisation, milling and packaging.

Vaborbactam is provided as sterile material for the manufacture of the finished product. The validation report of the sterilisation process has been provided for the site involved and includes the sterilisation step; process simulation data support the proposed process times.

No steps are defined as critical. The intermediate specifications were provided, have been justified and they are overall acceptable.

The characterisation of the active substance and its impurities are in accordance with the relevant ICH guidelines. The potential impurities are controlled in the active substance and intermediate specifications as well as in the in-process control during the manufacturing of the active substance by validated test methods. All in-process intermediates in the synthesis of vaborbactam as well as all organic impurities have been subjected to an in silico assessment of genotoxicity potential. The impurities' fate and controls have been discussed and the proposed control strategy ensures adequate control of their levels in the active substance.

The packaging for sterile vaborbactam (RPX7009) utilizes the Sterbag® system. The Sterbag® system is composed of three sterile bags. The first one (primary), made of low-density polyethylene (LDPE) and bottle-shaped is filled with the sterile product, placed under vacuum, sealed, labelled and placed into the secondary rectangular bag, made of high density polyethylene (HDPE). The secondary HDPE bag is sealed, placed under vacuum and inserted into a tertiary rectangular bag, made of four foils (low-density polyethylene, nylon, aluminium and polyester) joined together. This third bag is also sealed and placed under vacuum, so that the system is completely air-tight.

Specification

The finished product release specifications include appropriate tests and limits for appearance (visual), identification (HPLC, IR), assay (HPLC-UV), related substances (HPLC-UV), residual solvents (GC-FID), water content (Ph.Eur.), specific optical rotation (Ph.Eur.), particle size (Ph.Eur.), bulk density (Ph.Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The proposed limits for related substances have been toxicologically qualified and are therefore considered acceptable. It has been justified by batch analysis data and by the manufacturing process conditions that there is no need for a test for chiral purity in the vaborbactam substance. Particle size distribution and bulk density (untapped and tapped) are tested at release and reported for information only.

The analytical methods used in the control of the active substance have generally been satisfactorily described and validated in accordance with the relevant ICH guidelines. Information regarding the reference standards used in the analytical testing is satisfactory.

Batch analysis data have been provided for three commercial scale batches and also three validation batches. All results are within proposed specifications and confirm consistency of the manufacturing process from batch to batch.

Stability

Stability data on three production and three pilot scale batches of vaborbactam stored in the intended commercial packaging for up to 24 months under long term conditions (25°C/60% RH) and for up to 6 months under accelerated conditions (40°C/75% RH) was provided according to the ICH guidelines.

The stability batches were tested for appearance, specific optical rotation, water content, assay, related substances, sterility and bacterial endotoxins. The stability indicating capability of the methods has been demonstrated by forced degradation studies. All data reported from the accelerated and long term studies is within proposed specifications and no trends were seen.

Supportive stability data to support a re-test period of 36 months have been submitted for 12 batches of non-sterile vaborbactam stored at 25°C/60% RH for 18-48 months. The batches all comply with the acceptance criteria and no trends are observed.

Vaborbactam samples have been also exposed to forced degradation conditions. The substance was subjected to high temperature, acid, base, oxidation and photostability as per ICH Q1B. No significant

degradation was observed except for at the oxidative condition depending on treatment time. For all other treatments less than 1% total degradation was seen. With regard to photostability results no more than 0.3% total degradation was observed suggesting the substance is not photo sensitive.

Based on the overall stability results the proposed retest period of 36 months in the proposed container at 25°C/60% RH is accepted.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a sterile powder for concentrate for solution for infusion filled in single-use 50 ml Type I clear glass vials with 20mm bromobutyl rubber stoppers and sealed with 20 mm aluminium flip-off overcaps. The product is intended for intravenous administration after reconstitution and further dilution with 0.9% sodium chloride injection prior to use. There is a 3% overfill per vial to allow for delivery of the labelled content.

Meropenem chemical instability is well documented in the literature and its degradation takes place under various thermal, alkaline and acidic conditions, as well as in the presence of weak nucleophiles (like water) and/or metal ions. It contains an unstable, highly strained and reactive β-lactam amide bond. In aqueous solution, opening of the β-lactam ring by water forms Impurity A, whereas opening of the ring by a second molecule of meropenem forms Impurity B. Therefore, the product is developed as a sterile crystalline powder blend formulation to maximize stability. Vaborbactam is chemically stable in heat, acid, base and photolytic conditions, and is less stable to oxidative degradation.

Both active substances are used in their free acid form and need a counter ion in order to solubilise properly upon reconstitution. Sodium carbonate has been chosen for this purpose. It is also used for pH control. The sodium carbonate is crystalline and sterile and it complies with compendial requirements, e.g. Ph Eur. Nitrogen (Ph. Eur.) is used as process aid as an inert gas.

The information for the batches used in the clinical trials has been summarised and provided in the application.

Following interaction with regulatory agencies a strong preference for a single vial presentation containing both meropenem and vaborbactam in the same vial was expressed. Thus, the single vial presentation was developed. A lyophilized combination was not considered a viable option. Therefore, the product formulation has been developed to be manufactured as a sterile, crystalline powder blend.

Both meropenem and vaborbactam can be aseptically processed and isolated as sterile crystalline solids. The commercially available meropenem for injection is a sterile, crystalline powder blend with lyophilised sodium carbonate, having long-term stability in this format. Addition of vaborbactam to this formulation was considered a low risk approach to the development of a combination medicinal product.

The relevant physicochemical properties of the active substances and the excipient sodium carbonate have been addressed during development. The amount of sodium carbonate in the blend and its water content were also investigated.

As mentioned previously only one crystal form of meropenem trihydrate and vaborbactam (Form A) have been evaluated during development as only one form of each is manufactured at the commercial site. two different manufacturing methods were tested. Slightly better blend uniformity was achieved with lyophilised material (lab scale) and this manufacturing process was therefore chosen.

The components of the product are blended during manufacture and factors that may impact blend uniformity have been investigated. Given the limited batch experience with Vabomere manufacturing , the CHMP recommended that specifications for those parameters affecting blend uniformity, the specifications will be set after additional batches (n=6) have been produced and evaluated (see recommendations).

Given the known instability of meropenem in aqueous solution, hygroscopicity studies by dynamic vapour sorption have been performed in the components and the bulk blend. The results show that meropenem trihydrate and vaborbactam are not hygroscopic, but sodium carbonate is highly hygroscopic. The bulk blend was found to be hygroscopic, mainly due to the presence of sodium carbonate. The water content of sodium carbonate is limited at NMT 0.5% and this has proven sufficient with regards to control of degradation of meropenem.

The amount of sodium carbonate has been optimised in order to be sufficient to solubilize both substances but also adjusted so that there will be no pH extremes in the reconstituted product.

Vabomere is manufactured by bulk blending the three sterile components (meropenem trihydrate, vaborbactam and sodium carbonate) followed by packaging in a sterile, triple layered, vacuum-sealed Sterbag®.
A preliminary factorial experiment was initially conducted at small scale (30 g) to understand the factors contributing to acceptable blend content uniformity. From the results of this study blending time was defined, the type of manufacturing process was confirmed and the vaborbactam particle size was determined. Also, segregation tests were performed on the blend but no segregation was observed. Experiments were also performed on a slightly larger scale. Blending time is considered a critical process parameter.
The process was transferred to the commercial scale blender and the three registration batches were manufactured. Samples were tested for pH and assay. All individual values for content uniformity of both active substances were within their respective assay specifications. All data recorded were within their predefined acceptance criteria.

The Sterbags are then transferred to the vial filling line where they are opened under aseptic conditions and loaded into the hopper of an automated powder filling machine. The powder blend is filled into clean, sterilized and depyrogentated individual 50 mL glass vials, which are then stoppered and sealed. No specific discussion on the choice of sterilisation method is provided. As the proposed product is limited by the well-known instability of meropenem, this may be accepted.

The selection of the 50 ml glass vial is based on the goal to use the smallest vial possible and still be able to introduce sufficient volume of diluent without over-pressuring the vial and having acceptable reconstitution time and solution stability.

The finished product's primary packaging material constitutes a standard type I clear glass vial of 50 ml nominal volume with a bromobutyl rubber stopper and an aluminium flip-off overseal. The glass complies with Ph. Eur. 3.2.1 and the stopper with Ph Eur 3.2.9. The microbial barrier properties of the packaging are demonstrated by the microbial immersion test and the integrity of the stopper has been discussed; stability data supports the container closure system configuration.

Compatibility

The product is proposed to be reconstituted and diluted with 0.9 % saline prior to use. Tests are performed with the 3 registration batches at all long-term stability test points. The data showed that the reconstituted product (50 mg/ml) should be further diluted immediately; the diluted product can be used for up to 4h after dilution at room temperature and 22h under refrigeration. Following dilution, the infusion should be completed within 4 hours when stored at 25° C, or within 22 hours when refrigerated at 2-8 °C (SmPC 6.6).

Studies using 5% dextrose solutions as the reconstitution and dilution solvent were performed and the product was found to be chemically incompatible with this diluent. As such, the label provides instructions stating that only 0.9% sodium chloride solutions should be used as a diluent for Vabomere (SmPC 6.6).

Regarding the compatibility of the product following reconstitution with the vial and stopper, and dilution with commonly used infusion bag and line materials, apart from the expected chemical degradation of meropenem in solution observed in the in-use studies, no other incompatibility was observed. This means that the product does not impact on the closure materials during storage or administration and therefore the interaction studies per CPMP/QWP/4359/03 are not appropriate.

Manufacture of the product and process controls

The finished product manufacturing process comprises of blending the three sterile components meropenem trihydate, vaborbactam and sodium carbonate and subsequently filling them into Sterbags. The Sterbags are transported to the filling site where the powder blend is filled into vials under aseptic conditions. The process has been described in sufficient detail. The manufacturing process is performed at two sites; bulk blending in one site and vial filling under aseptic conditions in another.

Process validation data were provided and are acceptable. Media fill information is provided for all sites; adequate information on sterilisation of the equipment was provided. The process is non-standard and process validation data at commercial scale has been provided for 3 commercial scale batches regarding bulk blending and for 3 commercial scale batches of finished product for the vial filling under aseptic conditions. All validation data generated met acceptance criteria and are comparable between batches. They confirm that the process is well controlled and ensures that product of comparable quality is manufactured. The manufacturing process is considered validated.

Product specification

The finished product release specifications include appropriate tests and limits for appearance (visual), identification of meropenem (HPLC, UV), identification of vaborbactam (HPLC, UV), clarity and colour of solution (Ph. Eur.), reconstitution time (visual), constituted solution (Ph. Eur.), visible particles (USP), particulate matter (Ph. Eur.), pH (Ph. Eur.), water content (Ph.Eur.), uniformity of dosage forms (Ph. Eur.), assay of meropenem (HPLC), assay of vaborbactam (HPLC), assay of sodium (ICP-OES), related substances (HPLC), elemental impurities (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

The proposed limits for the specified impurities have been based on batch history and the levels qualified in toxicological studies.

The specification limits have been justified but given the limited batch data available to date the CHMP recommends the applicant to re-evaluate these limits once sufficient number of batches (n=6) is manufactured (see recommendations).

Regarding elemental impurities the acceptance criteria were derived from the permitted daily exposure (PDE) for parenteral drug products as per ICH Q3D. A total daily dose of 16.3 g product is assumed in line with the proposed posology. A summary of the risk assessment was provided that takes into account the active substance, excipients, packaging and equipment. Measured limits were provided and are well below the 30 % of limit threshold. Annual testing of one batch will therefore take place.

The finished product is released on the market following traditional final product release testing. The procedures for analytical methods used were provided. The non-compendial analytical methods were

validated according to current ICH guidance. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data on three commercial scale batches have been provided and all test results comply with the specification. There is good agreement between batches.

Stability of the product

Stability data from three commercial scale batches packaged in the proposed closure system and stored at long term (25°C/60% RH) and accelerated (40°C/75% RH) conditions according to ICH Q1A have been presented. Samples were stored in upright and inverted position. Also, data from one supportive laboratory scale batch has been included. The accelerated studies have been completed out to 6 months and data for up to 24 months data have been submitted under long term conditions. For the supportive laboratory scale batch, 18 months long term data are provided.

The stability batches were tested for appearance, clarity and colour of solution, pH, water content, reconstitution time, visible particles, assay of the active substances, impurities, particulate matter, bacterial endotoxins and sterility. The analytical methods were shown to be stability indicating by forced degradation studies.

All results obtained from the accelerated and long term studies are within proposed specifications and no significant changes or trends have been observed. No difference in the data is seen whether the vials are held in the upright or inverted position. It can be noted that there is no apparent increase in degradation products.

A photo-stability study has been conducted according to ICH Q1B Option 1 light on one commercial scale batch. No difference in results was seen for light exposed samples compared to unexposed and dark controls. Thus, the product is not considered as sensitive to light.

Forced degradation study has also been performed and samples of powder were exposed to heat, humidity, alkaline conditions, acid conditions and oxidative treatment with hydrogen peroxide. Although the active substances peaks were pure, degradation was observed for both substances in oxidising medium. While vaborbactam was stable under the other conditions, meropenem exhibits sensitivity to humid, alkaline and acid conditions.

Based on the stability data presented the proposed a shelf-life of 36 months and a storage condition “Do not store above 25 °C” (SmPC 6.3 and 6.4) is accepted.

Adventitious agents

No excipients of human or animal origin are used in the product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. The active substances and excipients are provided and used as sterile material in the manufacture of the finished product. Sufficient information regarding the sterilisation of the materials prior to entering the finished product manufacture has been provided. The finished product manufacturing process has been validated. The container closure system is considered suitable for this type of product and its intended use as per the SmPC. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-Given the limited batch experience with the manufacture of Vabomere, the finished product components specifications for those parameters affecting blend uniformity will be set after additional batches (n=6) have been produced and evaluated.

-Given the limited batch data available to date the finished product specification limits at shelf life will be re-evaluated once a sufficient number of batches (n=6) of Vabomere has been manufactured and tested for long-term stability.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

Meropenem is a well-established broad-spectrum (acting against Gram-positive, Gram-negative, and anaerobic bacteria), injectable carbapenem antibiotic that has been used worldwide for over 2 decades for the treatment of serious infections. It inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins (PBPs), which are bacterial enzymes involved in the biosynthesis of peptidoglycan.

Administering beta-lactamase inhibitor vaborbactam in combination with meropenem is intended to restore the activity of carbapenems against *Klebsiella pneumoniae* carbapenemase (KPC)-producing carbapenem-resistant Enterobacteriaceae (CRE).

Mechanistic studies with vaborbactam demonstrated that it behaves as a slow tight-binding inhibitor of KPC-2 with 1:1 stoichiometry and an extremely low off-rate, resulting in a residence time bound to enzyme measured in hours. Site-directed mutagenesis studies identified amino acids that play an important role in interaction of vaborbactam with KPC; furthermore, its distinct binding mode to KPC makes it different from other beta-lactamase inhibitors (Study MVAB-MOAMDCO-023, Study MVAB-MOA-MDCO-032, and Study MVAB-MOA-MDCO-033).

The applicant stated that recent prospective and retrospective surveillance studies that involved large global collections of clinical isolates of Enterobacteriaceae demonstrated that when vaborbactam was combined with meropenem *in vitro*, a marked enhancement of meropenem activity by vaborbactam against KPC-producing Enterobacteriaceae was evident. Vaborbactam did not enhance or reduce the *in vitro* activity of meropenem against a panel of clinical isolates of multidrug-resistant *Acinetobacter spp* and *P. aeruginosa* due to efflux of both vaborbactam and meropenem and other non-beta-lactamase mediated resistance mechanisms in non-fermenting bacteria.

The exposures of meropenem and vaborbactam producing antibacterial activity and suppressing the development of resistance against carbapenem-resistant, KPC-producing strains of Enterobacteriaceae with MICs of 8 mg/L and against P. aeruginosa with MICs up to 4 mg/L were identified in an *in vitro* hollow fibre pharmacodynamic model. Based on these experiments, a dosage regimen of meropenem 2g in combination with vaborbactam 2g administered every 8 hours by 3-hour infusion appeared to be the appropriate regimen for further clinical development.

The effect of vaborbactam on meropenem efficacy *in vivo* was investigated in neutropenic mouse thigh, ascending urinary tract infection model and pulmonary infection models due to KPC-producing, carbapenem-resistant strains of *K. pneumoniae*, *E. coli* and *Enterobacter cloacae*. In these models, the combination of vaborbactam and meropenem reduced bacterial counts at doses of meropenem that were ineffective when meropenem alone was administered. From a non-clinical perspective, CHMP agreed that the results from primary pharmacology studies support the rationale for the development of the proposed product – for which it appears that vaborbactam can restore the antibacterial effects of meropenem against carbapenem-resistant, KPC-producing strains of *K. pneumoniae*.

Secondary pharmacodynamic studies

Vaborbactam was screened *in vitro* for secondary pharmacologic activity by evaluating binding against a panel of receptors, transporters and ion channels as well as by evaluating inhibition of selected

human serine proteases. The applicant explained that the secondary pharmacology screen was completed early in the development and therefore the test concentration of vaborbactam in the off-target screening assay was below the later identified clinical Cmax. CHMP agreed that it would have been valuable to test the compound in secondary screens at relevant clinical concentrations, but was of the view that the *in vivo* toxicology studies, with exposure margins versus clinical exposure exceeding 40-50, indicate no findings of relevance for potential off-target pharmacologic effects. Furthermore, additional off-target assays using higher test concentrations of vaborbactam would not contribute to the human risk assessment at this point and such studies are therefore not considered necessary.

Safety pharmacology programme

As part of a general pharmacological evaluation, the effects of meropenem on the respiratory system, circulatory system, central nervous system, autonomic nervous system, smooth muscle, kidney function, blood and other biological systems were studied. Meropenem did not show any pharmacological effects of concern in any study. All data are published and will not be reviewed here.

A full package of safety pharmacology was completed for vaborbactam alone, which is in accordance with guideline CPMP/ICH/539/00 (ICH Topic S7A). In the Good Laboratory Practice (GLP) safety pharmacology studies; including the human hERG assay, functional observation battery, *in vivo* cardiovascular and *in vivo* respiratory safety pharmacology studies, vaborbactam had no apparent effects on the major organ systems. In vitro, hERG channel inhibition was reported at an IC50 value of >300 µM.

Since vaborbactam was shown not to adversely affect the antibacterial activity of meropenem and since there were no safety concerns for vaborbactam, CHMP agreed that combination safety pharmacology studies with vaborbactam-meropenem are not required.

Pharmacodynamic drug interactions

For the pharmacodynamic drug interactions related to the combination of vaborbactam and meropenem please see the clinical part of the report.

2.3.3. Pharmacokinetics

Absorption
Intravenously administered vaborbactam showed linear pharmacokinetics across all species tested following single-dosing. The oral bioavailability of vaborbactam in rodents was low, <10% in rats. Maximum vaborbactam concentrations were achieved immediately after dosing and decreased rapidly. The half-life tended to increase with dose, but remained relatively short across species at all doses; it ranged from 0.1 to approximately 2 hours. Clearance (CL) and steady-state volume of distribution (Vss) were independent of dose. Clearance was typically higher in rodents, ranging from 1.6 to 1.8 L/kg/hr, than in non-rodents (0.27 – 0.51 L/kg/hr). Differences between males and females could not be assessed, since all studies were conducted in males.

There was no evidence of accumulation with multiple vaborbactam doses or gender differences in serum PK parameters between males and females.

In a 14-day rat study, at the NOEL, maximum mean concentration (Cmax) and AUC(All) values at Day 14, were 2581 µg/ml and 1052 hr*µg/ml in the males respectively, and 2481 µg/ml and 899 hr*µg/ml in the females respectively. The systemic exposure of vaborbactam generally increased in a dose proportional manner without gender differences.

In dogs dosed for 14 days, toxicokinetic evaluation revealed the maximum plasma concentrations were observed at the end of the 15-minute infusion with a dose dependent increase in half-life. The mean clearance was comparable between sexes, decreasing slightly as the dose levels increased. The systemic exposure of vaborbactam generally increased in a dose proportional manner without differences between males and females. No accumulation was evident.

In the rabbit embryo-fetal development (EFD) study, following repeated daily RPX7009 intravenous infusion for 15 minutes (for 14 days), Cmax was achieved at the end of the infusion period, declining thereafter rapidly with dose dependent half-life of 0.42, 0.42 (determined in one animal only), and 2.24 hr at the low, mid, and high dose levels, respectively. The systemic exposure to vaborbactam on GD19 was similar as what was observed on GD7 with Cmax and AUC(all) mean values of 431, 1420, 4967 µg/ml, and 261, 926, and 4435 hr*µg/ml at dose levels of 100, 300, and 1000 mg/kg/day, respectively. No evidence of systemic accumulation between both sampling occasions was observed as confirmed by the absence of quantification of vaborbactam in the pre-dose samples, except for animal No. 3509, where a small amount was detected (0.676 µg/ml) and all of Group 4 (high dose) where the pre-dose samples ranged between 0.581 and 4.385 µg/ml. As observed following dosing on GD7, the Cmax values increase dose proportionally while the AUC(all) values increased in a slightly greater than dose proportional ratio.

Under the conditions of this study, vaborbactam was rapidly cleared from the plasma and well distributed with no evidence of systemic accumulation following repeated dosing. These results suggest that the systemic exposure to vaborbactam follow dose-dependent kinetics, possibly due to saturation in the drug elimination process at high doses.

Combination PK studies have been conducted in mice, rats (adult and juvenile) and dogs. Results from these studies, as well as toxicokinetic evaluations from 28-day repeat dose toxicology studies where vaborbactam was administered alone and in combination with meropenem, confirm that the PK profiles of meropenem and vaborbactam are similar and are unchanged when the two drugs are administered together. It was also confirmed that vaborbactam had no effect on the PK profile of the open-lactam metabolite (hydrolysed meropenem).

Distribution

Both meropenem (from the literature) and vaborbactam exhibited low binding to serum proteins (less than 40%) in animal and human serum. In SD rats administered 100 mg/kg C14-vaborbactam over a 30-minute infusion, a plasma drug derived half-life of 6.8hr was reported (females). Blood-to-plasma ratios suggested there was little to no uptake of radiolabelled drug from the plasma to the red blood cells. In the absence of in-vitro distribution data in blood cells from different species, it is agreed that measuring erythrocyte partitioning at this stage of development is not likely to generate data of importance for assessment of clinical concerns of vaborbactam. Radioactivity was widely distributed among tissues but with low mean drug-derived concentrations. The highest mean drug-derived tissue concentration was found in the kidneys, prostate, urinary bladder, seminal vesicle and liver, and the lowest in the spinal cord and brain. At 24 hours following the start of infusion, the radioactivity was eliminated from most tissues. Based on AUC0-96 values, the highest exposure to drug-derived radioactivity was in the large intestinal content, the kidneys and the urinary bladder, consistent with the presence of elimination through the hepatic pathway and the urinary excretion as the major route of elimination. Rapid elimination of the drug from tissues was apparent and confirmed by excretion data, where at 96 hr post-start of infusion period, a mean total recovery of 81% in urine, 7% in faeces and <1.0% (negligible) in carcasses and cage washes was reported.

The applicant has acknowledged the absence of in-vivo distribution data in pigmented animals and explains that vaborbactam is a free acid as well as a hydrophilic compound, which makes it less likely to bind to melanin as compared to lipophilic drugs. This is agreed. Moreover, there was no evidence of

ocular or cutaneous toxicity in pigmented beagle dogs and there have been no reports of increase in skin or ocular adverse events to vaborbactam in the clinic thus far.

It is reported that meropenem is excreted in breast milk. No data on milk distribution in pregnant animals treated with vaborbactam or placental transfer are reported, which is reflected in the SPC.

Metabolism

Vaborbactam was stable in rat, dog and human microsomes and hepatocytes. As no potential metabolites were identified during in vitro metabolic profiling of vaborbactam, the applicant did not measure metabolites in vivo. The applicant cites single-dose PK study data in male SD rats whereby it was determined that 90% vaborbactam was excreted unchanged in the urine over 24 hours and 6.6% in faeces. This is in line with human excretion data and hence supports the view that no further discussion on metabolic pathways is warranted.

In rat and dog pharmacokinetic studies using 14C meropenem, the ring-opened metabolite (H- 4295 or meropenem impurity A) was measured in both plasma and urine [Iba et al, 1992a].

Excretion

Vaborbactam is primarily eliminated through renal excretion of unchanged drug with 90% excreted unchanged in Sprague Dawley rats. Meropenem is also reportedly primarily eliminated via the renal system in rats and dogs. The applicant did not provide data on the excretion pattern in dogs due to comparability of in-vitro pharmacokinetic data and of the toxicity profile between the rat and the dog.

Drug interactions

Vaborbactam as perpetrator: For CYP inhibition and induction studies, the applicant did not initially discuss why the concentrations in these studies did not include the 50-fold of the mean unbound maximum plasma concentration (Cmax) obtained at steady state during treatment with the maximum therapeutic dose (for study 506 Cmax was 94.7 µg/ml = 318.7 µM of total drug = 245.5 µM of free drug assuming 33% protein binding). During the assessment the applicant has acknowledged that the concentrations used in the *in vitro* DDI studies do not meet the current requirements. The data already available suggest that vaborbactam may be an inhibitor of CYP2D6 at clinically relevant concentrations (Ki 200 uM, cut-off to exclude clinical relevance 8 mM).

The applicant has been requested by CHMP and has committed to complete the *in vitro* enzyme, transporter inhibition and induction studies post-authorization and to submit the results for assessment not later than November 2019. This was considered acceptable by CHMP. Moreover, the applicant proposal to update the information on the potential for DDIs in the SmPC section 4.5 (including the potential for risk of increased plasma concentrations of CYP2D6 substrates) to address the limitations of the current data is considered acceptable by CHMP. At the same time, CHMP requested the Applicant to list the medicinal products with narrow therapeutic window that are predominantly metabolised by CYP450 enzymes and to add examples for the medicinal products that are substrates for CYP2D6 in the Vabomere SmPC-this has been updated accordingly.

Regarding the renal/hepatic transporter Inhibition, the applicant proposed to conduct new Renal/Hepatic Transporter Inhibition studies at clinically relevant concentrations and to submit the results for assessment not later than November 2019. CHMP agreed to the proposal, considering that previous studies at lower concentrations showed that vaborbactam does not appear to be a substrate of OAT1, OAT3 or OCT2-mediated transport at up to 100 µM, nor is it a substrate of BCRP or P-gp at concentrations up to 300 µM. The current Vabomere SmPC caution of wording for co-administration of meropenem with probenecid is agreed upon by CHMP.

Vaborbactam as victim: Vaborbactam did not appear to be substrate for BCRP and P-gp in a concentration range of 30-300 µM. Vaborbactam also did not seem to be transported through OAT1, OAT3 and OCT2 over the same concentration range.

Meropenem was not found to be a substrate of OAT4, OCT1 or OCT2, but was found to be a substrate of OAT1 and OAT3. Based on this data, the only clinical PK interaction expected would be with probenecid. In a Phase I clinical trial in humans, administration of probenecid did increase the plasma half and AUC by 33% and 55%, respectively [Bax et al, 1989].

Combination PK

Combination PK studies have been conducted in mice, rats (adult and juvenile) and dogs. Results from these studies, as well as toxicokinetic evaluations from 28-day repeat dose toxicology studies where vaborbactam was administered alone and in combination with meropenem, confirm that the PK profiles of meropenem and vaborbactam are similar and are unchanged when the two drugs are administered together. It was also confirmed that vaborbactam had no effect on the PK profile of the open-lactam metabolite (hydrolysed meropenem).

Other pharmacokinetic studies

In the juvenile rats vaborbactam follows dose-dependent kinetics that increase in a greater than dose proportional manner, possibly due to the saturation of a clearance process at higher doses, and a rapid metabolism of meropenem to hydrolysed meropenem with similar dose-independent kinetics when administered alone or in combination. Exposures to both vaborbactam and meropenem were lower in juvenile rats (24 days old) compared to adult rats at the same doses, and half-lives of both drugs were shorter in juvenile rats.

2.3.4. Toxicology

As per ICH M3(R2) guidance, the repeat-dose toxicity studies, which were conducted both alone (vaborbactam) and in combination with meropenem for up to 28 days, with 28 days' recovery, are considered adequate to support registration of meropenem-vaborbactam treatment regimens of up to two weeks in duration. Based on the short duration of clinical treatment, carcinogenicity studies were not conducted, which was agreed upon by CHMP.

In the Vabomere SmPC it is stated that 4 g Vabomere (2 g meropenem/2 g vaborbactam) is administered every 8 hours by intravenous infusion over 3 hours. After identification of local toxicity in a 14-day rat study (Study 1011-0751) related to high vaborbactam osmolality, all subsequent repeat-dose toxicology studies of vaborbactam alone (up to 14 days) were conducted using lower concentrations of vaborbactam infused over 15 minutes. In these studies, doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in Beagle dogs were administered. The proposed clinical regimen is every 8 hours. During the assessment, the applicant has provided a rationale for limiting the dosing in the non-clinical species to once/day: i) it was made before the final dosing regimen was established; ii) to increase systemic exposure (which was greater than the clinical AUC); iii) to make it easier to dose multiple animals in an experiment; and iv) to minimize issues linked to maintaining indwelling infusion catheters over longer time periods. It is agreed that there are several pragmatic aspects surrounding repeat-dose infusions of animals, especially small animals. CHMP considered the provided reasons as more reasonable for rat exposures and somewhat less reasonable for dog exposures. The applicant explained that the periods without drug exposure can be mitigated by the fact that the plasma exposure profile provided considerably higher Cmax values (>20X) as well as 2 – 6 times higher AUC values relative to the clinical exposure. CHMP agreed the toxicological findings can still be viewed as relevant, since the large daily exposures allow target saturations (if applicable) and drug accumulation (if any) producing a visible readout (clinical chemistry and/or histopathology) as the period without

drug exposure (despite being 12 – 20 hours) would be too short for any recovery to be complete after 28 days of repeated dosing.

Single dose toxicity

Meropenem
Single dose, non-GLP toxicity studies with meropenem were conducted in mice, rats, and dogs (Kohda A et al, 1992). Overall, the lethal dose, 50% (LD50) values in mice and rats were 2650 mg/kg (males) and 2950 mg/kg (females) and 2850 mg/kg (males) and 3200 mg/kg (females), respectively. The acute lethal dose of meropenem is 2000 mg/kg in beagle dogs.

Vaborbactam
At vaborbactam concentrations used for bolus intravenous administration, the high osmolarity of the dosing solutions resulted in local vascular toxicity in rats. At lower concentrations (and osmolarity), using intravenous infusion over 15 to 30 minutes, local tolerability of vaborbactam or the combination of vaborbactam and a carbapenem was good. Based on maximum administrable volume and maximum feasible concentration, 1000 mg/kg was set as the maximum feasible dose in the toxicology studies.

Repeat dose toxicity

The applicant states there were no treatment related adverse effects from either vaborbactam or meropenem alone or in combination in rats or dogs. It was nevertheless noted that there are signs that vaborbactam may generate some hepatic inflammation in the 14d vaborbactam (study 1011-0762) and 28d+28d vaborbactam and meropenem dog (study 1013-1352) studies. It was alos noted that the dog AUC NOAEL systemic exposure margins to humans are low (14d study: 0.6x; 28d dog study: 1.8x). Furthermore, whilst classed as non-serious (i.e. not sufficient to stop treatment) and possibly influenced by confounders, some patients displayed slight increases in liver enzyme blood markers. At the CHMP request, the applicant agreed to amend the Vabomere Summary of Product Characteristics (SmPC) to include the following text in section 5.3:

In repeat dose toxicity studies in dogs, minimal hepatic inflammation was observed after 14 days and 28 days of exposure to vaborbactam alone or combined meropenem/vaborbactam.

Combination studies
Rats
After 28 days' administration of vaborbactam and meropenem (300/100 and 1000/300 mg/kg/day) to rats there were no clinical signs, body weights, food consumption, clinical pathology, organ weights changes or macroscopic and histopathologic effects that were considered related to the combination (study 1013-1341). Clinical signs including redness of the skin, thinning of the fur and scabs to the cervical region and/or axillaries and/or forepaws were considered related to the infusion jacket and considered procedural related. Statistically significant changes to various haematology parameters were considered incidental since they were noted in some control animals, changes were minimal, and/or reflected the normal inter-animal variation in this species. Incidental and no-adverse raised total bilirubin (BIL-T) concentration was noted at the end of the recovery period (Day 57) for high-dose females given vaborbactam/meropenem (1000/300 mg/kg/day), as there was an absence of any remarkable effect concentration at the end of the dosing period no correlating microscopic changes to the liver.

Infusion site changes in animals from all groups included various combinations of "firm material" and "soft material" adherent to the intima and "raised areas" frequently near or around the catheter tip and most likely indicative of the presence of a catheter *in situ*.

The applicant explained that although the liver was originally designated as a potential target organ, upon evaluation of the livers from all animals, especially the females, there was no clear test item-related effect nor was there any apparent dose relationship. Furthermore, findings, which consisted of minimal, focal/multifocal inflammation and/or minimal or mild hepatocellular vacuolation, were also present in some animals receiving the reference item. Based upon the distribution and severity of these liver changes, there was no effect of either test item, alone or in combination, on the liver. The NOAELs in this study for vaborbactam and meropenem (1000 and 300 mg/kg/day, respectively) were x2.37 and x0.16 (x3.94 for the metabolite – open lactam), respectively.

No new toxicities were associated with administration of vaborbactam spiked with impurities RPX800028 and RPX800027 in an additional 28-day study (study 1015-0201). Any reported clinical signs were considered incidental as they were sporadic across group and seen in control animals too with no dose-response relationship. As seen in the previous study, procedural-related findings included chronic organising thrombosis and intima proliferation at the infusion site. Reversible microscopic findings in the lung including mixed cell perivascular infiltrate and/or foreign body granuloma were noted occasionally in most treatment groups. The applicant explained that these findings are secondary to an indwelling catheter and infusion and were, therefore, considered procedure-related. The meropenem/vaborbactam NOAEL of 1000 mg/kg/500 mg/kg was associated with an average Day 28 vaborbactam Cmax and $AUC_{(0-12)}$ values of 1580 µg/mL and 1022 µg·hr/mL, respectively. This equates to approximate human safety margins of x2.14 and x0.27 (x7.29 for the metabolite – open lactam) for vaborbactam and meropenem, respectively.

Dogs

When dogs were administered vaborbactam, meropenem or a combination of the two for 28 days, clinical signs were noted in the scrotum of all groups (1013-1352): These changes included skin red in all groups including controls, skin scab (300 mg/kg/day RPX7009; 500 mg/kg/day meropenem; 300 mg/kg/day RPX7009/150 mg/kg/day meropenem), fur thinning (300 mg/kg/day and 1000 mg/kg/day RPX7009; 300 mg/kg/day RPX7009/150 mg/kg/day meropenem; 1000 mg/kg/day RPX7009/500 mg/kg/day meropenem), skin wound, skin wound with discharge and soft swelling. These changes were noted during the dosing period and some signs were still present during the recovery period (Group 5, 6 and 7 animals). These changes were of higher incidence in the 500 mg/kg/day meropenem dose (Group 5). These findings in two Group 5 and one Group 7 males did result in histopathological changes after the treatment period, but the findings were resolved after the recovery period: In the scrotum, moderate or marked ulceration was observed in 2/5 animals administered meropenem at 500 mg/kg/day alone and 1/5 in animals administered meropenem 500 mg/kg/day in combination with RPX7009 1000 mg/kg/day and correlated with macroscopic observations of wounds on the scrotum. The scrotal ulcers were associated with significant inflammation that extended to the epididymides and were accompanied with secondary changes of hypo/aspermatogenesis in the testes and aspermia/oligospermia in the epididymides of affected animals. As the severity and incidence was greater in the groups administered meropenem they were then considered possibly related to meropenem, although a spontaneous occurrence cannot be excluded. The applicant, however, theorised that as similar and less severe clinical observation were noted throughout all groups; the findings were possibly procedure related (daily dosing in slings), possibly related to meropenem or a spontaneous occurrence. Of note, since scrotal wounds were not observed macroscopically in recovery animals given 500 mg/kg/day of meropenem alone or in combination with RPX7009, the scrotum, which was not a standard study plan tissue, was not evaluated microscopically in recovery animals. There were changes in clinical chemistry (cholesterol elevations and changes in triglycerides, creatinine and albumin/globulin ratio) and urinalysis (presence of yeast) during the dosing period in this study, but these changes did not correlate with any histopathological findings and were not considered to be toxicologically significant. The NOAEL in this study was considered for vaborbactam, meropenem and meropenem-vaborbactam to be 1000, 500 and 500/1000 mg/kg/day, respectively. At the NOAEL the

margins of safety for humans following the proposed clinical posology are x6.57 vaborbactam alone, x3 (meropenem alone) and x5.6 for the meropenem metabolite.

Once daily 30-minute intravenous infusion of vaborbactam at doses of 100 and 1000mg/kg/day, biapenem (another carbapenem) at doses 30 and 100 mg/kg/day and vaborbactam/biapenem at doses 100/10, 300/30 and 1000/100 mg/kg/day to male and female Beagle dogs were studied for 28 days. Relative eosinophil (EOS) mean values were significantly elevated in all but 2 high-dose biapenem animals. Increases in globulin were also reported across treatment groups. These changes did not correlate with any histopathological findings and reversibility was observed of any changes following the 28-day recovery period, hence were not considered to be toxicologically significant. Clinical signs in high-dose biapenem animals included diarrhoea and emesis. No other treatment -related effects were reported. Vaborbactam at 1000 mg/kg/day, biapenem at 100 mg/kg/day and 1000 mg/kg/day vaborbactam /100 mg/kg/day biapenem were considered the NOAEL.

Genotoxicity

Vaborbactam and process impurities are not genotoxic. Genotoxicity of vaborbactam was assessed in a battery of *in vitro* and *in vivo* studies, in compliance with ICH S2. Two vaborbactam impurities, RPX800007 and RPX800026 were also evaluated in the Ames assay. All assays conducted met the criteria for validity and all were negative, including the Ames assays of the impurities. The results indicate that vaborbactam is not genotoxic.

New genotoxicity studies have not been conducted with meropenem and no evidence of mutagenic potential was found in any of the genotoxicity tests previously conducted for meropenem. No combination genotoxicity studies were conducted which is in accordance with EMEA guideline EMEA/CHMP/SWP/258498/2005.

Carcinogenicity

No carcinogenicity studies were conducted with vaborbactam alone or in combination with meropenem based on the intended short duration of therapy (<28 days). This is in line ICH guideline S1A: 'The Need for Carcinogenicity Studies of Pharmaceuticals' and is therefore considered acceptable by CHMP.

Reproduction Toxicity

Fertility

In the male fertility study (1014-0941), there were no adverse effects upon male reproduction and male reproductive assessments, which included epididymal sperm and testicular histopathological evaluation. Likewise, in the female fertility study (1011-1711) female SD rats displayed no adverse maternal effects on clinical signs, body weights, food consumption and gross pathology and no adverse effects on female reproduction. Therefore, based on these studies, the no observable adverse effect level (NOAEL) for male or female fertility and reproductive performance and early embryonic development, was 1000 mg/kg/day.

Regarding meropenem, the applicant cites Kawamura, 1992; where study results are reported following intravenous administration of meropenem to Alpk:ApfSD (Wistar) rats of the F0 generation to study the effects on the reproductive performance of male and females. Based on the published results, the NOAEL for male and female reproductive toxicity and early embryonic development was 1000 mg/kg/day.

Embryo-foetal development study

The administration of vaborbactam by intravenous infusion daily for 15 minutes from GD 6 to 17 inclusive to gravid female Sprague-Dawley rats at dose levels of up to 1000 mg/kg/day was generally well tolerated. There were no apparent adverse maternal effects on clinical signs, body weights and food consumption and no evidence of embryolethality, foetotoxicity or teratogenicity that could be attributed to treatment at doses up to 1000 mg/kg/day.

In the rabbit definitive EFD study (study 1011-1744), no treatment-related effects on pregnancy rates or viability reported at doses up to 1000 mg/kg administered between GD 7 and 19. Reported major external and internal malformations were considered not related to vaborbactam, although no findings were reported in control groups. No skeletal anomalies were treatment-related. There were no adverse maternal effects on clinical signs, body weights and food consumption. At the highest doses tested Cmax and $AUC_{0-\infty}$ values on GD19 were 4967 µg/mL and 4444 µg·hr/ml, respectively, in pregnant female rabbits [the margins of safety for humans following the proposed clinical posology are x7.05]. At the mid-dose Cmax and $AUC_{0-\infty}$ values on GD19 were 1420µg/ml and 919µg·hr/mL rabbits [the margins of safety for humans following the proposed clinical posology are x1.65].

Pre- and post-natal development study

In the pre- and post-natal development study (1013-0351), the administration of vaborbactam at 0, 100, 300 and 1000 mg/kg/day to pregnant female rats from GD 6 - PPD 20 was generally well tolerated. There were no adverse effects on reproduction performance of the F0 generation, or on the developmental performance (including sensory, behavioural and functional assessments) of the F1 generation. The F2 generation did not generally display adverse effects. Although pup deaths occurred (due to starvation); this was reported across all groups.

As this combination is intended to be used in the controlled environment of a hospital for short duration of dosing, CHMP agreed that the reproductive and developmental toxicology data suitably supports this application. In the absence of toxicokinetic data in the rat fertility (studies 1014-0941 and 1011-1711) and EFD (study 1011-1721) studies and pre- and post-natal development study (1013-0351), the applicant has bridged to the toxicokinetic data collated in the general toxicology studies where the doses and dosing intervals were also comparable. This approach was accepted by CHMP.

No reproductive studies were conducted with vaborbactam in combination with meropenem based on the results observed with the individual compounds. This is considered acceptable by CHMP.

Juvenile animals

It was unclear whether study 2015-0211 (non-GLP toxicokinetics study) was conducted retrospectively, due to the absence of the toxicokinetic analysis in the pivotal juvenile toxicology study (1015-0431) as it is not included in the toxicology written summary of the application. In the pivotal study neither meropenem nor vaborbactam administered alone or in combination had any effect on juvenile animals dosed from post-natal day 24 for 28 days. The NOEL in this study was, therefore, considered the high dose, 500 mg/kg of meropenem, 1000 mg/kg of vaborbactam and 1000/500 mg/kg of vaborbactam/meropenem. Assuming the purpose of the toxicokinetic study was to allow for bridging to the pivotal juvenile study to ascertain expected exposure levels that study, it could be assumed that the vaborbactam NOEL of 1000 mg/kg was associated with an average Day 1 Cmax and AUC_{0-12} values of 729 µg/mL and 41. µg·hr/mL, respectively. Likewise, the meropenem NOEL of 500 mg/kg/day was associated with averaged Day 1 Cmax and AUC_{0-12} values of 63 µg/mL and 25 µg·hr/ml, respectively. Moreover, the meropenem/vaborbactam combination (group 9) NOEL of 1000/500 mg/kg/day was associated with averaged Day 1 vaborbactam Cmax and AUC_{0-12} values of 631 µg/mL and 349 µg·hr/mL, respectively, and averaged Day 1 meropenem Cmax value of 71 µg/ml and AUC_{0-12} value of 29 µg·hr/ml.

For comparison, in the adult rat 28-day study GLP study (1013-1341), the vaborbactam NOAEL of 1000 mg/kg was associated with an average Day 1 Cmax and $AUC_{0-\infty}$ values of 1959.38 µg/ml and 1181.1 µg·hr/ml, respectively, for males and females combined. The meropenem NOAEL of 300 mg/kg/day was associated with averaged Day 1 Cmax and $AUC_{0-\infty}$ values of 154.95 µg/ml for males and females combined and 56.95 µg·hr/ml for females only.

In comparison, the meropenem/vaborbactam NOAEL of 1000/300 mg/kg/day was associated with averaged Day 1 vaborbactam Cmax and $AUC_{(0-\infty)}$ values of 1919.81 µg/ml and 1177.06 µg·hr/ml, respectively, and averaged Day 1 meropenem Cmax value of 143.91 µg/ml for males and females combined and $AUC_{(0-\infty)}$ value of 65.44 µg·hr/ml for males.

These results demonstrate considerably lower exposure levels in the juvenile animals (note that the top-dose of meropenem in the adult study was higher (500 mg/kg) than that studied in the juvenile study (300 mg/kg). As in the adult study the exposure levels in of the individual actives appear unaffected by concomitant administration.

Other toxicity studies

There was no evidence that the identified vaborbactam and meropenem impurities had a different toxicity profile from that of vaborbactam or meropenem itself. The applicant has not provided any data or discussion on the photo-reactivity potential for meropenem. Considering that the ICH S10 guideline (Photosafety Evaluation of Pharmaceuticals) was introduced recently (2013), i.e. after the introduction of the original meropenem products, CHMP agreed that it cannot be assumed that such data exist in the dossiers of previous products. CHMP therefore requested and the applicant committed to conducting an *in vitro* 3T3 neutral red uptake phototoxicity test for meropenem. The results of the study should be submitted for assessment not later than November 2019. This was considered acceptable by CHMP.

2.3.5. Ecotoxicity / environmental risk assessment

CHMP noted that during the assessment it could not be concluded that vaborbactam poses an aquatic environmental risk. As not all study reports have been provided, a full assessment of the ERA could not be conducted at this point. The applicant is required to provide OECD TG218 and TG308 study reports as soon as possible, but not later than June 2019.

Furthermore, the applicant's arguments that a limited definitive OECD TG209 test is enough for the ERA despite indications of max-concentration toxicity at 1000mg/L are not considered sufficient by CHMP. A full definitive OECD TG209 is required. Similarly, the Applicant's arguments that OECD TG106 sludge data can be considered sufficient with regard to the Phase IIB sediment risk assessment and that no additional OECD TG106 soil Koc data would be needed are also not considered acceptable by CHMP. Soil (or alternatively sediment) Koc data is required according to OECD TG106.

CHMP requested that all outstanding ERA data are submitted post-approval, no later than end of June 2019.

The applicant has not conducted a full ERA for meropenem. Although meropenem has not been previously authorised by the Centralised Procedure, it is currently authorised in 29 Member States of the European Economic Area through the Decentralized Procedure and no significant increase in environmental exposure in the EU is expected. This was considered acceptable by CHMP.

Table 1 Summary of main study results

Substance (INN/Invented Name): vaborbactam					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH5 log KOW -1.74 pH7 log KOW -2.68 pH9 log KOW -2.71			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				not B
	BCF	Not assessed			B/not B
Persistence	DT50 or ready biodegradability	missing			P/not P
Toxicity	NOEC or CMR	n/a			T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I -					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.151	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)		n/a			(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	Kd = 0.400-0.500L/kg Koc = 1.093-1.596L/kg			No adsorption into sludge from Denton WWTP or Easton WWTP.
Ready Biodegradability Test	OECD 301	No adequate data available			Not required (
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	No adequate data available			Summary provided but no full study submitted
Phase IIa Effect studies – no studies conducted					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	Growth rate NOEC LOEC EC50 Mean yield NOEC LOEC	 25 50 67 (59-75) 25 50	mg/L	

		EC50	55 (41-67)		
Daphnia sp. Reproduction Test	OECD 211	Mortality NOEC LOEC EC50 Reproduction NOEC LOEC EC50 Size (length) NOEC LOEC EC50	 10.9 >10.9 >10.9 10.9 >10.9 >10.9 10.9 >10.9 >10.9	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	Hatching NOEC LOEC Fry survival NOEC LOEC Size/weight NOEC LOEC	 11.5 >11.5 11.5 >11.5 11.5 >11.5	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	n/a	mg/L	missing
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	n/a	L/kg	Not required
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2	n/a		Not required
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	n/a	mg/kg	Not required
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	n/a	mg/kg	Not required
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	n/a	mg/kg	Not required
Collembola, Reproduction Test	ISO 11267	NOEC	n/a	mg/kg	Not required
Sediment dwelling organism		NOEC	n/a	mg/kg	Missing. To be supplied by Q2 2019

2.3.6. Discussion on non-clinical aspects

As per the guidance of ICH M3(R2), the repeat-dose toxicity studies, which were conducted both alone (vaborbactam) and in combination with meropenem for up to 28 days, with 28 days' recovery, are adequate to support registration of meropenem-vaborbactam treatment regimens of up to two weeks in duration. However, the applicant's argument that there were no treatment-related adverse effects from either vaborbactam or meropenem alone or in combination in rats or dogs was not accepted by CHMP. Subsequently, the applicant agreed to amend the Vabomere SmPC to include the following text in section 5.3:

'In repeat dose toxicity studies in dogs, minimal hepatic inflammation was observed after 14 days and 28 days of exposure to vaborbactam alone or combined meropenem/vaborbactam'

Regarding the environmental impact of Vaborbactam, the available data do not allow to conclude definitively on the potential risk of vaborbactam to the environment. Likewise, evaluation of the phototoxic potential of vaborbactam remains outstanding. All ERA outstanding data (results of studies OECD 218, 308, 209 and 106) will need to be submitted for assessment not later than the end of June 2019.

2.3.7. Conclusion on the non-clinical aspects

All non-clinical issues have been resolved. CHMP agreed that the non-clinical data do not point to any major concerns and that the clinically relevant findings have been adequately addressed in the Vabomere SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study; **Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number of Subjects Enrolled**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Safety and PK **Study 402**	To assess the safety, tolerability, and PK of single and multiple intravenous doses of vaborbactam when administered to healthy adult subjects.	Randomized, placebo-controlled, double-blind, single-ascending dose alone for first 6 cohorts followed by multiple ascending doses for remaining 4 cohorts	**SAD Phase** Placebo Vaborbactam 250 mg IV Vaborbactam 500 mg IV Vaborbactam 750 mg IV Vaborbactam 1 g IV Vaborbactam 1.25 g IV Vaborbactam 1.5 g IV **MAD Phase** Placebo Vaborbactam 250 IV q8h x 7 days Vaborbactam 1 g IV q8h x 7 days Vaborbactam 1.5 g IV q8h x 7 days Vaborbactam 2 g IV q8h x 7 days	80	Healthy	Up to 7 days

Type of Study; **Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number of Subjects Enrolled**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Safety and PK **Study 501**	To evaluate the safety, tolerability, and PK of meropenem and vaborbactam when administered alone and in combination as a single dose and in multiple doses to healthy adult subjects.	Randomized, placebo-controlled, double-blind, single- and multiple-ascending dose study	**Cohorts 1-5**: subjects received three 3-hour infusions of study drug first as single doses and then q8h for 7 days. **Cohort 6:** Subjects received 1-hour infusions of study drug first as single doses and then q8h for 7 days. Each dose cohort consisted of placebo, meropenem, and meropenem-vaborbactam groups. The first cohort also included a vaborbactam 250 mg treatment group, and the sixth cohort included a vaborbactam 2 g treatment group. The meropenem-vaborbactam doses were: 1 g-250 mg; 1 g/1 g; 1g-1.5 g; 1 g-2 g, and 2 g/2 g	94	Healthy	Up to 7 days

Type of Study; **Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number of Subjects Enrolled**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Safety and PK **Study 503**	Assessment of the safety and tolerability of 3 doses of meropenem-vaborbactam Assessment of plasma, ELF and AM concentrations of 3 doses of meropenem-vaborbactam to healthy adult subjects.	Open-label epithelial lining fluid study	Meropenem 2 g-vaborbactam 2 g IV q8h × 3 doses	26	Healthy	Three doses

Type of Study; **Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects Enrolled**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Safety and PK **Study 504**	To evaluate the serum and urine PK of a single dose of meropenem-vaborbactam when administered in patients with renal insufficiency and patients receiving HD therapy as compared to normal healthy volunteers. To evaluate the number and severity of TEAEs of a single dose of meropenem-vaborbactam when administered in patients with renal insufficiency and patients receiving HD therapy as compared to normal healthy volunteers.	Open-label, single-dose study of meropenem-vaborbactam in subjects with varying degrees of renal impairment	Meropenem 1 g-vaborbactam 1 g IV, single dose	41	Healthy; Patients with renal insufficiency	Single dose

Type of Study; **Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number of Subjects Enrolled**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Safety; Efficacy and PK **Study 505**	To assess the safety, tolerability, efficacy, and population PK of meropenem-vaborbactam in subjects with cUTI or AP	Multicenter, double-blind, double-dummy, randomized, parallel-group study of meropenem-vaborbactam versus piperacillin/tazobactam in the treatment of cUTI, including AP	Meropenem 2 g-vaborbactam 2 g IV q8h with each dose infused for 3 hours for up to 10 days Piperacillin 4 g/tazobactam 0.5 g IV infused in 100 mL normal saline over 30 min plus 250 mL normal saline IV infused over 3 hours q8h for up to 10 days After ≥15 IV doses, subjects could be switched to oral levofloxacin (500 mg q24h) to complete a total treatment course (IV plus oral) of 10 days. Treatment could go up to 14 days if clinically indicated in subjects with concurrent bacteremia.	550	Patients with cUTI, including AP	Minimum of 15 doses of IV therapy 10 days of total treatment (IV plus oral), but up to 14 days in subjects with baseline bacteremia

Type of Study; **Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number of Subjects Enrolled**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Safety, Efficacy and PK **Study 506**	To evaluate the safety, tolerability, efficacy, and PK of meropenem 2g-vaborbactam 2g in subjects with selected serious infections, suspected or known to be due to CRE	Randomized, open-label study of meropenem-vaborbactam versus best available therapy in the treatment of selected serious infections due to known or suspected CRE	Meropenem 2 g-vaborbactam 2 g IV q8h, with each dose infused for 3 hours for up to 14 days BAT with the following IV antibiotics either in combination or alone for up to 14 days: carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycosides (amikacin, tobramycin, or gentamicin), polymyxin B, and ceftazidime-avibactam	77	cUTI or AP, cIAI, HABP, VABP, and bacteremia	7 days to 14 days
Retrospective **Study 506NH**	Capture information and analyze the natural history, of patients with serious infections caused by CRE.	Retrospective	Not Applicable	257 cases reviewed	Patients with CRE	Not Applicable

2.4.2. Pharmacokinetics

The following table shows the clinical studies in which PK data were collected:

Table 2 Studies involving the examination of the PK properties of meropenem and/or vaborbactam

Study Number	Phase	Study Design	Dosing	PK Sampling Scheme(s)
Study 402	I	Phase I, randomized, double-blind, placebo-controlled, ascending single- and multiple-dose study evaluating safety, tolerability and PK in healthy adult subjects	Vaborbactam-single and multiple (q8h for 8 to 10 days); 250 – 2000 mg as 3-h infusion	Intensive blood sampling on Days 1 and 8/10; urine collected over 48 hours
Study 501	I	Phase I, randomized, double-blind, placebo controlled, single- and multiple-ascending-dose study in healthy adult subjects	Single and multiple doses of meropenem and vaborbactam alone or in combination (see summary for specifics)	Intensive blood sampling on multiple days; urine collected over 48 hours on multiple days (see summary for specifics)
Study 503	I	Phase I, single-center, randomized, open-label study evaluating the plasma, epithelial lining fluid and alveolar macrophage concentrations in healthy adult subjects	Meropenem 2g – vaborbactam 2g over 3-h q8h (3 doses)	Intensive blood sampling; BAL performed based upon randomized schedule
Study 504	I	Phase I, multicenter, open-label, single-dose study evaluating the pharmacokinetics and safety of meropenem and vaborbactam in subjects with varying degrees of renal impairment	Meropenem 1 g-vaborbactam 1 g over 3-h (1 dose)	Intensive blood sampling over 24 hours after the dose; urine collected over 72 hours
Study 505	III	Phase III, multicenter, randomized (1:1), parallel-group, double-blind, double dummy study	Meropenem 2 g-vaborbactam 2 g over 3-h q8h for at least 15 doses and up to 10 days (14 days in subjects with bacteremia)	Day 1 at 0.5 and 2-3 h after the end of the first infusion; Day 3 within 0.5 h of end of infusion
Study 506	III	Phase III, multicenter, randomized (2:1), open-label study of meropenem-vaborbactam versus best available therapy in subjects with serious infections due to known or suspected carbapenem-resistant Enterobacteriaceae	Meropenem 2 g-vaborbactam 2 g over 3-h q8h for 7-14 days	Day 1 at 0.5 and 2-3 h after the end of the first infusion; Days 3 and 5 within 0.5 h of end of infusion

Absorption

Study 402 was a double-blind, randomised, placebo-controlled, sequential ascending single and multiple dose study of vaborbactam (RPX7009) administered alone using 3-h intravenous infusions.

Table 3 Study design for single-ascending dose (SAD) cohorts 1-6 and multiple-ascending dose (MAD) cohorts 7-10

Cohort	Number of Subjects		Dose Level of	Single Dose	Multiple Dose
	RPX7009	Placebo	RPX7009 (mg)	(3 hour infusion)	(3 hour infusion, q8h)
1	6	2	250	Day 1	
2	6	2	500	Day 1	
3	6	2	750	Day 1	
4	6	2	1000	Day 1	
5	6	2	1250	Day 1	
6	6	2	1500	Day 1	
7	6	2	250	Day 1	Days 2 to 8
8	6	2	1000	Day 1	Days 2 to 8
9	6	2	1500	Day 1	Days 2 to 8
10	6	2	2000	Day 1	Days 4 to 10

Cmax for vaborbactam occurred at the end of the infusion. After single dose and after multiple dosing the mean Cmax and AUC_{0-8} increased in a dose-proportional manner (based on the linear regression model and the ANOVA model applied to group means of the dose-normalised Cmax and AUC_{0-t}.).

There was no evidence of accumulation in plasma after multiple dosing, consistent with the short $t_{1/2}$ (<2 hours). The mean ratio of Day 7/Day 1 Cmax was from 0.951 to 0.983 and that for Day 7 AUC_{0-t}/Day 1 AUC_{0-inf} was from 0.944 to 1.00.

The pre-infusion and the end-of-infusion plasma concentrations on Days 3, 5 and 7 in cohorts 7 through 9 and on Days 5, 7 and 9 in cohort 10 indicated that steady state was achieved prior to Day 3.

Table 4 Mean(SD) vaborbactam PK parameters following multiple IV infusions of vaborbactam-study 402

Parameter	250 mg q8h	1000 mg q8h	1500 mg q8h	2000 mg q8h
C_{max} (µg/mL)	4.81 (1.04)	21.3 (6.63)	33.4 (4.48)	40.9 (4.68)
AUC_{0-8} (µg•h/mL)	16.3 (3.56)	74.6 (17.9)	118 (15.3)	145 (15.8)
$t_{1/2}$ (h)	1.17 (0.131)	1.43 (0.359)	1.65 (0.262)	1.66 (0.0965)
CLt (L/h)	15.2 (2.56)	14.1 (3.42)	12.9 (1.71)	14.0 (1.78)
V_d (L)	25.7 (5.57)	28.0 (5.66)	30.3 (3.48)	33.4 (4.52)
fe_{0-8} (%)	79.9 (16.3)	82.8 (10.3)	86.8 (2.48)	91.6 (5.36)
CL_R (L/h)	12.7 (3.68)	11.7 (3.75)	11.2 (1.72)	12.8 (2.05)

Study 501 was a randomised, double-blind and placebo-controlled study intended to evaluate the effects of co-administering single and multiple doses of meropenem and vaborbactam. Doses of vaborbactam and meropenem evaluated were 250 mg/1 g; 1 g/1 g; 1.5 g/1g; 2 g/1 g; and 2 g/2 g.

- Cohorts 1-5 received 3-hour infusions as single doses and then every 8 hours for 7 days while Cohort 6 received 1-hour infusions.
- Cohort 1 included vaborbactam 250 mg alone and Cohort 6 included vaborbactam 2 g alone.

Peak and trough levels indicated that steady state was achieved by day 2 for each of meropenem, its open ring form and vaborbactam. All plasma samples were BLQ for meropenem and vaborbactam after the 12-h time point and all were BLQ for the meropenem open lactam metabolite after the 24-h time point.

Table 5 Geometric mean (geometric CV%) for select PK parameters-meropenem

Cohort/ Dose[a]	Treatment	N	C_{max}		AUC_{0-t}		AUC_{0-inf}		$t_{1/2}$	
			Single dose	Multiple dose	Single dose	Multiple dose	Single dose	Multiple dose	Single dose	Multiple dose
1 1000:250	Meropenem	32	16.85 (44.70%)	16.51 (57.98%)	51.09 (43.53%)	49.25 (55.68%)	51.63 (43.29%)	49.68 (55.41%)	1.020 (42.80%)	0.9676 (55.52%)
	Combination	16	18.57 (32.40%)	15.73 (34.45%)	55.63 (30.49%)	47.14 (32.51%)	56.10 (30.52%)	47.61 (32.50%)	0.9526 (28.81%)	0.9740 (33.41%)
2 1000:1000	Meropenem	13	18.58 (47.38%)	16.42 (38.40%)	57.60 (47.60%)	49.86 (39.25%)	58.12 (47.66%)	50.15 (39.10%)	0.9627 (35.28%)	0.8925 (20.34%)
	Combination	10	19.85 (46.60%)	16.97 (32.11%)	63.31 (50.88%)	53.92 (36.52%)	64.10 (50.97%)	54.43 (36.31%)	1.136 (45.15%)	0.9427 (24.04%)
3 1000:1500	Meropenem	19	20.90 (34.81%)	23.33 (59.08%)	64.19 (38.36%)	66.99 (55.90%)	64.64 (38.19%)	67.36 (55.73%)	0.8918 (31.49%)	0.8723 (33.21%)
	Combination	14	20.37 (48.31%)	19.91 (50.30%)	63.48 (47.91%)	64.49 (47.97%)	64.19 (48.42%)	64.94 (47.90%)	1.019 (44.37%)	0.8825 (28.88%)
4 1000:2000	Meropenem	19	17.28 (37.37%)	15.90 (43.85%)	53.19 (42.62%)	50.74 (32.70%)	53.74 (43.04%)	51.22 (32.03%)	1.013 (47.52%)	0.9759 (52.62%)
	Combination	14	17.53 (23.67%)	15.77 (29.17%)	54.55 (27.19%)	47.88 (20.70%)	55.01 (27.02%)	48.30 (20.62%)	0.9101 (45.54%)	1.067 (39.76%)
5 2000:2000	Meropenem	20	40.88 (53.56%)	46.00 (59.58%)	124.7 (49.10%)	133.7 (56.41%)	125.7 (48.93%)	135.1 (56.65%)	1.062 (54.91%)	1.004 (45.99%)
	Combination	16	45.70 (35.69%)	42.53 (48.50%)	137.3 (45.02%)	135.7 (46.81%)	139.3 (45.77%)	136.8 (46.66%)	1.304 (82.63%)	1.178 (56.46%)
6[b] 2000:2000	Meropenem	4	92.29 (13.62%)	88.95 (4.886%)	187.2 (11.71%)	178.6 (17.23%)	188.2 (10.94%)	180.4 (19.47%)	1.031 (31.18%)	1.287 (62.79%)
	Combination	16	90.11 (28.32%)	93.99 (21.60%)	204.4 (33.08%)	202.8 (34.09%)	205.8 (32.81%)	203.6 (33.82%)	1.021 (35.53%)	1.118 (40.76%)

There was a relatively wide range of meropenem clearance estimates from ~0.12 to 0.4 L/h/kg, which is consistent with a literature report of a mean meropenem clearance of 0.22 L/h/kg.

The meropenem mean plasma Cmax and AUC_{0-8} estimates after 2g/2g doses resembled values reported in the literature (39.8 µg/mL and 127 µg•h/mL) after administration of 2 g meropenem over 3 hours to healthy adults. The inactive metabolite of meropenem showed some accumulation with multiple dosing, especially after 2 g doses, but AUCs were generally about $1/5^{th}$ of those for parent drug.

When comparing PK between Cohorts 1-5 (3-h infusion) vs. Cohort 6 (1-h infusions), the meropenem and vaborbactam half-life estimates were similar. As expected, Cmax estimates for both were higher after the 1-h infusion. AUCs were also higher after 1-h infusions, which may reflect the PK sampling scheme early in the post-dose period, i.e. since CL of meropenem and vaborbactam is relatively rapid, taking the first PK sample at 1.5 h may result in an underestimation of AUC after 3-h infusions.

Table 6 Geometric mean (geometric CV%) for select PK parameters-vaborbactam(RPX7009)

Cohort/ Dose[a]	Treatment	N	C_{max}		AUC_{0-t}		AUC_{0-inf}		$t_{1/2}$	
			Single dose	Multiple dose	Single dose	Multiple dose	Single dose	Multiple dose	Single dose	Multiple dose
1 1000:250	RPX7009	40	5.182 (41.80%)	4.874 (36.97%)	16.74 (42.94%)	16.21 (46.77%)	17.19 (42.70%)	16.62 (46.87%)	1.088 (57.17%)	1.117 (50.27%)
	Combination	16	5.284 (40.19%)	4.568 (39.47%)	16.53 (38.96%)	14.60 (39.75%)	16.99 (38.29%)	15.07 (39.66%)	1.057 (52.01%)	1.158 (38.60%)
2 1000:1000	RPX7009	5	21.75 (42.33%)	—	74.59 (48.51%)	—	75.44 (48.01%)	—	1.459 (69.55%)	—
	Combination	10	23.34 (46.06%)	19.90 (29.65%)	77.99 (47.07%)	68.43 (38.95%)	79.37 (46.24%)	69.22 (39.04%)	1.503 (49.82%)	1.323 (61.84%)
3 1000:1500	RPX7009	7	36.25 (40.96%)	—	116.9 (37.31%)	—	117.8 (36.64%)	—	1.191 (49.33%)	—
	Combination	14	36.88 (36.99%)	32.60 (32.53%)	123.6 (40.37%)	114.7 (38.36%)	124.2 (40.36%)	115.4 (38.17%)	1.335 (44.72%)	1.431 (61.24%)
4 1000:2000	RPX7009	7	37.95 (28.83%)	—	125.0 (35.37%)	—	125.8 (35.05%)	—	1.272 (54.81%)	—
	Combination	14	40.00 (22.73%)	34.74 (34.55%)	132.1 (29.50%)	113.2 (29.78%)	132.8 (29.20%)	114.1 (29.58%)	1.373 (46.69%)	1.510 (56.32%)
5 2000:2000	RPX7009	8	49.53 (57.43%)	—	150.8 (54.52%)	—	151.9 (54.47%)	—	1.380 (37.65%)	—
	Combination	16	50.10 (42.55%)	54.65 (47.11%)	163.1 (43.90%)	192.6 (44.95%)	165.3 (45.18%)	194.6 (45.24%)	1.883 (61.94%)	1.639 (50.46%)
6[b] 2000:2000	RPX7009	4	95.51 (20.00%)	115.0 (19.39%)	190.7 (12.41%)	209.6 (9.477%)	191.5 (11.05%)	210.3 (9.335%)	1.185 (35.97%)	1.640 (46.31%)
	Combination	16	94.04 (42.59%)	115.9 (35.76%)	206.1 (43.16%)	225.8 (42.45%)	206.8 (43.13%)	226.7 (42.50%)	1.363 (40.17%)	1.589 (39.21%)

The ANOVA comparisons using data from Cohorts 1-5 for meropenem and vaborbactam showed that for Cmax, AUC_{0-t} and AUC_{0-inf} the 90% CI for the LS GMRs were within 0.8, 1.25, indicating that exposures were not significantly impacted by co-administration. In each case the means were slightly higher on co-administration for all three PK parameters. The weight normalised clearance values for meropenem and vaborbactam were generally similar regardless of co-administration, supporting the conclusion that there was no important interaction.

Qualitative comparisons of the geometric mean Cmax, AUC_{0-t} and AUC_{0-inf} by cohort suggested that the meropenem PK exposures increased in a greater than dose proportional manner. The trend was apparent but not so consistent with vaborbactam, for which the dose proportionality criteria for AUC_{0-inf}, AUC_{0-t} and Cmax were not strictly met for all comparisons but the 90% confidence for the power coefficient for AUC_{0-inf} did contain 1.00 and all other power coefficients were close to 1.00.

Distribution

Vaborbactam binding in serum was less than 30% in all animal species and 33% (range: 29 – 37%) in humans. Percent binding was independent of vaborbactam concentration. The plasma protein binding of meropenem is reported to be approximately 2%.

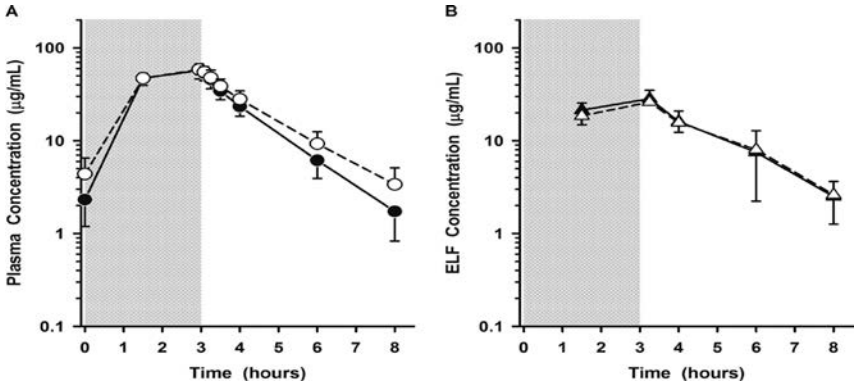
Study 503 included 26 healthy subjects (19 male; mean age 38.5 years) who received 3 IV doses of 2g/2g meropenem-vaborbactam as 3-hour infusions every 8 hours. Subjects were randomised to one of 5 bronchoscopy sampling time points after the start of the third infusion (at 1.5, 3.25, 4, 6 or 8 hours). There were 5 subjects per time group that completed dosing and BAL.

Following the third infusion the mean plasma meropenem Cmax and AUC_{0-8} were 58.2 µg/ml and 185.5 µg·h/mL, respectively. The mean concentrations of meropenem in plasma and ELF ranged from 1.36 to 41.2 µg/ml and 2.51 to 28.3 µg/ml, respectively. The concentrations of meropenem in the alveolar macrophages were below the quantifiable limit for all samples.

The mean Cmax and AUC_{0-8} for plasma vaborbactam were 59.0 µg/mL and 204.2 µg·h/ml, respectively. The mean concentrations of vaborbactam in plasma and ELF ranged from 2.74 to 51.1 µg/ml and 2.61 to 26.1 µg/ml, respectively. Alveolar macrophage concentrations of RPX7009 were measurable for all samples and ranged from 1.26 to 93.9 µg/ml.

Similar concentrations and time courses applied to meropenem and vaborbactam in plasma and ELF.

Figure 3 Mean (±SD) profile of Meropenem and Vaborbactam in Plasma (A) and Epithelial Lining Fluid (B) around the 3rd dose of meropenem (2 g) and vaborbactam (2 g); 3-h IV infusion



- The meropenem AUC_{0-8} values based on mean and median ELF concentrations were 111.7 and 102.4 µg·h/ml, respectively, and the ratio of ELF to total plasma meropenem concentrations based on the mean and median AUC_{0-8} values were 0.63 and 0.58, respectively.
- The ratios of ELF to unbound plasma meropenem concentrations (protein binding = 2%) based on the mean and median AUC_{0-8} values were 0.65 and 0.59, respectively.

Table 7 Ratios of ELF to total plasma concentrations of meropenem

BAL Sampling Time	ELF to Plasma
1.5-hour	0.525 ± 0.107
3.25-hour	0.590 ± 0.079
4-hour	0.705 ± 0.302
6-hour	1.037 ± 0.475
8-hour	2.133 ± 1.366

The mean ratios of ELF and AM to simultaneous plasma concentration for vaborbactam during the 8-hour period after drug administration ranged from 0.45 to 1.01 and 0.062 to 2.58, respectively. Two subjects in the 6-hour group had the highest reported concentrations in AM (35.4 and 93.9 µg/ml), which inflated the mean ratio at 6 hours. The report states that these results may have reflected very high concentrations of red blood cells in their BAL fluid.

- The AUC_{0-8} values based on mean and median ELF concentrations were 105.1 and 96.7 µg·hr/ml, respectively, and the ratio of ELF to total plasma concentrations based on the mean and median AUC_{0-8} values were 0.53 and 0.48, respectively.
- The ratios of ELF to unbound plasma concentrations (protein binding = 33%) based on the mean and median AUC_{0-8} values were 0.79 and 0.72, respectively.

Table 8 Ratios of ELF and plasma concentrations of vaborbactam (RPX7009)

BAL Sampling Time	ELF to Plasma	AM to Plasma
1.5-hour	0.450 ± 0.123	0.062 ± 0.029
3.25-hour	0.508 ± 0.096	0.165 ± 0.163
4-hour	0.570 ± 0.159	0.191 ± 0.101
6-hour	0.705 ± 0.329	2.58 ± 3.57
8-hour	1.009 ± 0.391	1.603 ± 1.103

Elimination

In **study 402** mean values for the percent urinary excretion fe_{0-8} following repeated dosing ranged from 79.9% for 250 mg to 91.6% for 2 g doses. Renal clearance constituted ~80-90% of total clearance. Most of the drug that appeared in urine did so within the first 4 hours and almost all appeared within 8 hours.

In **study 501** 40 to 60% of the meropenem dose and 75 to 95% of the vaborbactam dose was excreted intact in the urine over 24 to 48 h. There was a trend for the median renal clearance to be lower with combination therapy but the range of values was similar across all treatments (single- versus multiple-dose, alone or in combination). The high renal clearance of vaborbactam suggested a role for active secretion. The data from study 501 data indicated that the % of active renal secretion for meropenem is ~ 3% and for vaborbactam is ~ 36%.

Table 9 Active Renal Secretion of Meropenem and Vaborbactam in Study 501

Parameter	**Meropenem**	**Vaborbactam**
CLr (L/hr)	7.8	8.9
CLnr (L/hr)	7.3	2.0
CLtotal (L/hr)	15.1	10.9
fu (free fraction)	0.98	0.67
fu*GFR (L/hr)	7.35	5.03
% Active renal secretion	**3%**	**36%**

*GFR = 125 ml/min = 7.5 L/hr

Since the amount of active renal secretion for vaborbactam is estimated at > 25%, the applicant has committed to conduct new transporter studies to identify the transporter(s) responsible for the active secretion of vaborbactam.

Metabolism

- The potential for vaborbactam to be metabolised in the liver was evaluated in two *in vitro* studies in which it was incubated with liver microsomes from rats, dogs and humans at 37°C for 60 or 120 minutes. Vaborbactam was stable under these incubation conditions.

- Meropenem undergoes limited hydrolysis (~30%) *in vivo* to form an inactive open lactam metabolite via non-enzymatic degradation mechanisms. It is relatively stable to dehydropeptidase I, which is found mostly in renal tissue but occurs elsewhere, including in lung tissue.

The *in vitro* investigations relevant to metabolism reported in the application dossier were incomplete. The applicant has committed to address the deficiencies as a post-marketing commitment.

Population PK analyses

Separate POPPK models were developed for meropenem and vaborbactam. The initial models used pooled concentration-time data from studies 501 and 504 (93 healthy subjects) and sparse sampling from infected patients in 505 (N=271) and 506 (N=23). In response to CHMP's questions and comment, the revised models were based on 4264 meropenem concentrations from 413 subjects/patients and 4082 vaborbactam concentrations from 414 subjects/patients. In addition, 162 meropenem and 122 vaborbactam plasma concentrations that had previously been deemed outliers were included in the revised analyses.

In the original analyses, the inter-individual variability (IIV) in meropenem CL, Vc and Vp were 44.8, 44.3 and 11.3%, respectively, while the IIV in vaborbactam CL, Vc, CLd and Vp were 42.4, 35.6, 30.8 and 17.5%, respectively. In the updated analyses the IIV is increased due to the inclusion of the previously-identified outlier observations.

The applicant submitted the PC-VPC plots for the updated POPPK models. The prediction intervals of the simulated values were generally in good agreement with prediction corrected observed data. The meropenem model slightly under-estimated the data in moderate and severe renal impairment while the vaborbactam model generally over-estimated the data, which was more noticeable in the subset of data with normal renal function. However, these biases were limited and were considered unlikely to affect the overall conclusions from the POPPK analyses.

The covariates selected for evaluation were based upon prior experience with meropenem suggesting that body size and renal function were the only covariates of clinical relevance in this population. For vaborbactam, covariate analyses included a broader range of variables to assess the potential impact of age, infection status, body size, and renal function on the PK of vaborbactam.

Using the updated POPPK models, the predicted values were compared for healthy subjects and patients dosed with meropenem-vaborbactam 2g/2g q8h using 3-h infusions. The table below shows values only for patients with normal renal function (see footnotes). The pattern that was observed with the initial models (i.e. higher exposures in patients vs. healthy subjects) was maintained, with the highest values in patients from 506.

Table 10 Mean (CV%) meropenem and vaborbactam plasma steady-state PK parameters in infected patients and healthy volunteers

Study	C_{max} (µg/mL)	$AUC_{0-24, steady-state}$ (µg•h/mL)	$t_{1/2}$ [a] (h)	CL [b] (L/h)
Meropenem				

Study 501[c]	42.5 (48.5)	417[e] (45.8)	1.30 (82.6)	14.9 (45.8)
Study 505[d]	56.4 (53.3)	587 (54.7)	1.61 (21.4)	12.5 (54.4)
Study 506[e]	77.6 (40.1)	845 (42.4)	1.91 (24.1)	8.64 (50.2)
Vaborbactam				
Study 501[c]	54.7 (47.1)	496[f] (45.2)	1.64 (50.5)	10.7 (43.1)
Study 505[d]	74.6 (80.2)	941 (127)	1.95 (119)	9.27 (45.9)
Study 506[e]	117 (96.1)	1671 (104)	3.63 (104)	6.66 (67.1)

a. $t_{1/2}$ is based upon the terminal elimination phase.

b. clearance calculated by noncompartmental methods for Study 501 and derived from post-hoc PK parameters for Study 505 and Study 506.

c. N = 8, Cohort 5 from Study 501 who received meropenem 2 g/vaborbactam 2 g over 3 h.

d. N = 160 patients from Study 505 included in the population PK analysis who had eGFR greater than 80 ml/min/1.73 m^2.

e. N = 20, patients from Study 506 included in the population PK analysis who had eGFR greater than 80 ml/min/1.73 m^2.

f. $AUC_{0\text{-}24,\ steady\text{-}state}$ calculated as $AUC_{0\text{-}inf,\ Day\ 1}$ times 3 as a single dose was given on Day 1 in Study 501.

Analyses based on updated POPPK models including Phase 3 patients with renal impairment and data from outliers also demonstrated the difference between 505 and 506, as shown in the following tables:

Table 11 Summary [mean (CV%)] of key meropenem PK parameters in Phase 3 patients receiving meropenem 2 g – vaborbactam 2 g q8h derived from the fit of the updated meropenem population PK model

Parameter	Rempex 505 (n = 272[a])	Rempex 506 (n = 50[a])	Pooled (n = 322)
C_{max} (µg/ml)	57.4 (48.3)	90.3 (103)	62.5 (73.5)
$AUC_{0\text{-}24,\ Day\ 1}$ (µg•h/ml)	628 (50.5)	982 (102)	683 (74.1)
$AUC_{0\text{-}24,\ steady\text{-}state}$ (µg•h/ml)	610 (50.5)[b]	997 (82.7)[b]	668 (67.0)[b]
CL (L/h)	11.1 (61.6)	6.23 (66.0)	10.3 (65.0)
$t_{1/2,\ \alpha}$ (h)	0.769 (20.8)	0.907 (16.6)	0.790 (21.0)
$t_{1/2,\ \beta}$ (h)	1.88 (38.4)	3.05 (75.4)	2.06 (57.9)

a. Based upon protocol-mandated dose adjustment guidelines, 28 patients with renal impairment in Study 505 received a dose of meropenem 1 g – vaborbactam 1 g; similarly, nine patients in Study 506 received reduced doses of meropenem/vaborbactam due to renal impairment.

b. $AUC_{0\text{-}24,\ steady\text{-}state}$ estimates were not available for USUBJID 112004508 and 604004502 from Study 505 and USUBJID 300001616 and 300005602 from Study 506 as these four patients received less than three doses of meropenem/vaborbactam.

Table 12 Summary [mean (CV%)] of key vaborbactam PK parameters in Phase 3 patients receiving meropenem 2g – vaborbactam 2 g q8h derived from the fit of the updated

vaborbactam population PK model

Parameter	Rempex 505 (n = 272[a])	Rempex 506 (n = 50[a])	Pooled (n = 322)
C_{max} (µg/mL)	76.8 (72.7)	111 (86.1)	82.1 (78.7)
$AUC_{0\text{-}24,\ Day\ 1}$ (µg•h/ml)	895 (71.9)	1270 (87.3)	953 (78.1)
$AUC_{0\text{-}24,\ steady\text{-}state}$ (µg•h/ml)	969 (117)[b]	1640 (105)[b]	1070 (118)[b]
CL (L/h)	7.98 (53.4)	4.78 (78.8)	7.50 (57.9)
$t_{1/2,\ \alpha}$ (h)	0.370 (6.49)	0.373 (7.40)	0.371 (6.63)
$t_{1/2,\ \beta}$ (h)	2.62 (124)	5.81 (107)[c]	3.10 (129)[c]

a. Based upon protocol-mandated dose adjustment guidelines, 28 patients with renal impairment in Study 505 received a dose of meropenem 1 g – vaborbactam 1 g; similarly, nine patients in Study 506 received reduced doses of meropenem/vaborbactam due to renal impairment

b. $AUC_{0\text{-}24,\ steady\text{-}state}$ estimates were not available for USUBJID 112004508 and 604004502 from Study 505 and USUBJID 300001616 and 300005602 from Study 506 as these four patients received less than three doses of meropenem/vaborbactam

c. $t_{1/2,\ \beta}$ estimates were excluded for USUBJID 300001613 and 300001615 from Study 506 due to extremely high values (63.4 and 50.5 h, respectively).

Special populations

Impaired renal function

Study 504 evaluated single doses of 1g/1g meropenem-vaborbactam infused over 3h in 4 groups. Subjects on haemodialysis (HD; Group 5) received 2 doses immediately before and after the session. Groups were:

- Group 1: Mild renal insufficiency $eGFR_{MDRD}$ 60-89 mL/min/1.73m^2
- Group 2: Moderate renal insufficiency $eGFR_{MDRD}$ 30 to < 60 ml/min/1.73m^2
- Group 3: Severe renal insufficiency $eGFR_{MDRD}$ < 30 ml/min/1.73m^2 not receiving HD
- Group 4: Normal renal function $eGFR_{CG}$ ≥ 90 mL/min
- Group 5: ESRD receiving HD

In general, Cmax, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ for each of meropenem, the open ring form and vaborbactam increased with decreasing renal function along with the $t_{1/2}$. For both meropenem and vaborbactam the $Ae_{0\text{-}48}$ decreased with decreasing renal function. Linear regression analyses indicated that CLt and CLr increased with increasing renal function as measured using $eGFR_{MDRD}$.

Table 13 Geometric mean (geometric CV%) for select PK parameters-meropenem

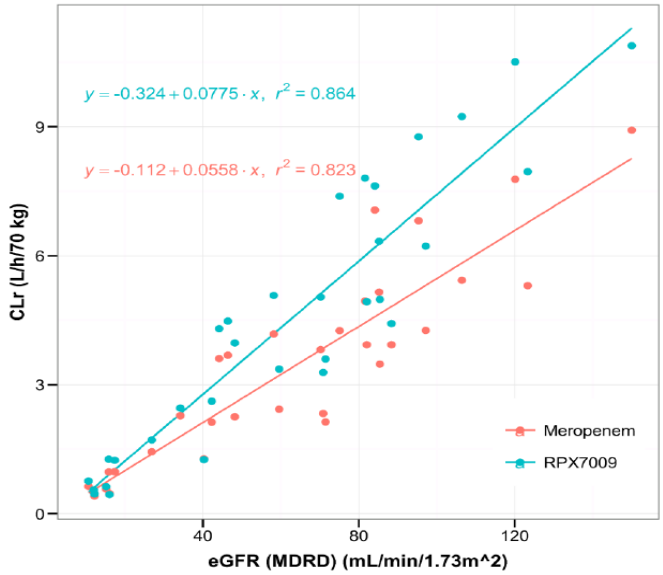
Group	N	C_{max} (µg/mL)	AUC_{0-t} (µg*h/mL)	AUC_{0-inf} (µg*h/mL)	CLt (L/h)	$t_{1/2}$ (h)
1: Mild impairment	8	31.7 (26.3%)	106 (30.4%)	107 (30.5%)	9.33 (30.5%)	1.42 (12.3%)
2: Moderate impairment	8	40.1 (15.4%)	169 (32.0%)	173 (32.9%)	5.80 (32.9%)	2.06 (37.1%)
3: Severe impairment	8	44.2 (25.8%)	355 (21.2%)	387 (24.3%)	2.59 (24.3%)	5.71 (38.6%)
4: Normal	8	26.7 (26.1%)	82.8 (31.9%)	83.5 (31.9%)	12.0 (31.9%)	1.28 (20.2%)
5: ESRD on dialysis (Day 1)	9	44.1 (18.0%)	268 (20.9%)	274 (21.1%)	3.65 (21.1%)	9.11 (25.2%)
5: ESRD off dialysis (Day 8)	8	46.6 (22.6%)	580 (32.0%)	603 (31.6%)	1.66 (31.6%)	9.28 (21.8%)

Table 14 Geometric mean (geometric CV%) for select PK parameters-vaborbactam

Group	N	C_{max} (µg/mL)	AUC_{0-t} (µg*h/mL)	AUC_{0-inf} (µg*h/mL)	CLt (L/h)	$t_{1/2}$ (h)
1: Mild impairment	8	29.2 (25.8%)	110 (25.9%)	112 (26.3%)	8.94 (26.3%)	1.86 (14.8%)
2: Moderate impairment	8	41.8 (17.4%)	212 (42.5%)	219 (44.2%)	4.56 (44.2%)	3.11 (50.3%)
3: Severe impairment	8	45.1 (25.9%)	524 (18.8%)	740 (36.1%)	1.35 (36.1%)	11.7 (58.3%)
4: Normal	8	27.1 (24.9%)	93.5 (34.0%)	94.7 (34.3%)	10.6 (34.3%)	1.62 (22.1%)
5: ESRD with dialysis (Day 1)	9	49.2 (20.0%)	519 (25.6%)	966 (62.7%)	1.04 (62.7%)	45.7 (78.7%)
5: ESRD between dialysis (Day 8)	8	55.0 (24.7%)	1550 (36.3%)	3550 (127%)[a]	0.282 (127%)[a]	54.3 (121%)[a]

For both compounds, $eGFR_{MDRD}$ explained significant portions of the inter-individual variability in CLr and CLt, with r^2 for the relationships above 0.85. The slope of the relationship between vaborbactam CLr and $eGFR_{MDRD}$ was steeper than that for the meropenem, which may be because vaborbactam non-renal clearance (CL_{NR}) is very low, resulting in a closer correlation between $eGFR_{MDRD}$ and CLt.

Figure 4 Relationship between eGFR and CLr of meropenem and vaborbactam



Note: linear regression analyses conducted separately for the two drugs. Data from Groups 1 through 4

Haemodialysis (HD) administered immediately following drug administration significantly increased the clearance of meropenem (mean 2.21-fold increase in CLt, $p<0.001$) and vaborbactam (mean 5.11-fold increase, $p=0.0235$) relative to administration on Day 8.

Other special populations

- Previous studies in subjects with hepatic impairment showed no effects of hepatic impairment on the PK of meropenem and studies in subjects with hepatic impairment have not been conducted for vaborbactam since there is no expected impact on vaborbactam PK.
- In the POPPK analyses sex was not a statistically significant predictor of the inter-individual variability (IIV) in meropenem or vaborbactam PK and AUC_{0-24} estimates were similar in males and females for both analytes.
- In the POPPK analyses race was not a statistically significant predictor of the IIV in meropenem or vaborbactam PK and AUC_{0-24} estimates were similar regardless of race for both analytes.
- For meropenem, body weight was a significant predictor of the IIV in both V_c and V_p but there was only a modest increase in V_c with increasing body weight and, although the relationship between V_p and body weight was tighter, the range of V_p values was small, especially in relation to V_c.
- For vaborbactam, height was a significant predictor of the IIV in CLt and BSA was a significant predictor of the IIV in V_c but relationships were less pronounced than for meropenem.
- In the POPPK analyses age was not a statistically significant predictor of the IIV in meropenem or vaborbactam PK.

Pharmacokinetic interaction studies

No clinical DDI studies were conducted. Vaborbactam is not a substrate for and does not inhibit or induce CYP isoenzymes. Vaborbactam does not appear to be a substrate of OAT1, OAT3 or OCT2, it was not a substrate of BCRP or P-gp under the study conditions and it did not significantly decrease the transport of probe substrates of BCRP, OAT1, OAT3, OCT2, OATP1B3 and BSEP.

Studies evaluating the potential for meropenem to interact with CYP450 enzymes are not available but there are no known interactions between carbapenems and substrates for CYP450 enzymes. A published study reported that meropenem is a substrate of OAT1 and OAT3.

2.4.3. Pharmacodynamics

Mechanism of action

Meropenem is a carbapenem that inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins (PBPs), which are bacterial enzymes involved in the biosynthesis of peptidoglycan.

Vaborbactam is a cyclic boronic acid pharmacophore that inhibits various class A and class C beta-lactamases but not Class B and D enzymes. In contrast to other approved beta-lactamase inhibitors (including avibactam) vaborbactam forms a covalent adduct between the boronate moiety and the catalytic serine residue. No ring-opening step is involved in this reversible inhibition. KPC inhibition by vaborbactam has an extremely slow reversal rate compared to that for other beta-lactamases and there is no inactivation of vaborbactam by KPC. Vaborbactam has no significant antibacterial activity at clinical concentrations.

Primary and Secondary pharmacology

In vitro activity and resistance

In vitro susceptibility testing was conducted using varying concentrations of meropenem in the presence of a fixed concentration of 8 µg/ml vaborbactam. The meropenem MIC determined in the presence of vaborbactam 8 µg/ml correlated better with efficacy in the *in vitro* PD model when simulating human PK on dosing with 2g/2g q8h using 3-hour infusions than the MIC determined in the presence of 4 µg/ml vaborbactam. The *in vitro* activity of meropenem-vaborbactam (MV) has been determined in 13 prospective and retrospective studies against a world-wide collection of >36,000 Gram-negative bacteria. Overall results for *Enterobacteriaceae* are shown in the following. Vaborbactam does not have a notable effect on the susceptibility of non-fermenters to meropenem.

Table 15 Summary of *in vitro* activities of meropenem-vaborbactam and meropenem against carbapenemase-negative strains of Enterobacteriaceae (N=105) with elevated carbapenem MIC

	Cumulative percent (%) of strains inhibited at each Meropenem MIC									
MIC (µg/mL)	**≤0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**>32**
MER	0.0	1.0	1.0	2.9	8.6	**51.4**	80.0	**95.2**	97.1	100.0
MER+VAB	6.7	12.4	32.4	**57.1**	72.4	89.5	**93.3**	98.1	99.0	100.0

A more major benefit for adding vaborbactam was observed when testing meropenem alone and the combination against ~1,900 KPC-producing enterobacteria with resistance to carbapenems.

Table 16 Summary of *in vitro* activities of meropenem-vaborbactam and meropenem against KPC-producing Enterobacteriaceae from various studies

		Cumulative percent (%) of strains inhibited at each Meropenem MIC									
Study (n)	**MIC (µg/mL)**	**≤0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**>32**
MVAB-MIC-JMI-031 (135)	MER	0.0	0.0	0.0	0.7	5.2	13.3	20.7	36.3	48.1	100
(Worldwide)	MER+VAB	59.3	77.0	91.1	96.3	98.5	99.3	100	100	100	100
MVAB-MIC-JMI-068 (203[a])	MER	0.0	0.0	0.0	1.9	7.4	21.2	33.0	47.8	59.1	100
(Worldwide)	MER+VAB	47.8	65.5	79.3	90.6	96.6	99.5	99.5	99.5	100	100
MVAB-MIC-SUNY-020 (125)	MER	0.0	1.7	2.5	6.6	19.8	44.6	73.6	78.5	85.1	94.2
(New York, US)	MER+VAB	80.2	86.0	90.1	97.5	99.2	99.2	99.2	99.2	99.2	99.2
MVAB-MIC-CHI-030 (129)	MER	0.0	0.0	0.0	0.0	0.0	1.6	8.5	25.6	38.0	42.6
(China)	MER+VAB	38.8	41.9	50.4	61.2	66.7	81.4	97.7	97.7	98.4	99.2
MVAB-MIC-JMI-004 (165)	MER	0.0	0.0	0.6	4.2	11.5	27.9	42.4	70.3	80.0	88.5
(Worldwide)	MER+VAB	83.0	86.1	92.1	93.9	97.0	98.8	98.8	100.0	100	100
MVAB-MIC-JMI-018 (150)	MER	0.0	0.0	0.0	0.0	2.7	13.3	32.7	56.7	70.00	76.7
(Worldwide)	MER+VAB	71.3	80.0	87.3	93.3	96.0	96.7	96.77	99.3	99.3	99.3
MVAB-MIC-IHMA-053 (991)	MER	0.0	0.0	0.0	0.0	4.1	11.9	24.5	39.6	53.7	100
(Worldwide)	MER+VAB	57.7	71.3	85.4	93.4	97.4	98.9	99.5	99.7	99.7	100

The MV MICs by KPC expressed displayed a trailing upper end of the distribution for KPC-2 and KPC-3.

Table 17 Frequency distribution (n) of MICs for meropenem-vaborbactam (vaborbactam at 8 mcg/mL) against KPC-producing Enterobacteriaceae by KPC variant

		MIC (µg/mL)											
Variant	N	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
KPC-2	612	295	42	39	67	79	46	27	11	4			2
KPC-3	371	159	13	18	68	58	34	12	4	2	2		1
KPC-5	2	1		1									
KPC-6	1	1											
KPC-9	2					2							
KPC-18	3	3											
Total	991	459	55	58	135	139	80	39	15	6	2		3

- The Ser130 residue of KPC-2 that is important for inhibition by avibactam does not play a role in its inhibition by vaborbactam. The Ki of vaborbactam decreased from 0.034 µM for the wild type KPC-2 to 0.011 µM for the Ser130Gly mutant.
- KPC mutants containing P174L or D179Y amino acid substitutions are resistant to ceftazidime potentiation with avibactam, but not with vaborbactam.
- The Trp105 residue plays a significant role in vaborbactam interaction with the KPC-2 enzyme but Trp105 substitutions had a minimal effect on the whole cell meropenem potentiation activity of vaborbactam.
- W105 substitutions significantly affect the kinetics of KPC-2-mediated hydrolysis. Meropenem potentiation by vaborbactam was not significantly affected by various W105 mutant proteins substitutions.
- Vaborbactam cannot restore susceptibility to meropenem in the presence of mechanisms of resistance to meropenem mediated by mutations in porin genes and multidrug resistance efflux pumps.

PK-PD analyses leading to meropenem dose selection

The PK-PD index is %*f*T>MIC and the PDT that best correlates with efficacy *in vitro*, in animals and in humans is a %*f*T>MIC of 30-40%. Using the maximum approved dose of meropenem (2 g q8h) and 3-hour infusions the PTA at a 40% %*f*T>MIC PDT is 100% of simulated subjects for meropenem MICs up to 8 µg/ml. In contrast the standard approved dose of 1 g q8h over 30 minutes achieves the target exposure for ~90% of simulated patients with MICs up to 1 µg/ml.

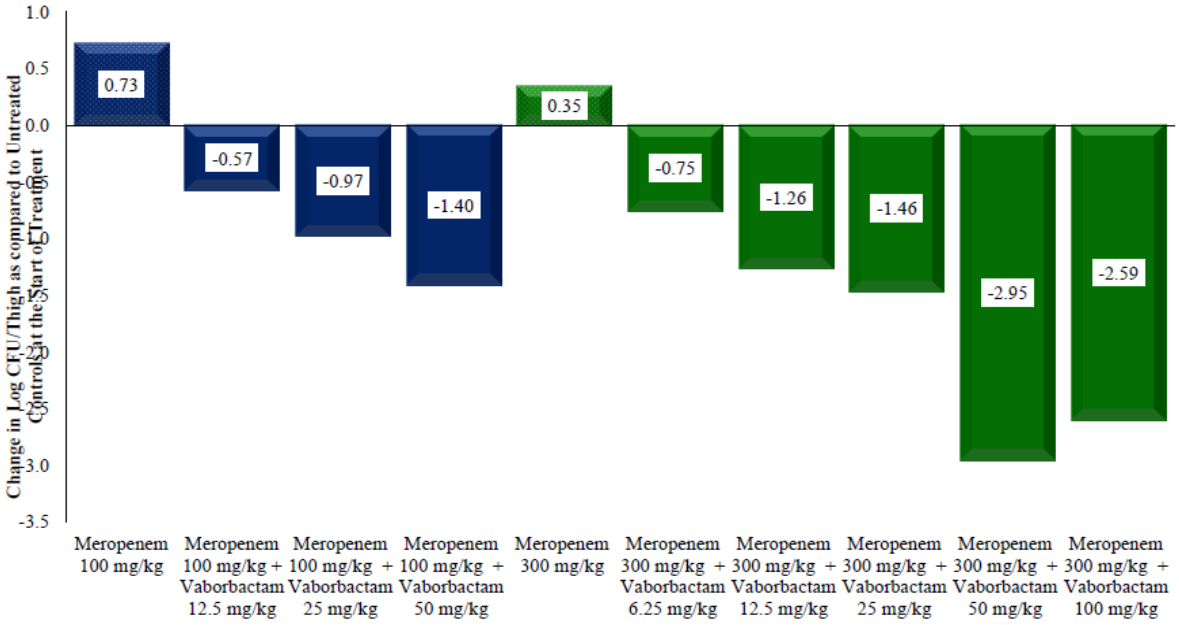
PK-PD analyses leading to vaborbactam dose selection

The approach was to simulate the exposure of meropenem in animal and *in vitro* models of infection to determine the vaborbactam exposure needed to achieve maximal bactericidal activity and suppresses resistance development in KPC-containing CRE with MV MICs up to 8 µg/ml. Based on the critical concentration determined in resistance development studies (8 mg/L), the minimum target exposure for vaborbactam fAUC0-24 was 192 mg*h/L (8x24). This approach assumed that the PD-linked variable for vaborbactam was its AUC, which was supported by PK-PD modelling studies (see below). In study 402 in healthy subjects vaborbactam 2 g q8h (3-h infusions) gave AUC0-8 of 145 µg.h/mL. With 33% protein binding this gives a mean 24 h fAUC of 291 mg*h/L (range 231 – 320 mg*h/L).

In a neutropenic mouse thigh infection model using KPC-producing strains and humanised dosage regimens (meropenem 300 mg/kg q2h and vaborbactam 50 mg q2h in mice give free drug plasma

exposures similar to those observed with 2g/2g q8h using 3 h infusions in humans) a reduction in bacterial counts was observed for all strains. Using fixed doses of meropenem and a KPC-producing K. pneumoniae strain (MV MIC 4 mg/L) the amount of bacterial killing increased with increasing doses of vaborbactam (see following figure).

Figure 5 Activity of meropenem alone and in combination with vaborbactam against carbapenem-resistant *K.pneumoniae* KP1094 in a 24h neutropenic mouse thigh infection model (meropenem MIC: alone ≥64 mcg/mL; w/ 4mcg/mL vaborbactam=32 mcg/mL; w/ 8 mcg/mL vaborbactam= 4mcg/mL)



Using a hollow fibre model, humanised dosage regimens of meropenem and vaborbactam were evaluated against carbapenem-resistant, KPC-producing strains of *K. pneumoniae*, *E. coli* and *E. cloacae* (inoculum ~10^8 CFU/mL) to assess the vaborbactam dose and to examine development of resistance. The model was used to mimic humanised dosage regimens of meropenem and vaborbactam of 1g/1g q8h, 1g/2g q8h and 2g/2g q8h each using 3-h infusions.

The 2g/2g regimen was tested against 17 carbapenem-resistant strains with MV MICs from ≤0.06 to 64 µg/mL. For strains with MV MICs ≤8 µg/ml >5 logs of bacterial killing were obtained with no regrowth. Four strains with MV MICs exceeding 8 µg/ml were studied. Bacterial regrowth was observed for 3 strains with MV MICs 16-64 µg/ml but the fourth strain did not show regrowth (MV MIC 16 µg/ml). Based on the results for the simulations of meropenem 2 g and vaborbactam 2 g administered q8h by 3-hour infusions, a vaborbactam *f*AUC of at least 200 mg*hr/L in combination with meropenem exposures that exceeded 8 mg/ml for 30% to 50% of the dosing interval was predicted to treat organisms with MV MICs of 8 µg/ml and prevent development of resistant subpopulations in carbapenem-resistant *K. pneumoniae* and *P. aeruginosa*.

PK-PD modeling of vaborbactam exposures considered the results from neutropenic mouse thigh and hollow fibre models. The dosage regimen for meropenem was designed to simulate a 2 g dose administered by a 3-hour infusion q8h, which was expected to produce meropenem concentrations that exceeded 8 µg/ml for 56% of an 8 hour dose interval (meropenem $fAUC_{0\text{-}24}$ 402 mg*h/L). The dosage regimens for vaborbactam were designed to produce 24 h vaborbactam *f*AUCs of 192, ~300 or 550 mg*h/L.

Data for the 4 *K. pneumoniae* isolates and the single *E. coli* isolate tested in the neutropenic mouse thigh model were pooled and used to determine the relationship between the change in Log CFU/thigh and %*f*vaborbactam >4 µg/ml, %*f*vaborbactam >8 µg/ml, 24 h vaborbactam *f*AUC and 24 h vaborbactam *f*AUC/M-V MIC. None of the indices described the data very well but the $fAUC_{0-24}$/MV MIC ratio performed best. For 1-log kill the ratio was 38. For the target MV MIC 8 µg/ml, the vaborbactam *f*AUC would need to be (38 x 8) 304 µg*h/ml, which is lower than the $fAUC_{0-24}$ in healthy subjects (mean 343 µg*h/ml) when using the proposed clinical dose regimen (2g/2g q8h and 3-h infusions).

Table 18 PK/PD indices, goodness of fit, and magnitude required for effect in the neutropenic mouse thigh infection model

PK-PD Index	Goodness of Fit (R^2)	Magnitude Required for		
		Stasis	1-log kill	2-log kill
%Free >4 µg/mL	0.66	21	54	95
%Free>8 µg/mL	0.60	12	35	62
Free 24h AUC	0.60	50	267	720
Free 24h AUC/M-V MIC	0.70	9	38	220

The data for the 13 *K. pneumoniae* isolates, the three *E. cloacae* and the single *E. coli* isolate tested in the in-vitro hollow fibre PK-PD model were pooled and used for the same Emax analysis. The *E*max model fit could be accomplished when fit to the 24 h vaborbactam *f*AUC/MV MIC ratio.

Table 19 PK/PD index, goodness of fit, and magnitude required for effect in the *in* vitro hollow fibre infection model

PK-PD Index	Goodness of Fit (R^2)	Magnitude Required for				
		Stasis	1-log kill	2-log kill	3-log kill	Resistance Prevention
Free 24h AUC/M-V MIC	0.81	12	18	25	36	>24

The magnitude of 24h *f*AUC/MIC to produce 1-log of bacterial killing in this model was 18 but suppression of resistance required a 24 h vaborbactam *f*AUC/MIC ratio >24. It was concluded that the vaborbactam 24h *f*AUC/MV MIC ratio gave the best correlation with antibacterial effect and the ratio required to suppress resistance was 36.

Table 20 Summary of the 24h free vaborbactam AUC/meropenem-vabobcatam MIC ratio in the neutropenic mouse thigh infection and in vitro hollow fibre models

Model	Ratio of the 24h Free Vaborbactam AUC:Meropenem-Vaborbactam MIC				
	Stasis	1-log kill	2-log kill	3-log kill	Regrowth Suppression
In Vitro Hollow Fiber Model	12	18	25	36	>24
Neutropenic Mouse Thigh Infection Model	9	38	220	Not Observed	Not Observed

Estimation of the probability of target attainment (PTA) was repeated during the assessment using the final POPPK models. The revised estimations also differed with respect to the PDTs as follows:

- In addition to the meropenem free-drug plasma %T>MIC targets of 30, 35 and 45%, which are associated with net bacterial stasis, and a 1- and 2-$\log_{10}$ CFU reduction from baseline, respectively, %T>MIC of 40% was included in the updated assessment.
- For vaborbactam, the free-drug plasma AUC/MIC ratio associated with a 1-$\log_{10}$ CFU reduction from baseline of 38 was evaluated.

The following approach was taken:

o The ability of meropenem alone to meet the meropenem PDT at meropenem MICs was first assessed. If the free meropenem T>MIC was 40% or greater at a specific meropenem MIC,

then target attainment was achieved and no further assessment based on meeting the vaborbactam PDT was done (i.e. a contribution from vaborbactam is not needed for efficacy).

- If the meropenem target was not met (i.e. the meropenem MIC was too high), then the ability of both meropenem and vaborbactam to meet their respective targets was assessed against the potentiated MIC (i.e. the meropenem-vaborbactam [MV] MIC).

For the first simulation, a population of 5,000 patients with varying degrees of renal function was generated by simulating eGFR values using a uniform probability distribution for the following renal function groups, each of which contained 1,000 simulated patients:

- ≥150 to 200 mL/min/1.73 m^2
- ≥50 to <150 mL/min/1.73 m^2
- ≥30 to <50 mL/min/1.73 m^2
- ≥15 to <30 mL/ min/1.73 m^2
- 0 to <15 mL/ min/1.73 m^2

Age was simulated according to a uniform distribution between 18 to 90 years (n = 1,000) and applied to each renal function group to maintain the same age distribution. Weight, height and BSA values were generated by applying a bootstrapping method in which 1,000 patients were randomly sampled with replacement from the Phase 3 PK analysis population. This set of demographic values was applied to each renal function group to maintain the same covariate distributions.

For the second simulation, 295 patients with cUTI or AP (122 and 173, respectively) from studies 505 and 506 that were in the data for the refined population PK models were replicated 11 times to generate a clinical population consisting of 3,245 simulated patients with cUTI or AP.

The first table below shows that for the applicant's proposed susceptibility criterion (MV MIC of 8 mg/L) the PTA exceeded 90% at each meropenem target and in each renal function group with the sole exception of PTA=88.4% for the 45% *f*T>MIC PDT in the moderate impairment group. PTA was inadequate for MV MIC 16 mg/L in almost all renal function subgroups at the 1-log kill PDT (35% *f*T>MIC). The second table below shows the PTA for the population of simulated patients with cUTI or AP. In this population, PTA exceeded 90% at MV MIC of 8 µg/ml and values exceeded 90% at MV MIC of 16 µg/ml for the %T>MIC ≥ 30 and 35 PDTs.

Table 21 Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall on Day 1 for meropenem-vaborbactam dosing regimens based on the assessment of four free-drug plasma meropenem %T > MIC targets and 11,599 Enterobacteriaceae isolates among simulated patients by renal function group

MV MIC (µg/mL)	Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC, free-drug plasma meropenem %T>MIC target[a], and renal function group defined by eGFR range (mL/min/1.73 m^2)																			
	Free-drug plasma meropenem %T>MIC ≥30					Free-drug plasma meropenem %T> MIC ≥35					Free-drug plasma meropenem %T> MIC ≥40					Free-drug plasma meropenem %T> MIC ≥45				
	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200
1	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99.9
4	99.9	100	100	100	100	99.6	100	100	100	100	99.6	99.9	100	100	99.9	99.5	99.8	99.5	99.8	99.8
8	97.3	99.6	97.9	100	99.9	96.7	99.2	96.3	99.7	99.7	95.9	97.8	92.9	99.0	98.7	93.8	96.6	88.4	96.8	95.3
16	74.5	89.7	75.0	95.2	93.5	71.2	86.0	68.6	91.8	88.2	66.5	81.6	60.8	86.0	81.5	62.0	76.1	52.8	76.0	71.7
32	29.9	52.9	30.3	66.7	61.5	26.9	47.1	26.3	59.5	54.6	23.6	40.9	20.5	50.4	45.2	20.4	35.4	16.7	39.9	34.6

Table 21 Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall on Day 1 for meropenem-vaborbactam dosing regimens based on the assessment of four free-drug plasma meropenem %T > MIC targets and 11,599 Enterobacteriaceae isolates among simulated patients by renal function group

MV MIC (µg/mL)	Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC, free-drug plasma meropenem %T>MIC target[a], and renal function group defined by eGFR range (mL/min/1.73 m^2)																			
	Free-drug plasma meropenem %T>MIC ≥30					Free-drug plasma meropenem %T> MIC ≥35					Free-drug plasma meropenem %T> MIC ≥40					Free-drug plasma meropenem %T> MIC ≥45				
	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200
64	1.70	7.10	1.30	14.2	10.9	1.50	5.90	0.90	9.30	7.90	1.00	4.70	0.50	6.40	5.90	0.80	3.50	0.30	4.60	3.20
Overall[b]	99.6	99.7	99.6	99.7	99.7	99.5	99.6	99.5	99.7	99.7	99.5	99.6	99.5	99.6	99.6	99.5	99.6	99.5	99.6	99.6

a. Based also on the assessment of a free-drug plasma vaborbactam AUC:MIC ratio target of 38, which was associated with a 1-$\log_{10}$ CFU reduction from baseline in a neutropenic murine thigh-infection model.
b. Represents the weighted percent probability of PK-PD target attainment over the meropenem-vaborbactam MIC distribution.

Table 22 Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall on Day 1 for meropenem-vaborbactam dosing regimens based on the assessment of four free-drug plasma meropenem %T > MIC targets and 11,599 Enterobacteriaceae isolates among simulated patients with cUTI or AP

MV MIC (µg/mL)	Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC, for free-drug plasma meropenem %T>MIC targets[a] among simulated patients with cUTI or AP			
	Free-drug plasma meropenem %T>MIC ≥30	Free-drug plasma meropenem %T> MIC ≥35	Free-drug plasma meropenem %T> MIC ≥40	Free-drug plasma meropenem %T>MIC ≥45
1	100	100	100	100
2	100	100	100	100
4	100	100	99.9	99.8
8	99.7	99.3	98.6	96.7
16	93.9	90.9	86.2	78.9
32	64.3	55.9	46.8	38.2
64	13.5	9.74	6.32	4.10
Overall[b]	99.7	99.7	99.6	99.6

a. Based also on the assessment of a free-drug plasma vaborbactam AUC:MIC ratio target of 38 which was associated with a 1-$\log_{10}$ CFU reduction from baseline in a neutropenic murine thigh-infection model.
b. Represents the weighted percent probability of PK-PD target attainment over the meropenem-vaborbactam MIC distribution.

The exercise was repeated for KPC-producing Enterobacteriaceae using the same PDTs and separately by renal function group and for patients with cUTI or AP. Due to high meropenem MICs for these organisms the joint target attainment had to be assessed against MV MICs.

At the meropenem 1-log kill PDT (35% *f*T>MIC), as well as at 40% and 45% *f*T>MIC, the joint PTA reliably exceeded 90% across all renal function sub-groups at MV MIC of 4 µg/ml but this was not achieved at the applicant's proposed susceptibility criterion of MV MIC 8 µg/ml.

Table 23 Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall on Day 1 for meropenem-vaborbactam dosing regimens based on the assessment of four free-drug plasma meropenem %T > MIC targets and 1,331 KPC-producing Enterobacteriaceae isolates among simulated patients by renal function group

MV MIC (µg/mL)	Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC, free-drug plasma meropenem %T>MIC target[a], and renal function group defined by eGFR range (mL/min/1.73 m^2)																			
	Free-drug plasma meropenem %T>MIC ≥30					Free-drug plasma meropenem %T> MIC ≥35					Free-drug plasma meropenem %T> MIC ≥40					Free-drug plasma meropenem %T> MIC ≥45				
	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200
1	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99.9
4	99.9	100	99.7	99.9	99.8	99.6	100	99.7	99.9	99.6	99.6	99.9	99.7	99.9	99.4	99.5	99.8	99.2	99.7	99.1
8	88.5	97.8	85.7	93.7	90.6	88.0	97.4	84.3	92.2	89.0	87.2	96.0	81.3	90.8	86.6	85.4	94.8	77.5	88.2	82.0
16	20.2	49.0	18.3	49.2	33.4	18.6	45.3	14.9	42.5	27.0	16.7	42.7	11.4	35.6	21.5	15.1	39.0	8.80	28.3	15.4
32	1.10	4.80	0.70	12.7	9.20	0.90	4.10	0.40	8.10	6.20	0.60	3.20	0.20	5.00	4.50	0.60	2.70	0.20	3.40	2.10
64	1.10	4.50	0.70	12.4	9.20	0.90	3.80	0.40	7.80	6.20	0.60	2.90	0.20	4.90	4.50	0.60	2.60	0.20	3.30	2.10
Overall[b]	99.5	99.6	99.5	99.6	99.6	99.5	99.6	99.5	99.6	99.5	99.5	99.6	99.5	99.6	99.5	99.5	99.6	99.4	99.5	99.5

a. Based also on the assessment of a free-drug plasma vaborbactam AUC:MIC ratio target of 38, which was associated with a 1-$\log_{10}$ CFU reduction from baseline in a neutropenic murine thigh-infection model.
b. Represents the weighted percent probability of PK-PD target attainment over the meropenem-vaborbactam MIC distribution.

Table 24 Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall on Day 1 for meropenem-vaborbactam dosing regimens based on the assessment of four free-drug plasma meropenem %T > MIC targets and 1,331 KPC-producing Enterobacteriaceae isolates among simulated patients with cUTI or AP

MV MIC (µg/mL)	Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC, for free-drug plasma meropenem %T>MIC targets[a] among simulated patients with cUTI or AP			
	Free-drug plasma meropenem %T>MIC ≥30	Free-drug plasma meropenem %T> MIC ≥35	Free-drug plasma meropenem %T> MIC ≥40	Free-drug plasma meropenem %T>MIC ≥45
1	100	100	100	100
2	100	100	100	100
4	100	100	99.9	99.7
8	94.9	93.7	92.0	89.6
16	46.3	41.4	35.4	29.7
32	11.3	8.01	4.90	3.14
64	11.0	7.83	4.75	3.02
Overall[b]	99.6	99.6	99.6	99.5

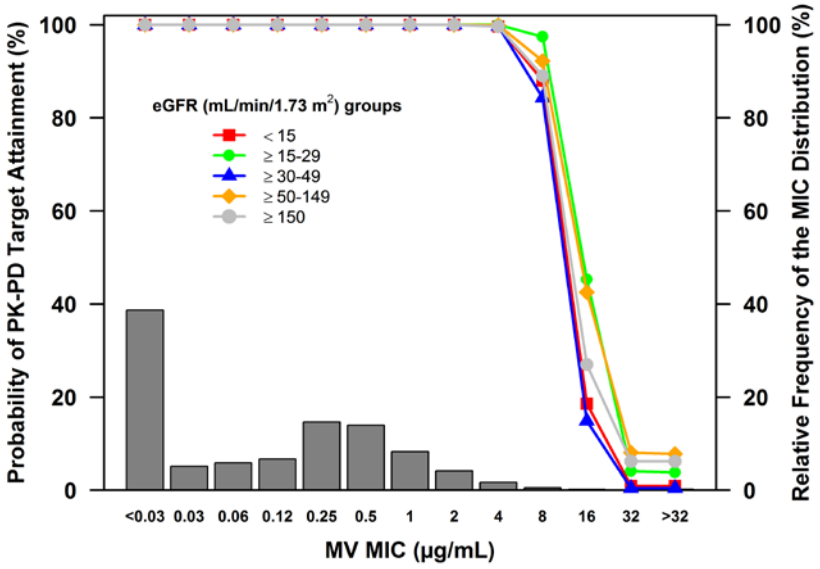
a. Based also on the assessment of a free-drug plasma vaborbactam AUC:MIC ratio target of 38 which was associated with a 1- $\log_{10}$ CFU reduction from baseline in a neutropenic murine thigh-infection model.
b. Represents the weighted percent probability of PK-PD target attainment over the meropenem-vaborbactam MIC distribution.

The exercise was further repeated for *P. aeruginosa*, which indicated satisfactory PTA across renal function groups at MV MIC 8 µg/ml, supporting the analysis across Enterobacteriaceae.

Using the revised POPPK analyses the analyses based on *Enterobacteriaceae* (as a whole) and *P. aeruginosa* indicate that PTA is satisfactory for meropenem PDTs associated with 1- and 2-$\log_{10}$ kill.

However, for the KPC producers, for which vaborbactam target attainment also becomes important, the joint PTA is >90% only up to MV MICs of 4 mg/L. As shown in the figure below, achieving >90% PTA for *joint target attainment* at the 1-$\log_{10}$ kill targets would still mean that the proposed dose regimen would suffice for the majority of KPC producers.

Figure 6 Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC for meropenem-vaborbactam dosing regimens based on free-drug plasma meropenem %T>MIC ≥ 35% among simulated patients by renal function group, overlaid upon the meropenem-vaborbactam MIC distribution for 1,331 KPC-producing Enterobacteriaceae isolates



Supplementary simulations and PTA using vaborbactam PDTs based on %fT>C_T

In this exercise, the selected PDTs were those associated with 1-$\log_{10}$ kill in the NMT model as follows:

- Meropenem %T>MIC ≥ 40%
- Vaborbactam AUC:MIC ratio ≥38, %T>threshold of 54% with C_T 4 µg/mL and 35% with C_T 8 µg/L

Firstly, a population of 5,000 simulated patients with varying degrees of renal function was generated by simulating eGFR using a uniform probability distribution for the following renal function groups, each of which contained 1,000 simulated patients: ≥150 to 200 ml/min/1.73 m^2; ≥50 to 149 ml/min/1.73 m^2; ≥30 to 49 ml/min/1.73 m^2; ≥15 to 29 ml/min/1.73 m^2; and <15 ml/min/1.73 m^2. Secondly, 295 patients with cUTI or AP (122 and 173, respectively) from Studies 505 and 506 that were included in the dataset for the refined population PK models were replicated 11 times to give 3,245 simulated patients with cUTI or AP. Meropenem-vaborbactam dosing regimens were assigned by baseline eGFR.

The table below shows that the PTA values for KPC-producing *Enterobacteriaceae* with MV MIC 8 µg/mL were >90% for vaborbactam T>C_T PDTs and higher than observed for the AUC/MIC ratio PDT.

The figure below shows PTA for the higher T>C_T PDT (i.e. 35% T> C_T=8µg/mL). For the simulated patient population with cUTI or AP, PTA was >90% regardless of PDT for MV MICs at 8 µg/ml.

Therefore, regardless of the PDT for vaborbactam selected from the 3 potential candidates identified from nonclinical studies, the PTA supported the proposed dose regimen and dose adjustment schema.

Table 25 Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC and overall on Day 1 for meropenem-vaborbactam dosing regimens based on the assessment of a free-drug plasma meropenem %T>MIC target≥40%, three free-drug plasma vaborbactam AUC:MIC ratio or %T>threshold targets, and 1331 KPC-producing Enterobacteriaceae isolates among simulated patients by renal function group

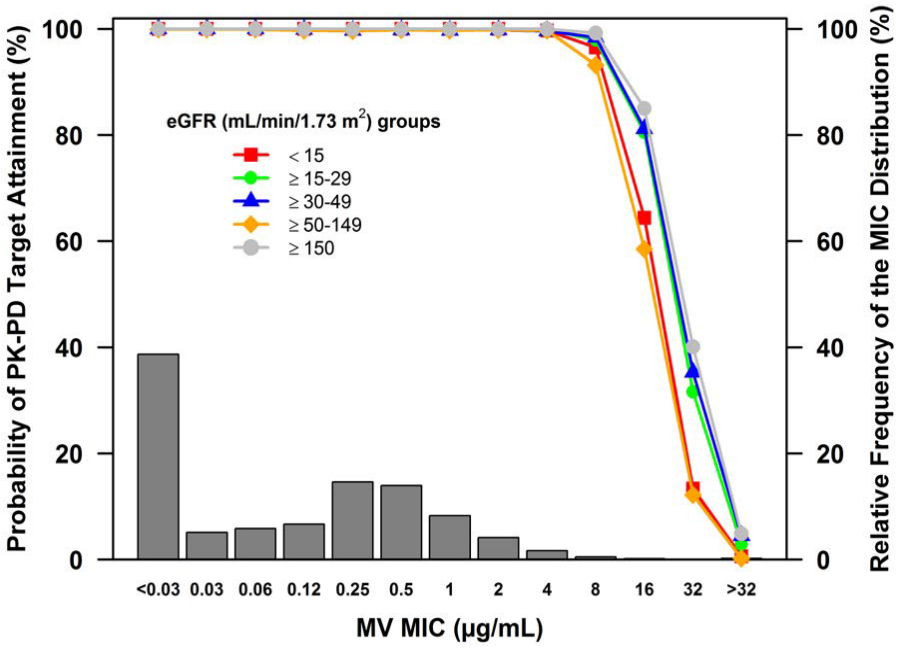
MV MIC (µg/mL)	Percent probabilities of PK-PD target attainment by meropenem-vaborbactam MIC, free-drug plasma vaborbactam AUC:MIC or %T>threshold target[a], and renal function group defined by eGFR range (mL/min/1.73 m^2)														
	Free-drug plasma vaborbactam AUC:MIC ≥ 38					Free-drug plasma vaborbactam %T>threshold of 4 mg/L ≥ 54%					Free-drug plasma vaborbactam %T>threshold of 8 mg/L ≥ 35%				
	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200	<15	≥15-29	≥30-49	≥50-149	≥150-200
0.06	100	100	100	100	100	100	100	99.9	99.5	99.5	100	100	99.9	100	99.9
0.12	100	100	100	100	100	100	100	99.7	99.3	97.9	100	100	99.7	100	99.9
0.25	100	100	100	100	100	100	100	99.6	98.9	97.5	100	100	99.6	100	99.7
0.5	100	100	100	100	100	100	100	99.7	99.0	97.4	100	100	99.8	100	99.8
1	100	100	100	100	100	100	100	99.7	99.0	97.6	100	100	99.7	100	99.7
2	100	100	100	100	100	100	100	99.7	99.0	97.4	100	100	99.8	100	99.8
4	99.6	99.9	99.7	99.9	99.4	99.7	99.9	99.6	98.9	97.5	99.7	99.9	99.7	100	99.6
8	87.2	96.0	81.3	90.8	86.6	96.5	97.9	93.2	98.0	95.9	96.5	97.9	93.2	99.2	98.4
16	16.7	42.7	11.4	35.6	21.5	64.4	80.5	58.5	83.8	78.7	64.4	80.5	58.5	85.0	81.2
32	0.60	3.20	0.20	5.00	4.50	13.4	31.6	12.1	39.0	33.3	13.4	31.6	12.2	40.1	35.3
64	0.60	2.90	0.20	4.90	4.50	0.60	2.90	0.20	4.90	4.50	0.60	2.90	0.20	4.90	4.50
Overall[b]	99.5	99.6	99.5	99.6	99.5	99.6	99.7	99.4	99.2	98.3	99.6	99.7	99.4	99.7	99.6

Note: Abbreviations are listed in the Abbreviation Listing.

a. Based on the assessment of the following free-drug plasma vaborbactam PK-PD targets associated with a 1-$\log_{10}$ CFU reduction from baseline in a neutropenic murine thigh-infection model: a free-drug plasma vaborbactam AUC:MIC target ≥ 38, a free-drug plasma vaborbactam %T> threshold of 4 mg/L ≥ 54%, and a free-drug plasma vaborbactam %T> threshold of 8 mg/L ≥ 35% [10].

b. Represents the weighted percent probability of PK-PD target attainment over the meropenem-vaborbactam MIC distribution.

Figure 7 Percent probabilities of PK-PD target attainment by MV MIC based on a free-drug plasma meropenem %T>MIC target ≥40%, a free-drug plasma vaborbactam %T>threshold of 8 mg/L≥35%, and the assessment for KPC-producing Enterobacteriaceae



Relationship between plasma concentration and effect

There were 11 ME patients with KPC-producing *Enterobacteriaceae* and sufficient PK data for analysis, of which 3 had KPC-producing *Enterobacteriaceae*, all with cUTI or AP. Meropenem MICs for these isolates ranged from 8 - >64 µg/ml but the MV MICs were ≤ 0.25 µg/ml. In these patients the 24h free vaborbactam AUC:MIC ratio exceeded 2,252, which is >100-fold higher than nonclinical targets for efficacy in mice and in the hollow fibre infection model.

The corresponding free-drug meropenem plasma concentrations exceeded the MV MIC for 100% of the dosing interval. All these patients had a clinical response at early, EOIVT and TOC endpoints.

There were 175 ME patients with cUTI and sufficient PK data for analysis, of which 154 patients had an enterobacterial baseline pathogen. More than 90% of patients with cUTI and with *Enterobacteriaceae* achieved meropenem %*f*T>MIC of 100% while 96.6% and 98.7% achieved the meropenem %*f*T>MIC target of 45%. The percentages with successful responses for the efficacy endpoints assessed across study visits, including TOC, ranged from 93 to 100% for clinical response and 76.3 to 100% for microbiological response. Overall response at both EOIVT and TOC was 100 and 79% for patients with cUTI and the subset with *Enterobacteriaceae*, respectively. Accordingly, univariable PK-PD relationships for efficacy endpoints based on data for these analysis populations were not identified.

Secondary pharmacology

The applicant did not conduct a TQT study.

In studies 402 and 501 ECGs were recorded at intervals including baseline and end of the infusion and were over-read and interpreted by the investigator. Analyses of placebo-corrected change-from-baseline QTcF (ΔΔQTcF) values by time point indicated that 2 g vaborbactam and 2 g meropenem does not cause clinically concerning QT prolongation. In study 505 ECGs were recorded before and at the end of infusion on several days and interpreted at a central ECG laboratory. ECGs showed a clear time-dependent effect on ΔQTcF in both treatment groups with no relation to plasma concentrations. Although there was a small increase during treatment in both groups the largest mean ΔQTcF was at the end of the IV treatment - 7.4 ms (90% CI 5.7 to 9.1) in the meropenem-vaborbactam group and 11 ms (90% CI 8.9 to 13.1) in the piperacillin/tazobactam group. The predicted QT effect at C_{max} did not exceed 5 ms.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics of IV meropenem+vaborbactam

Administration of vaborbactam alone showed that Cmax and AUC_{0-8} increased in a dose-proportional manner. With a short half-life, there was no evidence of accumulation in plasma after multiple dosing (including the clinical dose of 2 g q8h) and there were no significant differences among the group mean CL_{ss} and Vd values indicating that they did not change with increasing dose. After single doses the mean Ae_{0-24} was estimated at 2100 mg for the 2000 mg dose, giving a mean percent urinary excretion of 105% (2000 mg), most of which appeared in urine in the first 8 hours. The mean percent urinary excretion fe_{0-8} following repeated dosing at 2 g q8h was 91.6%. These data, as well as the lack of any metabolism of vaborbactam *in vitro* support the omission of a study with radiolabelled vaborbactam.

Co-administration of vaborbactam with meropenem at doses including 2g/2g q8h infused over 1 or 3 hours did not show any important effects of co-administration on meropenem, the open ring metabolite or vaborbactam. Although there was a trend for the median renal clearance to be lower with combination therapy, the overall range of values was similar across all treatments (single- versus multiple-dose, alone or in combination) for both meropenem and vaborbactam.

The data indicate generally similar pharmacokinetic properties for the two agents, including their partition coefficients. In addition, they both have relatively low or low protein binding in human sera (vaborbactam ~33% and meropenem ~2%).

Healthy volunteers vs. patients

Infected patients had higher exposures for both meropenem and vaborbactam compared to healthy subjects, with higher values in study 506 vs. study 505. The differences were apparent with or without including data from patients who had their dose adjusted in the model.

Dose adjustment for renal impairment

The dose adjustment schema for renal impairment that were used in studies 505 and 506 were different and neither study used the recommendations in the applicant's initial or revised SmPC.

The POPPK-predicted exposures (using the final models) and the PTA for various renal function categories broadly supported the dose adjustment recommendations and use of the standard dose for eGFR up to 200 ml/min/1.73m^2. The applicant was asked to re-calculate the BSA normalised eGFR to absolute GFR for all simulated patients and to update the PTA plots/tables during the procedure. These tables and plots included estimations of PTA at the extremes of each proposed renal impairment dose adjustment band. Overall, these PTA results supported the final dose adjustments in section 4.2 of the Vabomere SmPC based on CrCL (~absolute GFR).

However, the proposed cut-offs for dose adjustment categories (CrCL <40, <20 and <10 ml/min) were modified when changing from relative to absolute renal function. As the POPPK model does not describe the relationship between renal function and drug clearance in a reliable way due to the strong influence of age, the model cannot be used to simulate drug exposure in patients with different degrees of renal function. Thus, it cannot be used to support the proposed doses. Instead the applicant was asked to relate the proposed dose adjustments directly to the results of the dedicated renal impairment study.

The applicant plotted the relationship between CrCL in each participant and meropenem and vaborbactam clearance, respectively. In addition, a linear regression analysis of the relationship between renal function (CrCL) and drug clearance (meropenem and vaborbactam observed values, respectively) was presented. Using the linear regression model, the predicted AUCs at CrCL values just under and above the proposed cut-offs for dose adjustments were compared with anticipated exposures in a subject with typical renal function for the target patient population. The finding of reasonably similar AUCs in all renal function sub-groups (similar or up to ~2-fold) supported the recommended dose adjustment schema given the relatively large therapeutic window.

ELF penetration

In study 503 the plasma exposures in healthy subjects were similar to those reported in study 501 after dosing q8h with 2g/2g using 3-hour infusions. The intrapulmonary penetration of meropenem and vaborbactam based on AUC_{0-8} values of ELF and total drug concentrations were approximately 63% and 53%, respectively. When free drug (unbound) concentrations were considered, penetration was 65% and 79% for meropenem and vaborbactam, respectively. The assessment of penetration based on AUCs and not on ratios of plasma concentrations at single time points is appropriate. The estimates suggest that ELF penetration is of similar magnitude for the two agents and it is also relatively high compared to values reported for some other antibacterial agents.

The ELF penetration in patients with active lung infection has not been assessed. Further to the healthy subject data, the applicant calculated the ELF exposures to free meropenem and vaborbactam for patients in studies 505 and 506 by applying the ELF penetration ratios observed in study 503 (see following table).

Table 26 Concentrations of free meropenem and vaborbactam in ELF and plasma

	Free Meropenem ELF % T>MIC*^	Free Meropenem AUC (mg*h/L)			Free Vaborbactam ELF AUC/MIC Ratio *	Free Vaborbactam AUC (mg*h/L)		
		ELF	Plasma	E-P Ratio		ELF	Plasma	E-P Ratio
Single Dose (steady state)	55%	111.7	170.9	65%	13	105.1	132.3	79%
Estimated Daily Dose in Subjects from Study 505 ($AUC_{0\text{-}24,\ steady\text{-}state}$)	**55%**	**396**	609	65%	**53**	**422**	535	79%
Estimated Daily Dose in Subjects from Study 506 ($AUC_{0\text{-}24,\ steady\text{-}state}$)	**60%**	**572**	880	65%	**84**	**673**	852	79%

* MIC for the calculation is 8 mg/L.
^ Meropenem ELF concentrations were assumed to be proportional to exposures

Since there is an 8-h dose interval, the calculated mean free meropenem $AUC_{0\text{-}8}$ in ELF in healthy subjects gives a *f*T>MIC (where MIC= 8 mg/L) value of 55%, which exceeds the meropenem plasma PDT of *f*T>MIC 35% for 1-log kill and exceeds the more conservative PDTs of *f*T>MIC 40% and 45%.

If the healthy subject data in the first line of the table are multiplied by 3, the free vaborbactam ELF $AUC_{0\text{-}24}$ would be ~315 mg.h/L and the *f*AUC/MIC ratio would be ~39. This ratio is just about at the vaborbactam plasma PDT value of 38.

Regarding the second and third lines, the applicant has taken the revised POPPK estimates for total drug in plasma in patients and has calculated the plasma free drug $AUC_{0\text{-}24}$ values by applying the %protein bound values. The applicant then applied the mean ELF %penetration values from study 503 to the patient plasma free drug AUCs to derive the free drug AUCs in ELF. The meropenem *f*T>MIC and the vaborbactam *f*AUC/MIC ratio based on MV MIC=8 mg/L have been calculated using the mean free drug in ELF. The results have then been compared against the plasma PDTs for each agent.

The mean estimate for meropenem *f*T>MIC was consistent between healthy subjects and patients at about 55%. The applicant's estimates for mean vaborbactam *f*AUC/MIC are 53 based on study 505 and 84 based on study 506. Thus, both values are higher than the mean (~40) in healthy subjects. This calculated mean ELF *f*AUC/MIC ratio of ~40 in healthy subjects could be viewed as being representative of ELF penetration at the conservative end of the spectrum in patients with HAP/VAP, since the plasma exposures are lower in healthy subjects and it is possible that in the infected and inflamed lung the ELF penetration would be greater than that measured in healthy subjects in study 503. However, it must be remembered that all these calculations are based on mean values and that the patient data are founded on POPPK-predicted exposures.

Whilst PDTs relevant to ELF have not been identified, the applicant was asked to conduct exploratory simulations to estimate the PTA in ELF against the plasma PDTs for MV MIC=8 mg/L. For these analyses, simulated patients were uniformly assigned absolute eGFR values according to the ranges associated with dose adjustment and PTA at the extremes of each group were assessed. These exploratory analyses gave PTA ≥ 96.6% at a meropenem %T≥MIC target of 40% up to MIC=4 µg/ml. At MIC=8 µg/ml, PTA ranged from 84.2 to 96.8%, 72.1 to 96.7%, and 85.7 to 97.1%, for simulated patients among renal function groups based on the evaluation of all *Enterobacteriaceae*, KPC-producing

Enterobacteriaceae and *P. aeruginosa* isolates, respectively. Since it is the sufficiency of the vaborbactam dose that is of concern, it is notable that at the EUCAST-recommended susceptibility interpretive criterion (8 mg/L) the results for the KPC-producing enterobacteria indicate that even with augmented renal clearance the PTA (which here would reflect joint target attainment) exceeds 67% and at 4 mg/L the PTA exceeds 90%. Whilst the validity of this exploratory exercise is not substantiated for dose-finding purposes, the PTA results were considered supportive for the use of Vabomere to treat HAP/VAP.

Other PK issues

The drug-drug-interaction potential of vaborbactam appears to be low. The *in vitro* studies are in line with CHMP guidance operative at the time they were conducted. Some additional transporter studies, including those to identify the renal transporter(s) involved in the active secretion of vaborbactam, will be conducted post-approval. Meanwhile, the known DDIs for meropenem have been included in the Vabomere SmPC. It is acceptable that a hepatic impairment study has not been conducted. No effect of hepatic impairment on elimination of meropenem or vaborbactam is expected and both have low protein binding.

In-vitro activity

The investigation of the *in vitro* activity of meropenem-vaborbactam, including the added value of vaborbactam, has been extensive. *In vitro* susceptibility testing to determine the meropenem-vaborbactam (MV) MIC uses varying concentrations of meropenem in the presence of vaborbactam fixed at 8 µg/ml. The applicant has justified the use of this fixed vaborbactam concentration based on its relevance to the antibacterial effect shown in the *in vitro* PD model with simulated human PK for 2g/2g q8h using 3-hour infusions.

Due to the inherent stability of meropenem in the presence of ESBLs and AmpC enzymes, a benefit for adding vaborbactam is most apparent against *Enterobacteriaceae* expressing Class A serine-based carbapenemases. The most important of these are the *K. pneumoniae* carbapenemases (KPCs), which are no longer confined to this species and can be encoded on self-transmissible plasmids. At least 10 major KPC variants have been described so far (KPC-2 through KPC-11) and they differ among themselves by only one or two amino acids. They have ~45% homology with some other serine-based carbapenemases (e.g. SME and NMC/IMI) enzymes, which are of low or negligible clinical importance. Also, there are some Class C plasmid-borne serine-based carbapenemases. For example, CMY-10, which was first described in *Enterobacter aerogenes*, may be over-produced and confer resistance to carbapenems. However, vaborbactam inhibits these Class C serine-based carbapenemases.

Vaborbactam does not reduce meropenem MICs when resistance is due to Class B or D enzymes. It also has little or no effect when meropenem resistance is due to the other possible mechanisms of resistance to beta-lactams. For these reasons, it has little or no effect on the susceptibility of *P. aeruginosa* to meropenem.

The applicant points to the emergence of mutational resistance to avibactam and the lack of cross-resistance to vaborbactam. Nevertheless, the applicant has identified mutations in the laboratory that affect the inhibitory capacity of vaborbactam and it must be expected that with routine use clinical strains with these or similar mutations will be found. This inevitability underlines the need to make available several different inhibitors of carbapenemases for routine use with selected beta-lactam partners.

Selection of the vaborbactam PDT

The general approach taken by the applicant was rational. It included investigations of concentrations needed to minimize the risk of selection of resistance.

Based on the NMT model, the vaborbactam *f*AUC$_{0-24}$/MV MIC ratio gave the best relationship with bactericidal activity and the ratio for 1-log kill was 38. Although the *f*AUC$_{0-24}$/MV MIC ratio gave an R^2 value of 0.70, the %free vaborbactam > 4 mg/L gave an R^2 value of 0.66. For 1-log kill the model indicated that free vaborbactam should exceed 4 mg/L for 54% of the dose interval and should exceed 8 mg/L for 35% of the dose interval.

Based on the hollow fibre data the *f*AUC$_{0-24}$/MV MIC ratio was supported as the PK-PD index. Putting the results of the two methods together it was concluded that the vaborbactam *f*AUC/MV MIC ratio gave the best correlation with antibacterial effects and the ratio required to suppress resistance was finally concluded to be 36.

PTA and dose selection (see also re exploratory analysis for ELF above)

For meropenem alone used against meropenem-susceptible organisms the situation seems very clear. Using the maximum approved dose and 3h infusions there is very high PTA at meropenem MICs of up to 8 mg/L, even when PTA is determined using a PDT of 45% for %*f*T>MIC. The critical simulations are therefore for the meropenem-resistant organisms and the PTA when meropenem is dosed with vaborbactam. These simulations, with estimations of PTA, were revised during the assessment based on the updated POPPK models and using a vaborbactam PDT of *f*AUC/MIC=38.

The simulations of most importance to substantiate the vaborbactam dose are those for the KPC-producing *Enterobacteriaceae* by renal function sub-group. At MV MIC=8mg/L and for meropenem *f*T>MIC 35%, the PTA based on KPC-producers (which is the valid analysis since this requires that joint target attainment is displayed) is >90% except for subsets with end stage or moderate impairment or augmented renal function, for which the PTA is 84-89%. However, all subjects have >90% PTA at MV MIC=4 mg/L. Furthermore, for MV MIC=4 mg/L the PTA is >90% even for meropenem *f*T>MIC 45%.

Additional simulations using alternative vaborbactam PDTs were supplied during the assessment.

Using T>C_T values for MV MIC 4 and 8 µg/mL as the PDTs, supplementary simulations indicated that PTA was even higher for KPC-producing organisms than values obtained using he selected AUC/MIC ration PDT. These conclusions applied across renal function dose adjustment groups, lending further support to the adequacy of the vaborbactam dose.

The nonclinical data and the clinical ECG data support the omission of a TQT study.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic programme has been adequate for two agents that both have relatively simple pharmacokinetics and show no important interaction when they are co-administered. The microbiological investigations have been appropriate. The final Vabomere SmPC recommendations for dose adjustment by CrCL categories are considered acceptable. The rationale for selection of the meropenem dose is understood and is acceptable. The PK-PD approach to dose selection for vaborbactam has been rational. The revised simulations indicate that the vaborbactam regimen (2 g q8h and 3-hour infusions) is adequate to protect meropenem when the MV MICs are 4 mg/L and, in almost all patients, when the MV MIC= 8 mg/L.

2.5. Clinical efficacy

2.5.1. Main studies

Study 505 (TANGO I)

Methods

This was a phase III, multi-centre, randomized, double-blind, double-dummy study to evaluate the efficacy, safety, and tolerability of meropenem-vaborbactam compared to piperacillin/tazobactam in the treatment of complicated urinary tract infections (cUTI), including acute pyelonephritis (AP), in adults.

Study Participants

Eligible male and non-pregnant female adults of < 185 kg were to have cUTI or AP, expected to require at least 5 days of IV treatment.

Indication	Signs or symptoms evidenced by at least TWO of the following:	Pyuria evidenced by ONE of the following:	At least ONE of the following associated risks:
cUTI	• Chills, rigors, or fever (Fever must be documented within 24 h of the screening visit [oral or tympanic temperature ≥38°C {≥100.4°F} or rectal/core temperature ≥38.3°C {≥100.9°F}); observed and documented by a health care provider) • Elevated white blood cell count (>10,000/μL) or left shift (>15% immature PMNs) • Nausea or vomiting • Dysuria, increased urinary frequency, or urinary urgency • Lower abdominal pain or pelvic pain	• Positive LCE on urinalysis • White blood cell count ≥10 cells/μL in unspun urine • White blood cell count ≥10 cells/hpf in urine sediment	• Indwelling urinary catheter • Neurogenic bladder with presence or history of urine residual volume of ≥100 mL • Obstructive uropathy (eg, nephrolithiasis, tumor, fibrosis) that is expected to be medically or surgically treated within 48 h post-randomization • Azotemia due to intrinsic renal disease • Urinary retention in men due to previously diagnosed benign prostatic hypertrophy
AP	• Chills, rigors, or fever (Fever must be documented within 24 h of the screening visit [oral or tympanic temperature ≥38°C {≥100.4°F} or rectal/core temperature ≥38.3°C {≥100.9°F}); observed and documented by a health care provider) • Elevated white blood cell count (>10,000/μL), or left shift (>15% immature PMNs) • Nausea or vomiting • Dysuria, increased urinary frequency, or urinary urgency • Flank pain • Costo-vertebral angle tenderness on physical examination	• Positive LCE on urinalysis • White blood cell count ≥10 cells/μL in unspun urine • White blood cell count ≥10 cells/hpf in urine sediment	N/A

Any indwelling urinary catheters or instrumentation (including nephrostomy tubes and/or indwelling stents) were to be removed or replaced (if removal not clinically acceptable) within 12 hours after randomisation. Exclusions included:

- Presence of any of renal or perinephric abscess, polycystic kidney disease, chronic vesicoureteral reflux, renal transplantation, cystectomy or ileal loop surgery, prostatitis, orchitis, epididymitis, recent or planned urinary tract surgery (except to relieve an obstruction) or APACHE II >30
- Estimated $CrCL_{CG}$ <30 ml/min

Potentially therapeutic antibacterial agent within 48 hours before randomisation unless the patient had failed or had received a single dose of a short-acting agent (allowed in up to 25% of total enrolled)

Treatments

Patients were randomised to:

- 2g/2g q8h meropenem-vaborbactam over 3 h
- piperacillin/tazobactam 4.5 g q8h over 30 min

There was adjustment of meropenem-vaborbactam dose to 1g/1g q8h for patients with CrCL from ≥30 to 49 ml/min (which is not the final proposed dose adjustment in the SmPC).

Patients who met specified criteria for oral therapy and had received at least 15 IV doses could switch to oral levofloxacin 500 mg q24h.

Objectives

The pre-defined analysis populations were as follows:

- ITT = all randomised
- MITT = all treated
- m-MITT = MITT with a baseline bacterial pathogen(s) of $\geq 10^5$ CFU/mL in urine or the same bacterial pathogen present in concurrent blood and urine cultures. Patients with only a Gram-positive pathogen in the urine were not included in the m-MITT population.
- CE = MITT criteria with no major selection criteria violations, with a clinical outcome, had received ≥80% and ≤120% of expected IV doses or at least 6 doses if a failure and at least 9 doses if a cure.
- ME = those who met both MITT and CE criteria

Outcomes/endpoints

The primary efficacy endpoint for the EU submission was the proportion of patients in the co-primary m-MITT and Microbiological Evaluable (ME) Populations who achieved reduction in the baseline bacterial pathogen to $<10^3$ CFU/ml of urine at the TOC visit.

Secondary efficacy endpoints included the following:

- Proportion of subjects in the m-MITT and ME Populations with overall success at both the

EOIVT and TOC visits by infection type (cUTI or AP)

- Proportion of subjects with a clinical outcome of Cure in the m MITT, Clinical Evaluable (CE), and ME populations at Day 3, EOIVT, EOT, TOC, and LFU
- Proportion of subjects in the m-MITT and ME Populations with a microbiologic outcome of eradication at TOC to 10^3 CFU/ml of urine by infection type

Sample size

Assuming 60% in the m-MITT population, an overall success rate at EOIVT of 80% in both treatment groups and with a non-inferiority margin of 15%, the sample size of 500 patients provided 90% power to demonstrate the non-inferiority of meropenem-vaborbactam to piperacillin/tazobactam in the m-MITT population. Assuming 50% in the ME population the sample size provided 84% power to demonstrate non-inferiority of meropenem-vaborbactam to piperacillin/tazobactam in the ME population.

Randomisation

Randomisation (1:1) to 2g/2g q8h meropenem-vaborbactam over 3 h or to piperacillin/tazobactam 4.5 g q8h over 30 min was stratified by:

- AP, cUTI with removable source of infection [e.g. Foley catheter] or cUTI with non-removable source of infection [e.g. neurogenic bladder] and
- Geographic region (North America, Europe, Asia Pacific, Rest of World)

Enrolment was to be continued until at least 150 AP patients were enrolled (i.e. at least 30% of the total).

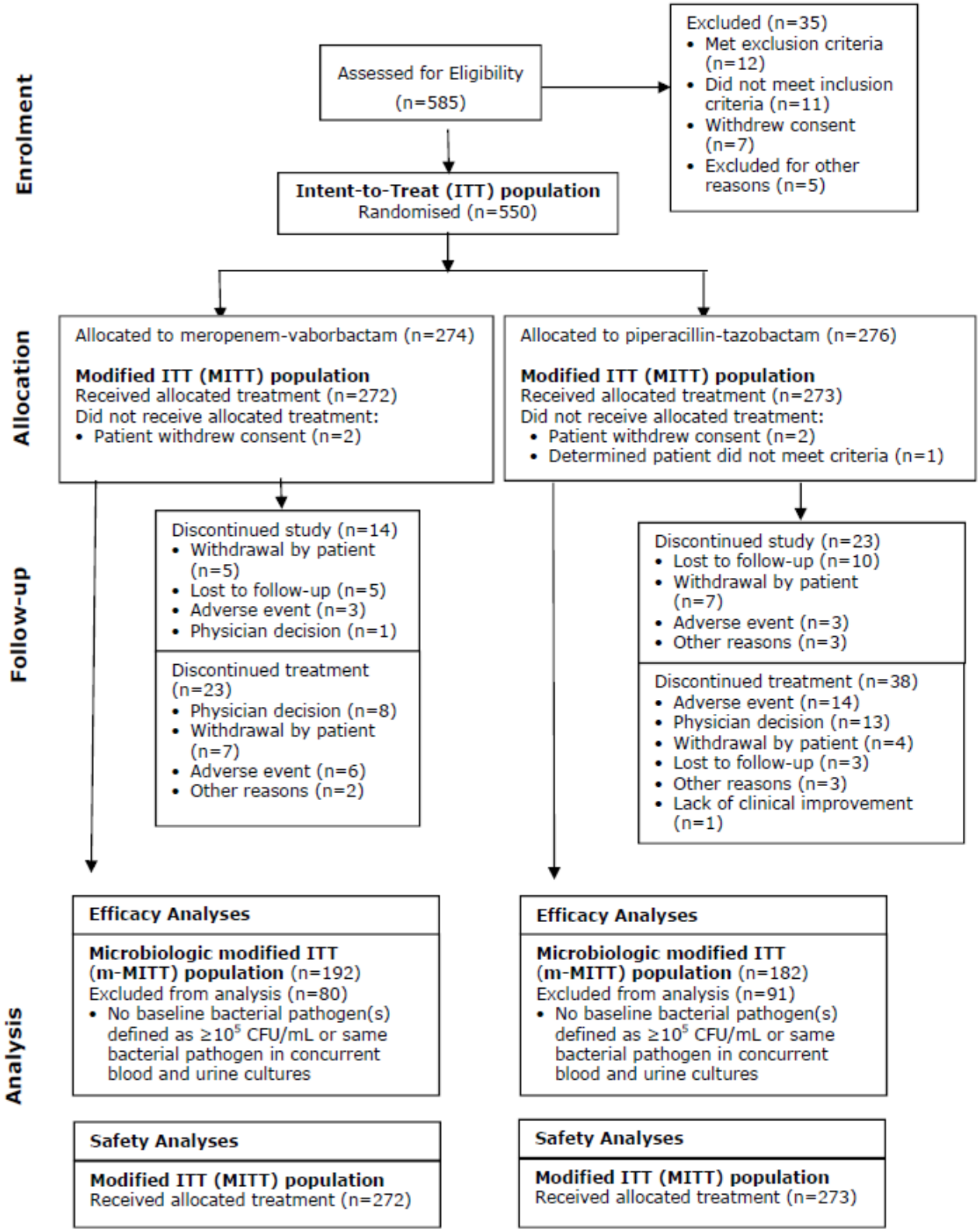
Blinding (masking)

This was a double-blind, double-dummy study.

Statistical methods

The proportion of subjects with overall success and the proportion of subjects with a microbiological outcome of eradication were summarized by group. The 95% two-sided confidence intervals (CIs) were presented for the between group differences (meropenem-vaborbactam minus piperacillin/tazobactam) based on the Miettinen and Nurminen method. The noninferiority margin was a difference of 15%. The secondary efficacy endpoints were analysed as described for the primary efficacy endpoints. CIs for the secondary efficacy endpoints were only presented when there were 5 or more subjects in each group.

Participant flow



Results

Of the 545 randomised and treated patients 88.8% completed treatment. Most patients who did not complete treatment withdrew during IV therapy. Just over half of patients switched to oral treatment and only 4 patients discontinued during this phase.

The MITT population showed similar baseline characteristics between the two treatment groups. More than 90% were white, >80% were enrolled in Europe, 66% were female, >60% were aged <65 years while 14.3% in the meropenem-vaborbactam group and 16.8% in the piperacillin/tazobactam group were ≥75 years of age. Mean age was 53.0 years and mean BMI was ~ 26 kg/m^2. CrCL ranged from 19-278 ml/min (4 patients had CrCL < 30 mL/min) but the mean and median values were around 90 ml/min.

About 30% met SIRS criteria and about 50% had Charlson co-morbidity scores ≥3. About 60% had AP and 40% had cUTI. Patients with AP were predominantly female (80.1% and 80.7%) and younger (mean ages of 47.3 years and 46.6 years). Patients with cUTI were predominantly male (53.1% and 56.3%) and older (mean ages of 61.4 years and 59.4 years in patients with a non-removable source of infection and 61.2 years and 63.3 years in patients with a removable source of infection). A higher proportion of AP patients had SIRS (37.9% and 43.5%) compared with cUTI patients (14.4% and 17.9%).

Most patients had single baseline pathogens (93.8% and 89.0%) and only one patient had 3 pathogens. *E. coli* was more common in AP (76.7% and 77.2%) than in cUTI but the reverse applied for *K. pneumoniae* (AP 12.5% and 8.9%).

For the four most commonly isolated species 3/164 baseline organisms obtained from patients assigned to meropenem-vaborbactam were resistant to meropenem (FDA or EUCAST criteria). In contrast, 32/164 baseline organisms in the piperacillin/tazobactam group were resistant to the assigned treatment based on EUCAST criteria and 19/164 based on FDA criteria.

The mean duration of total (IV/PO) treatment in the MITT population was 10.1 days in the meropenem-vaborbactam group (range 1 to 17 days) and 9.9 days in the piperacillin/tazobactam group (range 2 to 15 days). The mean duration of IV therapy was 8.0 days in both groups and most received ≥5 to 11 days.

Based on the EU primary endpoint non-inferiority was demonstrated in mMITT and ME populations with a lower bound of the 95% CI within -10%. Eradication rates were numerically higher in AP vs. cUTI patients.

Table 27 Eradication rate at TOC (m-MITT population and ME population)

Population	Meropenem-Vaborbactam n/N' (%)		Piperacillin/Tazobactam n/N' (%)
Overall			
m-MITT Population			
Eradication rate at TOC	128/192 (66.7)		105/182 (57.7)
Treatment difference [1]		9.0	
95% CI [1]		(-0.9, 18.7)	
ME Population			
Eradication rate at TOC	118/178 (66.3)		102/169 (60.4)
Treatment difference [1]		5.9	
95% CI [1]		(-4.2, 16.0)	
Acute pyelonephritis			
m-MITT Population			
Eradication rate at TOC	89/120 (74.2)		64/101 (63.4)
Treatment difference [1]		10.8	
95% CI [1]		(-1.4, 23.0)	
ME Population			
Eradication rate at TOC	83/111 (74.8)		62/92 (67.4)
Treatment difference [1]		7.4	
95% CI [1]		(-5.1, 20.0)	
cUTI with removable source of infection			
m-MITT Population			
Eradication rate at TOC	21/35 (60.0)		20/38 (52.6)
Treatment difference [1]		7.4	
95% CI [1]		(-15.4, 29.3)	
ME Population			
Eradication rate at TOC	20/34 (58.8)		19/34 (55.9)
Treatment difference [1]		2.9	
95% CI [1]		(-20.3, 25.9)	
cUTI with nonremovable source of infection			
m-MITT Population			
Eradication rate at TOC	18/37 (48.6)		21/43 (48.8)
Treatment difference [1]		-0.2	
95% CI [1]		(-21.7, 21.4)	
ME Population			
Eradication rate at TOC	15/33 (45.5)		21/43 (48.8)
Treatment difference [1]		-3.4	
95% CI [1]		(-25.3, 19.0)	

Percentage is calculated using N', the number of subjects in the corresponding population as the denominator.
Per EMA Criteria, a microbiologic outcome of Eradication is defined as the demonstration that the bacterial pathogen(s) found at baseline is reduced to $<10^3$ CFU/mL of urine.
[1] Treatment difference (meropenem-vaborbactam - piperacillin/tazobactam) is the estimate of the difference in the Eradication rate between the two treatment arms. The difference estimates and the 95% CIs are obtained based on Miettinen and Nurminen method [Miettinen and Nurminen, 1985].

Site 703-005 and Site 616-003 were identified by the applicant as having significant quality issues during the trial. After excluding data from the two sites the lower bound of the 95% CI remained within -10% for mMITT and ME populations.

Additional analyses of eradication at TOC using the EU cut-off ($<10^3$ CFU/mL) were provided that:

i) Excluded patients with baseline organisms *resistant to their assigned treatment*. For meropenem-vaborbactam the proposed breakpoint of 8 mg/L was applied (3 m-MITT and 3 ME patients affected) and for piperacillin/tazobactam the EUCAST and CLSI breakpoints were applied (36 and 23 m-MITT and 30 and 21 ME patients affected). The lower bounds of the 95% CI remained within -10%.

ii) Excluded patients with baseline organisms *resistant to piperacillin/tazobactam* when the EUCAST and CLSI breakpoints were applied (so affecting the same numbers in this group as reported above). In the m-MITT and ME populations the lower bounds of the 95% CI remained within -10%.

The eradication rates at TOC were higher in patients who switched to oral therapy vs. those who did not but were mostly numerically higher for meropenem-vaborbactam or were similar to the comparator rates. Exceptions were in cUTI patients with/without removable sources of infection who switched, in whom rates were numerically higher for piperacillin/tazobactam.

In contrast, among cUTI patients who did not switch the rates were numerically higher for meropenem-vaborbactam. These rates are all based on small denominators.

Eradication rates (EU cut-off) in the meropenem-vaborbactam and piperacillin/tazobactam groups decreased over time, especially between EOT and TOC. Non-inferiority was maintained throughout the visits shown below.

Table 28 Eradication rate (EMA's criterion of $<10^3$ CFU/mL of urine) by time point (m-MITT and ME populations)

	m-MITT Population		ME Population	
	Meropenem-Vaborbactam (N=192) n/N' (%)	Piperacillin/Tazobactam (N=182) n/N' (%)	Meropenem-Vaborbactam (N=178) n/N' (%)	Piperacillin/Tazobactam (N=169) n/N' (%)
Day 3				
Eradication	186/192 (96.9)	164/182 (90.1)	174/178 (97.8)	157/169 (92.9)
Difference	6.8		4.9	
95% CI	(1.9, 12.3)		(0.5, 10.0)	
EOIVT				
Eradication	188/192 (97.9)	168/182 (92.3)	178/178 (100.0)	166/169 (98.2)
Difference	5.6		1.8	
95% CI	(1.4, 10.7)		(-0.4, 5.1)	
EOT				
Eradication	169/192 (88.0)	158/182 (86.8)	160/178 (89.9)	156/169 (92.3)
Difference	1.2		-2.4	
95% CI	(-5.6, 8.1)		(-8.7, 3.8)	
TOC				
Eradication	128/192 (66.7)	105/182 (57.7)	118/178 (66.3)	102/169 (60.4)
Difference	9.0		5.9	
95% CI	(-0.9, 18.7)		(-4.2, 16.0)	
LFU				
Eradication	129/192 (67.2)	98/182 (53.8)	120/178 (67.4)	94/169 (55.6)
Difference	13.3		11.8	
95% CI	(3.4, 23.0)		(1.5, 21.8)	

The effects of age and gender on eradication rates shown below should be interpreted in terms of the distribution of AP and cUTI by these same factors. There were higher eradication and overall response rates in those with vs. without SIRS in the meropenem-vaborbactam group but this was not apparent in the control group.

Figure 8 Forest plot of eradication rate (EMA's CFU/mL criterion) at TOC by subgroup (m-MITT population)

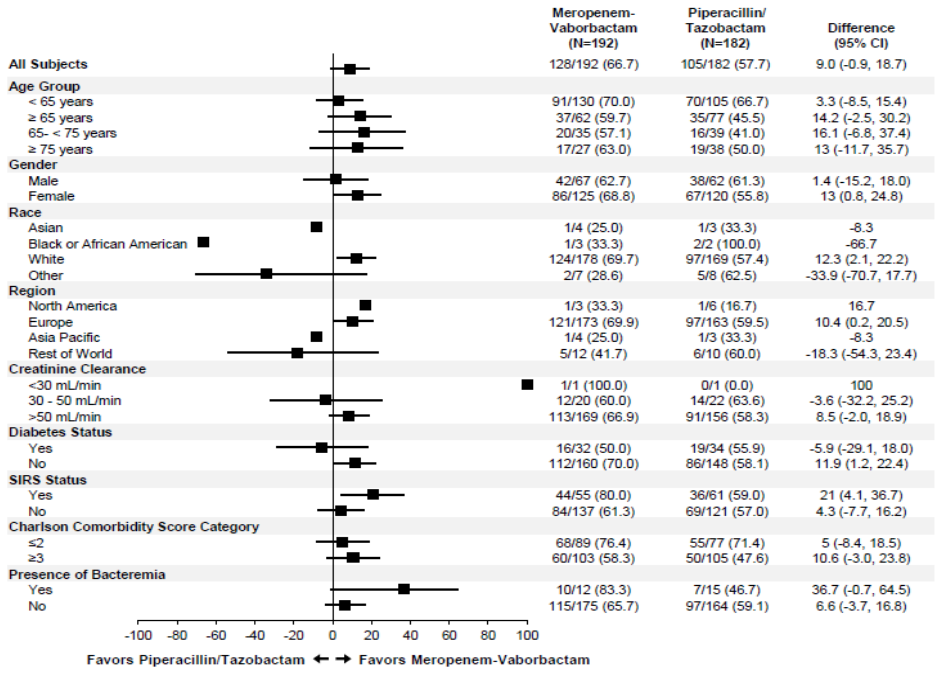


Figure 9 Eradication rates (EU criterion) by species (regardless of susceptibility) at TOC for the two treatment groups are shown below for the micro-MITT population.

Infection Type / Pathogen / Microbiological Outcome	Meropenem-Vaborbactam (N=192) n/N' (%)	Piperacillin/ Tazobactam (N=182) n/N' (%)
Overall		
Acinetobacter baumannii-calcoaceticus species complex		
Eradication	0/ 1 (0.0)	0/ 2 (0.0)
Persistence	0/ 1 (0.0)	0/ 2 (0.0)
Recurrence	0/ 1 (0.0)	0/ 2 (0.0)
Indeterminate	0/ 1 (0.0)	0/ 2 (0.0)
Citrobacter freundii species complex		
Eradication	2/ 2 (100.0)	3/ 3 (100.0)
Persistence	0/ 2 (0.0)	0/ 3 (0.0)
Recurrence	0/ 2 (0.0)	0/ 3 (0.0)
Indeterminate	0/ 2 (0.0)	0/ 3 (0.0)
Citrobacter koseri		
Eradication	1/ 1 (100.0)	1/ 1 (100.0)
Persistence	0/ 1 (0.0)	0/ 1 (0.0)
Recurrence	0/ 1 (0.0)	0/ 1 (0.0)
Indeterminate	0/ 1 (0.0)	0/ 1 (0.0)
Enterobacter cloacae species complex		
Eradication	9/ 10 (90.0)	3/ 5 (60.0)
Persistence	0/ 10 (0.0)	0/ 5 (0.0)
Recurrence	1/ 10 (10.0)	1/ 5 (20.0)
Indeterminate	0/ 10 (0.0)	1/ 5 (20.0)
Enterococcus faecalis		
Eradication	5/ 13 (38.5)	11/ 14 (78.6)
Persistence	0/ 13 (0.0)	0/ 14 (0.0)
Recurrence	7/ 13 (53.8)	3/ 14 (21.4)
Indeterminate	1/ 13 (7.7)	0/ 14 (0.0)
Escherichia coli		
Eradication	89/125 (71.2)	68/117 (58.1)
Persistence	0/125 (0.0)	0/117 (0.0)
Recurrence	21/125 (16.8)	21/117 (17.9)
Indeterminate	15/125 (12.0)	28/117 (23.9)

Klebsiella oxytoca		
Eradication	0/ 2 (0.0)	1/ 1 (100.0)
Persistence	0/ 2 (0.0)	0/ 1 (0.0)
Recurrence	0/ 2 (0.0)	0/ 1 (0.0)
Indeterminate	2/ 2 (100.0)	0/ 1 (0.0)
Klebsiella pneumoniae		
Eradication	19/ 30 (63.3)	14/ 28 (50.0)
Persistence	0/ 30 (0.0)	0/ 28 (0.0)
Recurrence	8/ 30 (26.7)	13/ 28 (46.4)
Indeterminate	3/ 30 (10.0)	1/ 28 (3.6)
Morganella morganii		
Eradication	0/ 1 (0.0)	3/ 3 (100.0)
Persistence	0/ 1 (0.0)	0/ 3 (0.0)
Recurrence	1/ 1 (100.0)	0/ 3 (0.0)
Indeterminate	0/ 1 (0.0)	0/ 3 (0.0)
Proteus mirabilis		
Eradication	3/ 6 (50.0)	9/ 12 (75.0)
Persistence	0/ 6 (0.0)	0/ 12 (0.0)
Recurrence	2/ 6 (33.3)	0/ 12 (0.0)
Indeterminate	1/ 6 (16.7)	3/ 12 (25.0)
Proteus vulgaris		
Eradication	1/ 1 (100.0)	1/ 1 (100.0)
Persistence	0/ 1 (0.0)	0/ 1 (0.0)
Recurrence	0/ 1 (0.0)	0/ 1 (0.0)
Indeterminate	0/ 1 (0.0)	0/ 1 (0.0)
Providencia stuartii		
Eradication	0/ 1 (0.0)	0/ 0
Persistence	0/ 1 (0.0)	0/ 0
Recurrence	0/ 1 (0.0)	0/ 0
Indeterminate	1/ 1 (100.0)	0/ 0
Pseudomonas aeruginosa		
Eradication	5/ 5 (100.0)	3/ 10 (30.0)
Persistence	0/ 5 (0.0)	1/ 10 (10.0)
Recurrence	0/ 5 (0.0)	5/ 10 (50.0)
Indeterminate	0/ 5 (0.0)	1/ 10 (10.0)
Pseudomonas putida		
Eradication	1/ 1 (100.0)	0/ 0
Persistence	0/ 1 (0.0)	0/ 0
Recurrence	0/ 1 (0.0)	0/ 0
Indeterminate	0/ 1 (0.0)	0/ 0
Staphylococcus saprophyticus		
Eradication	2/ 5 (40.0)	0/ 0
Persistence	0/ 5 (0.0)	0/ 0
Recurrence	0/ 5 (0.0)	0/ 0
Indeterminate	3/ 5 (60.0)	0/ 0

The three meropenem-resistant pathogens treated with meropenem-vaborbactam were eradicated at TOC and the patients had clinical cure. These pathogens were found to have porin deficiencies and/or to express efflux pumps affecting susceptibility to meropenem and to the combination.

Eradication rates at TOC for piperacillin/tazobactam-resistant (EU breakpoints) pathogens belonging to species for which there were at least 15 m-MITT patients were 16/36 (44%) for those treated with piperacillin/tazobactam and 25/38 (66%) for those treated with meropenem-vaborbactam.

Lower eradication rates at TOC were generally observed for organisms expressing ESBLs in both treatment groups.

Carbapenemases were identified in *Enterobacteriaceae* isolated from 3 meropenem-vaborbactam patients. One had *P. mirabilis* with VIM-1 but the MV MIC was 0.5 µg/ml. One had *K. pneumoniae* expressing OXA-48 (+CTX-M-15) with MV MIC 32 µg/ml and one had *P. stuartii* expressing KPC-2 alone with MV MIC ≤0.06 µg/ml. Two had “overall success” at TOC and the third had an outcome of indeterminate. One patient in the piperacillin/tazobactam group was infected with two different strains of *K. pneumoniae*, both producing KPC-2 (MV MICs 2 µg/ml and <0.06 µg/ml; +SHV-12) and failed due to microbiologic recurrence at TOC.

In the meropenem-vaborbactam group three patients were infected with *K. pneumoniae* that showed ≥4-fold increases in MV MIC (from 0.06 µg/ml to 0.25 µg/ml in 2; from 0.125 µg/ml to 0.5 µg/ml in 1). Whole genome sequence analysis demonstrated that the baseline and post-baseline isolates were likely the same. At TOC one had an indeterminate outcome and 2 failed.

Cure rates in the m-MITT, CE and ME Populations were numerically higher in the meropenem-vaborbactam group compared with the piperacillin/tazobactam group at Day 3, EOIVT, EOT, TOC and LFU. No differences were seen in cure rates over time between AP and cUTI patients. Overall success rates (clinical and FDA eradication criteria) were higher in both groups at EOIVT than at TOC due to return of the baseline pathogen in both groups at TOC. Relapse was defined as isolation of urine or blood culture with the same baseline urinary pathogen after prior eradication and accompanied by new or worsening signs and symptoms of infection requiring alternative antimicrobial therapy in the time period after EOT. One meropenem-vaborbactam and two piperacillin/tazobactam patients met these relapse criteria. No patients had new infections or superinfections.

Two patients in each treatment group died, including one piperacillin/tazobactam patient with septic shock. All four deaths were considered unrelated to treatment. The mean duration of ICU stay was shorter in the meropenem-vaborbactam group (9.3 vs. 11.1 days. For non-ICU patients, the mean durations of hospitalisation were 9.7 days and 9.9 days, and most were discharged home (96.9% and 94.0%).

Study 506 (TANGO II)

Study 506 was ongoing at the time of submission. It was terminated during the primary assessment period on the advice of the DSMB, which considered that their interim benefit-risk assessment did not support further randomisation of patients to best available therapy (BAT). The interim CSR was replaced with the final CSR during the procedure.

Methods

Study 506 was a Phase III, multicentre, randomized, open-label study of meropenem 2 g-vaborbactam 2 g versus BAT in the treatment of subjects with selected serious infections, specifically complicated urinary tract infections (cUTI) or acute pyelonephritis (AP), complicated intraabdominal infections (cIAI), hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), and bacteraemia, suspected or known to be caused by CRE.

Study Participants

Patients were to have any of cUTI/AP, cIAI, HABP, VABP or bacteraemia was suspected or known to be caused by CRE.

Treatments

Subjects randomized to the meropenem-vaborbactam group received meropenem 2 g-vaborbactam 2 g diluted in normal saline to a volume of 250 mL. After dilution, meropenem-vaborbactam was infused for 3 hours q8h using a programmable infusion pump.

Subjects randomized to BAT were treated with the following IV antibiotics, either alone or in combination: a carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycosides (amikacin, tobramycin, or gentamicin), polymyxin B, or ceftazidime-avibactam. The combinations for BAT were determined by the investigator, with the choice of BAT selected by the investigator before randomization to minimize potential selection bias. Investigators were instructed to select only country-approved therapies; the preparation, dose, and frequency of administration were recommended to be in accordance with the product labelling.

Study drug was infused for 7 days to 14 days. Changes to study drug were permitted within 72 hours based on susceptibility testing results. A change in study drug after 72 hours was considered a treatment failure and EOT procedures were performed.

Objectives

The objectives of the study were as follows:

- To evaluate the safety, tolerability, and efficacy of meropenem 2 g-vaborbactam 2 g in the treatment of subjects with selected serious infections, suspected or known to be due to CRE
- To assess the pharmacokinetics (PK) of meropenem and vaborbactam in subjects with selected serious infections, suspected or known to be due to CRE

Outcomes/endpoints

Efficacy endpoints differed across indications:

- the primary efficacy endpoint for subjects with HABP/VABP or bacteraemia was all-cause mortality

  at Day 28 in the microbiological carbapenem-resistant Enterobacteriaceae Modified Intent-to-Treat

  (mCRE-MITT) Population (i.e., all subjects who received at least one dose of study drug and who had Enterobacteriaceae at baseline that was confirmed as meropenem-resistant) for all subjects with HABP or VABP combined with all subjects with bacteraemia (not related to cUTI/AP or HABP/VABP);
- The primary efficacy endpoint for subjects with cUTI or AP in the EU was the proportion of subjects in the mCRE-MITT Population that demonstrated microbiologic eradication (ie, bacterial pathogen(s) found at baseline was reduced to <103 CFU/mL of urine).
- The primary endpoint for subjects with cIAI was the proportion of patients with a clinical outcome of cure in the mCRE-MITT population at TOC

Secondary efficacy endpoints for the indications of HABP/VABP, bacteraemia, and cUTI/AP included the following:

- All-cause mortality rate at Day 28 (cUTI/AP, HABP/VABP, and bacteraemia)
- Proportion of subjects with a clinical outcome of cure at TOC (HABP/VABP and bacteraemia)
- Proportion of subjects with a response of overall success at TOC (bacteraemia and cUTI/AP)
- Proportion of subjects with a clinical outcome of cure at TOC, where the use of aminoglycoside beyond 72 hours in subjects with a pathogen susceptible to meropenem-vaborbactam was assigned to failure (HABP/VABP and bacteraemia)
- Per pathogen outcome (HABP/VABP and bacteraemia)
- Relapse/recurrence rates (HABP/VABP, bacteraemia, and cUTI/AP)
- Proportion of subjects with a microbiologic outcome of eradication (bacteraemia and cUTI/AP)

Sample size

Due to the infeasibility of recruiting a large number of subjects infected with CRE pathogens, no formal power calculations were performed for this study. The sample size was based on practical considerations.

Randomisation

Randomisation (2 meropenem-vaborbactam: 1 BAT) was stratified by presenting indication (cUTI or AP, cIAI, HABP, VABP and bacteraemia) and by region (North America, Europe, Asia Pacific, Rest of World).

Blinding (masking)

This was an open-label study and the investigators, study coordinators, and pharmacy staff were not blinded. Subjects were not informed of their treatment assignment to ensure an unbiased assessment of outcomes for the meropenem-vaborbactam and BAT groups.

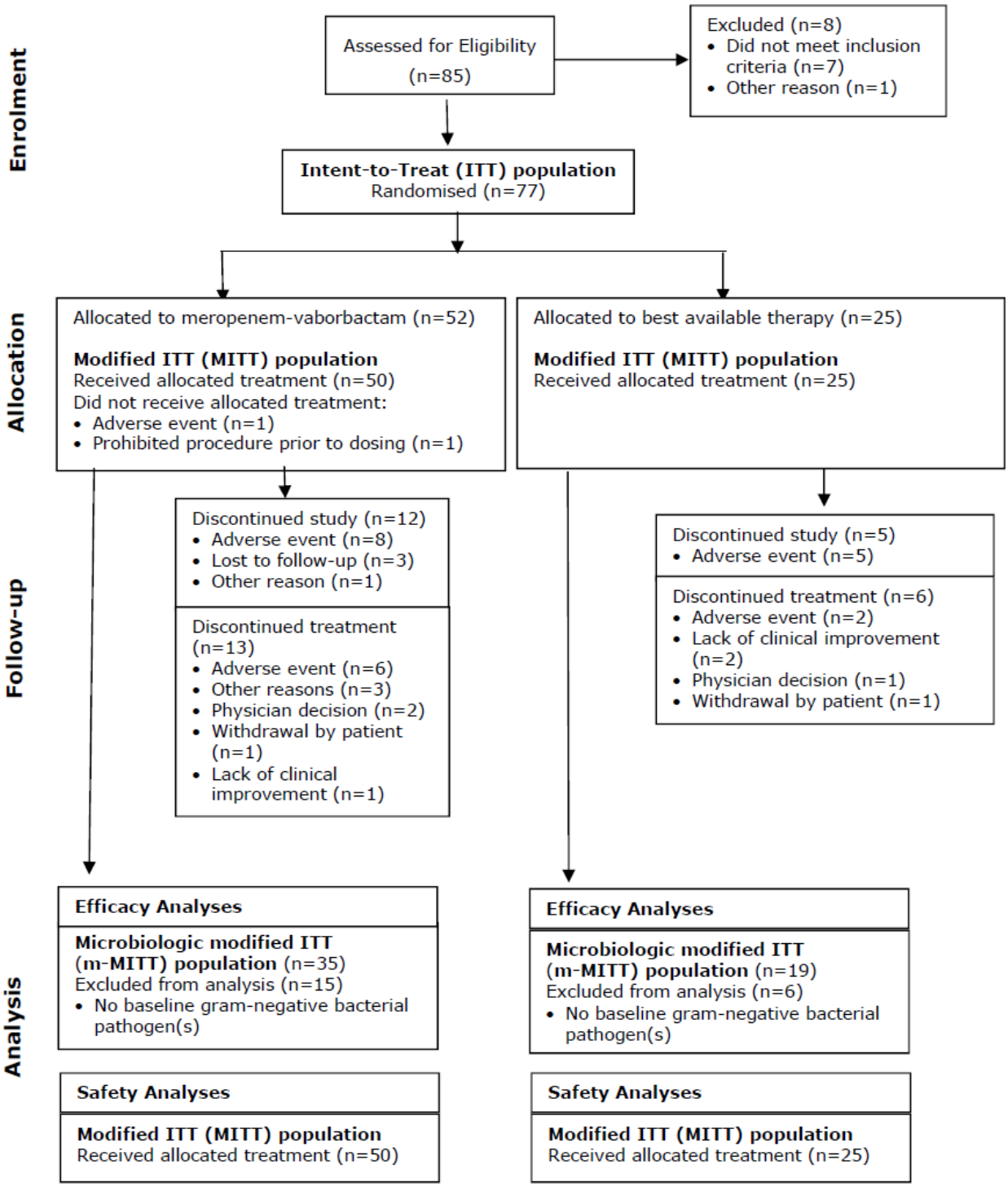
Statistical methods

Efficacy data were presented descriptively for:

- Microbiological Modified Intent-to-Treat (m-MITT) Population
- Microbiological Carbapenem-resistant *Enterobacteriaceae* Modified Intent-to-Treat (mCRE-MITT); this was the primary population for efficacy. CRE status was defined as follows:

CRE Status	Criteria
Known CRE:	• Had a known CRE infection based on evidence from CRE culture or other phenotypic or molecular testing within 72 hours prior to Day 1, alone or as a single isolate of a polymicrobial infection • Had received no more than 24 hours of an antimicrobial agent to which the known CRE was susceptible prior to enrollment OR • Had documented clinical evidence of failure (ie, clinical deterioration or failure to improve) after at least 48 hours of treatment with an antimicrobial agent to which the known CRE was susceptible
Suspected CRE:	• Had a suspected CRE infection based on evidence from CRE culture (KPC-producing, if known) or other phenotypic or molecular testing, alone or as a single isolate of a polymicrobial infection, from any source within 90 days prior to Day 1 • Had received no more than 24 hours of empiric antimicrobial therapy for gram-negative organisms prior to enrollment

Participant flow



Results

When the study was closed on the DSMB's advice there had been 77 patients (28 bacteraemia, 34 cUTI, 8 HAP/VAP, 7 cIAI) enrolled over 2.5 years. There was a high incidence of underlying comorbidities. About 40% were immunocompromised and 79% had a Charlson Comorbidity Score >5.

In the final population (52 meropenem, 25 BAT) 54 had a Gram-negative pathogen(s) isolated at baseline and were included in the m-MITT population and 47 had CRE (mCREMITT population), most of which were KPC-producers (median meropenem MIC 32 µg/ml vs. MV MIC 0.5 µg/ml).

There were trends toward mortality, clinical and microbiologic outcome benefits for monotherapy with meropenem-vaborbactam vs. BAT in the mMITT and mCRE populations across the indications. The benefit of meropenem-vaborbactam vs. BAT was particularly evident in those with HAP/VAP and bacteraemia. None of the deaths in the meropenem-vaborbactam group occurred in subjects with AEs of sepsis or septic shock vs. 3 of 4 deaths in the BAT group. At TOC in the mCRE-MITT Population, clinical cure rates and microbial eradication rates were 30.5% and 11.8% higher in the meropenem-vaborbactam group compared with the BAT group, respectively.

Table 29 Overview of efficacy results

Indication Endpoint	Population	Meropenem-Vaborbactam n (%)	BAT n (%)
All Indications			
All-cause mortality at Day 28	m-MITT	5/35 (14.3)	5/19 (26.3)
	mCRE-ITT	5/32 (15.6)	5/15 (33.3)
Clinical cure at TOC [1]	m-MITT	21/35 (60.0)	6/19 (31.6)
	mCRE-ITT	19/32 (59.4)	4/15 (26.7)
Microbial Eradication at TOC [2]	m-MITT	17/35 (48.6)	7/19 (36.8)
	mCRE-ITT	17/32 (53.1)	5/15 (33.3)
HAP/VAP or bacteremia			
All-cause mortality at Day 28	m-MITT	4/18 (20.0)	4/9 (44.4)
	mCRE-ITT	4/20 (22.2)	4/9 (44.4)
HAP/VAP			
All-cause mortality at Day 28	m-MITT	0/5 (0)	1/1 (100)
	mCRE-ITT	0/4 (0)	1/1 (100)
Clinical cure at TOC [1]	m-MITT	4/5 (80.0)	0/1 (0.0)
	mCRE-ITT	4/4 (100.0)	0/1 (0.0)
Microbial Eradication at TOC [2]	m-MITT	3/5 (60.0)	0/1 (0.0)
	mCRE-ITT	3/4 (75.0)	0/1 (0.0)
Bacteremia			
All-cause mortality at Day 28	m-MITT	4/15 (26.7)	3/8 (37.5)
	mCRE-ITT	4/14 (28.6)	3/8 (37.5)
Clinical cure at TOC [1]	m-MITT	9/15 (60.0)	2/8 (25.0)
	mCRE-ITT	8/14 (57.1)	2/8 (25.0)
Microbial Eradication at TOC [2]	m-MITT	8/15 (53.3)	3/8 (37.5)
	mCRE-ITT	7/14 (50.0)	3/8 (37.5)
cUTI or AP			
All-cause mortality at Day 28	m-MITT	1/ 13 (7.7)	0/8 (0.0)
	mCRE-ITT	1/ 12 (8.3)	0/4 (0.0)
Overall success at EOT [3]	m-MITT	10/ 13 (76.9)	4/ 8 (50.0)
	mCRE-ITT	9/ 12 (75.0)	2/ 4 (50.0)
Overall success at TOC [3]	m-MITT	4/ 13 (30.8)	4/8 (50.0)
	mCRE-ITT	4/ 12 (33.3)	2/4 (50.0)
Clinical cure at EOT [1]	m-MITT	10 (76.9)	4 (50.0)
	mCRE-ITT	9 (75.0)	2 (50.0)
Clinical cure at TOC [1]	m-MITT	6 (46.2)	4/8 (50.0)
	mCRE-ITT	5 (41.7)	2/4 (50.0)
Microbial Eradication at EOT [4]	m-MITT	9 (69.2)	3 (37.5)
	mCRE-ITT	8 (66.7)	2 (50.0)
Microbial Eradication at TOC [4]	m-MITT	3/13 (23.1)	2/8 (25.0)
	mCRE-ITT	3/12 (25.0)	2/4 (50.0)
cIAI			
All-cause mortality at Day 28	m-MITT	0/2 (0)	1/2 (50.0)
	mCRE-ITT	0/2 (0)	1/2 (50.0)
Clinical cure at TOC [1]	m-MITT	2/2 (100)	0/2 (0)
	mCRE-ITT	2/2 (100)	0/2 (0)
Microbial Eradication at TOC [2]	m-MITT	1/2 (50)	0/2 (0)
	mCRE-ITT	1/2 (50)	0/2 (0)
	mCRE-ITT	1/ 11 (9.1)	1/ 8 (12.5)

[1] Defined as complete resolution or significant improvement of the baseline signs and symptoms such that no further surgical intervention or antimicrobial therapy was warranted.
[2] Includes microbial eradication and/or presumed eradication where presumed eradication was defined as clinical cure and microbiological indeterminate.
[3] Defined as a clinical outcome of Cure and microbiologic outcome of Eradication.
[4] $<10^4$ CFU/mL of urine.

The higher proportion of subjects with missing data at the TOC visit in the meropenem-vaborbactam group compared with the BAT group makes outcomes for cUTI/AP subjects difficult to interpret. The mortality reductions seen with meropenem-vaborbactam monotherapy compared with BAT and the trend for increased clinical cure rates were seen in subjects aged ≥65 and ≥75 years, subjects who were immunocompromised, subjects who had a Charlson Comorbidity Score ≥4, and subjects who had SIRS at baseline (see below).

Cure rates were higher in the meropenem-vaborbactam group compared with the BAT group for subjects aged ≥65 and ≥75 years, subjects who had a Charlson Comorbidity Score ≥6, subjects who had impaired renal function (CrCl <50 ml/min) at baseline and subjects who had SIRS at baseline.

Table 30 Efficacy results by subpopulation across all indications (mCRE-MITT population)

	All-Cause Mortality at Day 28		Cures at TOC		Microbial Eradication at TOC	
	Meropenem-Vaborbactam	BAT	Meropenem-Vaborbactam	BAT	Meropenem-Vaborbactam	BAT
Age group						
< 65 years	1/ 17 (5.9)	1/ 9 (11.1)	14/ 17 (82.4)	4/ 9 (44.4)	1/ 17 (5.9)	4/ 9 (44.4)
≥65 years	4/ 15 (26.7)	4/ 6 (66.7)	5/ 15 (33.3)	0/ 6 (0.0)	2/ 15 (13.3)	0/ 6 (0.0)
≥75 years	1/ 7 (14.3)	3/ 3 (100.0)	1/ 7 (14.3)	0/ 3 (0.0)	0/ 7 (0.0)	0/ 3 (0.0)
SIRS status						
No	1/ 17 (5.9)	2/ 9 (22.2)	10/ 17 (58.8)	3/ 9 (33.3)	2/ 17 (11.8)	2/ 9 (22.2)
Yes	4/ 15 (26.7)	3/ 6 (50.0)	9/ 15 (60.0)	1/ 6 (16.7)	1/ 15 (6.7)	2/ 6 (33.3)
Charlson comorbidity score category						
<4	0/ 5 (0.0)	0/ 2 (0.0)	5/ 5 (100)	2/ 2 (100.0)	0/ 5 (0.0)	2/ 2 (100.0)
≥4	5/ 27 (18.5)	5/ 13 (38.5)	14/ 27 (51.9)	2/ 3 (66.7)	3/ 27 (11.1)	2/ 13 (15.4)
≥6	1/ 14 (7.1)	5/ 11 (45.5)	9/ 14 (64.3)	1/ 11 (9.1)	1/ 14 (7.1)	1/ 11 (9.1)
CrCl						
<50 mL/min	3/ 7 (42.9)	1/ 4 (25.0)	2/ 5 (40.0)	0/ 4 (0.0)	0/ 7 (0.0)	1/ 4 (25.0)
≥50 mL/min	2/ 24 (8.3)	4/ 9 (44.4)	17/ 24 (70.8)	4/ 9 (44.4)	3/ 24 (12.5)	3/ 9 (33.3)
Immunocompromised						
No	3/ 21 (14.3)	2/ 7 (28.6)	12/ 21 (57.1)	4/ 7 (57.1)	2/ 21 (9.5)	3/ 7 (42.9)
Yes	2/ 11 (18.2)	3/ 8 (37.5)	7/ 11 (63.6)	0/ 8 (0.0)	1/ 11 (9.1)	1/ 8 (12.5)

BAT = best available therapy; CrCl = creatinine clearance; SIRS = systemic inflammatory response syndrome; TOC = test of cure.

There were 7 subjects with HAP/VAP in the total study population of which 5 had a known CRE and 4/5 had *K. pneumoniae*. Meropenem MICs ranged from ≤0.03 µg/ml to >64 µg/ml in the meropenem-vaborbactam and BAT group while 2 and 1 in respective groups had KPC-producing isolates.

Seven subjects had cIAI of which 4 (2 per group) were in the m-MITT and mCRE-MITT populations. CRE pathogens at baseline included *K. pneumoniae* (3), *E. cloacae species complex* (1), *E. coli* (1), *Proteus mirabilis* (1) and an unspeciated coliform (1). The two in the meropenem-vaborbactam group but neither BAT subject were cures at EOT and one BAT subject died.

Microbiological outcomes for the m-MITT population are shown by pathogen in the following:

Table 31 Microbiological outcomes by pathogen (m-MITT population)

Infection Type Pathogen Microbiological Outcome	Meropenem-Vaborbactam (N= 35) n/N' (%)	Best Available Therapy (N= 19) n/N' (%)
Overall		
Acinetobacter baumannii-calcoaceticus species complex		
Eradication	0/ 1 (0.0)	0/ 0
Persistence	1/ 1 (100.0)	0/ 0
Recurrence	0/ 1 (0.0)	0/ 0
Indeterminate	0/ 1 (0.0)	0/ 0
Elizabethkingia meningoseptica/ elizabethkingia anophelis/ elizabethkingia miricola		
Eradication	1/ 1 (100.0)	0/ 0
Persistence	0/ 1 (0.0)	0/ 0
Recurrence	0/ 1 (0.0)	0/ 0
Indeterminate	0/ 1 (0.0)	0/ 0
Enterobacter cloacae species complex		
Eradication	1/ 1 (100.0)	2/ 2 (100.0)
Persistence	0/ 1 (0.0)	0/ 2 (0.0)
Recurrence	0/ 1 (0.0)	0/ 2 (0.0)
Indeterminate	0/ 1 (0.0)	0/ 2 (0.0)

Infection Type Pathogen Microbiological Outcome	Meropenem-Vaborbactam (N= 35) n/N' (%)	Best Available Therapy (N= 19) n/N' (%)
Overall		
Enterococcus faecalis		
Eradication	2/ 2 (100.0)	0/ 0
Persistence	0/ 2 (0.0)	0/ 0
Recurrence	0/ 2 (0.0)	0/ 0
Indeterminate	0/ 2 (0.0)	0/ 0
Enterococcus faecium		
Eradication	0/ 0	0/ 1 (0.0)
Persistence	0/ 0	1/ 1 (100.0)
Recurrence	0/ 0	0/ 1 (0.0)
Indeterminate	0/ 0	0/ 1 (0.0)
Escherichia coli		
Eradication	1/ 3 (33.3)	1/ 4 (25.0)
Persistence	2/ 3 (66.7)	3/ 4 (75.0)
Recurrence	0/ 3 (0.0)	0/ 4 (0.0)
Indeterminate	0/ 3 (0.0)	0/ 4 (0.0)
Klebsiella pneumoniae		
Eradication	14/ 30 (46.7)	4/ 14 (28.6)
Persistence	12/ 30 (40.0)	10/ 14 (71.4)
Recurrence	0/ 30 (0.0)	0/ 14 (0.0)
Indeterminate	4/ 30 (13.3)	0/ 14 (0.0)
Proteus mirabilis		
Eradication	0/ 0	0/ 2 (0.0)
Persistence	0/ 0	2/ 2 (100.0)
Recurrence	0/ 0	0/ 2 (0.0)
Indeterminate	0/ 0	0/ 2 (0.0)
Providencia stuartii		
Eradication	0/ 0	0/ 1 (0.0)
Persistence	0/ 0	1/ 1 (100.0)
Recurrence	0/ 0	0/ 1 (0.0)
Indeterminate	0/ 0	0/ 1 (0.0)
Pseudomonas aeruginosa		
Eradication	2/ 2 (100.0)	0/ 0
Persistence	0/ 2 (0.0)	0/ 0
Recurrence	0/ 2 (0.0)	0/ 0
Indeterminate	0/ 2 (0.0)	0/ 0
Serratia marcescens		
Eradication	1/ 1 (100.0)	1/ 1 (100.0)
Persistence	0/ 1 (0.0)	0/ 1 (0.0)
Recurrence	0/ 1 (0.0)	0/ 1 (0.0)
Indeterminate	0/ 1 (0.0)	0/ 1 (0.0)
Unspeciated coliform		
Eradication	0/ 0	0/ 1 (0.0)
Persistence	0/ 0	1/ 1 (100.0)
Recurrence	0/ 0	0/ 1 (0.0)
Indeterminate	0/ 0	0/ 1 (0.0)

- One patient with AP had a KPC-producing *K. pneumoniae* for which the MV MIC increased from 0.25 µg/ml at baseline to 1.0 µg/ml at TOC. Molecular analysis revealed that the TOC isolate could not have been directly selected from the baseline isolate. Therefore, two strains were likely present at baseline. The patient did not have eradication at TOC but did have a clinical outcome of cure at TOC.
- One had bacteraemia due to *K. pneumoniae* with an increase in meropenem MIC from 2 µg/ml at baseline to 8 µg/ml at EOT and an increase in MV MIC from 0.5 µg/ml to 2 µg/ml at EOT.

Neither isolate carried any carbapenemase genes, but both had the CTX-M-15 beta-lactamase gene and had defective porin OmpK36. The EOT isolate had a 3 to 4-fold increase in copy of CTX-M-15 compared to the baseline isolate. The patient had microbiologic recurrence and clinical failure at EOT due to death from a massive gastrointestinal haemorrhage on Day 5.

A third patient with HABP had two different strains of meropenem-resistant *P. aeruginosa* at baseline - one had meropenem and MV MICs of 8 µg/ml and one had MICs to both that were 16 µg/ml – and also had *A. baumannii*. On Day 3 the *A. baumannii* persisted and a strain of *P. aeruginosa* with a meropenem and MV MIC of 64 µg/ml was isolated. The baseline and Day 3 *P. aeruginosa* isolates were closely related and all three contained VIM carbapenemase. The Day 3 isolate was found to have insertional inactivation of the gene that encodes OprD. The *A. baumannii* and *P. aeruginosa* persisted at TOC and the patient was a clinical failure.

2.5.2. Discussion on clinical efficacy

Study 505 and the indication for treatment of cUTI, including AP

Study 505 was generally of an adequate design to meet the CHMP requirements for supporting the claimed indication except that the final pre-defined non-inferiority margin to be applied to the EU primary endpoint was 15%. The margin was increased from 10% to 15% by protocol amendment, reducing the projected sample size from 850 to 500 patients. This approach to the margin was taken because the programme, consisting of studies 505 and 506, was primarily intended to support use in patients with limited treatment options and not to support an additional standalone indication for cUTI and AP.

The study met the revised enrolment target. There were <15% in each group with CrCL < 50 ml/min, ~5% had concurrent bacteraemia and <5% had received prior antibacterial treatment for the infection under study. About 60% had AP and females accounted for 66% of the total population. Despite this, there was a good spread of ages including ~40% aged > 65 years. Overall about 30% had SIRS and about 50% had Charlson comorbidity scores ≥3. The applicability of the latter index to this patient population is unclear but this fact does not impact on the general acceptability of the patient population.

Although the pre-defined NI margin was 15% and the sample size had been adjusted, the primary analysis for the EU primary endpoint demonstrated that the lower bound of the 95% CI around the difference in eradication rates was well within -10% in the m-MITT and ME populations. The conclusions from the primary analysis were unchanged after removing data from the two sites where the sponsor identified problems during the study and in all the sensitivity analyses.

Although study 505 met its primary endpoint it must be remembered that effectively this study compared meropenem at the revised dosing regimen of 2 g q8h using 3-hour infusions with piperacillin-tazobactam because, as expected in the general cUTI/AP population, there were very few meropenem-resistant, MV-susceptible organisms detected at baseline. Thus, the study cannot provide support for the adequacy of the vaborbactam dose to protect meropenem from Class A and C beta-

lactamases. The vaborbactam dose can only be supported by the PK-PD analyses, which are of paramount importance for this application.

The imbalance in resistance to the assigned treatment was of concern for the overall validity of the primary analysis. Although piperacillin/tazobactam was a suitable comparator for a study that predominantly enrolled at European centres, it was clear that many more baseline organisms were resistant to the comparator whether the EUCAST or CLSI interpretive criteria were applied. After excluding patients infected with piperacillin-tazobactam resistant organisms the 10% NI margin was still met.

It is not surprising that some piperacillin/tazobactam-resistant organisms that were treated with this combination and three MV-resistant organisms treated with meropenem-vaborbactam were eradicated. The high concentrations achieved in urine as compared to plasma may sometimes have greatly exceeded the MIC at least for some period of the dose interval.

The study was not powered to demonstrate non-inferiority within patient subgroups with cUTI or AP. Nevertheless, the comparisons show that there was numerical superiority for meropenem-vaborbactam in each diagnostic subgroup except for the smallest group (cUTI with non-removable source of infection) in which the eradication rates were lowest (<50%) but comparable between treatments. In the largest subgroup of patients (i.e. those with AP) the margin was within -10%.

Patients could switch from IV to a defined PO treatment after at least 5 days IV if protocol-listed criteria were met. The mean duration of IV treatment was 8 days. The analysis of outcomes for the 57.4% meropenem-vaborbactam and 52.7% piperacillin/tazobactam patients who switched to oral treatment showed that eradication rates were higher in those who switched, but this observation is most likely driven by this sub-population being fastest to respond and generally the easiest to treat.

The responses at EOIVT and thereafter show a pattern that has been observed in other cUTI/AP studies, even when there was no oral switch. The eradication rates at EOIVT were very high and comparable between treatments, likely reflecting high concentrations of drugs in urine. In both groups the rates were lower at EOT and then lower again at TOC and FU visits. At each visit, there was no disadvantage for the meropenem-vaborbactam group. The largest drop was between EOT and TOC, with a more modest drop between EOIVT and EOT. The findings suggest that colony counts in samples taken while substantial drug concentrations persisted in urine resulted in falsely optimistic eradication rates. Only after withdrawal of drug were residual live organisms picked up in cultures.

The clinical outcomes are also of interest. These generally followed the patterns for the eradication rates and were lowest in both treatment groups for patients with cUTI and a non-removable source of infection. In addition, relapse was defined as isolation of urine or blood culture with the same baseline urinary pathogen after prior eradication *and accompanied by* new or worsening signs and symptoms of infection requiring alternative antimicrobial therapy after EOT. One meropenem-vaborbactam and two piperacillin/tazobactam patients met these relapse criteria. Almost all patients who had eradication at EOT but not at TOC were asymptomatic despite colony counts that exceeded 10^3 CFU/mL.

Eradication rates (EU criterion) by species (regardless of susceptibility) at TOC for the two treatment groups can support mention of *E. coli*, *K. pneumoniae* and *E. cloacae* species complex in section 5.1 of the SmPC as pathogens against which efficacy was demonstrated in the cUTI/AP trial. For other organisms there are either too few patients or the outcomes do not support convincing efficacy.

In conclusion, CHMP agreed that the results of study 505 support a standard indication for treatment of cUTI, including AP.

Study 506

Study 506 is viewed as a supplementary study in this application. Interpretation of efficacy data from such studies is difficult, but useful PK data can be generated in patients with infections outside of the urinary tract and a limited assessment of safety can be conducted, although the underlying condition of patients may complicate the analysis. As acknowledged in CHMP guidance, the critical information to support the use of the proposed dose regimen of meropenem-vaborbactam to treat the target MDR organisms must come from the PK-PD analyses.

Importantly, whilst this mixed infection study that was not designed for inferential testing cannot provide definitive evidence of efficacy, the DSMB recommended early study termination due to evidence of benefit in the meropenem-vaborbactam group. At the time of study closure 77 patients had been enrolled and 47 had evidence of CRE infection. The efficacy data show a consistent trend favouring meropenem-vaborbactam, which provides some broad support for the adequacy of the vaborbactam dose.

Patients with limited treatment options

Taken together, along with the revised PK-PD analyses, studies 505 and 506 can support the use of meropenem-vaborbactam to *treat infections due to aerobic Gram-negative pathogens in adults with limited treatment options*.

cIAI and HAP/VAP

There is no concern regarding the adequacy of the meropenem dose proposed for Vabomere to treat these infections, which have been claimed by the applicant. The following considerations focus on the justification for the vaborbactam dose:

cIAI

The applicant was asked to provide a detailed discussion on evidence considered to support this indication, which focussed on the fact that the PK properties of meropenem and vaborbactam are very similar.

Meropenem is recognised to be a very good treatment for cIAI and the extension of the infusion time can only be expected to potentially improve its performance in this type of infection. The data obtained with Vabomere in a small number cIAI patients in study 506 are promising but are far too limited to be able to say anything about the sufficiency of the vaborbactam dose.

Using the updated POPPK model, the volumes of distribution at steady-state were similar for meropenem (20.2 L) and vaborbactam (18.6 L), indicating that they distribute into a volume consistent with the extracellular fluid (ECF) compartment. At the same time, the protein binding for the two agents is estimated at 2% and 33%, respectively, and they have a similar partition co-efficient with low likelihood that penetration of vaborbactam into ECF will be affected significantly by transporters. Therefore, with broadly comparable plasma levels and ECF distribution, the concentration of free drug in the ECF is expected to be lower for vaborbactam than for meropenem.

Nevertheless, the nonclinical data using the neutropenic murine thigh infection model and humanised dosing regimens showed that there was at least ~1-log kill for most meropenem-resistant strains tested and that this was observed for MV MICs up to 4-8 mg/L. In the thigh model the penetration of both agents into ECF is a driving factor for efficacy. Therefore, the nonclinical data do support a conclusion that the vaborbactam dose regimen should suffice to treat cIAI, in which penetration of antibacterial agents into the peritoneal fluid is important.

In conclusion, based on considerations of the free vaborbactam levels that may be achieved in the ECF and the evidence provided from the nonclinical data using a humanised dose regimen in the

neutropenic murine thigh infection model, it could be agreed by CHMP that the vaborbactam dose should suffice to protect meropenem within the abdominal cavity should there be organisms resistant to meropenem alone due to production of serine carbapenemases.

HAP/VAP

The applicant's justification for this indication is based on free drug ELF penetration and comparisons between calculated ELF concentrations in infected patients and the plasma PDTs (there being no PDTs established specifically for ELF). Pls. also see the section and discussion on clinical pharmacology for the relevant data and discussion, including the exploratory estimations of PTA achieved in ELF against the plasma PDTs. Overall, CHMP agreed that that use of Vabomere in HAP/VAP could be accepted.

Treatment of bacteraemia in association with the above indications

The applicant has claimed this indication since it was granted for meropenem on conclusion of the Article 30 procedure. There is no concern regarding the meropenem dose to treat patients who have a bacteraemia in association with the approved indications for this agent.

It would not usually be considered appropriate to grant such an indication for a new product since the extent of clinical experience is almost always very limited and often restricted to one of the proposed indications for use. However, this situation is rather different since it is only the adequacy of the inhibitor dose that is potentially problematical. Furthermore, in study 505 there were 27 patients with bacteraemia and the eradication rates at TOC were 10/12 for meropenem-vaborbactam and 7/15 for piperacillin/tazobactam.

The final data from study 506 included 14 meropenem-vaborbactam and 8 BAT patients infected with CRE and with bacteraemia as the sole microbiological source at baseline. The mortality was 4/14 (28.6%) and 3/8 (37.5%) in respective groups. CHMP agreed that these results provide support for allowing this claim to be applied to meropenem-vaborbactam.

Reflection of the clinical and microbiological data in the Vabomere SmPC

The indication for use in patients with limited treatment options reflects treatment of infections due to aerobic Gram-negative pathogens, since this is the only broad group in which a benefit of adding vaborbactam to meropenem is expected.

CHMP agreed with the wording in section 4.4 of the Vabomere Product Information that reflects the limitations of the clinical data. The proposed list of organisms that have been successfully treated in clinical trials is short. It is accompanied by a list of organisms against which efficacy has not been demonstrated in clinical trials, but which may be expected to respond to Vabomere.

2.5.3. Conclusions on the clinical efficacy

CHMP agreed that, based on the data assessed in this applications, the following indications are supportable by a combination of microbiology, nonclinical efficacy, PK-PD analyses and clinical efficacy data:

- Complicated urinary tract infection (cUTI), including pyelonephritis
- Complicated intra-abdominal infection (cIAI)
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)
- Vabomere is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options (see sections 4.2, 4.4 and 5.1).
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be

associated with, any of the infections listed above.

2.6. Clinical safety

Patient exposure

At the time of filing the application there had been 407 individuals exposed to any dose of meropenem-vaborbactam in five clinical trials. An additional 70 healthy subjects were exposed to vaborbactam alone. Exposure to the intended clinical dose was limited to 272 patients in 505, 23 patients in 506 and 42 subjects in Phase 1 studies (N=337).

During the assessment, the final clinical study report for 506 (TANGO II) was provided by the applicant, which included a total of 50 patients exposed to meropenem-vaborbactam. The complete exposure to the intended clinical dose was increased to 364 patients (272 patients in 505, 50 patients in 506 and 42 subjects in Phase 1 studies).

The applicant's summary of safety described two patient pools:

- *Phase III pool:* Studies 505 (TANGO I) and 506 (TANGO II) pooled (322 meropenem-vaborbactam and 298 to any comparator)
- *All treated pool:* Studies 501, 503 and 504 plus studies 505 and 506. This dataset pools data from all individuals who received any dose of meropenem-vaborbactam (433) and it pools safety data from 347 individuals who received any comparator. It excludes those who received vaborbactam alone.

The following sections mainly describe the final data from 505 and 506

Adverse events

In **study 505** slightly higher proportions in the meropenem-vaborbactam group experienced at least one AE, study drug-related AEs and life-threatening AEs.

Table 32 Overview of adverse events (safety population)

	Meropenem-Vaborbactam (N=272)		Piperacillin/Tazobactam (N=273)		Total (N=545)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
All TEAEs	106 (39.0)	204	97 (35.5)	170	203 (37.2)	374
Drug-related TEAEs	41 (15.1)	56	35 (12.8)	45	76 (13.9)	101
TEAE by maximum severity						
Mild	49 (18.0)	79	45 (16.5)	69	94 (17.2)	148
Moderate	45 (16.5)	71	37 (13.6)	48	82 (15.0)	119
Severe	7 (2.6)	9	13 (4.8)	15	20 (3.7)	24
Life-Threatening	3 (1.1)	3	0 (0.0)	0	3 (0.6)	3
All SAEs	11 (4.0)	12	12 (4.4)	12	23 (4.2)	24
Drug-related SAEs	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Deaths	2 (0.7)	2	2 (0.7)	2	4 (0.7)	4
Discontinuation of study drug due to TEAEs [1]	7 (2.6)	8	14 (5.1)	16	21 (3.9)	24
Discontinuation from study due to TEAEs [2]	3 (1.1)	4	3 (1.1)	4	6 (1.1)	8

[1] Includes two subjects with fatal, serious AEs in the piperacillin/tazobactam group.
[2] Includes two subjects in the meropenem-vaborbactam group with fatal, serious AEs and 1 subject in the piperacillin/tazobactam group with a fatal, serious AE.

The most frequent AEs were headache, phlebitis/infusion site reaction, diarrhoea and nausea.

Table 33 Frequent (≥1% in either group) adverse events (safety population)

AE, n (%)	Meropenem-Vaborbactam (N=272) n (%)	Piperacillin/Tazobactam (N=273) n (%)	Total (N=545) n (%)
Headache	24 (8.8)	12 (4.4)	36 (6.6)
Diarrhoea	9 (3.3)	12 (4.4)	21 (3.9)
Nausea	5 (1.8)	4 (1.5)	9 (1.7)
Asymptomatic bacteriuria	4 (1.5)	4 (1.5)	8 (1.5)
Catheter site phlebitis[1]	5 (1.8)	3 (1.1)	8 (1.5)
Infusion site phlebitis	6 (2.2)	2 (0.7)	8 (1.5)
Urinary tract Infection	4 (1.5)	4 (1.5)	8 (1.5)
Hypokalaemia	3 (1.1)	4 (1.5)	7 (1.3)
Vaginal infection	1 (0.4)	6 (2.2)	7 (1.3)
Alanine aminotransferase increased	5 (1.8)	1 (0.4)	6 (1.1)
Anaemia	2 (0.7)	4 (1.5)	6 (1.1)
Aspartate aminotransferase increased	4 (1.5)	2 (0.7)	6 (1.1)
Hypertension	3 (1.1)	3 (1.1)	6 (1.1)
Pyrexia	4 (1.5)	2 (0.7)	6 (1.1)
Constipation	2 (0.7)	3 (1.1)	5 (0.9)
Dyspnoea	0 (0.0)	5 (1.8)	5 (0.9)
Renal cyst	1 (0.4)	3 (1.1)	4 (0.7)
Hypertensive crisis	0 (0.0)	3 (1.1)	3 (0.6)
Rash	0 (0.0)	3 (1.1)	3 (0.6)

[1]Catheter site phlebitis was phlebitis not associated with IV infusion of study drug.

Headache and phlebitis/infusion site reaction were the only AEs that occurred at a ≥2% higher rate in the meropenem-vaborbactam group and none was serious or resulted in discontinuation. Severe AEs were reported in 2.6% meropenem-vaborbactam and 4.8% piperacillin/tazobactam patients. No seizures or CDAD cases occurred in the meropenem-vaborbactam group.

AEs assessed by the investigator as related to study drug (either IV or oral therapy) were reported in 15.1% and 12.1% of the meropenem-vaborbactam and piperacillin/tazobactam groups, respectively, with more drug-related AEs occurring during IV treatment (14.7% and 12.1%; see table below) than during oral step-down treatment (1.1% and 0.7%). Frequent drug-related AEs during IV treatment (see table below) included headache (4.4% and 1.1%) and phlebitis (2.6% and 0.7%) in the meropenem-vaborbactam group and diarrhoea (1.1% and 2.2%) in the piperacillin/tazobactam group.

Table 34 Summary of drug-related treatment-emergent adverse events by system organ class and preferred term-safety population. Adverse events that started during IV treatment period

System Organ Class Preferred Term	Meropenem-Vaborbactam (N=272) n (%)	Piperacillin/Tazobactam (N=273) n (%)	Total (N=545) n (%)
Number of subjects with at least one TEAE	40 (14.7)	33 (12.1)	73 (13.4)
CARDIAC DISORDERS	0 (0.0)	1 (0.4)	1 (0.2)
ANGINA PECTORIS	0 (0.0)	1 (0.4)	1 (0.2)
GASTROINTESTINAL DISORDERS	5 (1.8)	12 (4.4)	17 (3.1)
ABDOMINAL DISTENSION	0 (0.0)	1 (0.4)	1 (0.2)
ABDOMINAL PAIN UPPER	1 (0.4)	0 (0.0)	1 (0.2)
DIARRHOEA	3 (1.1)	6 (2.2)	9 (1.7)
GASTRITIS	0 (0.0)	1 (0.4)	1 (0.2)
NAUSEA	1 (0.4)	3 (1.1)	4 (0.7)
STOMATITIS	0 (0.0)	1 (0.4)	1 (0.2)
VOMITING	0 (0.0)	1 (0.4)	1 (0.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	12 (4.4)	4 (1.5)	16 (2.9)
CATHETER SITE PHLEBITIS	2 (0.7)	1 (0.4)	3 (0.6)
CHEST DISCOMFORT	1 (0.4)	0 (0.0)	1 (0.2)
INFUSION SITE EXTRAVASATION	1 (0.4)	0 (0.0)	1 (0.2)
INFUSION SITE PHLEBITIS	6 (2.2)	2 (0.7)	8 (1.5)
INJECTION SITE PHLEBITIS	1 (0.4)	0 (0.0)	1 (0.2)
PYREXIA	1 (0.4)	1 (0.4)	2 (0.4)

IMMUNE SYSTEM DISORDERS	2 (0.7)	1 (0.4)	3 (0.6)
ANAPHYLACTIC REACTION	1 (0.4)	0 (0.0)	1 (0.2)
DRUG HYPERSENSITIVITY	1 (0.4)	0 (0.0)	1 (0.2)
HYPERSENSITIVITY	0 (0.0)	1 (0.4)	1 (0.2)
INFECTIONS AND INFESTATIONS	4 (1.5)	6 (2.2)	10 (1.8)
ORAL CANDIDIASIS	1 (0.4)	0 (0.0)	1 (0.2)
PSEUDOMEMBRANOUS COLITIS	0 (0.0)	1 (0.4)	1 (0.2)
URINARY TRACT INFECTION	1 (0.4)	0 (0.0)	1 (0.2)
VAGINAL INFECTION	0 (0.0)	3 (1.1)	3 (0.6)
VULVOVAGINAL CANDIDIASIS	2 (0.7)	1 (0.4)	3 (0.6)
VULVOVAGINAL MYCOTIC INFECTION	0 (0.0)	1 (0.4)	1 (0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.7)	1 (0.4)	3 (0.6)
INFUSION RELATED REACTION	2 (0.7)	0 (0.0)	2 (0.4)
PROCEDURAL NAUSEA	0 (0.0)	1 (0.4)	1 (0.2)
INVESTIGATIONS	3 (1.1)	5 (1.8)	8 (1.5)
ALANINE AMINOTRANSFERASE INCREASED	1 (0.4)	1 (0.4)	2 (0.4)
ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.4)	1 (0.4)	2 (0.4)
BLOOD CREATINE PHOSPHOKINASE INCREASED	1 (0.4)	1 (0.4)	2 (0.4)
BLOOD CREATINE PHOSPHOKINASE MB INCREASED	1 (0.4)	0 (0.0)	1 (0.2)
ELECTROCARDIOGRAM QT PROLONGED	1 (0.4)	1 (0.4)	2 (0.4)
LIPASE INCREASED	0 (0.0)	1 (0.4)	1 (0.2)
TRANSAMINASES INCREASED	0 (0.0)	1 (0.4)	1 (0.2)
NERVOUS SYSTEM DISORDERS	13 (4.8)	4 (1.5)	17 (3.1)
CONVULSION	0 (0.0)	1 (0.4)	1 (0.2)
DIZZINESS	1 (0.4)	0 (0.0)	1 (0.2)
HEADACHE	12 (4.4)	3 (1.1)	15 (2.8)
TREMOR	1 (0.4)	0 (0.0)	1 (0.2)
PSYCHIATRIC DISORDERS	1 (0.4)	0 (0.0)	1 (0.2)
HALLUCINATION	1 (0.4)	0 (0.0)	1 (0.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	1 (0.4)	1 (0.2)
DYSPNOEA	0 (0.0)	1 (0.4)	1 (0.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	3 (1.1)	3 (0.6)
PRURITUS	0 (0.0)	1 (0.4)	1 (0.2)
RASH	0 (0.0)	1 (0.4)	1 (0.2)
RASH PAPULAR	0 (0.0)	1 (0.4)	1 (0.2)
VASCULAR DISORDERS	3 (1.1)	1 (0.4)	4 (0.7)
HYPERTENSIVE CRISIS	0 (0.0)	1 (0.4)	1 (0.2)
HYPOTENSION	1 (0.4)	0 (0.0)	1 (0.2)
PHLEBITIS	1 (0.4)	0 (0.0)	1 (0.2)
VASCULAR PAIN	1 (0.4)	0 (0.0)	1 (0.2)

In **study 506** the overview of AEs is shown below for the final study population.

Table 35 Overview of adverse events (safety population)

	Meropenem-Vaborbactam (N=50) n (%)	BAT (N=25) n (%)	Total (N=75) n (%)
All TEAEs	42 (84.0)	23 (92.0)	65 (86.7)
Drug-related TEAEs	12 (24.0)	11 (44.0)	23 (30.7)
TEAE by maximum severity			
Mild	11 (22.0)	4 (16.0)	15 (20.0)
Moderate	11 (22.0)	5 (20.0)	16 (21.3)
Severe	7 (14.0)	7 (28.0)	14 (18.7)
Life-threatening	3 (6.0)	1 (4.0)	4 (5.3)
All SAEs	17 (34.0)	11 (44.0)	28 (37.3)
Drug-related SAEs	0 (0.0)	2 (8.0)	2 (2.7)
Deaths	10 (20.0)	6 (24.0)	16 (21.3)
Discontinuation of study drug due to TEAEs	5 (10.0)	3 (12.0)	8 (10.7)
Discontinuation from study due to TEAEs	8 (16.0)	5 (20.0)	13 (17.3)

Percentage was calculated using the number of subjects in the column heading as the denominator.
Drug-related includes possibly related to study drugs and probably related to study drugs.
TEAEs are AEs with start date and time on or after the first dose of study drug.

AEs occurred most frequently in the SOCs of Infections and Infestations (M-V, 26.0%; BAT, 56.0%) and Gastrointestinal Disorders (M-V, 34.0%; BAT, 32.0%). SOCs with a ≥10% difference between the groups were Infections and Infestations (as above), Investigations (M-V, 10.0%; BAT, 24.0%), Nervous System Disorders (M-V, 12.0%; BAT, 24.0%), Psychiatric Disorders (M-V, 6.0%; BAT,

20.0%), Musculoskeletal and Connective Tissue Disorders (M-V, 12.0%; BAT, 0%) and Renal and Urinary Disorders (M-V, 8.0%; BAT, 28.0%).

Diarrhoea (M-V, 12.0%; BAT, 16.0%), anaemia (M-V, 10.0%; BAT, 12.0%) and hypokalaemia (M-V, 10.0%; BAT, 8.0%) were the most frequent AEs in the meropenem-vaborbactam group. Sepsis (M-V, 4.0%; BAT, 20.0%), septic shock (M-V, 2.0%; BAT, 16.0%) and diarrhoea (M-V, 12.0%; BAT, 16.0%) were the most frequent AEs in the BAT group. AEs indicative of renal failure occurred in a lower proportion of subjects in the meropenem-vaborbactam group compared with the BAT group (about half received colistin); these events included renal failure (0% and 4.0%, respectively), renal failure acute (2.0% and 12.0%, respectively) and renal impairment (2.0% and 8.0%, respectively).

The proportion of subjects with a severe AE was lower in the meropenem-vaborbactam group compared with the BAT group (14.0% and 28.0%, respectively). This difference between groups was not due to a single AE, but several different AEs in the BAT group that were not seen in the meropenem-vaborbactam group. There was no drug-related AE with a >10% difference between the groups.

Drug-related AEs reported by 2 subjects were diarrhoea (M-V, 4.4%; BAT, 4.0%) and leukopenia (M-V, 4.0% BAT, no subjects) in the meropenem-vaborbactam group and *C. difficile* colitis (M-V, 2.0%; BAT, 8.0%) and increased transaminases (M-V, no subjects; BAT, 8.0%) in the BAT group.

The most frequent AE leading to study discontinuation in the meropenem-vaborbactam and BAT groups was sepsis/septic shock (6.0% and 16.0%, respectively).

Serious adverse event / deaths / other significant events

Based on the final data from 506, There were 20 fatal AEs (12 subjects [3.7%] in the meropenem-vaborbactam group and 8 subjects [2.7%] in the comparator group) reported across the meropenem-vaborbactam development programme and all occurred in Phase III trials.

None of the patients treated with meropenem-vaborbactam was assessed by the Investigator as related to study drug. They were determined to be complications of the underlying infection (sepsis, septic shock) or aggravation of the underlying condition in critically-ill patients (general physical health deterioration, haemorrhagic shock or multiorgan failure). In the comparator arms a higher proportion of deaths were due to infectious conditions (6 died of septic shock or sepsis vs. 3 in the meropenem-vaborbactam arm).

Table 36 SAEs Leading to Death by Preferred Term in the Phase III Pool

Preferred Term	Meropenem-Vaborbactam (N=322) n (%)	Comparators (N=298) n (%)
Subjects with any AE leading to death	12 (3.7)	8 (2.7)
Cardiac arrest	2 (0.6)	0 (0.0)
General physical health deterioration	2 (0.6)	0 (0.0)
Multiple organ dysfunction syndrome	1 (0.3)	0 (0.0)
Sudden cardiac death	1 (0.3)	0 (0.0)
Sepsis	2 (0.6)	1 (0.3)
Septic shock	1 (0.3)	5 (1.7)
Glioblastoma	1 (0.3)	0 (0.0)
Cerebral haemorrhage	0 (0.0)	1 (0.3)
Aspiration	1 (0.3)	0 (0.0)
Pulmonary embolism	0 (0.0)	1 (0.3)
Shock haemorrhagic	1 (0.3)	0 (0.0)

Phase III Pool: Studies 505 and 506 pooled

Subject Number	Study	Treatment	Age/ Race/ Gender	Day of IV	Day died	AE PT	Related
076-003-510	505	M-V	76/W/M	9	14	Aspiration	Not related
203-002-503	505	M-V	74/W/M	8	11	Sudden cardiac death	Not related
076-003-604	506	M-V	48/AA/M	10	60	Glioblastoma	Not related
300-001-601	506	M-V	69/W/F	3	4	Cardiac arrest	Not related
300-001-609	506	M-V	65/W/F	8	35	Septic shock	Not related
300-001-610	506	M-V	88/W/F	3	4	Sepsis	Not related
300-001-616	506	M-V	70/W/F	2	2	Cardiac arrest	Not related
300-001-622	506	M-V	77/W/F	20	22	Sepsis	Not related
376-001-602	506	M-V	73/W/F	7	36	General physical health deterioration	Not related
376-001-605	506	M-V	53/W/F	3	3	General physical health deterioration	Not related
376-005-603	506	M-V	74/W/F	4	5	Shock haemorrhagic	Not related
840-019-603	506	M-V	61/W/M	12	12	Multiple organ dysfunction syndrome	Unlikely related
300-001-514	505	P/T	86/W/F	1	2	Septic shock	Not related
703-005-509	505	P/T	81/W/F	3	3	Pulmonary embolism	Not related
300-001-617	506	BAT	75/W/F	5	11	Septic shock	Not related
300-001-621	506	BAT	51/W/M	14	16	Cerebral haemorrhage	Not related
376-005-602	506	BAT	81/W/M	3	3	Sepsis	Not related
826-002-601	506	BAT	75/A/M	3	11	Septic shock	Not related
840-001-603	506	BAT	70/W/M	20	43	Septic shock	Not related
840-004-601	506	BAT	67/W/M	11	12	Septic shock	Not related

In the Phase III pool, the incidence of SAEs was similar in the meropenem-vaborbactam and comparator groups (8.7% and 7.7%, respectively). Four SAEs (one M-V; three comparators) were considered related to study therapy by the investigator but none was considered unexpected for that treatment group. The related SAEs were an infusion related reaction for meropenem/vaborbactam and *Clostridium difficile* colitis, seizure and sepsis for the comparators. The report of sepsis was not due to the initial bacteria identified in blood cultures but was due to *Enterococcus faecium* detected in the subject's urine culture post treatment completion.

Apart from the malignancies that were discovered and not deemed related to therapy, the remaining SAEs were expected in critically ill, older subjects with severe infections and multiple co-morbidities.

Table 37 All SAEs in the Phase III Pool

Preferred Term	Meropenem-Vaborbactam (N=322) n (%)	Comparators (N=298) n (%)
Number of subjects with any SAE	28 (8.7)	18 (7.7)
Anaemia	0 (0.0)	1 (0.3)
Cardiac arrest †	2 (0.6)	0 (0.0)
Cardiac failure congestive	1 (0.3)	1 (0.3)
Gastrointestinal haemorrhage	1 (0.3)	0 (0.0)
General physical health deterioration†	2 (0.6)	0 (0.0)
Multiple organ dysfunction syndrome†	1 (0.3)	0 (0.0)
Sudden cardiac death†	1 (0.3)	0 (0.0)
Bacterial sepsis	0 (0.0)	1 (0.3)
Clostridium difficile colitis	0 (0.0)	1 (0.3)
Enterococcal bacteraemia	1 (0.3)	0 (0.0)
Gangrene	1 (0.3)	0 (0.0)
Klebsiella bacteraemia	1 (0.3)	0 (0.0)
Peritonitis	0 (0.0)	1 (0.3)
Pneumonia	0 (0.0)	1 (0.3)
Postoperative wound infection	0 (0.0)	1 (0.3)
Pyelonephritis	0 (0.0)	1 (0.3)
Salpingo-oophoritis	1 (0.3)	0 (0.0)
Sepsis (2†)	3 (0.9)	4 (1.3)
Septic shock (1†)	2 (0.6)	5 (1.7)
Superinfection bacterial	1 (0.3)	0 (0.0)
Urinary tract infection	0 (0.0)	2 (0.7)
Urosepsis	1 (0.3)	0 (0.0)
Infusion related reaction	1 (0.3)	0 (0.0)
Colon cancer	1 (0.3)	1 (0.3)
Glioblastoma †	1 (0.3)	0 (0.0)
Rectal neoplasm	1 (0.3)	0 (0.0)
Cerebral haemorrhage †	0 (0.0)	1 (0.3)
Lacunar stroke	0 (0.0)	1 (0.3)
Seizure	0 (0.0)	2 (0.7)
Acute kidney injury	0 (0.0)	1 (0.3)
Azotaemia	1 (0.3)	0 (0.0)
Ureterolithiasis	1 (0.3)	0 (0.0)
Aspiration†	1 (0.3)	0 (0.0)
Pneumonia aspiration	1 (0.3)	0 (0.0)
Pulmonary embolism†	1 (0.3)	1 (0.3)
Pulmonary oedema	1 (0.3)	0 (0.0)
Arterial haemorrhage	1 (0.3)	0 (0.0)
Deep vein thrombosis	1 (0.3)	0 (0.0)
Hypotension	0 (0.0)	1 (0.3)
Shock haemorrhagic†	1 (0.3)	0 (0.0)
Thrombophlebitis superficial	0 (0.0)	1 (0.3)

†: includes fatal reports

Laboratory findings

In **study 505** few patients had potentially clinically significant changes in haematology values and the numbers were comparable between groups.

Table 38 Potentially clinically significant postbaseline hematology findings (safety population)

Laboratory Abnormality	Meropenem-Vaborbactam (N=272) n (%)	Piperacillin/Tazobactam (N=273) n (%)	Total (N=545) n (%)
Absolute Lymphocyte Count <0.5 x 10^9/L	5/253 (2.0)	2/246 (0.8)	7/499 (1.4)
Absolute Neutrophil Count <1.0 x 10^9/L	1/176 (0.6)	3/168 (1.8)	3/168 (1.8)
Hematocrit ≤0.75X LLN	2/251 (0.8)	8/248 (3.2)	10/499 (2.0)
Hematocrit ≥1.25X ULN	0/251 (0.0)	0/248 (0.0)	0/499 (0.0)
Hemoglobin ≤11.5 g/dL (≤115 g/L) for Male, ≤9.5 g/dL (≤95 g/L) for Female	16/226 (7.1)	25/226 (11.1)	41/452 (9.1)
Hemoglobin ≥18.0 g/dL (≥180 g/L) for Male, ≥16.0 g/dL (≥160 g/L) for Female	0/226 (0.0)	2/226 (0.9)	2/452 (0.4)
Platelet Count ≤75 x10^9/L	0/250 (0.0)	1/249 (0.4)	1/499 (0.2)
Platelet Count ≥700 x10^9/L	3/250 (1.2)	10/249 (4.0)	13/499 (2.6)
Red Blood Cell Count ≤0.75X LLN	4/251 (1.6)	8/248 (3.2)	12/499 (2.4)
Red Blood Cell Count ≥1.25X ULN	0/251 (0.0)	0/248 (0.0)	0/499 (0.0)

Percentages are calculated using N' as the denominator, where N' is the number of subjects with at least one postbaseline assessment and baseline values were not potentially clinically significant.

Mean changes from baseline over time and shifts in liver function tests were minimal and similar between the groups. No patient met Hy's law criteria. The incidence of potentially clinically significant liver function test abnormalities was low and comparable between the groups. Most of the patients shown in the table below had onset before EOIVT. No patient had study drug discontinued due to the liver function test elevations and all resolved following treatment completion.

One patient in the meropenem-vaborbactam group had an ALT or AST ≥10X ULN. At EOIVT there was an increase in ALT from 45 U/L at baseline to 464 U/L (≥10X ULN) and an increase in AST from 62 U/L to 219 U/L (≥5X ULN) but total bilirubin was 5.6 µmol/L. ALT and AST were decreased at EOT (204 U/L and 39 U/L, respectively) and at TOC (ALT 73 U/L). ALT and AST increased were reported as AEs starting on Day 7 with resolution on Day 19. Both AEs were considered moderate, non-serious and possibly related to study drug.

Table 39 Potentially clinically significant postbaseline liver function findings at any time postbaseline (safety population)

Laboratory Abnormality	Meropenem-Vaborbactam (N=272) n (%)	Piperacillin/Tazobactam (N=273) n (%)	Total (N=545) n (%)
ALT			
≥3X ULN	8/265 (3.0)	5/262 (1.9)	13/527 (2.5)
≥5X ULN	2/265 (0.8)	2/262 (0.8)	4/527 (0.8)
≥10X ULN	1/265 (0.4)	2/262 (0.8)	3/527 (0.6)
≥20X ULN	0/265 (0.0)	0/262 (0.0)	0/527 (0.0)
AST			
≥3X ULN	5/265 (1.9)	4/260 (1.5)	9/525 (1.7)
≥5X ULN	2/265 (0.8)	3/260 (1.2)	5/525 (1.0)
≥10X ULN	0/265 (0.0)	2/260 (0.8)	2/525 (0.4)
≥20X ULN	0/265 (0.0)	0/260 (0.0)	0/525 (0.0)
ALT (U/L) or AST (U/L)			
≥3X ULN	9/266 (3.4)	5/262 (1.9)	14/528 (2.7)
≥5X ULN	3/266 (1.1)	3/262 (1.1)	6/528 (1.1)
≥10X ULN	1/266 (0.4)	2/262 (0.8)	3/528 (0.6)
≥20X ULN	0/266 (0.0)	0/262 (0.0)	0/528 (0.0)
Total Bilirubin (mg/dL)			
≥1.5X ULN	4/263 (1.5)	1/257 (0.4)	5/520 (1.0)
≥2X ULN	1/263 (0.4)	0/257 (0.0)	1/520 (0.2)
Alkaline Phosphatase (ALP) (U/L)			
≥1.5X ULN	5/260 (1.9)	6/258 (2.3)	11/518 (2.1)
≥3X ULN	0/260 (0.0)	2/258 (0.8)	2/518 (0.4)
ALT, AST, ALP (U/L) and Total Bilirubin (mg/dL)			
ALT or AST ≥3X ULN and Total Bilirubin ≥2X ULN	0/266 (0.0)	0/264 (0.0)	0/530 (0.0)
ALT or AST ≥3X ULN and Total Bilirubin ≥2X ULN and ALP≤2X ULN	0/266 (0.0)	0/264 (0.0)	0/530 (0.0)
ALT ≥3X ULN and TBIL ≥2X ULN and (ALT/ULN)/(ALP/ULN) ≥5	0/266 (0.0)	0/264 (0.0)	0/530 (0.0)

Proportions with potentially clinically significant changes in clinical chemistry are shown below.

Table 40 Potentially clinically significant postbaseline kidney function findings

Laboratory Abnormality	Meropenem-Vaborbactam (N=272) n (%)	Piperacillin/Tazobactam (N=273) n (%)	Total (N=545) n (%)
Blood urea nitrogen ≥10.7 mmol/L	12/248 (4.8)	7/243 (2.9)	19/491 (3.9)
Creatinine ≥2.0 mg/dL (≥176.83 µmol/L)	0/257 (0.0)	3/253 (1.2)	3/510 (0.6)

Table 41 Potentially clinically significant postbaseline chemistry findings (safety population)

Laboratory Abnormality	Meropenem-Vaborbactam (N=272) n (%)	Piperacillin/Tazobactam (N=273) n (%)	Total (N=545) n (%)
Calcium ≤7.0 mg/dL (≤1.75 mmol/L)	1/265 (0.4)	9/263 (3.4)	10/528 (1.9)
Calcium ≥15.5 mg/dL (≥3.87 mmol/L)	0/265 (0.0)	0/263 (0.0)	0/528 (0.0)
Creatine phosphokinase ≥3 xULN	6/261 (2.3)	8/259 (3.1)	14/520 (2.7)
Glucose ≤50 mg/dL (≤2.8 mmol/L)	2/227 (0.9)	1/219 (0.5)	3/446 (0.7)
Glucose ≥180 mg/dL (≥10.0 mmol/L)	10/227 (4.4)	14/219 (6.4)	24/446 (5.4)
Potassium ≤3.0 mmol/L	2/237 (0.8)	6/232 (2.6)	8/469 (1.7)
Potassium ≥5.5 mmol/L	15/237 (6.3)	21/232 (9.1)	36/469 (7.7)
Sodium ≤125 mmol/L	0/265 (0.0)	1/262 (0.4)	1/527 (0.2)
Sodium ≥150 mmol/L	0/265 (0.0)	3/262 (1.1)	3/527 (0.6)

In **study 506** shifts in haematology values over time did not reveal any major differences between the meropenem-vaborbactam and BAT groups. Abnormalities in a haematology parameter reported as an AE in the meropenem-vaborbactam and BAT groups included anaemia (10.0% and 12.0%, respectively), leukocytosis (2.0% and 4.0%), leukopenia (4.0% and 4.0%), thrombocytopenia (4.0% and 8.0%) and decreased platelet count (2.0% and none).

No meropenem-vaborbactam patients had a shift in ALT from normal at baseline to high. No patient met Hy's law criteria. Liver function test abnormalities reported as AEs in the meropenem-vaborbactam and BAT groups were ALT increased (0% and 4%, respectively), transaminases increased (0% and 8.0%), blood ALP increased (2.0% and 4.0%), hyperbilirubinaemia (4.0% and 0%) and blood bilirubin increased (0% and 4.0%). These events were non-serious and did not result in discontinuation.

One meropenem-vaborbactam patient and 2 BAT patients had acute kidney injury as defined by RIFLE criteria. Renal AEs of renal failure, renal failure acute, and renal impairment were reported in a lower percentage in the meropenem-vaborbactam group compared with the BAT group (4.0% and 24.0%, respectively). Renal AEs in the meropenem-vaborbactam group included moderate renal impairment linked to disease-related multiorgan failure in a cUTI subject and moderate acute renal failure that was reported as unrelated to study drug in a VABP subject. Two additional subjects in the meropenem-vaborbactam group had other signs of reduced renal function: non-serious and mild events of oliguria, anuria and decreased urinary output in the context of recurrent haemorrhages in one subject with bacteraemia and a mild decreased urine output in a cIAI subject with a gastrointestinal bleed and ischemic colitis. None was considered related to study therapy. Few subjects had potentially clinically significant changes in other serum chemistry parameters.

Safety in special populations

Rates for all and drug-related AEs were higher in the meropenem-vaborbactam group for ≥ 65 years.

Phase III Pool						
	Meropenem- Vaborbactam (N= 322)			Comparator (N= 298)		
Number of subjects	<65 (N=211) n (%)	≥65 (N=59) n (%)	≥75 (N=52) n (%)	<65 (N=184) n (%)	≥65 (N=61) n (%)	≥75 (N=53) n (%)
All TEAEs	96 (45.5)	25 (42.4)	27 (51.9%)	74 (40.2)	21 (34.4)	25 (47.1)
Drug-related TEAEs	37 (17.5)	6 (10.2)	10 (19.2)	32 (17.4)	9 (14.8)	5 (9.4)
TEAEs leading to death	3 (7.4)	6 (10.2)	3 (5.7)	1 (0.5)	2 (3.3)	5 (9.4)
Subjects with SAEs	9 (4.3)	12 (20.3)	7 (13.5)	10 (5.4)	6 (9.8)	7 (13.2)
Drug-related SAEs	0	1 (1.7)	0	1 (0.5)	2 (3.3)	0
TEAEs leading to study drug discontinuation	6 (2.8)	4 (6.8)	2 (3.8)	9 (4.9)	5 (8.2)	3 (5.7)
TEAEs leading to study discontinuation	3 (1.4)	5 (8.5)	3 (5.7)	2 (1.1)	1 (1.6)	5 (9.4)

In the meropenem-vaborbactam group SAEs were reported more often by males (11.5% vs. 4.2% females) but females had higher rates than males for all and drug-related AEs (the data below represents the Phase III Pool including interim data from Study 506 that was submitted with the initial application).

	Phase III Pool			
Number of Subjects	Meropenem-Vaborbactam (N=295)		Comparator (N=289)	
	Male (N=104) n (%)	Female (N=191) n (%)	Male (N=105) n (%)	Female (N=184) n (%)
All TEAEs	42 (40.4)	84 (44.0)	34 (32.4)	77 (41.8)
Drug-related TEAEs	15 (14.4)	32 (16.8)	12 (11.4)	32 (17.4)
TEAEs leading to death	3 (2.9)	4 (2.1)	3 (2.9)	2 (1.1)
Subjects with SAE	12 (11.5)	8 (4.2)	7 (6.7)	11 (6.0)
Drug-related SAE	1 (1.0)	0 (0.0)	1 (1.0)	2 (1.1)
TEAEs leading to study drug discontinuation	3 (2.9)	7 (3.7)	4 (3.8)	12 (6.5)
TEAEs leading to study discontinuation	3 (2.9)	5 (2.6)	3 (2.9)	3 (1.6)

- There were higher rates for AEs, deaths, SAEs and AEs leading to study drug or study discontinuation in patients with creatinine clearance ≥30 to 49 mL/min vs. those with values ≥50 mL/min but there were too few with values <30 mL/min for comment.

Immunological events

After updating the database with complete study 506 data, 13 subjects from the Phase III pool were identified using the Hypersensitivity Broad SMQ to which was added the PT infusion related reaction. Nine were determined to be hypersensitivity/infusion related reactions to meropenem-vaborbactam after review of the reports. The four excluded events were drug hypersensitivity to levofloxacin, contrast media reaction, generalised oedema and stomatitis, all due to causes other than meropenem-vaborbactam.

Table 42 TEAEs of Hypersensitivity and Infusion Related Reaction (Phase III Pool)

	Phase III Pool	
High-Level Term / **Preferred Term**	**Meropenem-Vaborbactam (N=322) n (%)**	**Comparator (N=298) n (%)**
Subjects with hypersensitivity/infusion related reactions	13	13
Hypersensitivity	11	13
Infusion related reactions	2	0
Hypersensitivity	11 (3.4)	13 (4.4)
Anaphylactic reaction	1 (0.3)	0 (0.0)
Bronchospasm	1 (0.3)	0 (0.0)
Contrast media reaction*	1 (0.3)	0 (0.0)
Drug hypersensitivity*	1 (0.3)	1 (0.3)
Erythema	1 (0.3)	0 (0.0)
Generalised oedema*	1 (0.3)	2 (0.7)

Table 42 TEAEs of Hypersensitivity and Infusion Related Reaction (Phase III Pool)

	Phase III Pool	
High-Level Term **Preferred Term**	**Meropenem-Vaborbactam (N=322) n (%)**	**Comparator (N=298) n (%)**
Hypersensitivity	1 (0.3)	1 (0.3)
Pruritus	1 (0.3)	2 (0.7)
Rash	1 (0.3)	3 (1.0)
Rash macular	0 (0.0)	1 (0.3)
Skin exfoliation	0 (0.0)	1 (0.3)
Stomatitis*	1 (0.3)	2 (0.7)
Urticaria	1 (0.3)	0 (0.0)
Infusion related reaction	2 (0.6)	0 (0.0)

*these were determined not to be hypersensitivity reactions to meropenem-vaborbactam;

Four of the nine subjects with hypersensitivity reactions to meropenem-vaborbactam discontinued or had an interruption of treatment and all recovered.

Table 43 Hypersensitivity Reactions Requiring IV Treatment Discontinuation

	Meropenem/ vaborbactam N=322 (n %)	Comparator N=298 (n %)
Hypersensitivity	1 (0.3)	1 (0.3)
Infusion related reaction	2 (0.6)	0 (0.0)
Anaphylactic reaction*	1 (0.3)	0 (0.0)

*action taken with meropenem-vaborbactam recorded as interrupted but never re-introduced.

Discontinuation due to adverse events

In **study 505** AEs leading to study drug discontinuation were reported in 2.6% and 5.1% of the meropenem-vaborbactam and piperacillin/tazobactam groups, respectively.

Table 44 Adverse events leading to study drug discontinuation

System Organ Class Preferred Term	Meropenem-Vaborbactam (N=272) n (%)	Piperacillin/Tazobactam (N=273) n (%)	Total (N=545) n (%)
Number of subjects with at least one AE leading to study drug discontinuation [1]	7 (2.6)	14 (5.1)	21 (3.9)
Cardiac disorders	0 (0.0)	1 (0.4)	1 (0.2)
Angina pectoris	0 (0.0)	1 (0.4)	1 (0.2)
Gastrointestinal disorders	0 (0.0)	1 (0.4)	1 (0.2)
Vomiting	0 (0.0)	1 (0.4)	1 (0.2)
General Disorders And Administration Site Conditions	1 (0.4)	1 (0.4)	2 (0.4)
Pyrexia	1 (0.4)	1 (0.4)	2 (0.4)
Immune system disorders	2 (0.7)	2 (0.7)	4 (0.7)
Drug hypersensitivity	1 (0.4)	1 (0.4)	2 (0.4)
Hypersensitivity	1 (0.4)	1 (0.4)	2 (0.4)
Infections and infestations	1 (0.4)	3 (1.1)	4 (0.7)
Postoperative wound infection	0 (0.0)	1 (0.4)	1 (0.2)
Pseudomembranous colitis	0 (0.0)	1 (0.4)	1 (0.2)
Salpingo-oophoritis	1 (0.4)	0 (0.0)	1 (0.2)
Septic shock	1 (0.4)	1 (0.4) [2]	2 (0.4)
Injury, poisoning and procedural complications	2 (0.7)	0 (0.0)	2 (0.4)
Infusion related reaction	2 (0.7)	0 (0.0)	2 (0.4)
Investigations	0 (0.0)	2 (0.7)	2 (0.4)
Blood bilirubin increased	0 (0.0)	1 (0.4)	1 (0.2)
Blood creatinine increased	0 (0.0)	1 (0.4)	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0)	1 (0.4)	1 (0.2)
Colon cancer	0 (0.0)	1 (0.4)	1 (0.2)
Nervous system disorders	1 (0.4)	1 (0.4)	2 (0.4)
Cerebrovascular accident	0 (0.0)	1 (0.4)	1 (0.2)
Tremor	1 (0.4)	0 (0.0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (0.7)	2 (0.4)
Dyspnoea	0 (0.0)	1 (0.4)	1 (0.2)
Pulmonary embolism	0 (0.0)	1 (0.4) [2]	1 (0.2)
Rash	0 (0.0)	1 (0.4)	1 (0.2)
Vascular disorders	0 (0.0)	1 (0.4)	1 (0.2)
Hypertensive crisis	0 (0.0)	1 (0.4)	1 (0.2)

[1] Includes no subjects in the meropenem-vaborbactam group and 2 subjects in the piperacillin/tazobactam group with fatal, serious AEs.
[2] Event was a fatal, serious AE.

AEs leading to study discontinuation were reported in 1.1% per group (3 patients each). One meropenem-vaborbactam patient was discontinued after receiving 7 doses because the serum pregnancy test conducted on Day 1 was positive. The pregnancy was terminated by an elective abortion 7 days later.

In **study 506** AEs leading to study drug discontinuation are summarised in the following table.

Table 45 Adverse events leading to study drug discontinuation (safety population)

System Organ Class Preferred Term	Meropenem-Vaborbactam (N=50) n (%)	BAT (N=25) n (%)	Total (N=75) n (%)
Discontinuations of study drug due to an AE	5 (10.0)	3 (12.0)	8 (10.7)
Cardiac disorders	2 (4.0)	0 (0.0)	2 (2.7)
Cardiac arrest	2 (4.0) [1]	0 (0.0)	2 (2.7)
Gastrointestinal disorders	1 (2.0)	0 (0.0)	1 (1.3)
Gastrointestinal haemorrhage	1 (2.0)	0 (0.0)	1 (1.3)
General disorders and administration site conditions	2 (4.0)	0 (0.0)	2 (2.7)
General physical health deterioration	1 (2.0) [1]	0 (0.0)	1 (1.3)
Multi-organ failure	1 (2.0) [1]	0 (0.0)	1 (1.3)
Infections and infestations	0 (0.0)	1 (4.0)	1 (1.3)
Pseudomonal bacteraemia	0 (0.0)	1 (4.0)	1 (1.3)
Nervous system disorders	0 (0.0)	1 (4.0)	1 (1.3)
Somnolence	0 (0.0)	1 (4.0)	1 (1.3)
Renal and urinary disorders	0 (0.0)	1 (4.0)	1 (1.3)
Renal impairment	0 (0.0)	1 (4.0)	1 (1.3)
Vascular disorders	1 (2.0)	0 (0.0)	1 (1.3)
Shock haemorrhagic	1 (2.0)[1]	0 (0.0)	1 (1.3)

[1] Fatal AEs.

AEs leading to study discontinuation were reported in 8 and 5 patients with 3 and 4 of these patients discontinuing due to sepsis/septic shock.

Post marketing experience

There was no post-marketing experience for vaborbactam during the assessment of the MAA.

2.6.1. Discussion on clinical safety

The dose of meropenem in Vabomere is the highest approved dose in the EU and the safety profile of meropenem is well described. It is possible that some recognised ADRs (e.g. seizures) could occur at a higher rate when using this maximum dose, especially if there is inadequate dose adjustment for renal impairment. However, there is already a warning about seizures and reflection in section 4.8.

The limitation of the safety database pertains to vaborbactam. Exposure to the intended clinical dose (2g/2g meropenem-vaborbactam using 3-h infusions) is limited to 364 patients (322 in the Phase III studies and 42 in the Phase I studies).

In study 505 the general picture is of broadly similar safety profiles between meropenem-vaborbactam and piperacillin/tazobactam. The AEs indicated that infusion site reactions and phlebitis were slightly more common with meropenem-vaborbactam although it does not appear that local tolerance was a major issue that triggered withdrawals.

In the Phase III pool, the rate of AEs assessed by the investigator as related to study drug that had onset during IV treatment was slightly higher in the meropenem-vaborbactam group (16.1% vs. 14.8%) for the Phase III pool. Much of the difference in rates is represented by headache (4.0% vs. 1.0%) and phlebitis (3.0% vs. 1.0%). The applicant revised the table of ADRs in section 4.8 of the SmPC during the procedure.

Increased ALT or AST were more often reported as AEs with meropenem-vaborbactam although rates were < 2%. These PTs are reflected in the table in section 4.8. No patient met Hy's law criteria. One young male patient had marked increases from baseline to EOIVT in ALT (≥10X ULN) and AST (≥5X ULN) that subsequently declined, suggesting a relationship to meropenem-vaborbactam but his total bilirubin at EOIVT was within the reference range (5.6 µmol/L).

There was no testing for Coomb's test seroconversion during studies 505 and 506 but this has been observed with meropenem and therefore it has been added as a possible ADR to section 4.8.

2.6.2. Conclusions on the clinical safety

CHMP agreed that there are no major safety concerns which would impact on the benefit-risk balance of Vabomere.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Serious hypersensitivity *Clostridium difficile*-associated diarrhoea Seizures Hepatotoxicity
Important potential risks	Development of resistance to meropenem/vaborbactam
Missing information	Safety profile in patients with severe renal impairment

Pharmacovigilance plan

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Global Microbiology surveillance study: Antimicrobial activity of meropenem/ vaborbactam tested against a global collection of Gram-negative organisms Category 3	To monitor the activity of meropenem/vaborbactam at fixed 8 µg/ml and various comparator agents when tested against Gram-negative clinical isolates collected in United States, European Union, Latin America, and Asia Pacific medical centres as part of the SENTRY Antimicrobial Surveillance Program.	Development of resistance to meropenem/ vaborbactam	Annual reports	First annual report due 30 April 2019

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious hypersensitivity	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • A recommendation to discontinue treatment if a severe allergic reaction occurs is included in SmPC Section 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction Additional pharmacovigilance activities: • None
Clostridium difficile-associated diarrhoea	Routine risk communication: • SmPC Section 4.8 • PL Section 2 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations to discontinue treatment with meropenem/vaborbactam, administer specific treatment for *Clostridium difficile*, and prevent the use of medicinal products that inhibit peristalsis are included in SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction Additional pharmacovigilance activities: • None
Seizures	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Section 2 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warnings against concomitant treatment with meropenem and valproic acid, sodium valproate, and valpromide and recommendations that supplemental anticonvulsants are administered if treatment with both therapies are required are included in SmPC Sections 4.4 and 4.5. • Dose adjustment in patients with renal impairment is discussed in SmPC Section 4.2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction Additional pharmacovigilance activities: • None
Hepatotoxicity	Routine risk communication • SmPC Section 4.8 • PL Section 2 • PL Section 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning for the hepatic function to be closely monitored during treatment with meropenem/vaborbactam due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) are included in SmPC Section 4.4	• None Additional pharmacovigilance activities: • None
Development of resistance to meropenem/vaborbactam	Routine risk communication: • SmPC Section 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk: • A recommendation that the official guidance on appropriate use of antibacterial agents should be considered is included in SmPC Section 4.1. • A recommendation that meropenem/vaborbactam should only be administered after consulting with a physician with appropriate experience in the management of infectious diseases is included in SmPC Section 4.2. • A specification of the type of carbapenemases that are not inhibited by vaborbactam is included in the SmPC Section 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Global Microbiology surveillance study
Safety profile in patients with severe renal impairment	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Necessary dose adjustments for patients with varying degrees of renal impairment are presented by CrCl in SmPC Section 4.2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 29.08.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of vaborbactam with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers vaborbactam to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vabomere (meropenem-vaborbactam) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Vabomere is proposed by the applicant for the treatment of the following infections in adults:

- Complicated urinary tract infection (cUTI), including pyelonephritis
- Complicated intra-abdominal infection (cIAI)
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Vabomere is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

The types of infections to be treated are commonplace, except for those due to organisms that are resistant to multiple classes of antibacterial agents, which are discussed further below. Acute pyelonephritis may result from an ascending uncontrolled bladder infection or may be haematogenous, while complicated UTIs are usually associated with anatomical abnormalities or foreign bodies placed in the tract, such as catheters and renal stents. Complicated intraabdominal infections (cIAI) are common infections encountered in general surgery and have been estimated to be responsible for 20% of all severe sepsis episodes in the intensive care unit. Overall mortality rates in cIAIs remain as high as 25% with subjects who develop tertiary peritonitis experiencing even higher rates. HAP/VAP is a major resource-consuming problem especially associated with patients who have had a complication of an underlying illness or medical intervention. Mortality rates are commonly at least 20%. In each case the severity of the underlying disease and inappropriate antimicrobial therapy, due in part to increased antimicrobial resistance, significantly contribute to the mortality rates.

3.1.2. Available therapies and unmet medical need

Successful treatment of cUTI and HAP/VAP are especially threatened by rising rates of antimicrobial resistance among common urinary pathogens. The threat is somewhat less for AP and cIAI, since they often have an acute onset outside of hospital settings. This makes it less likely that the causative pathogens have been subjected to the degree of selective pressure that typically affects nosocomial organisms.

Beta-lactam antibacterial agents are very commonly used to manage the above types of infections when they involve Gram-negative pathogens. Increasing resistance to beta-lactams, including the carbapenems, frequently co-exists with resistance to many other classes so that reports of organisms that are effectively untreatable or treatable only with resource to colistin have increased in recent years. Although carbapenem resistance remains at relatively low levels, for most EU countries increasing trends for the period 2011 to 2014 were observed for seven EU Member States. As of March 2013, *K. pneumoniae* carbapenemase was the most widely disseminated carbapenemase across the EU. There remains an unmet medical need for treatments for patients infected with CRE.

3.1.3. Main clinical studies

Study 505 is the pivotal clinical trial for this application. It was a randomised, double-blind trial versus piperacillin/tazobactam in complicated urinary tract infections and acute pyelonephritis. In line with CHMP guidance and scientific advice, this trial did not require that patients were infected with MDR/XDR pathogens, since that would have made the study design unfeasible. The study was designed in accordance with CHMP requirements to support a standalone and unqualified indication for treatment of cUTI and AP except that the pre-defined non-inferiority margin was 15%. The primary analysis however met the required margin of 10%. Nevertheless, with almost no meropenem-resistant, meropenem-vaborbactam susceptible organisms treated, this study cannot substantiate the adequacy of the vaborbactam dose. Its value rests in providing comparative safety data versus. another beta lactam/betalactamase inhibitor combination product and PK data from patients treated with the recommended dose.

Study 506 may be regarded as supportive. This randomised open-label study vs. BAT allowed enrolment of patients with any of cUTI/AP, cIAI, HABP, VABP and bacteraemia if the infection was suspected or known to be caused by CRE. The study was intended only for a descriptive comparison of efficacy.

3.2. Favourable effects

In study 505, about 60% had acute pyelonephritis and ~40% had complicated UTI, with a good spread of ages including ~40% aged above 65 years. The primary analysis for the EU primary endpoint demonstrated that the lower bound of the 95% CI around the difference in eradication rates was well within -10% in the m-MITT and ME populations. The conclusions from the primary analysis were unchanged after removing data from two study sites where the sponsor identified problems during the study.

Although piperacillin/tazobactam was a suitable comparator for a study that predominantly enrolled at European centres, it was clear that many more baseline organisms were resistant to the comparator whether the EUCAST or CLSI interpretive criteria were applied. Additional analyses of the EU primary endpoint after excluding patients infected with piperacillin-resistant pathogens or pathogens resistant to the assigned treatment still met the 10% margin. Furthermore, although the study was not powered to demonstrate non-inferiority within patient subgroups with cUTI or AP, the comparisons showed numerical superiority for meropenem-vaborbactam in each diagnostic subgroup except for the smallest group (cUTI with non-removable source of infection) in which the eradication rates were lowest (<50%) but comparable between treatments. In the largest subgroup of patients (i.e. those with AP) the margin was within -10%. The clinical outcomes generally followed the patterns for the eradication rates.

Patients could switch from IV to a defined PO treatment after at least 5 days IV and when protocol-listed criteria were met. The mean duration of IV treatment was 8 days. In both treatment groups the eradication rates at TOC were higher in those who switched to oral treatment, most likely driven by this sub-population being fastest to respond and generally the easiest to treat. Most sub-group comparisons, which must be viewed with caution, showed numerical superiority for meropenem-vaborbactam. A table of eradication rates (EU criterion) by species (regardless of susceptibility) at TOC indicates that clinical efficacy has been sufficiently demonstrated to support mention of only three organisms in section 5.1 of the SmPC (*E. coli*, *K. pneumoniae* and *E. cloacae* complex).

Although study 506 was not designed for inferential testing, the DSMB reviewed interim data and recommended early study termination due to evidence of benefit in the meropenem-vaborbactam group. The final CSR provided a consistent trend favouring meropenem-vaborbactam over BAT.

It would not usually be considered appropriate to grant a separate indication for a new product that endorses use in patients who have bacteraemia in association with an approved indication since the extent of clinical experience is almost always very limited. However, the situation for meropenem-vaborbactam is rather different since it is only the adequacy of the inhibitor dose that is in question.

To support this use, there were 27 patients in study 505 with bacteraemia and the eradication rates at TOC were 10/12 for meropenem-vaborbactam and 7/15 for piperacillin/tazobactam. Additionally, the final data from study 506 included 14 meropenem-vaborbactam and 8 BAT patients infected with CRE and with bacteremia as the sole microbiological source at baseline. The mortality was 4/14 (28.6%) and 3/8 (37.5%) in respective groups. The results provide support for allowing this claim to be applied to meropenem-vaborbactam.

3.3. Uncertainties and limitations about favourable effects

Vaborbactam cannot protect meropenem from Class B and D beta-lactamases. In addition, it cannot restore susceptibility to meropenem if resistance is mainly or wholly due to impermeability of the outer membrane and/or an efflux pump.

Although study 505 met its primary endpoint, it must be remembered that this study compared meropenem at the revised dosing regimen of 2 g q8h using 3-hour infusions with piperacillin-tazobactam because there were very few meropenem-resistant, meropenem/vaborbactam-susceptible organisms detected at baseline. This study has value in supporting the revised regimen for meropenem and in generating safety and PK data in infected patients treated with the proposed meropenem-vaborbactam regimen. However, since it cannot support the adequacy of the vaborbactam dose to protect meropenem from Class A and C beta-lactamases, the PK-PD analyses are of paramount importance to support the application.

During the procedure, the POPPK analyses and the PK-PD analyses were revised, with re-estimation of the PTA. The results based on the KPC-producing organism, for which joint target attainment has been assessed, do support the dose regimen. However, PTA was < 90% (although > 84%) for some patient subgroups defined by renal function at MV MIC=8 mg/L. PTA at MV MIC=4 mg/L was highly satisfactory for all renal function subgroups. It should be noted that for most patients the dose is predicted to be adequate regardless of renal function and that there are very few KPC-producing organisms with MV MICs > 4 mg/L.

Effectively, since patient numbers in study 506 were too small, there are very few clinical data to support the use of meropenem-vaborbactam to treat cIAI or HAP/VAP, so that these indications for use are actually based on the efficacy of meropenem alone and the PK-PD analyses.

For complicated IAI, using the updated POPPK model, the general PK and the volumes of distribution at steady-state were similar for meropenem (20.2 L) and vaborbactam (18.6 L), indicating that they distribute into a volume consistent with the extracellular fluid (ECF) compartment. At the same time, the protein binding for the two agents is estimated at 2% and 33%, respectively. Therefore, with broadly comparable plasma levels and ECF distribution, the concentration of free drug in the ECF is expected to be lower for vaborbactam than for meropenem. Nevertheless, the nonclinical data using the neutropenic murine thigh infection model, in which ECF levels are important for efficacy, and humanised dosing regimens showed that there was at least ~1-log kill for most meropenem-resistant strains tested at MV MICs up to 4-8 mg/L. Therefore, despite the limitations regarding clinical data, the

nonclinical data and PK-PD considerations do support a conclusion that the vaborbactam dose regimen should suffice to treat cIAI.

The justification for the HABP/VABP indication is based on free drug ELF penetration and comparisons between calculated ELF concentrations in infected patients and the plasma PDTs (there being no PDTs established specifically for ELF). The calculations are based on mean values and the patient data are founded on POPPK-predicted exposures. The applicant also conducted exploratory simulations to estimate the PTA in ELF against the plasma PDTs for MV MIC=8 mg/L, which gave very satisfactory results overall and for KPC-producing *Enterobacteriaceae*. Based on the above, CHMP agreed that the use of Vabomere in HABP/VABP is acceptable.

3.4. Unfavourable effects

In study 505, the general picture is of broadly similar safety profiles between meropenem-vaborbactam and piperacillin/tazobactam. The adverse events indicated that infusion site reactions and phlebitis were slightly more common with meropenem-vaborbactam, although local tolerance was not a major issue that triggered withdrawals from the study. The rate of AEs assessed by the investigator as related to study drug that had onset during IV treatment was slightly higher in the meropenem-vaborbactam group (14.7% vs. 12.1%). Much of the difference reflected rates for headache (4.4% vs. 1.1%) and phlebitis (2.6% vs. 0.7%).

Increased ALT or AST were more often reported as AEs with meropenem-vaborbactam although rates were less than 2%. No patient met Hy's law criteria. One young male patient had marked increases from baseline to EOIVT in ALT (≥10X ULN) and AST (≥5X ULN) that subsequently declined, suggesting a relationship to meropenem-vaborbactam, but his total bilirubin at EOIVT was within the reference range (5.6 µmol/L).

In study 506 adverse events occurred most frequently in the SOCs of Infections and Infestations (meropenem/vaborbactam (M-V), 26.0%; BAT, 56.0%) and Gastrointestinal Disorders (M-V, 34.0%; BAT, 32.0%). Diarrhoea (M-V, 12.0%; BAT, 16.0%), anaemia (M-V, 10.0%; BAT, 12.0%) and hypokalaemia (M-V, 10.0%; BAT, 8.0%) were the most frequent AEs in the meropenem-vaborbactam group. Sepsis (M-V, 4.0%; BAT, 20.0%), septic shock (M-V, 2.0%; BAT, 16.0%) and diarrhoea (M-V, 12.0%; BAT, 16.0%) were the most frequent AEs in the BAT group. AEs indicative of renal failure occurred in a lower proportion of subjects in the meropenem-vaborbactam group compared with the BAT group; these events included renal failure (0% and 4.0%, respectively), renal failure acute (2.0% and 12.0%) and renal impairment (2.0% and 8.0%).

There was no drug-related adverse event with a more than 10% difference between the groups. Drug-related adverse events reported by 2 subjects were diarrhoea (M-V, 4.4%; BAT, 4.0%) and leukopenia (M-V, 4.0% BAT, no subjects) in the meropenem-vaborbactam group and *C. difficile* colitis (M-V, 2.0%; BAT, 8.0%) and increased transaminases (M-V, no subjects; BAT, 8.0%) in the BAT group. Overall, CHMP agreed that in this complicated patient population, there were no major concerns regarding the safety profile of meropenem-vaborbactam.

3.5. Uncertainties and limitations about unfavourable effects

The safety database pertaining to vaborbactam is limited. Exposure to the intended clinical dose (2g/2g meropenem-vaborbactam using 3-h infusions) is limited to 364 patients and there are no post-marketing data available.

3.6. Effects Table

Effects Table for Vabomere

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Bacterial eradication in urine	$<10^3$ CFU/mL in urine at TOC visit	n/N (%)	Meropenem-vaborbactam m-MITT 128/192 (66.7%) ME 118/178 (66.3%)	Piperacillin/tazobactam m-MITT 105/182 (57.7%) ME 102/169 (60.4%)	95% CI -0.9, 18.7 95% CI -4.2, 16 All sensitivity analyses supported the primary analysis	Study 505
All-cause mortality at day 28	Alive at day 28	n/N (%)	Meropenem-vaborbactam m-MITT 5/35 (14.3%) CRE-mITT 5/32 (15.6%)	BAT m-MITT 5/19 (26.3%) CRE-mMITT 5/15 (33.3%)		Study 506
Unfavourable Effects						
All AEs		n/N (%)	Meropenem-vaborbactam 148/322 (46.0%)	Pooled comparators 120/298 (40.3%)		Phase 3 pool
ADRs			53/322 (16.5%)	46/298 (15.4%)		
SAEs			28/322 (8.7%)	23/298 (7.7%)		
Deaths			12/322 (3.7%)	8/298 (2.7%)		
Discontinuations due to AEs			12/322 (3.7%)	17/298 (5.7%)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is an unmet need in terms of paucity of well tolerated antibacterial agents that are active against aerobic Gram-negative organisms that express Class A and C carbapenemases. The microbiological data and non-clinical models provided in this marketing authorisation application support a conclusion that vaborbactam can protect meropenem from inactivation by these beta-lactamases in the absence of other types of carbapenem resistance. Vabomere cannot wholly solve the problem of carbapenem resistance, but it provides a potentially useful alternative for treatment of many infections due to carbapenem-resistant enterobacteria.

Study 505 was conducted in a typical complicated UTI/AP patient population and included very few meropenem-resistant organisms. It provides good evidence for the adequacy of the meropenem regimen of 2 g q8h using 3-hour infusions, but it cannot provide clinical evidence for the adequacy of the vaborbactam regimen.

At the time of closing study 506, there were 77 patients enrolled and 47 were infected with CRE. This study was not designed to provide definitive clinical evidence to support the meropenem-vaborbactam dose regimen, although the results do broadly support the vaborbactam regimen. Therefore, the justification for the vaborbactam dose must come from PK-PD analyses. The approach to these analyses was broadly rational and the revised PTA estimates indicate that the dose should cover the majority of enterobacteria producing Class A or C carbapenemases with MV MICs up to 8 mg/L.

The safety database for the combination is relatively small but it does not indicate any major concerns resulting from addition of vaborbactam to meropenem.

The use of meropenem-vaborbactam to treat patients infected with aerobic Gram-negative organisms with limited treatment options was agreed upon by CHMP. Furthermore, CHMP agreed that study 505 provides good support for a standalone unqualified indication for treatment of cUTI/AP. The claim that meropenem-vaborbactam could be used to treat these two indications when patients are bacteraemic was also supported.

The scientific justification for the vaborbactam dose to treat cAI and HAP/VAP comes from the revised PK-PD analyses and calculations of the concentrations of vaborbactam in the ELF in infected patients. CHMP agreed that these findings support the adequacy of the vaborbactam dose to protect meropenem.

3.7.2. Balance of benefits and risks

The overall benefit-risk of Vabomere is positive for the indications claimed.

3.7.3. Additional considerations on the benefit-risk balance

Vaborbactam cannot be expected to protect meropenem against Class B and D beta-lactamases or to restore susceptibility when resistance is wholly or partly due to impermeability or efflux mechanisms. It is very important that the user understands these limitations. The Vabomere Product Information conveys the limitations and recommends that use of Vabomere to treat patients with limited treatment options is overseen by an appropriately experienced infectious disease specialist.

3.8. Conclusions

The overall B/R of Vabomere is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vabomere is favourable in the following indication:

“treatment of the following infections in adults:

- Complicated urinary tract infection (cUTI), including pyelonephritis

- Complicated intra-abdominal infection (cIAI)
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP).

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Vabomere is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

Consideration should be given to official guidance on the appropriate use of antibacterial agents."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that vaborbactam is a new active

substance as it is not a constituent of a medicinal product previously authorised within the European Union.