21 March 2024
EMA/147600/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Emblaveo

International non-proprietary name: Aztreonam / Avibactam

Procedure No. EMEA/H/C/006113/0000

Note

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

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List of abbreviations

Abbreviation	Term
%*f*T>C_T	percent of time that free plasma concentrations are above the threshold concentration over a dosing interval
%*f*T>MIC	percent of time that free plasma concentrations are above the minimum inhibitory concentration over a dosing interval
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AmpC	a Class C β-lactamase (Amp = ampicillin)
APACHE	acute physiologic assessment and chronic health evaluation
ARC	augmented renal clearance
ASMF	active substance master file = drug master file
AST	aspartate aminotransferase
ATLAS	Antimicrobial Testing Leadership and Surveillance
ATM	Aztreonam
ATM-AVI	aztreonam-avibactam
AUC	area under the plasma concentration curve
$AUC_{(0\text{-}6)}$ or AUC_6	area under plasma concentration vs. time curve from time point zero to 6 hours
$AUC_{(0\text{-}last)}$ or AUC_{last}	area under plasma concentration vs. time curve from time point zero up to the time for the last measured concentration above limit of quantification
$AUC_{0\text{-}\tau}$or AUC_{tau}	area under the plasma concentration-time curve from time zero to time tau (τ), the dosing interval
$AUC_{0\text{-}24,ss}$, $AUC_{24,ss}$	area under the plasma concentration-time curve from time zero to 24 hours at steady-state
$AUC_{0\text{-}t}$ or AUC_t	area under the plasma concentration-time curve from time zero to time t
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AVI	avibactam
BAT	best available therapy
BL	beta-lactam
BLI	beta-lactamase inhibitor
BMI	body mass index
BSI	blood stream infections

Abbreviation	Term
CAZ	ceftazidime
CAZ-AVI	ceftazidime-avibactam
CE	clinically evaluable
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cIAI	complicated intra-abdominal infection
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
CLr	renal clearance
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady-state
COL	colistin
CrCL	creatinine clearance
cUTI	complicated urinary tract infection
CV	coefficient of variation
CXL	ceftaroline avibactam combination
CYP	cytochrome
DDI	drug-drug interaction
DEHP Di(2-ethylhexyl)	phthalate
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ELD	extended loading dose
ELF	epithelial lining fluid
EMA	European Medicines Agency
ESBL	extended-spectrum β-lactamase
ESRD	end stage renal disease
EU	European Union
FDA	Food and Drug Administration
FMEA	failure mode effects analysis
GC	gas chromatography
GGT	gamma-glutamyl transferase

Abbreviation	Term
GVP	good pharmacovigilance practices
HAP	hospital-acquired pneumonia
HDPE	high density polyethylene
HFIM	hollow fibre infection model, hollow fibre system
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	inductively coupled plasma mass spectrometry
ICP-OES	inductively coupled plasma - optical emission spectrometry
ICU	intensive care unit
IMP	imipenemase
IR	iInfrared
ITT	intent-to-treat
IV	intravenous
KF	Karl Fischer titration
KPC	*Klebsiella pneumoniae* carbapenemase
LC	liquid chromatography
LD	loading dose
LDPE	low density polyethylene
MAA	marketing authorisation application
MBL	metallo-β-lactamase
MD	maintenance dose
MDD	maximum daily dose
MDR	multi-drug resistance
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MER	meropenem
MIC	minimum inhibitory concentration
MIC_{90}	minimum inhibitory concentration at which 90% of isolates are inhibited
$MIC_{ATM\text{-}AVI}$	minimum inhibitory concentration of ATM in the presence of AVI
micro-ITT	microbiologically intent-to-treat

Abbreviation	Term
micro-MITT/mMITT	microbiologically modified intent-to-treat
MITT/mITT	modified intent-to-treat
MO	major objection
MTZ	metronidazole
N/A	not applicable
NDM	New Delhi metallo-β-lactamase, A Class B β-lactamase
NF	National Formulary
NMT	not more than
NP	nosocomial pneumonia
NXL104	previous name for avibactam
OAT	organic anion transporter
OOS	out of specification
OXA	oxacillin
PBP	penicillin binding protein
PBRER	periodic benefit risk evaluation report
PCS	potentially clinically significant
PD	pharmacodynamic
PDE	permitted daily exposure
PE	polyethylene
PES	polyethersulfone
PG	parallel group
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
PMAR	p modelling analysis report
PO	PO polyolefin
PP	polypropylene
PT	preferred term
PTA	probability of target attainment
q6h, q8h, q12h	every 6 hours, every 8 hours, every 12 hours
QTc	QT interval corrected for heart rate
QTPP	quality target product profile

Abbreviation	Term
QWP	Quality Working Party
RH	relative humidity
RMP	risk management plan
SAE	serious adverse event
SD	standard deviation
SmPC	summary of product characteristics
SMQ	standardised MedDRA queries
SOC	MedDRA system organ class
$t_{1/2}$	terminal phase half-life
TAMC	total aerobic microbial count
TEAE	treatment emergent adverse event
TOC	test of cure
TYMC	total combined yeasts/moulds count
uHPLC	ultra-high performance liquid chromatography
UK	United Kingdom
ULN	upper limit of normal
US	United States
USP	United States Pharmacopoeia
USPI	United States Prescribing Information
UTI	urinary tract infection
UV	ultraviolet
VAP	ventilator-associated pneumonia
Vss	steady-state volume of distribution
XR(P)D	X-ray (powder) diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe Ma EEIG submitted on 17 August 2023 an application for marketing authorisation to the European Medicines Agency (EMA) through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004 for Emblaveo.

The applicant applied for the following indication:

treatment of the following infections in adult patients (see sections 4.4 and 5.1):

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

Emblaveo is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (see sections 4.2, 4.4, and 5.1).

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

1.2. Legal basis

The legal basis for this application refers to:

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

The application submitted is a fixed combination medicinal product.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0553/2022) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0553/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.4.2. New active substance status

The applicant initially requested that the combination of the active substances Aztreonam and

Avibactam contained in the above medicinal product to be considered as a new active substance. The applicant withdrew their claim for new active substance status during the procedure.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
17 January 2013	EMEA/H/SA/2422/1/2012/III	*Kerstin Wickström, Mair Powell*
23 April 2015	EMEA/H/SA/2422/2/2015/I	*Kerstin Wickström, Valentina Mantua*
23 April 2015	EMEA/H/SA/2422/1/FU/1/2015/III	*Kerstin Wickström, Mair Powell*
23 June 2022	EMA/SA/0000086610	*Mair Powell, Anders Lignell*

The scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

- *Strategy regarding manufacturing plant for ATM-AVI to address GMP requirements.*
- *Preclinical toxicology programme to support registration.*
- *Dose selection for ATM-AVI.*
- *Clinical pharmacology package.*
- *PK/PD package to support registration including:*
  - *In vitro and in vivo models.*
  - *Global surveillance data for susceptible Gram-negative pathogens, including MBL-producing isolates, plus susceptibility data obtained in the clinical studies.*
  - *POP PK model and PTA.*
- *Clinical data package to support registration.*
- *Design of the phase 3 studies:*
  - *C3601002, a Prospective, Randomized, Multicentre, Open Label, Central Assessor Blinded, Parallel Group, Comparative Study to Determine the Efficacy, Safety and Tolerability of Aztreonam Avibactam (ATM-AVI) ± Metronidazole (MTZ) Versus Meropenem ± Colistin (Mer ± Col) for the Treatment of Serious Infections due to Gram Negative Bacteria, Including Metallo β-Lactamase (MBL) Producing Multidrug Resistant Pathogens, for Which There are Limited or no Treatment Options*
  - *C3601009, a Prospective, Randomized, Open-Label, Comparative Study to Assess the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) and Best Available Therapy for the Treatment of Serious Infections due to Multi-Drug Resistant Gram-Negative Bacteria Producing Metallo β -Lactamase (MBL)*

The clinical studies mainly relevant to the applied indications are study C3601002 and study C3601009 to provide comparative safety data (and some efficacy data) and PK-data from patients to update the population-PK model for probability of target attainment (PTA) analyses and study D4280C00009 to provide AVI PK-data from epithelial lining fluid (ELF) to support treatment of lung infections.

It should be noted that phase 3 studies evaluating a BL at its approved dose combined with a BLI may not provide stand-alone efficacy data to support the dose regimen for the BLI. This is because it is not a strict requirement to confine such studies to infections caused by pathogens resistant to the BL but susceptible to the BL-BLI combination. Therefore, the PK/PD analyses incorporating the non-clinical PK/PD data and patient PK data are generally considered pivotal to support the dose regimen of the BLI for the proposed indications.

The Applicant stated that the ATM-AVI development programme was conducted in accordance with CHMP guidance. The Applicant (and the former sponsor AstraZeneca) received CHMP scientific advice in 2012, 2015 and 2022. Overall, the advice given has been followed and the CHMP agreed that the development programme could be sufficient to support MAA for treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment option.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	17 August 2023
Accelerated Assessment procedure was agreed-upon by CHMP on	20 July 2023
The procedure started on	14 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 November 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	24 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 November 2023
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	08 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	20 February 2024

The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	08 March 2024
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 Emblaveo on	21 March 2023

2. Scientific discussion

2.1. Problem statement

The prevalence of metallo-β-lactamases (MBL) producing pathogens is currently relatively low in the US and EU. However, sporadic cases are being reported regularly in the global literature, with concern that these infections will soon present a challenge given the current paucity of antibacterial agents active against these isolates in a variety of patients with different diagnoses of infectious disease.

Enterobacterales resistant to carbapenems by producing metallo enzymes have become more prevalent in clinical settings worldwide. Infection with MBL-producing Enterobacterales is related to high mortality.

The unmet medical need for new treatment options exists because current treatment options for MBL-based infections are essentially limited to colistin, tigecycline, and lately, cefiderocol. These agents are used because of their demonstrated *in vitro* activity against some MBL-producing pathogens. However, colistin and tigecycline therapies have been associated with tolerability and safety concerns.

Although ATM is not inactivated by MBLs, as a single agent it has limited utility because the vast majority of MBL-producing pathogens also express the serine-β-lactamases that do inactivate it. With AVI's ability to inhibit Class A, Class C, and some Class D serine-β-lactamase enzymes, restoration of ATM's activity against pathogens that co-produce MBLs and serine enzymes has been demonstrated.

The safety profiles of the individual components of ATM-AVI suggest that the combination may offer substantial benefits compared to colistin or tigecycline, thus presenting another treatment option for patients with MBL-producing pathogens.

2.1.1. Disease or condition

Emblaveo was proposed by the applicant to be indicated for the treatment of the following infections in adults:

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

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

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

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 cUTI is 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. 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 UTIs are UTIs complicated by involvement of the upper urinary tract (pyelonephritis) or by underlying functional or anatomic abnormalities of the urinary tract. Common uropathogens causing cUTI are *Escherichia coli*, other Enterobacterales and *Pseudomonas aeruginosa*.

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 encountered in cIAI are *E. coli*, other Enterobacterales, *P. aeruginosa* and anaerobic organisms such as *Bacteroides fragilis*.

HAP and VAP are infections in hospitalised (or recently hospitalised) patients. Colonisation of the respiratory tract with a variety of Gram-positive and Gram-negative bacteria may lead to infection. Among the most encountered pathogens in HAP/VAP are *Staphylococcus aureus*, Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

2.1.4. Clinical presentation, diagnosis

Infection types included in the proposed indications are diagnosed based on clinical presentations and radiologic imaging in addition to microbiologic investigations to characterise the pathogens causing the infections.

2.1.5. Management

Treatment of cUTI/acute pyelonephritis, cIAI and HAP/VAP is in general initially empirically chosen based on the knowledge of the main causative pathogens and their likelihood of carrying resistance mechanisms. The selection of antibacterial agent(s) is further guided by results of pathogen identification and susceptibility testing.

Beta-lactam antibacterial agents are commonly used to manage 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 a limited selection of

antibacterial agents such as colistin, tigecycline, cefiderocol and newer BL/BLI combinations. However, there are limitations also to these agents. Importantly, acquired resistance occurs also against these agents. Treatment-emergent nephrotoxicity is of concern for colistin. Tigecycline is not active against *Pseudomonas* spp. Moreover, safety concerns of an increased risk of death with tigecycline have limited its use.

The newer beta-lactam/beta-lactamase (BL/BLI) combinations such as ceftolozane/tazobactam (TOL/TAZ), ceftazidime/avibactam (CAZ/AVI), meropenem/vaborbactam (MEM/VAB) and imipenem/relbactam (IMI/REL) are possible options for the treatment of some carbapenem-resistant Gram-negative organisms but none of them are universal or active against class B (metallo-beta-lactamase) producers. Overall, there is still an unmet medical need for additional antibacterial agents addressing carbapenem resistance in Gram-negative organisms especially those producing class B beta-lactamases.

2.2. About the product

Aztreonam (ATM) is a monocyclic beta-lactam (BL) antibacterial agent (monobactam) that inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins (PBPs).

Avibactam (AVI) is a non-β-lactam beta-lactamase inhibitor (BLI) with inhibitory activity against certain beta-lactamases which prevents the hydrolysis of ATM.

The proposed dose in patients with a creatinine clearance >50 mL/min is a loading dose of 2 g/0.67 g ATM/AVI administered as an intravenous infusion over 3 hours followed by maintenance doses of 1.5 g/0.5 g ATM/AVI beginning at the next dosing interval and administered as intravenous infusions over 3 hours every 6 hours.

The treatment duration is 5 to 14 days depending on the site of the infection.

Dose and dosing interval adjustments are proposed in patients with renal impairment.

2.3. Type of application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the assessment of the request provided by the applicant and the CHMP guideline on the procedure for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) no 726/2004.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 1.5 g of aztreonam and 0.5 g of avibactam as active substances.

The only other ingredient is arginine.

The product is available in glass vial (Type I) closed with a rubber (chlorobutyl) stopper and aluminium seal with flip-off cap as described in section 6.5 of the SmPC.

2.4.2. Active Substance – Avibactam sodium

2.4.2.1. General information

The chemical name of avibactam sodium is [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate; (CAS) Sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-(aminocarbonyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester, sodium salt (1:1) corresponding to the molecular formula $C_7H_{10}N_3O_6SNa$. It has a molecular weight of 287.23 and the following structure:

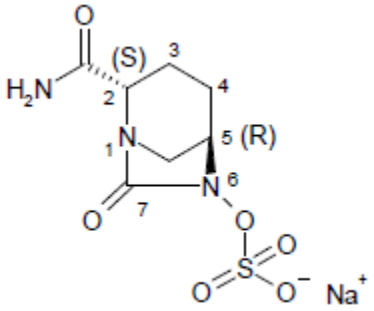


Figure 1: active substance structure

There are 3 chiral centres present in the molecule, but only 2 chiral centres (at the 2- and 5-positions) are stereogenic. Therefore, there are only 4 possible stereoisomers. The chiral centre at the 1-position is not stereogenic as the stereochemistry at the bridgehead nitrogen (the 1-position) is dictated by the stereochemistry at the 5-position bridgehead carbon and therefore does not generate new stereoisomers. Avibactam sodium is the (2*S*,5*R*)-enantiomer of the trans-diastereoisomer, as shown in the structure above.

The absolute stereochemical configuration of the active substance is defined by the starting material, and by the stereospecific nature of the manufacturing process and isolations. The absolute stereochemical configuration of the active substance has been confirmed by single crystal XRD.

The chemical structure of the active substance was elucidated by a combination of infrared, NMR and UV/Vis spectroscopy, mass spectrometry, and X-ray powder diffraction.

The active substance is a non-hygroscopic white to pale yellow powder freely soluble in water.

Avibactam sodium is produced as an anhydrous crystalline form. Extensive polymorph screening studies identified other crystalline solid forms of avibactam sodium. The form selected is kinetically more accessible and is routinely isolated during manufacture. Active substance stability studies have shown that the form selected and manufactured does not convert to any other solid form under the proposed storage conditions.

2.4.2.2. Manufacture, characterisation and process controls

Avibactam sodium is manufactured by one manufacturer. The active substance is synthesised in four main steps using a well-defined starting material with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, the starting material and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes have been presented in sufficient detail and have been justified.

The manufacturing route in early development used the same intermediates and the same starting material as those used in the commercial manufacturing route. During late development, an additional isolation point was introduced, and the processing stages between two intermediates were redeveloped. These changes improved the operability and processing and also the quality of the avibactam sodium produced.

Avibactam sodium is packaged under nitrogen in a container closure system comprised of three bags as follows:

1. An inner low-density polyethylene (LDPE) bottle-shaped bag, which is the product contact inner bag.
2. A middle high-density polyethylene (HDPE) bag.
3. An outer multi-layer aluminum bag, which protects the active substance from humidity and light.

The inner LDPE bag, middle HDPE bag and outer multi-layer aluminum bag conform with both current European Pharmacopoeia (Ph. Eur.) and United States Pharmacopoeia (USP) requirements.

2.4.2.3. Specification

The active substance specification includes tests for description, identification (IR, LC), assay (LC), organic impurities (LC), residual solvents (GC), water content (KF), sodium (ICP-OES), bacterial endotoxins (Ph. Eur.)

Impurity specifications were established in accordance with the principles of ICH Q3A; impurities present at higher content than the qualification threshold were qualified and appropriate specifications have been set.

Limits for residual solvents have been set in line with ICH Q3C requirements. A risk assessment for elemental impurities was performed in line with ICH Q3D principles and the risk of elemental impurities is considered negligible.

The justification for the absence of routine controls for microbiological quality, residue on ignition and potential polymorphism is accepted. Batch analyses data from numerous pilot scale batches and four commercial scale batches manufactured with the commercial process have been provided.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for active substance and related impurities testing has been presented.

Batch analyses data from numerous pilot scale batches manufactured throughout development, and four commercial scale batches manufactured with the commercial process have been provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three commercial scale batches of active substance manufactured with the proposed commercial process by the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, assay, organic impurities, water content and microbial quality (TAMC, TYMC). The analytical methods used were the same as for release and were stability indicating.

An avibactam-related impurity has been observed to increase under long-term, accelerated and stressed storage conditions studies for the solid form of the avibactam sodium. Under long term storage conditions all tested parameters were within the specifications. At the accelerated condition of 40ºC /75% RH out of specification results were observed for assay and impurities at the 6 month timepoint. Variation in levels of impurities among the batches was also observed. The most probable root cause was lack of control of the oxygen and humidity levels during the packaging of the stability samples and a variation in the length of time that it took for stability samples to be packaged. As requested by CHMP, the applicant has confirmed that they are now controlling the conditions during packaging and has initiated stability studies at intermediate conditions on three new commercial batches.

A photostability study was carried out according to the ICH Guideline Q1B on Photostability Testing of New Drug Substances and Products on one primary stability batch. Samples were tested for description, assay and organic impurities. All parameters remained unchanged. Therefore it was concluded that avibactam sodium is not light sensitive and does not require a protect from light restriction.

Forced degradation experiments were performed on avibactam sodium active substance to establish the extent and nature of potential degradation pathways and to confirm the suitability of the LC assay and purity method.

Solid avibactam sodium active substance samples were exposed to thermal and photolytic stress (2X ICH). No significant degradation was observed at under thermal and photostability (2X ICH).

Solutions of avibactam sodium active substance were exposed to acid, base, hydrogen peroxide, 2,2’-Azobis (2-methylpropionitrile) (AIBN, (free-radical initiator) and $FeCl_3$. Degradation was observed in avibactam sodium active substance samples exposed to acid, base, hydrogen peroxide, AIBN, $FeCl_3$ and thermal humidity. Avibactam sodium active substance is stable to photolytic stress.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 16 months at or below 25ºC in the proposed container.

2.4.3. Active Substance - Aztreonam

2.4.3.1. General information

The chemical name of aztreonam is (Z)-2-[[[(2-Amino-4-thiazolyl)[[(2S,3S)-2-methyl-4-oxo-1-sulfo-3-

azetidinyl]carbamoyl]methylene]amino]oxy]-2-methylpropionic acid corresponding to the molecular formula C13H17N5O8S2. It has a relative molecular mass of 435.43 and the following structure:

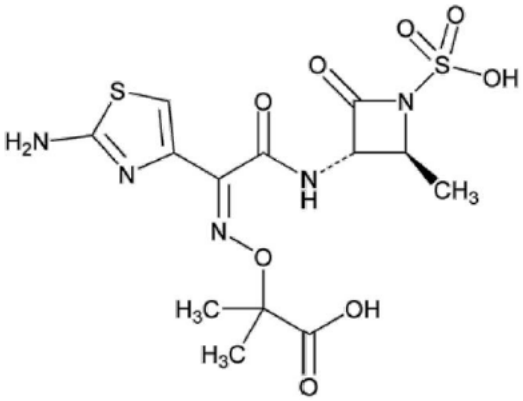


Figure 2: active substance structure

The chemical structure of aztreonam was elucidated by a combination of the following methods: IR, UV, ^{1}H-NMR, ^{13}C-NMR, elemental analysis, MS, DSC, TGA, XRPD. The solid-state properties of the active substance were measured by XRPD.

The active substance is a white crystalline powder, slightly soluble in water at pH 3-5 and sparingly soluble at pH 7, which is close to the intravenous physiological pH (7.4) where the finished product is administered by infusion. Aztreonam β form, which is the polymorphic form manufactured as the active substance, is slightly hygroscopic.

Aztreonam exhibits stereoisomerism due to the presence of 2 chiral centres. The stereochemistry of these chiral centres originates from one of the starting materials. Enantiomeric purity is controlled routinely by specific optical rotation. The pertinent stereoisomer is also controlled among the related substances by HPLC.

Polymorphism has been observed for aztreonam. Four polymorphic forms (α, β, γ, and δ) are described in the literature. The intended polymorphic form of aztreonam to be manufactured is the beta polymorphic form. The polymorph form manufactured is routinely controlled in the specification of the active substance by an in-house method using XRPD.

There is no monograph of aztreonam in the European Pharmacopoeia.

2.4.3.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Aztreonam active substance and the intermediate are manufactured at two different locations by the same ASMF holder.

Aztreonam is synthesised in 2 main steps using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Solvents used during the synthesis of the active substance are tested by GC as residual solvents on the active substance in accordance with ICH Q3C.

As per ICH Q3D, a risk assessment on elemental impurities was conducted covering all potential sources of metal contamination such as but not limited to, production equipment and evaluation of starting materials, raw materials and reagents used in the route of synthesis of the active substance and the potential risk from the active substance primary packaging materials. The evaluation was conducted on 3 commercial batches. As an outcome of the review process the appropriate controls have been put in place for elemental impurities.

During the procedure, a major objection (MO) was raised to request that the full detailed risk assessment on nitrosamines impurities is presented. A detailed risk analysis on the formation of nitrosamines impurities in the active substance was presented in the restricted part of the ASMF as per the guidance in the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products. The risk of potential presence of nitrosamines related to the active substance manufacturing process, the raw materials used and the combination of them was evaluated in accordance with current requirements and identified no risk of nitrosamine formation in the active substance. No analytical evaluation or control action is therefore required on the active substance.

In compliance with Commission Regulation (EU) 10/2011 as amended, the active substance is packaged in a sealed food-grade polyethylene bag. This bag is put in another low-density polyethylene bag heat sealed that is itself placed in an aluminium laminated bag also heat sealed, and then placed into a sealed metal drum.

2.4.3.3. Specification

The active substance specifications includes tests for: appearance (visual), identification (IR, HPLC, XRPD), water (Karl-Fisher), residue on ignition (Ph. Eur.), specific optical rotation (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), formic acid (IC), nickel content (ICP-MS), bacterial endotoxins (Ph. Eur.), TAMC (Ph. Eur.), TYMC (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Impurities tested under related substances are process-related impurities or degradation products that may be present in the active substance and are controlled according to the existing USP monograph.

During the procedure, the CHMP raised an MO on the aztreonam specification applied by the finished product manufacturer requesting the applicant to provide full validation information on the methods which were not from Ph. Eur. The applicant addressed it by including relevant Ph. Eur. test method references and full validation information on the non-pharmacopoeial methods.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 6 commercial scale batches of the active substance are provided by the ASMF holder. The results are within the specifications and consistent from batch to batch.

The applicant also provided batch analyses results on 6 commercial scale batches, proving that the finished product manufacturer can control the active substance according to the specifications, with the exception of results from an alternative identification test and specific heavy metal content. The applicant subsequently provided the data for these tests. The results are within the specifications and consistent from batch to batch.

2.4.3.4. Stability

Stability data from 3 batches of active substance manufactured under aseptic conditions using the same manufacturing method from the proposed manufacturer stored in a container closure system representative of that intended for marketing for up to 18 months under long term conditions (+5°C (± 3°C)) and for up to 6 months under accelerated conditions 25°C (± 2°C) / 60% RH (± 5%) according to the ICH guidelines were provided from the primary stability study. The use of material manufactured under aseptic conditions in lieu of material manufactured under non aseptic conditions (i.e. commercial manufacturing conditions) for the primary stability studies is justified on the basis that active substances manufactured under either condition are chemically and physically equivalent.

Additional stability data from three validation batches manufactured under non-aseptic conditions from the proposed manufacturer stored in a container closure system representative of that intended for marketing for up to 12 months under long term conditions (+5°C (± 3°C)) and for up to 6 months under accelerated conditions 25°C (± 2°C) / 60% RH (± 5%) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification by IR, water content, identification by HPLC, assay on anhydrous and solvent free basis, related substances. At long term conditions samples were also tested for identification by XRPD, bacterial endotoxins, TAMC and TYMC. The analytical methods used were the same as for release and were stability indicating.

In the primary stability study, all tested parameters were within the proposed specifications under long term conditions, however under accelerated conditions out-of-specifications for unspecified impurities were observed on 2 batches. In the additional validation batches placed on stability, all tested parameters remained within the specification for long-term conditions at all timepoints, however outof-specifications were observed under accelerated conditions at the 6-month timepoint for 3 batches for unspecified impurities.

Photostability testing following the ICH guideline Q1B was performed on 4 batches. As described in the literature, the aztreonam beta form yellowed and its aztreonam E-isomer content increased due to the influence of light on isomerization. These results demonstrates that aztreonam beta form is light sensitive and need to be protected from light. The current proposed container provides adequate light protection.

Results on stress conditions: heat, acidic, basic, and oxidative conditions were also provided on one batch of the active substance to study the stability of aztreonam and the stability indicating power of HPLC method for assay and related substances. The active substance was found to be sensitive in all conditions, meaning that for all stress conditions the total amount of impurities and the degradation products significantly increased beyond the specification limits. The most sensitive conditions for aztreonam were the acidic and the alkaline conditions where total impurities and degradation products increased the most. In conclusion, the HPLC method is stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 18 months when stored at +5°C (± 3°C) in the proposed container.

2.4.4. Finished Medicinal Product

2.4.4.1. Description of the product and pharmaceutical development

The finished product is presented as a sterile white to slight-yellow powder for concentrate for solution for infusion for single use containing 1.5 g of aztreonam and 0.5 g of avibactam as active substances.

The excipient used is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur. Standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

The finished product is intended to be reconstituted with 10 mL of water for injection and diluted with 0.9% sodium chloride, 5% dextrose, or lactated Ringer's infusion solution prior to administration.

The qualitative and quantitative composition of the finished product has been presented. There is an overfill, to ensure that the entire labelled content can be used. Medicinal products containing avibactam sodium or aztreonam as a single active substances are available in the EU. The aim of the pharmaceutical development for Emblaveo was to develop a fixed dose combination of the two active substances to: i) provide greater accuracy in their dosing, not depending on the reconstitution and mixing of products from multiple vials, and ii) reduce the risk of confusion between reconstitution instructions and volumes of reconstituted individual products which could lead to incorrect dosing.

A number of finished product characteristics were determined to ensure that the commercial formulation would meet the requirements stated in the quality target product profile (QTPP) defined as: a sterile lyophilised powder for intravenous infusion containing 1.5 g aztreonam/0.5 g avibactam which meets Ph. Eur. and ICH requirements, with a minimum shelf life of 24 months. The formulation and manufacturing development was evaluated through the use of risk assessment, laboratory studies, process modelling tools and manufacturing experience to identify the critical product quality attributes and critical process parameters and identify operating ranges. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes.

Attributes which were defined as critical (critical quality attributes or CQAs) are: appearance, identification, assay, content uniformity, degradation products, pH, water content, reconstitution time, appearance of reconstituted solution, particulate matter, sterility and bacterial endotoxins.

For Phase 1, 2 and 3 clinical studies, aztreonam and avibactam were supplied in separate vials for co-administration as a combined single infusion solution. For the proposed fixed-dose commercial formulation, a 3:1 weight ratio of aztreonam to avibactam was selected. The ratio is the same as the ratio applied during clinical trials.

Characteristics of the aztreonam product used in clinical trials were leveraged for formulation development.

Formation of impurities due to interaction between aztreonam and arginine excipient is known, and the impurities were identified. Specifications for these impurities were established and conform to ICH Q3B and supported by a toxicological qualification study.

The compatibility of avibactam and arginine was studied for the proposed commercial product, Emblaveo. Two finished product degradants were identified. Specifications for these impurities were established and conform to ICH Q3B and supported by a toxicological qualification study.

Water for injection is used during formulation as a solvent/vehicle and removed during lyophilisation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

An evaluation has been performed with the aim to demonstrate the pharmaceutical equivalence between infusion solutions prepared from clinical trial formulations and the proposed commercial formulation. Three batches of each were studied, parameters investigated were assay, related substances, appearance, pH, and sub-visible particulates.

the results confirm that infusion solutions prepared from the proposed commercial product have composition that was quantitatively and qualitatively identical to infusion solutions prepared from the clinical product.

Two concentrations of the infusion solution were evaluated to bracket the potential range of the administration concentration of the finished product. A low concentration of aztreonam and avibactam, and a high concentration of aztreonam and avibactam was employed during clinical studies and was used for evaluation of pharmaceutical equivalence and the selected in-use stability timepoint. The pH, osmolality and viscosity of reconstituted diluted product (with 0.9% saline, 5% glucose, lactated Ringer's) to produce infusion solutions with a concentration of 40 mg/mL aztreonam and 13.3 mg/mL avibactam or 1.5 mg/mL aztreonam and 0.5 mg/mL avibactam have been discussed and it is concluded that these parameters are appropriate for infusion formulations.

Aseptic processing was selected as the sterilisation method for Emblaveo based on the decision tree for sterilisation choices for dry powder products in the CHMP guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015). The justification of the choice of sterilisation method originally provided by the applicant was deficient and the CHMP raised a MO. In response, the applicant demonstrated that upon exposure to dry heat discoloration of the lyophilised cake occurred, indicating significant chemical degradation. The resulting product did not meet the intended release specification for appearance. This, together with the measured glass transition temperature (Tg) of the product and known temperature sensitivity of aztreonam above 25° C as evidenced in the out of specification observed in the stability studies (see aztreonam active substance stability section of this report), led to the conclusion that terminal sterilisation by dry heat was not to be a viable option for the finished product, and alternative combinations of time and temperature dry heat cycles to achieve a SAL of ≤10-6 were not explored.

Type 1 glass is known to be susceptible to gamma radiation induced discoloration, providing challenges determining the appearance and colour of the lyophilised cake and the reconstituted solution. Moreover, gamma irradiation inherently produces local heating as a part of the sterilisation process; as noted above aztreonam is known to be unstable above 25°C. Therefore gamma irradiation was also deemed not to be a viable option for terminal sterilisation of the product. As a result, a combination of sterile filtration and aseptic processing was selected and validated for the finished product manufacture.

The primary packaging is a 30 mL glass vial (Type I) sealed with a chlorobutyl lyophilisation double vent rubber stopper and a 20 mm aluminum flip off overseal. The material complies with Ph.Eur. and EC requirements. A functional secondary packaging container (paperboard carton) is also used to protect the formulation from light. The choice of the container closure system has been validated by stability data, extractables and leachables and container closure integrity studies and is adequate for the intended use of the product.

A comprehensive study was undertaken to evaluate the in-use stability and compatibility of the finished product with common infusion diluents (sodium chloride, 5% dextrose, and lactated Ringer's

solution), intravenous (IV) bags and infusion lines, administration sets and extension sets. The results from this study support the handling instructions included in the SmPC.

2.4.4.2. Manufacture of the product and process controls

The manufacturing process consists of seven main steps: weighing, compounding, sterile filtration, aseptic filling, lyophilisation, capping, inspection and packaging. The process is considered to be a non-standard manufacturing process.

Several hold time limits are applied during the manufacture of Emblaveo. These have been described and validated.

Process validation data for three commercial scale batches have been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.4.4.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of lyophilised cake (visual), appearance of reconstituted solution (visual, Ph. Eur.), reconstitution time (visual), pH (Ph. Eur.), colour of solution (Ph. Eur.), identification of avibactam and aztreonam, (HPLC), assay of arginine, avibactam and aztreonam (HPLC), related substances of avibactam and aztreonam (HPLC), ethanol (GC), uniformity of content (Ph. Eur.), water content (Karl Fischer, Ph. Eur.), visible particulates (Ph. Eur.), particulate matter (subvisible) (Ph. Eur.), sterility (Ph. Eur.) and endotoxin (BET) (Ph. Eur.).

The assay specification limits for avibactam and aztreonam have been justified based on pertinent development information, batch analysis history and stability data.

Acceptance criteria of the specified impurities have been qualified in nonclinical toxicity studies.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three commercial scale batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.4.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (5ºC) and for up to 6 months under accelerated conditions (25ºC / 60% RH) according to the ICH guidelines were provided. The batches of Emblaveo are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were stores in upright and inverted positions.

Samples were tested for appearance of lyophilised cake, appearance of reconstituted solution, reconstitution time, pH, colour of solution, assay of arginine, avibactam and aztreonam, related substances of avibactam and aztreonam, water content, particulate matter (subvisible), sterility and endotoxin. The analytical procedures used are stability indicating. Some of the specified degradation products showed increased levels in either accelerated or both accelerated and long-term conditions, but no out of specification results were observed.

Supportive stability data from three development batches stored for 6 months at accelerated conditions, and 18, 24 and 36 months, respectively under long term conditions was also provided. Results were within the proposed specification limits.

In addition, one batch commercial scale batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were exposed in the horizontal orientation.

Samples were tested for appearance of lyophilised cake, appearance of reconstituted solution, reconstitution time, pH, colour of solution, assay of arginine, avibactam and aztreonam, related substances of avibactam and aztreonam and water content.

No significant changes were observed in any of the parameters measured for the confirmatory photostability study for samples packaged in the proposed commercial packaging.

Significant changes were observed in some parameters for the exposed samples that were not protected with the secondary packaging. Therefore, it is concluded that the finished products are protected from light.

Based on available stability data, the proposed shelf-life of 24 months when stored at 5°C protected from light in the proposed commercial packaging as stated in the SmPC (section 6.3) are acceptable.

An in-use stability study for Emblaveo was conducted for both the reconstituted solution and the infusion (admixture) solution in three diluents (0.9% saline, 5% dextrose and lactated Ringer's) at the upper and lower range of the potential administration concentrations for each diluent. Samples were tested for appearance of solution, colour of solution (for reconstituted solution only), pH, assay of avibactam, assay of aztreonam, avibactam related substances, aztreonam related substances, and particulate matter.

After reconstitution with water (prior to admixture into IV diluents for use as an infusion solution), the product concentrate was stored at 30°C under ambient light for 60 minutes. The reconstituted solution was tested immediately after dissolution of the cake, after 30 minutes and after 60 minutes. All test parameters met acceptance criteria. This supports the shelf-life after reconstitution in SmPC that the reconstituted vial should be used within 30 minutes for preparation of the infusion bag or stock solution that delivers the appropriate dose for intravenous infusion. The in-use stability study of Emblaveo in the different IV diluents concluded that Emblaveo diluted in 0.9% saline and lactated

Ringer's is stable for 24 hours at 5°C followed by 12 hours at 30°C under ambient light. Emblaveo diluted in 5% dextrose is stable for 24 hours at 5°C followed by 6 hours at 30°C under ambient light, as described in the SmPC.

In accordance with the Note for Guidance on in-use stability testing of human medicinal products, CPMP/QWP/2934/99 and the Quality of Medicines: Part 2 Q&A, in-use stability testing of Emblaveo during shelf-life was requested. The applicant confirmed that the study is being performed on two primary stability batches stored at the 5°C long-term stability condition. In-use stability data after 4 months and 12 months storage was presented for the reconstituted lyophilised cake and the infusion (admixture) solution in three diluents (0.9% saline, 5% dextrose and lactated Ringer's) at the upper and lower range of the potential administration concentrations of aztreonam and avibactam for each diluent. The data and calculations provided support the proposed instructions for handling included in section 6.6. of the SmPC. The applicant will continue the study up to the end of shelf-life (24 months).

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA (ref. 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union).

2.4.4.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.5. Discussion on chemical, pharmaceutical and biological aspects

The finished product consists of a fixed dose combination of avibactam sodium and aztreonam to facilitate the administration of these active substances. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Three major objections were raised during the procedure on the lack of detailed risk assessment on nitrosamine impurities, the finished product manufacturer specification for aztreonam (specifically the lack of references to Ph. Eur. test methods and full validation of the non Ph. Eur. methods) and the justification of the sterilisation method for the finished product. These were satisfactorily addressed during the procedure. 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.

2.4.6. 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.

2.4.7. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

For AVI, a complete non-clinical study package was submitted. The same study programme was evaluated by CHMP in 2016 as part of the registration package of AVI in combination with ceftazidime. No new assessment of the data is made in this AR, although brief summaries based on the EPAR for the AVI/CAZ (ceftazidime) fixed-dose combination are presented.

For ATM, the non-clinical programme is mainly composed of literature data. In general, the non-clinical information provided by the applicant on ATM, whilst sparse, was considered acceptable given that ATM is a marketed antibiotic with a well-established clinical safety profile and that the systemic ATM exposure following Emblaveo administration seems covered by the systemic ATM exposure following ATM monotherapy.

A few new studies have been completed with ATM and AVI in combination. The ATM/AVI combination has been tested in a non-GLP 2-week intravenous (IV) dose range-finding study and two 4-week repeat-dose (one non-GLP and one GLP) IV studies in rats. In addition, a 2-week impurity qualification was also conducted with ATM/AVI in rats, and haemolysis was investigated *in vitro*.

In addition, environmental risk assessments for ATM and AVI were provided.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Primary pharmacodynamic are presented in section 2.6.2.2.

2.5.2.2. Secondary pharmacodynamic studies

No information on the secondary pharmacodynamics of ATM was presented.

AVI was tested in an off-target screening panel of 50 targets at a single concentration of 100 µM (or 27 µg/mL unbound or 2.1x the projected unbound C_{max} of AVI of 12.7 µg/mL at the MRHD for ATM/AVI; molecular weight of 265.24 was used for AVI). No significant activity, defined as >50% inhibition, was detected. AVI was also tested at a single concentration of 1000 µM (or 265 µg/mL unbound or 21x the projected unbound C_{max} of AVI at the MRHD for ATM/AVI) in 12 assays of serine protease activity. AVI had no significant activity. In addition, the activity of AVI at three serine proteases, chymotrypsin, plasmin and thrombin, was assessed over 5 concentrations up to a maximum of 10 mM (or 2650 µg/mL unbound or >200x the projected unbound C_{max} of AVI at the MRHD for ATM/AVI). AVI had no significant activity at plasmin or thrombin proteases while an IC_{50} of 1.49 mM (or 395 µg/mL unbound or 31x the projected unbound C_{max} of AVI at the MRHD for ATM/AVI) was defined for chymotrypsin.

2.5.2.3. Safety pharmacology programme

The applicant stated that ATM has been tested for potential effects on neuro-pulmonary, cardiovascular and renal function, however no further details have been presented. One *in vitro* study report has been provided indicating that ATM has a low potency (IC_{50} >10 mM, corresponding to 4354 µg/mL) interactions with hK v11.1, hCav1.2/β2/α2δ, hKv7.1/hKCNE1. No blockade of hNav1.5 or hKv4.3/hKChIP2.2 could be detected up to a maximum test concentration of 10 mM. Given that ATM is

a marked antibiotic with a well-established clinical safety profile and that the systemic ATM exposure following Emblaveo administration seems covered by the systemic ATM exposure following ATM monotherapy, the information presented on safety pharmacology was considered acceptable.

AVI has been tested in a complete safety pharmacology package in rats (CNS, renal, respiratory and GI) and dogs (CV), in compliance with GLP. All studies were conducted using IV administration with exception on the rat GI study in which oral administration was used.

In rats, AVI had no significant effects on autonomic, motor and behavioural parameters in the Irwin screen at the highest tested dose of 1000 mg/kg administered by IV bolus. AVI had no effects on respiratory function at the highest tested dose of 1000 mg/kg by 30-minute IV infusion. AVI had no effect on renal function in rats with the exception of a dose-dependent increase in sodium excretion, which may be attributed to administration of its sodium salt. A dose of 1000 mg/kg corresponds to ~70x the projected exposure of AVI based on total C_{max} at the MRHD.

Following oral administration of AVI in rats, a delay in mean intestinal transit was observed at 2000 mg/kg (C_{max} 83 µg/mL and $AUC_{(0-t)}$ 114 µg/mL·h).

AVI had no effect on hERG current in HEK293 cells at unbound concentrations 21x the projected exposure of AVI based on unbound C_{max} at the MRHD. No significant changes were observed in cardiovascular and ECG parameters in conscious telemetered dogs up to 1000 mg/kg. Although AVI did induce an increase in blood pressure following bolus IV administration in the rat, the effect was very transient, lasting only approximately 2 minutes from the end of dosing.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies with ATM/AVI, ATM or AVI have not been conducted.

2.5.3. Pharmacokinetics

New data generated to support the development of the combination consists of analytical methods for ATM/AVI in rats, TK data for combination toxicity studies in rats, *in vitro* assays of plasma protein binding for ATM, and transporter interaction data for ATM. Remaining ATM data included in this submission is based on information provided in the SBA, label, and published literature. AVI data included in this document is from AVI alone groups included in the combination toxicity studies as well as relevant information from the registration package for the fixed dose combination avibactam/ceftazidime.

2.5.3.1. Methods

A HPLC-MS/MS assay was validated for the determination of ATM and AVI in K_2EDTA rat plasma using protein precipitation and negative ion mode detection. The was method has been validated according to guidelines and in compliance with GLP. The range was 20 to 20000 nmol/L ATM and 40 to 40000 nmol/L AVI, and the lower limit of quantification set at 20 nmol/L for ATM and 40 nmol/L for AVI. Short- and long-term stabilities were sufficient to support the ATM/AVI combination toxicity studies in rats.

2.5.3.2. Absorption

ATM and AVI are administered intravenously and exhibit short half-lives in plasma.

There was no evidence of accumulation of ATM or AVI following repeat dosing in 14-day and 28-day combination toxicity studies. Administration of ATM and AVI in combination did not change the systemic exposure to either analyte compared to dosing alone, and systemic exposure to ATM and AVI was similar between sexes.

2.5.3.3. Distribution

Neither ATM nor AVI are highly bound to plasma proteins in preclinical species or in humans.

Protein binding of ATM was low to moderate in rat plasma, with a mean value of 60.7% bound (39.3% unbound) and was concentration independent. In mouse serum, ATM showed concentration dependent binding (concentration range 56 to 977 µM with the fraction bound ranging from 90.8 to 35.6% (9.2% to 64.4% unbound). Binding to human plasma proteins was concentration independent between 5 and 500 µM, with a mean value of 38.4% bound (61.6% unbound). An average value of 38% bound (62% unbound) is used when calculation of unbound ATM in human plasma is needed.

Protein binding of AVI was low, < 22.1% (>77.9% unbound) across mouse, dog, rabbit and rat and was concentration-dependent (concentration range 0.94 to 9400 µM). Binding of AVI in human plasma was concentration-independent and ranged between 5.7% and 8.2% bound (91.8% and 94.3% unbound). An average value of 8% bound (92% unbound) is used when calculation of unbound AVI in human plasma is needed.

After SC dosing in the rat, concentrations of ATM in kidneys and liver were higher than or similar to serum concentrations. Concentrations in all other tissues and organs were lower than serum.

After IV dosing in the rat, tissue concentrations of AVI related radioactivity were higher in kidneys, urinary bladder and whole blood than plasma. Concentrations in all other tissues and organs were less than plasma. Higher exposure in kidneys and urinary bladder is consistent with a drug that is cleared by renal elimination.

Both ATM and AVI are reported to cross the placental barrier and to be excreted in milk. However, the data presented for ATM are scarce. In SmPC section 4.6 it is stated that aztreonam is excreted in breast milk in concentrations that are less than 1% of those in simultaneously obtained maternal serum. This statement is in agreement with Fleiss et al (1985) reporting a study on ATM serum and milk concentrations in 12 lactating and healthy subjects over an 8-hour period following IM or IV administration.

2.5.3.4. Metabolism

ATM was not extensively metabolised in preclinical species or in humans. Urinary excretion was the primary route of elimination of ATM.

In vitro, AVI was metabolically stable in mouse, rabbit, dog and human liver microsomes. In vivo metabolism appeared to be <26% in rats and <20% in dogs indicating metabolic mediated elimination to be a minor clearance pathway.

Unchanged parent AVI was the major drug-related component in human plasma and urine. There was no evidence of any circulating metabolites in man.

2.5.3.5. Elimination

Metabolism is not a major route of elimination for either ATM or AVI, and both drugs are primarily eliminated unchanged in the urine in preclinical species and in humans.

2.5.4. Toxicology

The toxicological potential of AVI has been characterised in studies of single- and repeat-dose toxicity, *in vitro* and *in vivo* genotoxicity, reproduction toxicity, phototoxicity, local tolerance and immunotoxicity. These studies have previously been evaluated as part of the registration package of AVI in combination with ceftazidime (CAZ). No new assessment of the data has been performed, thus summaries based on the EPAR of the fixed dose combination CAZ/AVI is presented.

The ATM/AVI combination has been tested in a non-GLP 2-week intravenous (IV) dose range-finding study and two 4-week repeat-dose (one non-GLP and one GLP) IV studies in rats. In addition, a 2-week impurity qualification was also conducted with ATM-AVI in rats that included an *in vivo* micronucleus assessment of two drug product impurities, the AVI-arginine adduct 1 and AVI-arginine adduct 2. In addition, some AVI/ATM-related impurities were evaluated *in silico*.

The rat was selected as the single species for the combination toxicity studies because target organs of toxicity associated with ATM are evident in this species. In previous registration packages, 2 species (rats and dogs) were utilised for toxicity evaluations for ATM alone and AVI alone. These species have a comparable metabolic profile to humans.

The combination toxicity studies in rats utilised a 30-minute IV infusion to mimic the loading IV infusion for the clinic. The rats were dosed less frequently each day than in the clinic (e.g., once per day versus every 6 hours in the clinic).

2.5.4.1. Single dose toxicity

No single-dose toxicity studies have been conducted with the ATM/AVI combination. This is considered acceptable.

In the 14-day IV ATM/AVI combination toxicity study, a single dose of 2000 mg/kg ATM delivered over 30 minutes by IV infusion was not tolerated as evidenced by severe clinical signs that included abnormal gait, hunched posture, shallow breathing, liquid faeces, drinking excessively, erected fur, and cold to touch. These signs were more severe in males than females and prompted euthanasia of these animals on Day 2 after a single dose. Intolerance was associated with a total C_{max} of 4000 µg/mL ATM and total AUC_{24} of 9580 µg•h/mL ATM (Day 1 combined sexes) or 61x and 8.7x, respectively, the projected exposure associated with the MRHD of ATM in combination with AVI.

The acute toxicity of AVI following IV administration is low.

2.5.4.2. Repeat dose toxicity

ATM/AVI repeat-dose IV combination studies in rats for up to 4 weeks with recovery have been conducted. The key targets identified in repeat-dose combination toxicity studies in rats with ATM/AVI were the kidney and liver.

Mortality

ATM at a single dose of 2000 mg/kg was not tolerated in male rats in the first 2-week dose-finding study, see section single-dose toxicity above. In the subsequent 4-week study, IV infusion of ATM at 1500 mg/kg/day, with or without AVI was not tolerated in male rats due to adverse clinical signs. Dosing in males was suspended on Day 2, and all males were terminated on Study Day 8.

Kidney

Increases in kidney weight were observed in the ATM/AVI combination toxicity studies up to 4 weeks in duration in rats at ATM/AVI doses of ≥750/300 mg/kg/day. The increase in kidney weight (up to 1.10x control) in the 1-month GLP study was associated with cortical tubular vacuolation that was primarily minimal in severity. In addition, there was a marginally increased incidence of minimal hyaline casts in some studies. These findings were attributed to ATM since the same findings were observed in the ATM alone groups and not in the AVI alone groups. Kidney changes reversed in the 12-week recovery phase of the GLP 4-week study.

In addition, tubular necrosis was observed in all 6 rats that received a single dose of 2000 mg/kg ATM. This dose was not tolerated and resulted in moribund euthanasia of all rats prior to the second dose. This finding was not observed at lower ATM doses in studies up to 1 month in duration.

Liver

Increases in liver weights were observed in combination toxicity studies up to 1-month in duration in rats at ATM/AVI doses of ≥750/300 mg/kg/day that were associated with AUC_{24} exposure margins of ≥1.4x based on the MRHD of ATM. The increases in liver weight (up to 1.14x control) in the 1-month GLP study did not have a microscopic correlate while the increase in liver weight (up to 1.24x control) in the 2-week study was associated with minimal centrilobular hepatocellular hypertrophy in the 1500/600 mg/kg/day ATM/AVI group. Liver changes reversed in the 12-week recovery phase of the second 1-month study.

In addition, centrilobular necrosis was observed in 2 of 6 rats that received a single dose of 2000 mg/kg ATM. This dose was not tolerated and resulted in moribund euthanasia of all rats prior to the second dose. This finding was not observed at lower ATM doses in studies up to 1 month in duration.

2.5.4.3. Genotoxicity

ATM is stated to be devoid of mutagenic and clastogenic potential *in vitro* (bacterial reverse mutation assay, mouse lymphoma forward mutation assay, gene conversion assay, chromosome aberration assay in human lymphocytes) and *in vivo* (mouse bone marrow cytogenetic assay).

AVI was negative in the Ames assay, unscheduled DNA synthesis, chromosomal aberration assay and the rat micronucleus test.

2.5.4.4. Carcinogenicity

Carcinogenicity studies have not been conducted with ATM/AVI, ATM by the IV route or AVI. A 104-week rat inhalation toxicology study to assess the carcinogenic potential of ATM demonstrated no drug-related increase in the incidence of tumours. Due to the short duration of treatment, carcinogenicity studies are not warranted (ICH S1A).

2.5.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity studies have not been conducted with the ATM/AVI combination. This was however considered acceptable.

For ATM, no effect on fertility was observed in a 2-generation study in rats at daily doses of 150, 600, or 2400 mg/kg ATM by SC injection given prior to and during gestation and lactation. Based on body surface area, the high dose is 3.2x the MRHD of 6.5 g per day. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dose, but not in

offspring of rats that received the lower doses of ATM. In embryo-foetal developmental studies in pregnant rats and rabbits with daily SC doses of ATM up to 1800 and 1200 mg/kg, respectively, there was no evidence of embryotoxicity or fetotoxicity. These doses, based on body surface area, are 2.7x and 3.6x the MRHD for adults of 6.5 g ATM per day. A peri- and post-natal development study in rats with ATM by SC injection revealed no drug-induced changes in any maternal, fetal, or neonatal parameters. The highest dose used in this study, 1800 mg/kg/day, is 1.8x the MRHD based on body surface area.

AVI has been tested in a full reproductive toxicity study package following IV administration. AVI did not affect female fertility/reproductive performance or embryofoetal development following repeat IV administration to rats at doses up to 250 mg/kg/day corresponding to ~1.7x the projected AUC exposure at the MRHD. In male rats, small decreases in epididymal and prostate weights were observed at 1000 mg/kg/day and considered to be a secondary effect to a decrease in bodyweight gain at all doses. There were no effects on male reproductive performance or fertility up to 1000 mg/kg/day corresponding to ~4.5x the projected AUC exposure at the MRHD.

In a rat embryo-foetal development study, there were two malformed foetuses at 500 mg/kg/day (one with domed head, protruding tongue, mal-rotated right hind limb and hyperextension of the right forepaw and a second with scoliosis) and at 1000 mg/kg/day (anophthalmia). Since there were no malformations and no overall effects on embryo-foetal development at 250 mg/kg/day, the exposures at this dose were considered as an appropriate reference for a NOEL for embryo-foetal changes in the rat, corresponding to ~1.7x the projected AUC exposure at the MRHD.

In a rabbit embryofoetal development study, there was an increased post-implantation loss at 1000 mg/kg/day and lower mean foetal weights with slightly retarded ossification of the metacarpal of the first digit, tarsal bone and sixth sternebra was observed at 300 mg/kg/day and above. There were no other overt findings at 100 mg/kg/day and this dose is therefore deemed to be the NOEL for embryo-foetal changes in the rabbit and the NOAEL for maternal toxicity, corresponding to ~1.1x the projected AUC exposure at the MRHD.

AVI administered during pregnancy and lactation to F0 rats was associated with a dose-related increase in the incidence of renal pelvic dilatation and ureter dilatation, with no associated pathological changes to the renal parenchyma. There was no evidence of recovery in the renal pelvic dilatation but the ureteric dilations were not seen in the young adult offspring. These findings were considered associated with administration of AVI. The dose of 120 mg/kg/day is considered to be the NOEL for the unilateral or bilateral renal pelvic dilatation and/or luminal dilatation of the ureters, corresponding to ~0.6x the projected AUC exposure at the MRHD.

Juvenile toxicity

Both ATM and AVI given separately are approved in children, but no paediatric indication is currently proposed for the combination product.

2.5.4.6. Toxicokinetic data

Toxicokinetics was included in the ATM/AVI IV combination repeat-dose studies in rats. The plasma concentrations of ATM and AVI were determined after a 30-minute IV infusion to rats that received ATM alone, AVI alone or ATM in combination with AVI in repeat doses up to 4 weeks in duration. The systemic exposure to ATM and AVI (as assessed by C_{max} and AUC_{24}) increased with increasing dose, were comparable between Day 1 and the end of the study, and similar in males and females. Administration of ATM and AVI in combination did not change the systemic exposure to either analyte compared to dosing alone, and systemic exposure to ATM and AVI was similar between sexes.

Exposure margins are based on total exposure values since ATM and AVI are not highly bound and protein binding data with ATM or AVI are comparable between humans and toxicology species. AUC exposure multiples of the projected exposure at the MRHD were reached at the NOAEL in the 4-week GLP compliant combination toxicity study (~2x for AVI and ~4x for ATM).

2.5.4.7. Local tolerance

A stand-alone local tolerance study with ATM/AVI have not been conducted. However, IV injection sites were evaluated microscopically in the GLP-compliant 1-month repeat-dose toxicity study in rats and no test article-related findings were observed with ATM/AVI at doses up to 1500-600 mg/kg/day (100-40 mg/mL), ATM at doses up to 1500 mg/kg/day (100 mg/mL), and AVI at doses up to 600 mg/kg/day (40 mg/mL). Although no overt tolerability concerns have been identified, the main issue identified with AVI in previous repeat-dose toxicity studies in rats and dogs was local tolerance at the injection site.

2.5.4.8. Other toxicity studies

Impurities

The maximum daily dose of Emblaveo is 6.5 g ATM and 2.17 g AVI and thus according to ICH Q3B (R2) the qualification threshold is 0.15%. However, as further discussed in the Quality AR, a 0.2% limit for unspecified degradation products is proposed and found acceptable.

There are several ATM-related impurities having a shelf-life specification above the qualification threshold; desulfated ATM (NMT 1.5%), open-ring desulfated ATM (NMT 0.5%), open-ring ATM (NMT 2.0%), E-isomer (NMT 1.0%), impurity I (NMT 2.0%), impurity J (NMT 2.0%), in-house impurity 1 (NMT 1.0%), in-house impurity 2 (NMT 2.0%), in-house impurity 3 (NMT 0.3%) and open-ring amide (NMT 0.5%). These ATM-related impurities are all concluded as non-mutagenic based on *in silico* data. Furthermore, all impurities with exception of open-ring desulfated ATM have been adequately qualified *in vivo*. This structure bears similarities to both open-ring ATM and desulfated ATM that have been qualified *in vivo*. *In silico* analysis revealed no structural alerts for the open-ring desulfated ATM. Given that both the desulfated and the open-ring structure have been qualified separately, the arguments provided by the applicant are agreed.

AVI-related impurities specified above the qualification threshold include AVI decarbonyl (PF-07866682, NMT 2.0%), AVI arginine adduct 1 (PF-07921322, NMT 1.0%) and AVI arginine adduct 2 (PF-07921944, NMT 0.8%). All these AVI-related impurities are concluded as non-mutagenic based on *in silico* and/or *in vitro* data. Further, they have all been qualified *in vivo*.

Phototoxicity

ATM was not evaluated for phototoxicity since ICH S10 guidance does not apply to marketed drugs unless there is a new cause for concern. AVI does not absorb in the appropriate spectrum and was concluded as negative in an *in vitro* phototoxicity study in Balb/c3T3 fibroblasts.

Haemolysis, clumping and plasma precipitation

In an *in vitro* haemolysis assay, mixing of ATM (133 mg/mL) and ATM/AVI formulation (133/40 mg/mL) and its control article (Water for Injection) with rat whole blood did not cause haemolysis, clumping or plasma precipitation. The tested ATM and AVI concentrations correspond to the commercial formulation concentration after reconstitution.

2.5.5. Ecotoxicity/environmental risk assessment

- **Aztreonam**

The $logD_{ow}$ values of ATM were below 4.5 (ranging from -2.73 to -2.98) at all environmentally relevant PHs (i.e. 5, 7 and 9).

The Phase 1 $PEC_{surfacewater}$ (refined based on treatment regime) of ATM (1.4 µg/L) exceeded the action limit of 0.01 µg/L, triggering Phase II environmental fate and effect assessments.

For the Tier A aquatic effects assessment, standard long-term toxicity tests in algae, cyanobacteria, *Daphnia* and fish were performed in accordance with the appropriate OECD Test Guidelines and GLP.

The cyanobacteria was the most sensitive species tested and the NOEC = 830 µg/L was used in the $PNEC_{surfacewater}$ calculation. As per guidance, the chronic NOEC for *Daphnia* (8.2 mg/L) was used to calculate the $PNEC_{groundwater}$ and the the NOEC for sludge (100 mg/L) was used to calculate the $PNEC_{microorganisms}$.

The Koc_{ads} for ATM (345 L/kg) was below 3700 L/kg and it is concluded that exposure to the terrestrial compartment as a result of spreading of sludge on soil is low and Tier B assessment of the terrestrial compartment is not required.

In OECD308, aztreonam remains predominantly in the water phase, in sediment only small amounts of 6.3% parent in maximum are detected. Therefore, the trigger values for freshwater are relevant and the DT_{50}-total system can be transferred to the trigger values of 40 days (P) and 60 days (vP). As the DT50 total system, 12 °C amounts to 45 and 89 days (Brandywine Creek clay loam and Choptank River sand respectively) the vP trigger for the water phase (> 60 days) is exceeded and aztreonam is to be considered as very persistent. The vP -trigger value is also fulfilled in the water phase itself (DT_{50} water, 12 °C = 41 / 83 days).

Total radioactivity in the extractable and unextractable sediment in the OECD 308 test was >10%, and therefore the toxicity of ATM to sediment-dwelling organisms was investigated in Tier B.

The NOEC value for emergence ratio and development rate of *Chironomus riparius* was determined to be 1500 mg/kg. This value was used to derive the $PNEC_{sediment}$ and the resulting PEC/PNEC ratio for ATM did not exceed relevant trigger, and therefore a risk to sediment-dwelling organisms was concluded to be low.

The applicant has agreed to submit an updated ERA with a revised $PEC_{surfacewater}$ value for aztreonam. The updated ERA will be provided by December 2024 (see section 7.2).

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of aztreonam to the environment. However, aztreonam is considered very persistent (vP) in the environment.

Table 1: Summary of main study results for aztreonam

Substance (INN/Invented Name): Aztreonam			
CAS-number (if available): 78439-06-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Dow (pH 5) = -2.73 Log Dow (pH 7) = -2.97 Log Dow (pH 9) = -2.98	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**

Bioaccumulation	log D_{ow}	<3.0	Not B (according to screening criterion)
Persistence	DT_{50} water	$DT_{50\ fresh\ water}$ (12°C) = 83 d $DT_{50\ total\ system}$ (12°C) = 89 d	vP
Toxicity	NOEC	0.83 mg/L	Not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$ (refined)	1.4	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			Antibiotic
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Kd=no sorption (sludge) Kd=no sorption (HOM soil) Kd=no sorption (LOM soil) Kd=14.5 (HOM sediment) Koc=345 (HOM sediment) Kd=no sorption (LOM sediment)	Study with two soils, two sediments and one sludge
Hydrolysis	OECD 111		Estimated half-life at pH 7, 25ºC is 262 days, using Arrhenius equation
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	HOM test system: $DT_{50,\ water}$ = 19 d at 20°C $DT_{50,\ water}$ = 41 d at 12°C $DT_{50,\ sediment}$ = 3.0 d at 20°C $DT_{50,\ sediment}$ = 6.3 d at 12°C $DT_{50,\ total\ system}$ = 21 d at 20°C $DT_{50,\ total\ system}$ = 45 d at 12°C Mineralization (180 days) = 49% % shifting to sediment = 48.3 LOM test system: $DT_{50,\ water}$ = 39 d at 20°C $DT_{50,\ water}$ = 83 d at 12°C $DT_{50,\ sediment}$ = 3.4 d at 20°C $DT_{50,\ sediment}$ = 7.3 d at 12°C $DT_{50,\ total\ system}$ = 42 d at 20°C $DT_{50,\ total\ system}$ = 89 d at 12°C Mineralization (180 days) = 37% % shifting to sediment = 13.7 (1) = Brandywine Creek sediment, clay loam, (2) = Choptank River sediment, sand % NER = 32.9% (1), 4.8% (2) Transformation products >10% = YES, (1) 'Peak at RT 6.5 min (HPLC)' = 14.5% (max. at d 102) Proposed molecular formula: $C_9H_{12}N_4O_4S$	DT50 at 12°C calculated using Arrhenius equation At end test

		(2) 'Peak at RT 7.5 min (HPLC)' = 39.7% (max. at d 180) Proposed molecular formula: 'RT 7.5min: $C_{13}H_{19}N_5O_9S_2$			
Biodegradation in activated sludge	OECD 314B	18.6% mineralization after 28 days DT_{50} = ~ 1 minute			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test (*Raphidocelis subcapitata*)	OECD 201	EC_{50} EC_{10} NOEC	>8.6 >8.6 8.6	mg/L	Growth rate
Blue Green Alga (*Anabaena flos-aquae*)	OECD 201	EC_{50} EC_{10} NOEC	2.6 1.5 0.83	mg/L	Growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC LOEC EC_{10}	8.2 >8.2 ND	mg/L	Survival, reproduction, length
Fish, Early Life Stage Toxicity Test *(Pimephales promelas)*	OECD 210	NOEC LOEC EC_{10}	3.7 9.0 5.7	mg/L	Hatch, survival, length, weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100	mg/L	
Phase IIb Studies					
Sediment dwelling organism (*Chironomus riparius*)	OECD 218	NOEC LOEC	1500 >1500	mg/kg	Corrected to 10% organic carbon

- **Avibactam**

The $logD_{ow}$ values of AVI were below 4.5 (ranging from -1.39 to -1.30) at all environmentally relevant PHs (i. e. 5, 7 and 9). Thus, AVI is not identified as persistent, bioaccumulative and toxic (PBT) or a very persistent and very bioaccumulative (vPvB) substance.

The Phase 1 $PEC_{surfacewater}$ (refined based on treatment regime) of AVI (0.48 µg/L) exceeded the action limit of 0.01 µg/L, triggering Phase II environmental fate and effect assessments, however this has not been provided. A summary of main study results for avibactam have been provided, but no avibactam study reports. The applicant has agreed to submit an updated Phase II ERA for avibactam with revised $PEC_{surfacewater}$ values for avibactam and aztreonam including an additional study OECD TG 201 using cyanobacteria for avibactam. The updated ERA will be provided by December 2024 (see section 7.2).

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of avibactam to the environment.

Table 2: Summary of main study results for avibactam

Substance (INN/Invented Name): Avibactam			
CAS-number (if available): 119249-61-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OECD107	Log Dow (pH 5) = <-1.39 Log Dow (pH 7) = <-1.36 Log Dow (pH 9) = <-1.30	Not PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		Not B
	BCF		B/not B

Persistence	DT_{50} or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$ (refined)	0.48	μg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			Antibiotic
PBT-statement:	Avibactam is not considered as PBT nor vPvB		

Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$ (refined)	0.48	μg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Soil 1: (%foc = 1.93) Sediment 1: (%foc = 5.6) Sediment 2: (%foc = 0.014) Sludge 1: Totnes %foc = 44.1)	OECD 106	Kd=no sorption (soil) Kd= no sorption (HOM sediment) Kd=no sorption (LOM sediment) Kd= 5.1 (sludge, est.)	Currently not assessed
Hydrolysis	OECD 111	36 days	Currently not assessed
Aerobic and Anaerobic Transformation in Aquatic Sediment systems (100 days) (1) = HOM %foc = 7.2 (2) = LOM %foc = 0.2	OECD 308	1 - HOM test system: $DT_{50,total\ system}$ = 7 d at 20 °C $DT_{50,total\ system}$ = 15 d at 12 °C % shifting to sediment (max) = 37% Mineralization (100 days) = 72% NER = 35% 2 - LOM test system: $DT_{50,total\ system}$ = 16 d at 20 °C $DT_{50,total\ system}$ = 34 d at 12 °C % shifting to sediment (max) = 28% Mineralization (100 days) = 73% NER = 25% Transformation products >10% = NO	Currently not assessed
Aerobic Biodegradation	OECD 301B	Not readily biodegradable	Currently not assessed

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test (*Raphidocelis subcapitata*)	OECD 201	NOEC	120	mg/L	Currently not assessed
Blue Green Alga (*Anabaena flos-aquae*)	OECD 201		TBD	mg/L	Currently not assessed
Daphnia sp. Reproduction Test	OECD 211	NOEC LOEC	100 >100	mg/L	Currently not assessed

Fish, Early Life Stage Toxicity Test *(Pimephales promelas)*	OECD 210	NOEC LOEC	2 >2	mg/L	Currently not assessed
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1	mg/L	Currently not assessed
Phase IIb Studies					
Sediment dwelling organism (*Chironomus riparius*)	OECD 218	NOEC LOEC	300 >300	mg/kg	Currently not assessed

2.5.6. Discussion on non-clinical aspects

Overall, the scope of the non-clinical study package is considered acceptable. Overall, the non-clinical documentation of ATM is considered sparse. This is largely considered acceptable given that ATM is a marked antibiotic with a well-established clinical safety profile and that the systemic ATM exposure following Emblaveo administration seems covered by the systemic ATM exposure following ATM monotherapy.

No information on the secondary pharmacodynamics of ATM has been presented. Furthermore, the applicant states that ATM has been tested for potential effects on neuro-pulmonary, cardiovascular and renal function, but no further details have been presented. One *in vitro* report was provided indicating that no blockade of hNav1.5 or hKv4.3/hKChIP2.2 could be detected up to a maximum test concentration of 10 mM, corresponding to 108x the projected exposure of ATM based on unbound C_{max} at the MRHD. The sparse information is considered acceptable given the established clinical safety profile of ATM at relevant clinical exposures.

The data presented for AVI suggests a low potential for inducing off-target effects at the clinical exposure.

AVI has been tested in a complete safety pharmacology package in rats (CNS, renal, respiratory and GI) and dogs (CV).

In rats, no significant effects on autonomic, motor, behavioural and respiratory parameters were observed at the highest tested dose of 1000 mg/kg administered by IV bolus, corresponding to 70x the clinical C_{max} at the MRHD. No effect was observed on renal function in rats at up to 1000 mg/kg with the exception of a dose-dependent increase in sodium excretion, potentially be attributed to administration of its sodium salt. Following oral administration of AVI in rats, a delay in mean intestinal transit was observed at 2000 mg/kg (C_{max} 83 µg/mL and $AUC_{(0-t)}$ 114 µg/mL·h) corresponding to 6x the clinical C_{max} at the MRHD. As Emblaveo is intended for IV administration, the clinical relevance of the delayed intestinal transit observed following oral administration is unclear. In clinical trials with Emblaveo, *Clostridioides difficile*-associated diarrhoea was observed (SmPC section 4.8).

AVI had no effect on hERG current in HEK293 cells at unbound concentrations 21x the projected exposure of AVI based on unbound C_{max} at the MRHD. No significant changes were observed in cardiovascular and ECG parameters in conscious telemetered dogs up to 1000 mg/kg (250x the projected exposure of AVI based on total C_{max} at the MRHD).

the systemic exposure levels of the mono-components seem to cover the expected human exposures of ATM and AVI following treatment with the combination and increased exposures of ATM or AVI are not expected when given in combination. The findings from the combination toxicity study in rats indicate that neither ATM nor AVI alter the exposure of each other in rats, and there is no signs of synergistic toxicity. Therefore, the lack of AVI/ATM safety pharmacology combination studies are acceptable. Altogether, a risk of potential effects on vital signs following administration of Emblaveo appears to be low.

New pharmacokinetic data generated to support the development of ATM for combination with AVI consists of analytical methods for ATM-AVI in rats, TK data for combination toxicity studies in rats, *in vitro* assays of plasma protein binding for ATM, and transporter interaction data for ATM.

The ATM-AVI combination has been tested in a 2-week non-GLP range-finding study and two 4-week repeat-dose (one non-GLP and one GLP) IV studies in rats. Given the proposed short duration of clinical treatment (<28 days) the combination study with IV administration of ATM and AVI in a single species (rat) for 28 days is appropriate and in line with the recommendations in ICH M3(ICH M3(R2) guidance, 2009) and the guideline on the non-clinical development of fixed combinations of medicinal products (CHMP/EMEA/CHMP/SWP/258498/2005).

The combination toxicity studies in rats utilised a 30-minute IV infusion to mimic the loading IV infusion for the clinic. The rats were dosed less frequently each day than in the clinic (eg, once per day versus every 6 hours in the clinic). The ratio of ATM:AVI was 2.5:1 in the studies while the clinical ratio is 3:1. This slight difference of ATM:AVI dose ratio from the clinical dose ratio is not expected to impact the validity of the combination toxicity studies.

In the ATM/AVI combination studies, the key target organs identified were the kidney and liver observed in test groups receiving ATM only, or in combination with AVI.

ATM (with or without AVI) was not tolerated at doses ≥1500 mg/kg/day. At 1500 mg/kg/day, the ATM C_{max} and AUC_{24} exposures ranged between 5370 to 6120 µg/mL and 16100 to 16700 µg•h/mL, respectively, corresponding to approximately 80x and 14x, the clinical therapeutic exposure. Although the AUC margin to a moribund condition seems low, there is extensive clinical experience of ATM exposures following ATM monotherapy in the same range as that resulting from Emblaveo.

The findings in kidneys included slight increases in weight and primarily minimal cortical tubular vacuolation at ATM/AVI doses of ≥750/300 mg/kg/day. These renal findings were fully reversible and were not considered adverse because of the minimal nature of the changes and because of the lack of changes in renal function. These doses were associated with AUC_{24} exposure margins of ≥2.1x based on the MRHD of ATM. These findings were attributed to ATM since the same findings were observed in the ATM alone groups and not in the AVI alone groups. Both ATM and AVI are predominantly eliminated by the kidney, partly by active tubular secretion.

In liver, increased weights were observed at ATM/AVI doses of ≥750/300 mg/kg/day that were associated with AUC_{24} exposure margins of ≥1.4x based on the MRHD of ATM. In the 1-month GLP study no microscopic correlates were observed while the increase in liver weight in the 2-week study was associated with minimal centrilobular hepatocellular hypertrophy in the 1500/600 mg/kg/day ATM/AVI group. In the GLP study, the liver findings were considered non-adverse because of the minimal nature of the change and because of the lack of change in liver function and were attributed to ATM. Liver changes reversed in the 12-week recovery phase of the second 1-month study. In the clinic, ATM is well known to have liver side effects, usually asymptomatic serum transaminase elevations that are self- limiting and resolve rapidly upon discontinuation.

AUC exposure multiples of the projected exposure at the MRHD were reached at the NOAEL in the 1-month GLP compliant combination toxicity study (~2x for AVI and ~4x for ATM).

The same target organs are reported from previously conducted IV repeat-dose studies in rats and dogs with ATM. In previous IV repeat-dose studies with AVI in rats and dogs, the main issue identified was local tolerance at the injection site but no major systemic toxicity was observed. Overall, the majority of findings appear to relate to administration of ATM, with or without AVI. There was no evidence to suggest that AVI altered the toxicity of ATM for any of the parameters, and there were no adverse findings noted for AVI alone. Moreover, administration of ATM and AVI in combination did not change the systemic exposure to either analyte compared to dosing alone.

ATM is stated to be devoid of genotoxic potential with reference given to an ATM label. An *in silico* mutagenicity assessment was performed using two complementary (Q)SAR methodologies, one expert rule-based (DEREK) and one statistical-based (SARAH) where ATM was predicted to be inactive (non-mutagenic). This information in conjunction with the known lack of genotoxicity for ATM can be considered sufficient and the information given in SmPC section 5.3 is agreed.

Carcinogenicity studies have not been conducted with ATM/AVI, ATM by the IV route or AVI, and due to the short duration of treatment, carcinogenicity studies are not warranted.

Regarding reproductive toxicity of ATM, three relevant publications were found in the public domain; one fertility study, one embryo-foetal development study, and one pre- and postnatal development study, all performed in Sprague-Dawley rats (Furuhashi et al, 1985). The publications are in Japanese but English translations were provided. Overall, all three studies seem well conducted in terms of animal numbers, dosing period and parameters evaluated but the GLP status is unclear. In the fertility study it is reported that no effects were found in male or female fertility parameters and the NOAEL on male and female fertility and early embryonic development was concluded at 750 mg/kg/day. In the teratology study, no adverse effects are reported in embryonic or foetal parameters at any dose level, and the NOAEL on embryo-foetal development was set at 750 mg/kg/day. Finally, in the perinatal and postnatal study, no apparent adverse effects are reported in pup parameters at any dose level and the NOAEL on pre- and post-natal development was set at 750 mg/kg/day. Margin calculations based on body surface area have been provided indicating that rats were administered doses around and slightly above the maximal human recommended dose. Overall, the data presented in these publications are in agreement with information presented in the SmPCs of other ATM products, and the proposed text in the Emblaveo SmPC is agreed.

For AVI, a dose-related lower mean foetal weight and delayed ossification was observed in pregnant rabbits at 300 and 1000 mg/kg/day. The findings are potentially related to maternal toxicity. Plasma exposure levels at maternal and foetal NOAEL (100 mg/kg/day) indicate low margins of exposure. In the rat, no adverse effects were observed on embryo-foetal development or fertility. Following administration of avibactam throughout pregnancy and lactation in the rat there was no effect on pup survival, growth or development; however, there was an increase in incidence of dilation of the renal pelvis and ureters in less than 10% of the rat pups at maternal exposures greater than or equal to approximately the human therapeutic AUC exposure. The text proposed in the SmPC is in agreement with that of the fixed dose combination CAZ/AVI.

No reproductive studies were conducted with ATM and AVI in combination based on the results observed with the individual compounds. This seems acceptable. Considering the seriousness of the indications and lack of therapeutic options in the case of some pathogens, the use of Emblaveo during pregnancy seems necessary in situations when treatment is clearly indicated. Overall, the information given in SmPC 4.6 and 5.3 is agreed.

The non-clinical data supporting the proposed drug product specification of ATM- and AVI-related impurities is considered satisfactory.

2.5.7. Conclusion on the non-clinical aspects

All non-clinical concerns have been satisfactorily addressed by the applicant, and from a non-clinical perspective approval can be recommended.

The applicant commits to provide an updated ERA, including a Phase II assessment for avibactam and a new OECD TG 201 study in cyanobacteria, by December 2024 (see section 7.2).

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical overview includes the following statement:

> "*All studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and in compliance with the International Council on Harmonization Good Clinical Practices Guidelines. Each investigational centre obtained approval from their Institutional Review Board or Independent Ethics Committee. All patients gave informed written consent before entering the studies. In addition, all local regulatory requirements were followed.*"

The applicant has furthermore 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.

No need for a GCP inspection was identified.

Table 3: Tabular overview of clinical studies

The clinical development programme for ATM-AVI included the following studies:

Study Number	Study Description
PK in Healthy Participants	
D4910C00001	Single and multiple dose study of ATM-AVI in young and elderly
NXL104-1001	Single ascending dose study of AVI alone and in combination with CAZ
NXL104-1002	Multiple ascending dose study of AVI
D4280C00008	Single dose ^{14}C-avibactam to assess mass balance, metabolite profile and elimination
D4280C00009	Single-center study of CAZ and AVI in ELF and plasma
CXL-PK-01	Single and multiple IV doses of ceftaroline fosamil and AVI
CXL-PK-05	Tissue penetration of multiple IV doses of ceftaroline fosamil and AVI
Intrinsic Factors	
Renal Function	
C3601006	Multiple doses ATM-AVI in participants with severe renal impairment & normal renal function
NXL104-1003	Single dose of AVI in participants with normal renal function and varying degrees of renal impairment
CXL-PK-04	Single dose of ceftaroline fosamil and AVI in adults with augmented renal clearance
Race/Ethnicity	
C3601007	Single & multiple dose study of ATM-AVI in healthy Chinese participants
D4280C00010	Single and multiple ascending dose study of AVI alone and in combination with CAZ in healthy Japanese male participants
Age/Gender/ Obesity	

NXL104-1004	Single dose of AVI in young males; elderly males; young females; elderly females
CXL-PK-06	Single dose of ceftaroline fosamil in healthy participants who were normal to overweight and in obese classes I, II, and III
Extrinsic Factors	
D4280C00011	Multiple dose PK and DDI Study of AVI and CAZ
D4280C00012	Multiple dose PK and DDI Study of CAZ-AVI and Metronidazole
PD in Healthy Participants	
D4280C00007	Single dose, thorough QTc study (CAZ-AVI, CXL)
PK and Exposure-Response in Patients	
C3601001	A Phase 2a, prospective, open-label, three cohorts, multicenter study to determine the PK, safety and tolerability of ATM-AVI for the treatment of cIAI in hospitalized adults.
C3601002	A Phase 3, prospective, randomized, multicenter, open-label, central assessor-blinded, PG, comparative study to determine the efficacy, safety, and tolerability of ATM-AVI±MTZ versus MER ± COL in the treatment of hospitalized adults with cIAI or HAP/VAP.
C3601009	A Phase 3, prospective, randomized, multicenter, open-label, PG, comparative study to determine the efficacy, safety, and tolerability of ATM-AVI+ MTZ versus best available therapy (BAT) in the treatment of hospitalized adults with cIAI, HAP/VAP, cUTI, or BSI due to MBL-producing Gram-negative bacteria.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Aztreonam/avibactam was developed as a fixed dose combination of aztreonam 1.5 g and avibactam 0.5 g for administration by intravenous (IV) infusion. Both active substances are previously approved in the EU. The product is submitted as a complete application, and thus the disposition of the substances should be described and subgroups where an altered exposure can be expected based on the pharmacokinetic properties should be identified. Potential interactions should also be evaluated. In this case, the application partly relies on previous data with ATM and AVI given separately and partly on new studies with the combination of ATM and AVI.

The *in vivo* studies submitted that were performed as part of other development programmes where AVI was dosed alone or in combination with other antibiotics than ATM as well as the AVI *in vitro* studies were already submitted and assessed in the application for the fixed dose combination CAZ/AVI and will be summarised, but no new assessment will be made. The new studies submitted as part of this application are three phase 1 studies (D4910C00001, C3601006 and C3601007), the phase 2a study (C3601001) and the two phase 3 studies (C3601002 and C3601009) as well as three new *in vitro* studies for ATM.

Absorption

Absorption is not applicable as this product is for IV infusion only. The clinical studies were performed using separate vials of the two active substances and not with the commercial fixed-dose combination product. The powder formulations used are however dissolved into solutions and diluted before administration, and there are no excipients that interact with the drug substance (e.g. complex formation). The reconstituted and diluted solution used during the clinical trials is also identical to the one obtained following reconstitution and dilution of the commercial formulation. No PK comparison between formulations used in the clinical studies and commercial formulation is needed.

Distribution

The apparent mean Vss determined in healthy volunteers and patients in the ATM-AVI programme, based on noncompartmental analysis, ranged from 12.3 to 23.7 L for ATM and from 14.3 to 37.4 L for AVI. The steady state distribution volumes stated in the SmPC are those observed in the phase 2 study in cIAI patients (study C361001) using the intended ATM/AVI dose, about 20L for ATM and about 24L for AVI.

The human protein binding of avibactam and aztreonam is concentration independent and low, approximately 8 and 38%, respectively.

Penetration of aztreonam into the intact blood-brain barrier is limited, resulting in low levels of aztreonam in the cerebrospinal fluid (CSF) in the absence of inflammation; however, concentrations in CSF are increased when the meninges are inflamed.

Avibactam distributed to infected subcutaneous tissues. AVI is also distributed into human ELF, but the exposure in this compartment is lower than that in plasma, around 30%. Penetration of aztreonam into pulmonary epithelial lining fluid (ELF) has not been studied clinically.

Elimination

The terminal half-lives ($t_{½}$) of both aztreonam and avibactam are approximately 2 to 3 hours after intravenous administration.

ATM is not significantly metabolised. In healthy subjects, ATM is excreted in the urine by active tubular secretion and glomerular filtration. Approximately 75-80% of an intravenous or intramuscular dose was recovered in the urine. The components of urinary radioactivity were unchanged ATM (65% was recovered by 8 hours), the inactive β-lactam ring hydrolysis product of ATM (approximately 7%) and unknown metabolites (approximately 3%). Urinary excretion of a single parenteral dose was essentially complete by 12 hours after injection. About 12% of a single intravenous radiolabelled dose was recovered in the faeces. Unchanged ATM and the inactive β-lactam ring hydrolysis product of ATM were present in faeces. Approximately 20% of the dose was eliminated as metabolites, with the monobactam ring-opened product being the primary identified metabolite. This metabolite accounted for about 7% in urine and 3% in faeces (Swabb et al, 1983).

AVI is predominantly renally cleared and metabolism has little contribution to its excretion. Single 500-mg doses of AVI were given to 6 healthy volunteers by IV infusion over 60 min with a target dose of radioactivity of no more than 300 µCi (11.1 MBq) [^{14}C]avibactam (Study D4280C00008). An average of 97% (range, 95% to 98%) of administered radioactivity was recovered from the urine, over 95% within 12 hours of dosing. Only 0.2% (range: 0.17% to 0.23%) of administered radioactivity was recovered from the faeces. The AVI and total radioactivity plasma concentrations were similar up to 8 hours after the start of the infusion (the geometric mean ratio was 1.15 at 8 hours), suggesting that

there was very limited contribution of metabolites or breakdown products *in vivo*, which is consistent with the high proportion of urine total radioactivity that was attributable to AVI.

An average of 85% (range, 67% to 101%) of administered AVI was recovered from the urine, with over 50% being recovered within 2 hours of the start of the infusion. Renal clearance was 158 mL/min (9.48 L/h) on average, which is greater than glomerular filtration rate suggesting active tubular secretion (Study D4280C00008).

In vitro, AVI underwent minimal metabolism in mouse, rabbit, dog and human liver microsomes. Unchanged parent AVI was the major drug-related component in human plasma and urine. There was no evidence of any circulating metabolites in man.

Dose proportionality and time dependencies

Study D4910C00001 (Part B) investigated single and multiple doses of ATM-AVI. Results are presented in the tables below. Mean t½ for ATM and AVI were approximately 2 to 3 hours across cohorts. ATM and AVI clearance values were relatively constant across doses and dosing regimens. Comparison of Day 1 and Day 11 C_{max} and AUC values within each cohort revealed similar values, indicating little or no accumulation following repeated q6h dosing. AUC and C_{max} of both ATM and AVI increased in a dose-proportional manner in the studied dose range (ATM 1500-2000 mg, AVI 375-600 mg) (linearity indices close to 1.00). The % unchanged drug excreted in urine was independent of administered dose and accounted for 64.2% to 75.9% of the administered ATM dose, and 83.8% to 100% of the AVI dose, respectively, at steady state (Day 11). Renal clearance accounted for most of plasma clearance.

Table 4: Summary of Aztreonam PK Parameters from Study D4910C00001 (part B)

	Treatment	N	Parameter (Geometric Mean [%CV])				
			C_{max} (µg/mL)	AUC_{0-6} (µg•h/mL)	AUC (µg•h/mL)	CL (L/h)	$t_{½}$ (h)
Part B							
Cohort 1 Day 1	2000 mg aztreonam +	8	123 (16.7)	299 (14.5)	345 (16.3)	5.79 (16.3)	2.24 (16.6)
Cohort 1 Day 11	375 mg avibactam over 1 h infusion	8	124 (9.0)	NC	275 (14.0)[a]	7.27 (14.0)	NC
Cohort 2 Day 1	2000 mg aztreonam +	4	123 (6.2)	286 (4.5)	326 (5.5)	6.15 (5.5)	1.98 (3.3)
Cohort 2 Day 11	600 mg avibactam over 1 h infusion	2	NC	NC	NC	NC	NC
Cohort 3 Day 1	1500 mg aztreonam +	8	82.4 (16.0)	245 (15.4)	283 (17.7)	5.29 (17.8)	1.90 (16.2)
Cohort 3 Day 11	600 mg avibactam over 2 h infusion	7	80.9 (12.9)	NC	231 (15.9)[a]	6.49 (15.9)	NC
Cohort 4 Day 1	1500 mg aztreonam +	10	63.2 (9.4)	222 (8.6)	270 (9.8)	5.56 (9.9)	2.14 (21.2)
Cohort 4 Day 11	450 mg avibactam over 3 h infusion	10	62.6 (9.1)	NC	223 (7.9)[a]	6.72 (7.9)	NC
Cohort 5 Day 1	1500 mg aztreonam +	10	59.2 (13.1)	205 (13.0)	250 (13.3)	5.99 (13.4)	2.28 (25.9)
Cohort 5 Day 11	410 mg avibactam over 3 h infusion	10	55.7 (9.0)	NC	203 (11.1)[a]	7.39 (11.1)	NC

Table 5: Summary of Avibactam PK Parameters from Study D4910C00001 (part B)

	Treatment	N	Parameter (Geometric Mean [%CV])				
			C_{max} (µg/mL)	AUC_{0-6} (µg•h/mL)	AUC (µg•h/mL)	CL (L/h)	$t_{½}$ (h)
Part B							
Cohort 1 Day 1	2000 mg aztreonam + 375 mg	8	16.0 (10.1)	29.4 (12.3)	31.8 (12.5)	11.8 (12.4)	2.17 (30.9)
Cohort 1 Day 11	avibactam over 1 h infusion	8	14.5 (15.9)	NC	26.1 (13.0)[a]	14.3 (13.1)	NC
Cohort 2 Day 1	2000 mg aztreonam + 600 mg	4	25.1 (5.8)	44.9 (11.5)	47.8 (12.5)	12.5 (12.7)	2.82 (41.1)
Cohort 2 Day 11	avibactam over 1 h infusion	2	NC	NC	NC	NC	NC
Cohort 3 Day 1	1500 mg aztreonam + 600 mg	8	19.3 (16.4)	49.0 (13.3)	53.1 (12.9)	11.3 (12.8)	2.61 (10.0)
Cohort 3 Day 11	avibactam over 2 h infusion	7	17.6 (12.2)	NC	43.3 (11.7)[a]	13.8 (11.7)	NC
Cohort 4 Day 1	1500 mg aztreonam + 450 mg	10	9.99 (11.2)	32.0 (11.0)	35.7 (11.8)	12.6 (11.9)	2.26 (30.1)
Cohort 4 Day 11	avibactam over 3 h infusion	10	8.69 (9.9)	NC	29.0 (10.2)[a]	15.5 (10.4)	NC
Cohort 5 Day 1	1500 mg aztreonam + 410 mg	10	8.68 (14.0)	27.9 (14.3)	31.4 (14.7)	13.1 (14.8)	1.85 (27.4)
Cohort 5 Day 11	avibactam over 3 h infusion	10	8.36 (16.5)	NC	26.7 (12.6)[a]	15.4 (12.7)	NC

Previous data regarding ATM: ATM peak serum concentrations increased in proportion to dose following single IV doses of 500 mg to 2000 mg; distribution and elimination parameters were independent of dose consistent with linear PK (Swabb & Sugerman, 1983).

Previous data regarding AVI: AVI plasma C_{max} and AUC_t increased in direct proportion to dose within the dose range of 50 to 1000 mg (Study NXL104/1001). When considering the whole dose range from 50 to 2000 mg, the relationships are also approximately dose proportional, with a doubling in dose resulting in 2.07-fold increases in C_{max} and 2.08-fold increases in AUC_t. There was little or no accumulation following repeated (q8H) doses. When AVI was given alone in the dose range 500 to 1000 mg 3 times daily q8h for 5 days, steady-state PK parameters of AVI were predictable from single-dose data, suggesting dose-linear and time-invariant kinetics.

Table 6: PK Parameters of AVI following IV Infusion in Healthy Participants

Dose (No. of Participants)	Time Point	Median (Range)	Geometric Mean (CV%)				
		t_{max} (h)	C_{max} (mg/L)	AUC_{0-t} (mg.h/L)	$t_{½}$ (h)	V_{ss} (L)	CL (L/h)
Study NXL104/1002, Part A (multiple dosing)							
500 mg AVI (n = 8)	Day 1	0.50 (0.50-0.50)	37.3 (70%)	52.2 (28%)	1.45 (9%)	15.27 (24%)	9.41 (19%)
	Day 5	0.50 (0.50-0.75)	36.3 (111%)	50.6 (32%)	1.67 (11%)	16.66 (28%)	9.87 (21%)
750 mg AVI (n = 8)	Day 1	0.50 (0.50-0.75)	40.8 (36%)	60.5 (18%)	1.38 (8%)	20.03 (23%)	12.19 (18%)
	Day 5	0.50 (0.50-4.00)	44.4 (26%)	68.1 (23%)	1.35 (22%)	19.18 (19%)	11.01 (21%)
1000 mg AVI (n = 8)	Day 1	0.50 (0.50-0.50)	57.5 (20%)	81.2 (23%)	1.37 (15%)	20.14 (38%)	12.07 (23%)
	Day 5	0.50 (0.50-0.75)	50.9 (41%)	82.1 (21%)	1.48 (6%)	20.94 (32%)	12.18 (19%)
Study NXL104/1001 (single dosing)							
2000 mg AVI (n = 8)	Day 1	0.50 (0.50-1.00)	120.3 (23%)	183.7 (15%)	2.71 (5%)	20.78 (20%)	10.88 (14%)

Study C3601006 (RI study): Steady-state PK parameters of ATM and AVI in healthy adults with normal renal function administered the intended dose for registration consisting of a loading dose (2000 mg/667 mg) and maintenance doses of 1500 mg/500 mg administered every 6 hours as 3-hour infusions are summarised in Table 4.

Table 7: Steady-State PK Parameters (Geometric Mean [%CV]) in Healthy Adults with CrCL >80 mL/min to 150 mL/min after Multiple Intravenous 3-hour Infusions of 1500 mg/500 mg ATM-AVI

	ATM (n=6)	**AVI** (n=6)
$AUC_{0\text{-}6,ss}$ (mg*h/L)	230.8 (16)	41.19 (18)
C_{max} (mg/L)	57.34 (13)	11.08 (14)
CL (L/h)	6.5 (16)	12.16 (18)
$t_{½}$ (h)[a]	2.605 (0.349)	3.188 (0.071)
[a]Arithmetic mean (SD) reported for $t_{½}$ Source: C3601006		

Variability

In the phase 2 study C3601001 between-patient variability in systemic exposure to AVI, was high, with CV% estimates of 74.0% and 79.2% in cohort 1 and cohort 2 and 3, respectively for AUC(0-6) and 164.5% and 61.2%, respectively for Cmax. For ATM the variability was also high with estimates of 60.6 % and 54.6 % in cohort 1 and cohort 2 and 3, respectively for AUC(0-6) and 146.9 % and 42.6%, respectively for Cmax.

The between-variability in systemic exposure was considerably lower in study D4910C00001 (Part B) in healthy volunteers where CV% values of AUC(0-6) and Cmax for AVI and ATM were below 20%.

Pharmacokinetics in target population

Study C3601001 (phase 2a study, REJUVENATE, in cIAI patients): This study included a PK subset with rich PK sampling. The maintenance doses of both ATM and AVI used in cohort 2 and 3 are the same as those proposed in the current SmPC for patients with CrCL >50 mL/min and 31 to 50 mL/min, respectively (while a lower AVI dose was used in cohort 1). Only one subject with CrCL 31-50 ml/min was included in the study and this subject was excluded on day 2, thus this study provided data on steady state exposure in cIAI patients with CrCl >50 mL/min with the intended maintenance dose.

Table 8: ATM-AVI Dosing Regimens in study C3601001

Cohort	**Loading dose**	**Extended loading infusion**	**Maintenance infusion**
Patients in Cohort 1 with normal renal function or mild renal impairment (CrCl >50 mL/min)	500 mg ATM plus 137 mg AVI by IV infusion over a 30 minute period	Not applicable	1500 mg ATM plus 410 mg AVI over a 3 hour period (to be administered every 6 hours)
Patients in Cohorts 2 and 3 with normal renal function or mild renal impairment (CrCl >50 mL/min)	500 mg ATM plus 167 mg AVI by IV infusion over a 30 minute period	Not applicable	1500 mg ATM plus 500 mg AVI over a 3 hour period (to be administered every 6 hours)
Patients in Cohorts 2 and 3 with moderate renal impairment (CrCl 31 – 50 mL/min)	500 mg ATM plus 167 mg AVI by IV infusion over a 30 minute period	Extended loading infusion of 1500 mg ATM plus 500 mg AVI over a 3 hour period	750 mg ATM plus 250 mg AVI over a 3 hour period (to be administered every 6 hours)

CrCl, creatinine clearance; ATM, aztreonam; AVI, avibactam; IV, intravenous
The first maintenance dose was started immediately following the loading dose.
Source: Section 16.1.1

PK data for aztreonam and avibactam (based on subject with intensive PK sampling and NCA analysis) in the cIAI participants are shown in the tables below. The PK parameters of ATM and AVI in this study were largely similar to what has been reported previously in healthy volunteers.

Table 9: Geometric Mean (CV%) Pharmacokinetic Parameters of Aztreonam Following IV Infusion of Aztreonam-Avibactam on Day 4, Intensive PK Sampling, Study C3601001

PK Parameter (Units)	Lower AVI Dose (Cohort 1) (N=13)	Higher AVI Dose (Cohort 2+3) (N=8)
AUC_{0-6} (h•µg/mL)	235.2 (60.6)	234.7 (54.6)
AUC_{last} (h•µg/mL)	235.9 (60.4)	234.3 (54.7)
C_{max} (µg/mL)	62.5 (146.9)	55.4 (42.6)
T_{max} [a] (h)	2.9 (0.5-3.5)	2.4 (2.0-3.0)
$t_{½}$ [b] (h)	2.3 (1.06)[c]	2.8 (2.05)
CL (L/h)	6.4 (35.4)	6.4 (35.5)
V_{ss} (L)	20.3 (16.9)[c]	19.6 (31.8)
Source: Module 5.3.5.1 C3601001 Table 14.4.5.1.1 a. Median (Min-Max) b. Arithmetic mean (SD) c. n=11		

Table 10: Geometric Mean (CV%) Pharmacokinetic Parameters of Avibactam Following IV Infusion of Aztreonam-Avibactam on Day 4, Intensive PK Sampling, Study C3601001

PK Parameter (Units)	Lower AVI Dose (Cohort 1) (N=13)	Higher AVI Dose (Cohort 2+3) (N=8)
AUC_{0-6} (h•µg/mL)	40.4 (74.0)	47.5 (79.2)
AUC_{last} (h•µg/mL)	40.5 (73.8)	47.4 (79.3)
C_{max} (µg/mL)	11.6 (164.5)	12.1 (61.2)
T_{max} [a] (h)	2.9 (0.5-3.8)	2.8 (2.0-3.3)
$t_{½}$ [b] (h)	1.8 (0.59)[c]	2.2 (1.85)
CL (L/h)	10.1 (42.6)	10.5 (41.4)
V_{ss} (L)	26.0 (22.0)[c]	23.7 (29.7)
Source: Module 5.3.5.1 C3601001 Table 14.4.5.1.2 a. Median (Min-Max) b. Arithmetic mean (SD) c. n=11		

PopPK: The steady-state population PK parameters of ATM and AVI in Phase 3 patients with normal renal function (defined as CrCL >80 mL/min to 150 mL/min), 97 with cIAI and 28 with NP (including HAP and VAP), after 3-hour infusions of 1500 mg/500 mg administered every 6 hours are summarised in the tables below. In general, the PK of both ATM and AVI is comparable between patients and healthy adults, however there are modest differences between infection types predicted from the population PK analysis.

Table 11: Population PK Parameters (Geometric Mean [% CV]) of ATM and AVI in Phase 3 cIAI Patients with CrCL >80 mL/min to 150 mL/min Following 1500 mg/500 mg q6h as 3-hour Infusions

	ATM (n = 97)	AVI (n = 97)
$AUC_{0-24,ss}$ (mg·h/L)	776 (47.2)	151.8 (49.6)
$C_{max,ss}$ (mg/L)	51.1 (42.0)	10.5 (46.7)
CL (L/h)	7.10 (45.0)	12.3 (47.9)
Source: Module 5.3.3.5 PMAR-EQDD-C360a-DP3-1245 Amendment, Table A10.1		

Table 12: Population PK Parameters (Geometric Mean [% CV]) of ATM and AVI in Phase 3 NP Patients with CrCL >80 mL/min to 150 mL/min Following 1500 mg/500 mg q6h as 3-hour infusions

	ATM (n = 28)	AVI (n = 28)
$AUC_{0\text{-}24,ss}$ (mg·h/L)	1022 (27.7)	194 (28.4)
$C_{max,ss}$ (mg/L)	63.7 (27.1)	12.7 (29.5)
CL (L/h)	5.56 (29.4)	9.87 (30.3)
Source: Module 5.3.3.5 PMAR-EQDD-C360a-DP3-1245 Amendment, Table A10.2		

The table below shows predicted ATM and AVI steady exposures by renal function group across infection type.

Table 13: Summary of ATM and AVI Exposures at Steady-State for Phase 3 Participant by Renal Function Groups

	Aztreonam			Avibactam		
	N	Cmax,ss (mg/L)	AUC24,ss (mg·h/L)	N	Cmax,ss (mg/L)	AUC24,ss (mg·h/L)
Augmented Renal Function						
Mean (SD)	45	51.61(27.1)	800.67(527.69)	46	11.24(6.93)	168.21(123.12)
Median (Range)	45	44.56(15.53-194.22)	659.3(70.45-3779.55)	46	9.13(3.05-44.79)	135.86(13.68-805.91)
GM (CV%)	45	47.34(41.09)	703.23(55.92)	46	9.97(49.04)	143.08(62.08)
Normal Renal Function						
Mean (SD)	127	57.64(18.7)	900.85(338.36)	127	11.83(4.16)	175.47(68.63)
Median (Range)	127	55.38(6.47-135.02)	845.81(91.38-2263.32)	127	11.43(1.04-29.94)	164.65(15.77-462.7)
GM (CV%)	127	54.16(40.83)	832.76(45.83)	127	11.01(44.86)	161.42(47.5)
Mild Renal Impairment						
Mean (SD)	62	73.04(23.19)	1203.43(423.1)	63	15.36(5.95)	243.07(105.74)
Median (Range)	62	71.78(17.3-153.66)	1139.28(267.16-2541.53)	63	14.59(3.2-39.01)	214.83(52.14-737.23)
GM (CV%)	62	69.39(34.48)	1132(37.6)	63	14.29(41.85)	224.16(42.73)
Moderate Renal Impairment						
Mean (SD)	27	78.07(44.6)	1396.22(821.31)	27	19.22(11.84)	341.8(210.89)
Median (Range)	27	63.94(30.15-231.36)	1093.57(517.23-4279.76)	27	14.21(6.04-64.15)	281.4(102.42-1131.12)
GM (CV%)	27	68.45(54.54)	1220.4(55)	27	16.82(53.55)	299.05(53.68)
Severe Renal Impairment						
Mean (SD)	8	52.26(17.96)	928.97(413.99)	8	16.38(8.01)	318.04(189.58)
Median (Range)	8	47.94(36.79-90.61)	822.26(588.53-1839.74)	8	15.77(8.34-33.88)	310.45(138.27-742.58)
GM (CV%)	8	50.01(31.37)	865.86(39.65)	8	14.98(46.12)	279.63(56.51)

Repository artifact ID FI-53597155. Lines 1–2 substituted.

ATM = aztreonam; AVI = avibactam; Cmax,ss = maximum concentration at steady-state; AUC24,ss = area under concentration-time curve over 24 hours at steady-state; SD = standard deviation; GM = geometric mean; CV = coefficient of variation

Simplified loading dose: In the adult Phase 3 studies (C3601002 and C3601009), the dose regimens consisted of a LD (infusion over 30 minutes) followed immediately by an ELD (infusion over 3 hours), and MD starting at the next dose interval. This LD/ELD was combined into one infusion bag, necessitating a change in infusion rate after the first 30 minutes to a slower infusion for 3 hours. These regimens have potential for dosing administration errors in clinical practice. Simulations were therefore performed to simplify the LD, proposed as one constant rate infusion over 3 hours (SLD) with the same total LD as the Phase 3 doses (LD+ELD). A regimen without an initial loading dose was also evaluated. Predicted joint PTA (Table 14) reached >90% for the PK/PD target in both LD scenarios. When no LD was administered, the predicted joint PTA was <90% in the first dosing interval for all renal function groups except mild renal impairment.

The predicted geometric mean (geometric coefficient of variation (CV)%) of ATM and AVI PK exposures after different LD scenarios in the first dosing interval (Cmax and AUC_T) and at steady-state (Cmax,ss and AUC24,ss) for cIAI subjects with various degrees of renal function are shown in the tables below.

Comparing exposures of ATM and AVI across various degrees of renal function, a loading dose administered as one constant rate infusion over 3 hours (SLD) gave a higher Cmax compared to Phase 3 LD/ELD (S1) and ranged from 9% to 19% higher in the first dosing interval. Given the total loading dose administered was not different, AUCτ values were the same for SLD and Phase 3 LD/ELD. Exposure parameters at steady-state were unaffected by LD scenarios.

Table 14: Summary of joint PTA (%) (ATM 60%fT>MIC of 8 mg/L and AVI 50%fT>CT of 2.5 mg/L) for Adult Patients across Renal Function Groups following LD Scenarios of ATM-AVI as IV Infusion

	First Dosing Interval	Steady-State
Augmented Renal Clearance		
S1 (LD 0.5h/ELD 3h)	94.92	89.36
SLD (LD 3h)	93.26	90.24
MD	79.24	90.24
Normal Renal Function		
S1 (LD 0.5h/ELD 3h)	97.72	96.76
SLD (LD 3h)	97.04	96.74
MD	89.12	96.74
Mild Renal Impairment		
S1 (LD 0.5h/ELD 3h)	99.36	99.36
SLD	99.28	99.32
MD	96.32	99.32
Moderate Renal Impairment		
S1 (LD 0.5h/ELD 3h)	99.8	95.24
SLD (LD 3h)	99.8	95.04
MD	73.38	95.04
Severe Renal Impairment		
S1 (LD 0.5h/ELD 3h)	98.58	90.4
SLD (LD 3h)	97.94	91.22
MD	68.34	91.22
End Stage Renal Disease		
S1 (LD 0.5h/ELD 3h)	99.6	99.16
SLD (LD 3h)	99.48	99.14
MD	86.06	99.14

Repository artifact ID FI-42579479. Line 1 substituted.

Values are percent of patients based on summary of 5000 simulated patients. LD = loading dose; ELD = extended loading dose; S1 = Phase 3 LD/ELD; SLD = simplified loading dose; MD = maintenance dose (it was the first MD); PTA = probability of target attainment.

Table 15: Summary of ATM Exposures for Adult Patients Across Renal Function Groups Following LD Scenarios of ATM-AVI as IV Infusion

	First Dosing Interval				Steady-State	
	GM_C_{max} (mg/L)	GMR_C_{max}	GM_AUC_{τ} (mg·h/L)	GMR_AUC_{τ}	GM_$C_{max,ss}$ (mg/L)	GM_$AUC_{24,ss}$ (mg·h/L)
Augmented Renal Clearance						
S1 (LD 0.5h/ELD 3h)	42.1 (42.4)		171 (42.3)		42.2 (42.3)	660 (44.2)
SLD (LD 3h)	49.2 (42.4)	1.17	174 (41.7)	1.02	42.4 (42.0)	666 (44.0)
MD	36.9 (42.4)	0.88	130 (41.7)	0.76	42.4 (42.0)	666 (44.0)
Normal Renal Function						
S1 (LD 0.5h/ELD 3h)	51.0 (42.8)		208 (42.6)		52.2 (42.7)	843 (44.7)
SLD (LD 3h)	58.2 (43.1)	1.14	209 (42.3)	1	51.9 (42.5)	838 (44.6)
MD	43.7 (43.1)	0.86	156 (42.3)	0.75	51.9 (42.5)	838 (44.6)
Mild Renal Impairment						
S1 (LD 0.5h/ELD 3h)	60.9 (43.7)		250 (43.4)		65.1 (43.0)	1095 (44.8)
SLD	68.8 (44.3)	1.13	252 (43.0)	1.01	65.0 (42.7)	1094 (44.5)
MD	51.6 (44.3)	0.85	189 (43.0)	0.76	65.0 (42.7)	1094 (44.5)
Moderate Renal Impairment						
S1 (LD 0.5h/ELD 3h)	69.5 (44.0)		287 (43.6)		39.8 (42.5)	703 (44.4)
SLD (LD 3h)	77.4 (45.1)	1.11	291 (43.4)	1.01	39.7 (42.6)	699 (44.4)
MD	29.0 (45.1)	0.42	109 (43.4)	0.38	39.7 (42.6)	699 (44.4)
Severe Renal Impairment						
S1 (LD 0.5h/ELD 3h)	50.0 (46.4)		291 (44.6)		40.2 (44.3)	647 (46.5)
SLD (LD 3h)	59.5 (47.1)	1.19	284 (44.0)	0.98	40.3 (43.0)	646 (44.9)
MD	29.8 (47.1)	0.59	142 (44.0)	0.49	40.3 (43.0)	646 (44.9)
End Stage Renal Disease						
S1 (LD 0.5h/ELD 3h)	58.4 (46.8)		356 (45.6)		55.8 (44.9)	998 (47.3)
SLD (LD 3h)	67.0 (49.6)	1.15	346 (46.3)	0.97	56.2 (44.9)	1008 (47.4)
MD	33.5 (49.6)	0.57	173 (46.3)	0.49	56.2 (44.9)	1008 (47.4)

Repository artifact ID FI-42579480. Lines 1–2 substituted.

GM = geometric mean; ATM = aztreonam; AVI = avibactam; LD = loading dose; ELD = extended loading dose; S1 = Phase 3 LD/ELD; SLD = simplified loading dose; MD = maintenance dose (for this scenario, it was the first MD); GMR = ratio of geometric mean to S1 scenario; Cmax = maximum concentration; AUCτ = area under concentration-time curve from time zero to τ; Cmax,ss = maximum concentration at steady-state; AUC24,ss = area under concentration-time curve over 24 hours at steady-state; IV = intravenous

Table 16: Summary of AVI Exposures for Adult Patients Across Renal Function Groups Following LD Scenarios of ATM-AVI as IV Infusion

	First Dosing Interval			Steady-State		
	GM_C_{max} (mg/L)	GMR_C_{max}	GM_AUC_{τ} (mg·h/L)	GMR_AUC_{τ}	GM_$C_{max,ss}$ (mg/L)	GM_$AUC_{24,ss}$ (mg·h/L)
Augmented Renal Clearance						
S1 (LD 0.5h/ELD 3h)	8.43 (49.0)		34.0 (48.8)		8.39 (48.7)	127 (48.1)
SLD (LD 3h)	10.0 (49.9)	1.19	34.6 (48.1)	1.02	8.45 (48.3)	128 (47.9)
MD	7.53 (49.9)	0.89	25.9 (48.1)	0.76	8.45 (48.3)	128 (47.9)
Normal Renal Function						
S1 (LD 0.5h/ELD 3h)	10.2 (48.9)		41.2 (48.7)		10.3 (48.4)	160 (47.9)
SLD (LD 3h)	11.8 (50.6)	1.16	41.2 (48.7)	1	10.2 (48.6)	158 (48.3)
MD	8.84 (50.6)	0.87	30.9 (48.7)	0.75	10.2 (48.6)	158 (48.3)
Mild Renal Impairment						
S1 (LD 0.5h/ELD 3h)	12.8 (50.4)		52.6 (49.9)		13.8 (48.7)	229 (48.7)
SLD	14.7 (52.2)	1.14	53.0 (49.6)	1.01	13.8 (48.7)	229 (48.8)
MD	11.0 (52.2)	0.86	39.8 (49.6)	0.76	13.8 (48.7)	229 (48.8)
Moderate Renal Impairment						
S1 (LD 0.5h/ELD 3h)	16.2 (52.6)		67.6 (51.8)		10.3 (48.6)	190 (49.2)
SLD (LD 3h)	17.9 (54.7)	1.1	68.3 (51.5)	1.01	10.3 (48.2)	188 (48.6)
MD	6.71 (54.7)	0.41	25.6 (51.5)	0.38	10.3 (48.2)	188 (48.6)
Severe Renal Impairment						
S1 (LD 0.5h/ELD 3h)	12.6 (56.0)		77.0 (54.2)		13.0 (51.9)	237 (52.8)
SLD (LD 3h)	14.5 (59.3)	1.15	74.8 (53.7)	0.97	13.0 (50.0)	237 (50.6)
MD	7.25 (59.3)	0.58	37.4 (53.7)	0.49	13.0 (50.0)	237 (50.6)
End Stage Renal Disease						
S1 (LD 0.5h/ELD 3h)	15.1 (59.3)		97.5 (57.9)		27.2 (56.0)	571 (57.8)
SLD (LD 3h)	16.5 (63.7)	1.09	93.9 (59.1)	0.96	27.4 (56.4)	576 (58.2)
MD	8.25 (63.7)	0.55	46.9 (59.1)	0.48	27.3 (56.2)	574 (57.9)

Repository artifact ID FI-42579481. Lines 1–2 substituted.

ATM = aztreonam; AVI = avibactam; GM = geometric mean; LD = loading dose; ELD = extended loading dose; S1 = Phase 3 LD/ELD; SLD = simplified loading dose; MD = maintenance dose (for this scenario, it was the first MD); GMR = ratio of geometric mean to S1 scenario; Cmax = maximum concentration; AUCτ = area under concentration-time curve from time zero to τ; Cmax,ss = maximum concentration at steady-state; AUC24,ss = area under concentration-time curve over 24 hours at steady-state; IV = intravenous

Special populations

Impaired renal function

Study C3601006 (Effect of Severe Renal Impairment on ATM-AVI): This was an open-label, parallel-group pharmacokinetic study of multiple intravenous doses of ATM and AVI in male subjects with severe renal impairment (n=5) and demographically matched subjects with normal renal function (n=6). An IV loading dose (30 minutes infusion) followed by multiple IV doses (3 hours infusion) of ATM-AVI were administered. For participants with normal renal function (eGFR ≥80 ml/min), the loading dose was 500 mg ATM plus 167 mg AVI infused over a 30-minute period, immediately followed by an extended loading dose of 1500 mg ATM plus 500 mg AVI over a 3-hour period. Three hours after the extended loading dose was completed, a maintenance dose of 1500 mg ATM and 500 mg AVI was infused over 3 hours and administered q6h. For participants with severe renal impairment (eGFR >15 - ≤30 mL/min), the loading dose was 675 mg ATM plus 225 mg AVI infused over 30 minutes, immediately followed by an extended loading dose of 675 mg ATM plus 225 mg AVI infused over 3 hours. Five hours after the extended loading dose was completed, a maintenance dose of 675 mg ATM plus 225 mg AVI was infused over 3 hours and administered q8h. Results are presented in the tables below.

Table 17: Descriptive Summary of Plasma and Urine Aztreonam PK Parameters by Renal Function Group - Parameter Analysis Set, Study C3601006

Parameter (Unit)[a]	Normal Renal Function Group (N=6)	Severe Renal Impairment Group (N=5)
Plasma		
N2, N3	6, 6	5, 5
$AUC_{24,ss}$ (ug.hr/mL)	922.9 (16)	733.5 (16)
AUC_{tau} (ug.hr/mL)	230.8 (16)	244.3 (16)
CL (L/hr)	6.499 (16)	2.761 (16)
C_{max} (ug/mL)	57.34 (13)	43.34 (11)
C_{tau} (ug/mL)	21.43 (19)	18.55 (24)
$t_{½}$ (hr)	2.605 ± 0.34944	4.902 ± 1.4286
T_{max} (hr)	2.92 (2.00-2.92)	2.92 (2.92-3.75)
V_{ss} (L)	23.70 (29)	18.46 (19)
V_z (L)	24.25 (23)	18.79 (21)
Urine		
N2	6	5
Ae_{tau} (mg)	1047 (11)	361.2 (19)
Ae_{tau} (%)	69.68 (11)	53.51 (19)
CL_r (L/hr)	4.527 (18)	1.477 (23)

a. Geometric mean (geometric %CV) for all except median (range) for T_{max} and arithmetic mean± SD for $t_{½}$.

Source: Table 9, C3601006 CSR

N = Total number of participants in the treatment group in the indicated population.

N2 = Number of participants contributing to the summary statistics.

N3 = Number of participants contributing to the summary statistics for $t_{½}$, CL, V_{ss} and V_z.

Table 18: Descriptive Summary of Plasma and Urine Avibactam PK Parameters by Renal Function Group - Parameter Analysis Set, Study C3601006

Parameter (Unit)[a]	Normal Renal Function Group (N=6)	Severe Renal Impairment Group (N=5)
Plasma		
N2, N3	6, 6	5, 5
$AUC_{24,ss}$ (ug.hr/mL)	164.8 (18)	204.6 (20)
AUC_{tau} (ug.hr/mL)	41.19 (18)	68.31 (20)
CL (L/hr)	12.16 (18)	3.295 (20)
C_{max} (ug/mL)	11.08 (14)	11.35 (14)
C_{tau} (ug/mL)	3.100 (24)	5.597 (39)
$t_{½}$ (hr)	3.188 ± 0.071391	6.524 ± 1.6469
T_{max} (hr)	2.46 (2.00-2.92)	2.92 (2.00-3.25)
V_{ss} (L)	37.37 (30)	27.78 (16)
V_z (L)	55.83 (19)	30.14 (16)
Urine		
N2	6	5
Ae_{tau} (mg)	465.6 (11)	270.0 (17)
Ae_{tau} (%)	93.19 (11)	119.9 (17)
CL_r (L/hr)	11.30 (20)	3.948 (36)

Source: Table 11, C3601006 CSR

a. Geometric mean (geometric %CV) for all except median (range) for T_{max} and arithmetic mean± SD for $t_{½}$.

N = Total number of participants in the treatment group in the indicated population.

N2 = Number of participants contributing to the summary statistics.

N3 = Number of participants contributing to the summary statistics for $t_{½}$, CL, V_{ss} and V_z.

ATM total daily exposure ($AUC_{24,ss}$) and peak exposure (C_{max}) were ~21% and ~24% lower in participants with severe renal impairment, compared to the normal renal function group. AVI total daily exposure ($AUC_{24,ss}$) was ~24% higher in participants with severe renal impairment, compared to the normal renal function group. Peak exposures (C_{max}) were comparable between the two groups.

Pop-PK: No dose adjustment is proposed in patients with CrCL 50-80 ml/min. The predicted $AUC_{24,ss}$ was approximately 30% higher for ATM and 40% higher for AVI in patients with CrCL 50-80 ml/min compared to patients with normal renal function (CrCL 80-150 ml/min). Dose adjustments are proposed in patients with CrCL <50 ml/min. On average, AVI $AUC_{24,ss}$ was predicted to be 14% greater in patients with moderate renal impairment (defined by the applicant as CrCL >30 to 50 mL/min; given maintenance dose of ATM 750 mg/AVI 250 mg), and 47% greater in patients with severe renal impairment (CrCL >15 to ≤30 mL/min; given maintenance dose of ATM 675/AVI 225 mg) compared to patients with normal renal function. This increase in AVI exposure in patients with moderate and severe renal impairment was not considered to be of clinical consequence according to the applicant. Patients with ESRD (CrCL≤15 mL/min) were not included in the ATM-AVI clinical trials but dose adjustments for this group is proposed. AVI exposures at steady-state are the highest of the renal function groups. Only 2 patients with ESRD with AVI PK were included in the popPK dataset however.

Previous data with ATM: The PK of ATM alone has been studied in patients with renal impairment where all participants received a single 1 g IV dose with frequent blood sampling for at least 24 hours post-dose for drug concentration and PK analysis. One study included patients with various degrees of chronic renal failure (n = 12; mean ± SD CrCL 17.8 ±13.5 mL/min; range 4.8-49.9 mL/min) (el Guinaidy et al, 1989). In this study the $t_{½}$ (mean ±SD) was significantly increased (p <0.001) from 1.8 ±0.14 hours in participants with normal renal function to 4.9±1.06 hours in patients with chronic renal

failure. The corresponding statistically significant decreases (p <0.001) in ATM CL were 84.2 ±7.8 mL/h/kg in participants with normal renal function to 30.2 ±9.2 mL/h/kg in patients with chronic renal failure.

Another study of ATM included 4 groups (n = 6/group) with CrCL of >80 mL/min, 30-80 mL/min, 10-29 mL/min, and <10 mL/min, respectively (Mihindu et al, 1983). The terminal $t_{½}$ (mean ±SD) increased (p <0.001) with decreasing renal function, from 1.98 ±0.12 h (normal renal function), to 3.42 ±0.80 h, 4.76 ±0.85 h, and 6.02 ±1.53 h, respectively. ATM CL decreased from 107 mL/min (6.42 L/h) in participants with normal renal function to 29 mL/min (1.74 L/h) for functionally anephric patients. Urinary excretion (urine collected in intervals up to 48 hours post-dose) of ATM was also determined in this study. Urinary recovery of ATM ranged from 58% of the administered dose in normal participants to 1.4% in uremic patients.

Previous data with AVI: The PK of AVI (100 mg, single 50 mL IV infusion over 30 minutes) in renally impaired participants compared to subjects with normal renal function was assessed in the CAZ-AVI programme (Study NXL104/1003).

Group 1: normal renal function (creatinine clearance >80 mL/min)
Group 2: mild to moderate renal impairment (creatinine clearance 50 to 79 mL/min)
Group 3: moderate renal impairment (creatinine clearance 30 to 49 mL/min)
Group 4: severe renal impairment (creatinine clearance <30 mL/min) but not requiring any type of dialysis
Group 5: end-stage renal failure requiring haemodialysis

AVI exposure (expressed by AUC_{inf}) increased with increasing level of renal impairment by approximately 2.6-, 3.8-, 7.0-, and 19.5-fold for Groups 2 to 5, respectively, compared to group 1. This was associated with a decrease in AVI clearance with increasing severity of renal impairment, consistent with renal CL being the dominant elimination route. The half-life increased from less than 2 hours in participants with normal renal function (Group 1) up to about 8 hours for participants with severe renal disease (Group 4) and 23 hours in participants with end-stage renal failure (Group 5).

Augmented renal clearance (ARC): The PK of AVI was studied in a Phase 1 study of patients with ARC and sepsis (Study CXL PK-04). AVI was administered as a single dose in combination with ceftaroline fosamil (ceftaroline fosamil 600 mg + AVI 600 mg; 60-minute IV infusion) to hospitalised patients (3 females and 9 males; mean age of 34 years) with ARC and sepsis. Patients with an estimated CrCL ≥ 115 mL/min (by Cockcroft-Gault) were eligible to be enrolled in the study, and ARC was confirmed by a measured urinary CrCL ≥140 mL/min (from an 8-hour, or longer, urine collection). The measured urinary mean ±SD CrCL was 194.85 ±76.09 mL/min. The mean AVI CL was 16.6 L/h, Vss 26.9 L, and $t_{½}$ of 1.67 hours. The gmean clearance of AVI increased by 39.5% in ARC compared with healthy subjects in a previous study, CXL-PK-01. ARC was associated with a 37.8% lower Cmax and 28.4% lower AUC0-t for AVI.

The impact of ARC (CrCL >150 mL/min) on the PK of ATM and AVI was assessed by population PK analysis. In the updated population PK models with inclusion of Phase 3 data (approximately 46 patients with ARC), the relationships between time-varying nCRCL and CL were described by power and linear functions for both drugs. For nCRCL ≥80 mL/min/1.73 m^2, ATM and AVI CL were found to increase slowly with increasing nCRCL, such that an increase of 100 mL/min/1.73 m^2 in nCRCL led to a 38.3% and 31.3% increase in ATM and AVI CL, respectively, suggesting that the exposures only decrease modestly at high CRCL values.

Dose adjustments are not proposed for ATM-AVI in patients with ARC based on population PK analysis and Phase 3 patient data.

Proposed dosage adjustment in RI

Dose adjustments for ATM-AVI are recommended in patients with CrCL≤50 mL/min based on totality of data for ATM and AVI in renal impairment. Population PK simulations have been conducted to assess the probability of PK/PD target attainment for different dosing regimens of ATM-AVI in patients with mild, moderate, and severe renal impairment as well as ESRD to support proposed dosing recommendations. It was accepted that daily exposures to AVI in patients with moderate or severe renal impairment would be modestly higher than AVI exposure in patients with normal renal function in order to maintain target ATM exposure.

The proposed dosage in patients with renal impairment is as follows:

No dosage adjustment is required in patients with mild renal impairment (estimated CrCL > 50 to ≤ 80 mL/min).
(Normal dose in patients with CrCL > 50 mL/min: Loading dose 2.0 g/0.67 g, maintenance dose 1.5 g/0.5 g every 6 hours.)

Table 19: Recommended dose adjustments for patients with estimated creatinine clearance ≤ 50 mL/min:

Estimated CrCL (mL/min)[a]	Dose of Aztreonam-Avibactam[b,c]		Infusion Time	Dosing Interval
	Loading	Maintenance		
> 30 to ≤ 50	2.0 g/0.67 g	0.75 g/0.25 g	3 hours	Every 6 hours
> 15 to ≤ 30	1.35 g/0.45 g	0.675 g/0.225 g	3 hours	Every 8 hours
≤ 15 mL/min, including on haemodialysis[d]	1.0 g/0.33 g	0.675 g/0.225 g	3 hours	Every 12 hours

a Calculated using the Cockcroft-Gault formula.
b Aztreonam-avibactam is a combination product in a fixed 3:1 ratio (see section 6.6). A single loading dose is followed by maintenance doses beginning at the next dosing interval.
c Dose recommendations are based on PK modelling and simulation.
d Both aztreonam and avibactam are removed by haemodialysis; Emblaveo should be administered after the haemodialysis session on haemodialysis days.

There are insufficient data to make dosing adjustment recommendations for patients undergoing renal replacement therapy other than haemodialysis (e.g. continuous veno-venous haemofiltration or peritoneal dialysis). No dose adjustment is proposed in patients with ARC.

Impaired hepatic function

PK of AVI or ATM-AVI has not been studied in patients with hepatic impairment. The $t_{½}$ of ATM was only slightly prolonged in patients with biliary or alcoholic cirrhosis, 2.2 and 3.2 hours, respectively (compared to 1.9 h in the normal group) since the liver is a minor pathway of excretion (MacLeod et al, 1984).

Gender and race

In Study NXL104/1004 male participants had 18% lower AVI C_{max} values (no gender effect for AUC), which was not considered to be clinically meaningful.

The plasma concentration-time course of AVI in Japanese participants was comparable to Western healthy participants.

In study C3601007, the PK, safety and tolerability of ATM-AVI administrated as single and repeated IV doses was evaluated in healthy Chinese participants. Day 4 ATM and AVI geometric mean plasma CL was 5.3 L/h and 11.3 L/h, respectively, comparable to CL values reported from other ATM-AVI PK

studies in healthy participants. The geometric means of C_{max} in Chinese population were 28.0% (ATM) and 21.0% (AVI) higher than Western population (Study C3601006, normal renal function group), respectively; the geometric means of AUC_{tau} were 19.1% (ATM) and 7.3% (AVI) higher than Western population (Study C3601006, normal renal function group), respectively. This difference between ethnic groups is considered not clinically significant and may be attributed to differences in body weight between the populations.

The pharmacokinetics of aztreonam-avibactam is not significantly affected by gender or race and no dose adjustment is proposed based on these aspects.

Weight

The impact of obesity on the PK of AVI was explored in healthy participants (Study CXL-PK-06). In participants under obese classes I, II, and III, the geometric mean C_{max} of AVI was 13.5%, 19.7%, and 38.4% lower, respectively, than C_{max} value in participants who were normal to overweight. The geometric mean AUC of AVI was lower by 10.5%, 18.4%, and 20.0%, and apparent volume of distribution was higher in participants who were obese than in participants who were normal to overweight.

In the population PK analysis, there were no obvious differences for the ATM and AVI exposures between obese (defined as BMI≥30 kg/m^2) and non-obese Phase 3 patients. Based on the results from Study CXL-PK0-06 and the ATM-AVI population PK analysis, dosing adjustments for ATM-AVI due to obesity are not warranted in obese Class I, II, and III patients.

Age

Table 20: Summary of Participants treated with ATM-AVI in Older Age Categories in Phase 1 ATM-AVI PK Trials

PK Trial	Age 65-74 n/N (%)	Age 75-84 n/N (%)	Age ≥85 n/N (%)
C3601006	3/11 (27.3)	1/11 (9.1)	0/11 (0)
C3601007	0/12 (0)	0/12 (0)	0/12 (0)
D4910C00001	8/65 (12.3)	0/65 (0)	0/65 (0)

In study D4910C00001 (part C), ATM-AVI PK was evaluated in healthy young (18 to 45 years) male and in elderly (>65 years old) male and female participants following multiple infusions. Steady-state exposure parameters of both ATM and AVI when co-administered suggested an increase in healthy elderly versus healthy young participants. For ATM, AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$ increased by approximately 23%, 16% and 54%, respectively. Corresponding increases were observed for AVI, where AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$ were increased by approximately 33%, 31% and 74%, respectively. An ad-hoc analysis was carried out for both ATM and AVI, including CrCL as a continuous variable, since lower systemic and renal CL were observed in the healthy elderly participants. After adjusting for CrCL, exposure (AUC_{ss} and $C_{max,}$ss) of ATM and AVI when administered in combination appeared to be similar in healthy elderly versus healthy young participants.

In study NXL104/1004, AVI PK profiles showed that elderly participants have a somewhat longer terminal $t_{½}$ and 17% higher AUC.

No dosage adjustment of ATM-AVI is required in elderly patients based on age; the dose should be selected based on renal function.

Children

No data in children was included in this submission and no paediatric indication is proposed.

Pharmacokinetic interaction studies

Based on study D4910C00001 there is no indication of an interaction between the two active substances in the combination product, avibactam and aztreonam. When comparing AUC_{inf} and Cmax for each active substance given in combination with the other active substance versus given alone, the results were within standard BE criteria.

Previous data with AVI demonstrated absence of interaction between ceftazidime and avibactam, between metronidazole and avibactam and between ceftaroline fosamil and avibactam.

Pharmacokinetics using human biomaterials

As the product is for IV administration, the relevant cut-off for assessment of DDI potential *in vivo* is 50*Cmax, u. Regarding ATM, using a Cmax value of 73.4 µg/mL or 65.1 µg/mL, an fu value of 0.62 and the Mw of 435.43 g/mol, the relevant cut-off would be approximately 5 mM. Regarding AVI, using a Cmax value of 12.4 µg/mL or 13.8 µg/ml, an fu value of 0.92 and the Mw of 287.23 g/mol, the relevant cut-off would be approximately 2 mM. For the fixed dose combination CAZ/AVI, the Cmax value stated was 14 µg/mL, i.e. similar to the value used for Emblaveo.

ATM is not metabolised by CYPs, thus interactions with CYP inhibitors or inducers are not expected. Regarding ATM as perpetrator of drug-drug interactions, the SmPC of IV aztreonam includes no information on interactions due to CYP inhibition or induction.

ATM was demonstrated to be a substrate of OAT1 and OAT3 *in vitro*. Concomitant administration of probenecid or furosemide with ATM has been reported to result in clinically insignificant increases in ATM exposure, but co-administration with probenecid is not recommended due to avibactam. There is an *in vitro* signal for OAT1 inhibition and potentially also for OAT3 inhibition by ATM. No interaction was observed between ATM and AVI in the clinical study.

Based on *in vitro*-data, AVI was not a reversible or time-dependent inhibitor of human CYP enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5) and also not an inducer of CYP enzymes.

AVI was not an inhibitor of the following hepatic and renal transporters evaluated *in vitro*: Pgp, BCRP, OATP1B1, OATP1B3, BSEP, MRP4, OCT1 and OCT2. AVI was an inhibitor of OAT1 and OAT3 but would not be expected to inhibit OAT1/3 in the clinically relevant exposure range.

No metabolism of AVI was observed, thus interactions with inhibitors/inducers of CYPs or other enzymes are not expected. AVI was not a substrate of Pgp, BCRP, MRP4 or OCT2, but was a substrate of human OAT1 and OAT3 kidney transporters. Use with probenecid is not recommended.

Exposure relevant for safety evaluation

In subjects with normal renal function, the following steady state exposure is predicted (geometric mean (CV%)):

For ATM Cmax of 54.2 mg/L (40.8) and AUC24 of 833 mg*h/L (45.8) and for AVI Cmax of 11.0 mg/L (44.9) and AUC24 of 161 mg*h/L (47.5).

In mild RI (for which no dosage adjustment is proposed), the following steady state exposure is predicted (geometric mean (CV%)):

For ATM Cmax of 69.39 mg/L (34.48) and AUC24 of 1132 mg*h/L (37.6) and for AVI Cmax of 14.29 mg/L (41.85) and AUC24 of 224.16 mg*h/L (42.73). (See Table 13)

2.6.2.2. Pharmacodynamics

This section highlights the studies that describe the *in vitro* activity of aztreonam (ATM) and avibactam (AVI), the potentiation of ATM activity by the addition of AVI *in vitro* and *in vivo* and the most important studies and analyses for dose selection of the single components of the fixed-dose-combination (FDC).

As laid out in the *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 3)* for a clinical development programme evaluating a licensed beta-lactam (BL) at the approved dose in combination with a beta-lactamase inhibitor (BLI) it should be noted that the PK/PD analyses incorporating non-clinical PK/PD data and patient PK data are generally considered pivotal to support the dose regimen of the BLI for the proposed indications.

Mechanism of action

ATM is a monocyclic beta-lactam antibacterial agent (monobactam) that inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins (PBPs).

AVI is a non-β-lactam BLI with inhibitory activity against certain beta-lactamases which prevents the hydrolysis of ATM.

Primary pharmacology

In vitro activity studies

Antimicrobial susceptibility testing

In vitro susceptibility testing was conducted using CLSI methodology with ATM-AVI by testing varying concentrations of ATM in the presence of 4 mg/L of AVI.

Antibacterial spectrum

ATM exerts antibacterial activity against aerobic gram-negative pathogens that mainly include Enterobacterales and to a lesser extent also *P. aeruginosa*. Although ATM is subject to hydrolysis by class A extended spectrum beta-lactamases (ESBLs) and carbapenemases, class C (AmpC) beta-lactamases and class D oxacillinases and carbapenemases, it is generally stable to hydrolysis by class B carbapenemases (metallo-beta-lactamases; MBLs).

AVI inhibits class A ESBLs and carbapenemases, class C β-lactamases and some class D oxacillinases and carbapenemases. It has no inhibitory activity against the class B metallo-enzymes. In-vitro studies evaluating AVI activity gave IC_{50} values <200 nM except for some class D and all class B enzymes tested (ceftazidime-avibactam EPAR). AVI alone has weak antibacterial activity with MIC values of ≥16 mg/L against most isolates.

The *in vitro* spectrum of activity of ATM-AVI have been determined against clinical isolates from surveillance programmes, isolates from clinical trials and challenge sets of isolates enriched in specific resistance mechanisms.

Table 21 shows the MIC summary statistics of ATM-AVI and comparators for Enterobacterales isolates in ATLAS surveillance years 2017-2021. The addition of AVI to ATM potentiated the activity of ATM with a reduction of MIC_{90} from >64 mg/L to 0.25 mg/L.

Table 21: Activities of ATM-AVI and Comparator Antimicrobial Agents when Tested against 102,837 Isolates and Enterobacterales in ATLAS Surveillance Studies – 2017-2021

Antimicrobial Agent	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
Aztreonam-Avibactam[b,c]	≤0.015 – >64	0.06	0.25	Na	na	na	na	na	na
Meropenem	≤0.004 – >16	≤0.06	0.12	93.3	0.6	6.1	93.9	1.2	4.9
Imipenem	≤0.03 – >8	0.25	2	82.9	7.1	10.0	90.0	3.9	6.0
Tigecycline[d]	≤0.015 – >8	0.5	2	96.4	3.1	0.6	75.2	0.0	24.8
Amikacin	≤0.25 – >64	2	8	95.8	0.9	3.3	93.8	0.0	6.2
Aztreonam	≤0.015 – >128	0.12	>64	72.3	2.4	25.3	69.3	3.0	27.7
Cefepime	≤0.12 – >32	≤0.12	>32	74.6	5.7	19.7	72.8	4.3	22.9
Ceftazidime	≤0.015 – >128	0.25	>64	72.5	2.8	24.7	68.5	4.0	27.5
Ceftriaxone	≤0.06 – >16	≤0.06	>16	70.0	0.7	29.2	70.0	0.7	29.2
Colistin	≤0.06 – >8	0.25	>8	0.0	81.5	18.5	81.5	0.0	18.5
Levofloxacin	≤0.03 – >8	≤0.25	>8	67.9	5.3	26.8	67.9	5.3	26.8
Piperacillin-Tazobactam	≤0.12 – >128	2	>64	78.5	4.4	17.1	78.5	0.0	21.5

Source: Module 5.3.5.4 Study report ATM-AVI-M2-060

[a] Criteria as published by CLSI [2022] and EUCAST [2022]

[b] In the ATM-AVI combination, AVI was at a fixed concentration of 4 mg/L.

[c] ATM-AVI n=100,228 as ATM-AVI was not on Trek panels for India and China in 2017 and 2018 giving a difference in n's for ATM and ATM-AVI.

[d] Tigecycline - Breakpoints from FDA Package Insert.

Enterobacterales Organisms (n=102,837) include: *Citrobacter amalonaticus* (89), *Citrobacter braakii* (306), *Citrobacter diversus* (3), *Citrobacter farmeri* (55), *Citrobacter freundii* (2729), *Citrobacter freundii* complex (19), *Citrobacter gillenii* (8), *Citrobacter koseri* (2195), *Citrobacter murliniae* (7), *Citrobacter sedlakii* (47), *Citrobacter* sp. (159), *Citrobacter youngae* (8), *Cronobacter sakazakii* (1), *Cronobacter* sp. (1), *Enterobacter asburiae* (539), *Enterobacter bugandensis* (590), *Enterobacter cancerogenus* (3), *Enterobacter cloacae* (6707), *Enterobacter cloacae* complex (562), *Enterobacter gergoviae* (1), *Enterobacter hormaechi* (45), *Enterobacter kobei* (192), *Enterobacter ludwigii* (82), *Enterobacter* sp. (2294), *Enterobacter xiangfangensis* (197), *Escherichia coli* (31042), *Escherichia* sp. (1), *Escherichia vulneris* (1), *Hafnia alvei* (1), *Klebsiella aerogenes* (3189), *Klebsiella oxytoca* (4385), *Klebsiella pneumoniae* (28615), *Klebsiella* sp. (268), *Klebsiella variicola* (1677), *Kosakonia* (Enterobacter) *cowanii* (1), *Lelliottia amnigena* (2), *Morganella morganii* (3127), *Pantoea agglomerans* (4), *Pantoea dispersa* (2), *Pantoea septica* (1), *Pantoea* sp. (1), *Pluralibacter gergoviae* (11), *Proteus hauseri* (322), *Proteus mirabilis* (4282), *Proteus penneri* (34), *Proteus rettgeri* (2), *Proteus* sp. (171), *Proteus vulgaris* (1401), *Providencia alcalifaciens* (25), *Providencia rettgeri* (1070), *Providencia rustigianii* (2), *Providencia* sp. (90), *Providencia stuartii* (1221), *Raoultella ornithinolytica* (76), *Raoultella planticola* (12), *Raoultella terrigena* (1), *Salmonella* sp. (7), *Serratia ficaria* (1), *Serratia fonticola* (1), *Serratia liquefaciens* (18), *Serratia marcescens* (4650), *Serratia rubidaea* (1), *Serratia* sp. (268), *Serratia ureilytica* (16).

MBLs were found in 28 species of Enterobacterales in the surveillance years between 2017 and 2021. MIC_{90} values for ATM-AVI ranged from ≤0.015 to 8 mg/L, with the highest values observed for MBL-positive *E-coli*. MIC_{90}s were at least 8-fold lower for ATM-AVI relative to ATM.

The vast majority of the MBL-producing isolates of Enterobacterales were found to co-carry beta-lactamases of different classes. Only 8.0% of all MBL-positive Enterobacterales carried an MBL gene alone and in the other isolates all combinations of enzymes from classes A, B, C; and D were observed (Table 22). The ATM-AVI MIC_{90} values were all ≤8 mg/L.

Table 22: Comparative Activity of ATM and ATM AVI for 2,530 MBL-Producing Enterobacterales with or without Additional β-Lactamase Enzymes

	ATM		ATM-AVI	
	MIC (mg/L)			
MBL Group (ATM n/ ATM-AVI n)[a,b]	MIC_{90}[c]	Range	MIC_{90}	Range
All MBL (2,530/2,449)	128	≤0.015 - >128	1	≤0.015 - >64
MBL (188/185)	32	≤0.015 – >128	0.5	≤0.015 – >64
MBL + AmpC (98/97)	>64	≤0.015 – >64	8	≤0.015 – >64
MBL + AmpC + ESBL (25/23)	128	2 – 128	4	≤0.015 – 16
MBL + AmpC + ESBL + OSBL (150/142)	>128	0.5 – >128	2	≤0.015 – 16
MBL + AmpC + OSBL (115/112)	>64	≤0.015 – >128	8	≤0.015 – 32
MBL + ESBL (174/168)	>128	≤0.015 – >128	2	≤0.015 – >64
MBL + ESBL + OSBL (938/915)	>128	0.06 – >128	0.5	≤0.015 – 16
MBL + GES Carbapenemase + ESBL + OSBL (21/21)	>128	2 – >128	0.25	≤0.015 – 0.5
MBL + GES Carbapenemase + OSBL (1/1)	-	0.5 – 0.5	-	0.03 – 0.03
MBL + KPC (12/12)	>64	0.12 – >128	0.12	0.06 – 0.12
MBL + KPC + AmpC + ESBL (2/2)	-	>64 – >64	-	0.25 – 0.25
MBL + KPC + AmpC + ESBL + OSBL (9/9)	-	64 – >128	-	0.06 – 1
MBL + KPC + AmpC + OSBL (9/9)	-	>64 – >128	-	0.25 – 2
MBL + KPC + ESBL (6/6)	-	>64 – >64	-	0.06 – 0.5
MBL + KPC + ESBL + OSBL (24/24)	128	32 – >128	0.5	0.03 – 0.5
MBL + KPC + OSBL (30/30)	>64	4 – >64	0.5	0.03 – 0.5
MBL + OSBL (169/167)	64	≤0.015 – >128	0.5	≤0.015 – 4
MBL + OXA Carbapenemase (7/7)	-	≤0.03 – 8	-	≤0.015 – 0.25
MBL + OXA Carbapenemase + AmpC + ESBL (3/3)	-	>64 – >128	-	0.5 – 2
MBL + OXA Carbapenemase + AmpC + ESBL + OSBL (47/46)	>128	16 – >128	4	0.06 – 16
MBL + OXA Carbapenemase + AmpC + OSBL (15/15)	>64	0.5 – >64	4	0.25 – 4
MBL + OXA Carbapenemase + ESBL (9/9)	-	64 – >64	-	0.06 – 8
MBL + OXA Carbapenemase + ESBL + OSBL (439/410)	>128	4 – >128	0.5	≤0.015 – >64
MBL + OXA Carbapenemase + OSBL (39/36)	32	0.06 – >64	1	0.06 – 1

Source: Module 5.3.5.4 Study report ATM-AVI-M2-060

[a] In the ATM-AVI combination, AVI was at a fixed concentration of 4 mg/L.

[b] ATM-AVI was not on Trek panels for India and China in 2017 and 2018 giving a difference in n's for ATM and ATM-AVI in some MBL enzyme groups.

[c] MIC_{90} values are not calculated for n's <10.

Table 23 shows the MIC summary statistics of ATM-AVI and comparators for MBL-containing Enterobacterales isolates.

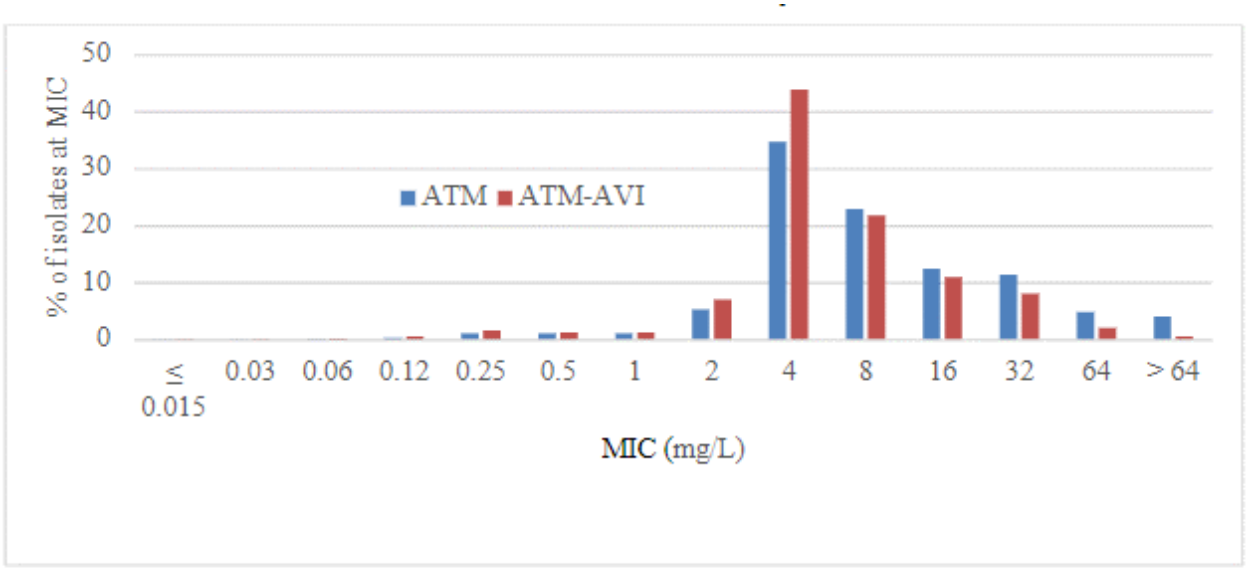
Table 23: Activities of ATM-AVI and Comparator Antimicrobial Agents when Tested Against 2,530 Isolates of MHL-Containing Enterobacterales in ATLAS Surveillance Studies – 2017-2021

Antimicrobial Agent	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
Aztreonam-Avibactam[b,c]	≤0.015 – >64	0.25	1	na	na	na	Na	na	na
Meropenem	≤0.06 – >16	>16	>16	3.6	2.8	93.6	6.4	14.1	79.5
Imipenem	≤0.06 – >8	>8	>8	1.1	1.8	97.0	3.0	5.2	91.9
Tigecycline[d]	0.06 – >8	1	2	91.8	6.8	1.3	46.7	0.0	53.3
Amikacin	≤0.25 – >64	32	>64	46.7	4.6	48.7	36.8	0.0	63.2
Aztreonam	≤0.015 – >128	>64	128	17.6	2.2	80.2	13.8	3.8	82.4
Cefepime	≤0.12 – >32	>32	>32	0.8	2.8	96.4	0.5	1.4	98.1
Ceftazidime	2 – >128	>64	>128	0.1	0.1	99.8	0.0	0.1	99.9
Ceftriaxone	16 – >16	>16	>16	0.0	0.0	100.0	0.0	0.0	100.0
Colistin	≤0.06 – >8	0.5	>8	0.0	80.6	19.4	80.6	0.0	19.4
Levofloxacin	≤0.03 – >8	>8	>8	11.0	6.8	82.2	11.0	6.8	82.2
Piperacillin-Tazobactam	1 – >128	>64	>64	1.1	0.7	98.3	1.1	0.0	98.9

Source: Module 5.3.5.4 Study report ATM-AVI-M2-060.
[a] Criteria as published by CLSI [2022] and EUCAST [2022]
[b] In the Aztreonam-Avibactam combination, Aztreonam was at a fixed concentration of 4 m/L.
[c] ATM-AVI, n=2,449 as ATM-AVI was not on Trek panels for India and China in 2017 and 2018 giving a difference in n's for ATM and ATM-AVI.
[d] Tigecycline - Breakpoints from FDA Package Insert
MBL-containing Organisms (n=2,536) include: *Citrobacter amalonaticus* (1), *Citrobacter farmeri* (2), *Citrobacter freundii* (70), *Citrobacter koseri* (2), *Citrobacter sedlakii* (2), *Citrobacter* sp. (1), *Enterobacter asburiae* (6), *Enterobacter bugandensis* (7), *Enterobacter cloacae* (213), *Enterobacter cloacae* complex (11), *Enterobacter kobei* (1), *Enterobacter* sp. (67), *Enterobacter xiangfangensis* (3), *Escherichia coli* (333), *Klebsiella aerogenes* (7), *Klebsiella oxytoca* (33), *Klebsiella pneumoniae* (1488), *Klebsiella* sp. (6), *Klebsiella variicola* (7), *Morganella morganii* (9), *Proteus mirabilis* (36), *Proteus vulgaris* (1), *Providencia rettgeri* (80), *Providencia* sp. (11), *Providencia stuartii* (82), *Raoultella ornithinolytica* (2), *Serratia marcescens* (47), *Serratia* sp. (2).

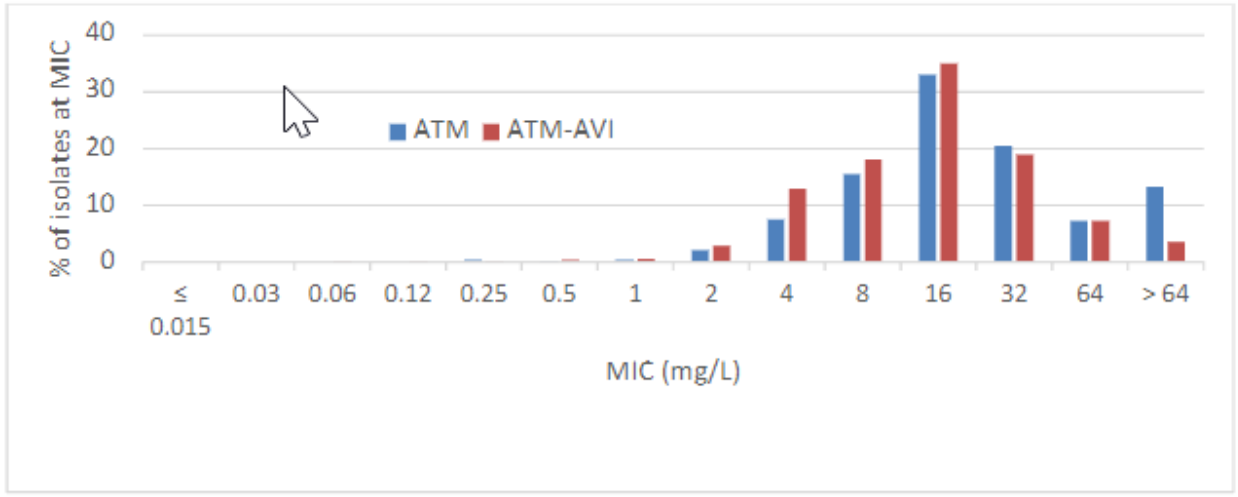
ATM-AVI showed moderate activity against *P. aeruginosa* in world-wide surveillance studies, with MIC_{90}s of 16 –32 mg/L which was near identical to that of ATM alone (32 mg/L) (Figure 3 and Figure 4).

Figure 3: Activity of ATM (n=36833) and ATM-AVI (n=36147) against P. aeruginosa Isolates from the ATLAS Surveillance Study (2017-2021)



Source: Module 5.3.5.4 Study report ATM-AVI-M2-060
For ATM-AVI MIC evaluation, avibactam was tested at a fixed concentration of 4 mg/L.

Figure 4: Activity of ATM (n=933) and ATM-AVI (n=908) against MBL-containing P. aeruginosa Isolates from the ATLAS Surveillance Study (2017-2021)



Source: Module 5.3.5.4 Study report ATM-AVI-M2-060
For ATM-AVI MIC evaluation, AVI was tested at a fixed concentration of 4 mg/L.

Stenotrophomonas maltophilia is a nosocomial pathogen that is resistant to many β-lactams due to the production of two β-lactamases; L1, which is a metallo-β-lactamase, and L2, a Class C cephalosporinase. ATM-AVI *in vitro* activity against *S. maltophilia* was assessed in the years 2020 and 2021 (n=181 and 183, respectively). ATM-AVI and ATM demonstrated MIC_{90} values of 4 mg/L and >16 mg/L, respectively, each year.

Resistance to ATM-AVI

Mechanisms of resistance to ATM-AVI include production of beta-lactamases that can hydrolyse ATM and which are not inhibited by AVI, porin mutations which affect outer membrane permeability, overexpression of efflux pumps and mutations in the penicillin-binding protein genes.

Laboratory selection of resistance

The frequencies of spontaneous resistance to ATM-AVI were measured in isolates of Enterobacterales and *P. aeruginosa* isolates. The frequency of emergent colonies that could grow in the presence of a concentration of ATM-AVI that represented 4-fold and 8-fold the agar dilution MIC was low, with resistant mutants only being isolated in seven Enterobacterales isolates and one *P. aeruginosa* strain. The frequency in *P. aeruginosa* was $3.3x10^{-8}$ and ranged from $1.3x10^{-8}$ to $6.7x10^{-11}$ for the isolates of Enterobacterales.

The emergence of resistance to ATM-AVI during serial passage was determined with representative isolates of *E. coli* and *K. pneumoniae* carrying the metallo-β-lactamase NDM- 1 in conjunction with other serine β-lactamase enzymes. Growth of E. coli ARC3600 (NDM 1, OXA-1, CMY-6) and K. pneumoniae ARC3802 (NDM-1, TEM-1, OXA-1, CTX-M-15, SHV-2a, DHA 1) was observed over multiple passages in liquid medium containing sub- inhibitory concentrations (0.5-fold MIC) of ATM-AVI. After twenty passages, resistant mutants of *E. coli* ARC3600 and *K. pneumoniae* ARC3802 were isolated that displayed 128-fold decreases in susceptibility over the starting culture, from 0.25 mg/L to 32 mg/L and from 0.125 mg/L to 16 mg/L, respectively. This decrease in susceptibility to ATM-AVI was associated with a corresponding 16-fold decrease in susceptibility to ATM alone for *E. coli* ARC3600, from 8 mg/L to 128 mg/L. Paradoxically, the trend of susceptibility to ATM alone for the *K. pneumoniae* ARC3802 variants was the opposite, with the variants from the later passages showing a 4- to 8-fold increase in susceptibility to ATM.

In this investigation, these two Enterobacterales strains were also serially passed in sub-inhibitory concentrations of tigecycline and colistin. After twenty passages, *E. coli* ARC3600 variants were 256-fold and 128-fold less susceptible to tigecycline and colistin, respectively. The *K. pneumoniae* ARC3802 variants were 1024-fold less susceptible to both comparator compounds, and the resistance to colistin to that level was seen after only five passages.

Mutations associated with MIC-changes has been demonstrated in AmpC influencing the binding affinity of AVI, resulting in decreased activity to ATM-AVI. Moreover, a four-amino-acid insertion into PBP3 has also been demonstrated resulting in reduced access to ATM and decreases susceptibility.

Emergence of resistance in the clinical studies

No Enterobacterales post-baseline isolate with an increase (≥4-fold) in ATM-AVI MIC, relative to baseline MIC, was found in the clinical studies. Two participants with *P. aeruginosa* at baseline in study C3601002 had post-baseline *P. aeruginosa* pathogens that had an increase in ATM-AVI MIC (≥4-fold MIC at baseline). Whole genome sequencing was not performed. Therefore, genetic relatedness to the baseline pathogen and possible genetic changes that may have mediated the increased ATM-AVI MICs could not be elucidated.

Effects of human body fluids on susceptibility to ATM-AVI

The *in vitro* activity of ATM-AVI was generally unaffected by the presence of human urine, human serum and lung surfactant.

Summary of support for dose selection

Dose regimen selection for ATM-AVI was guided by approved dosing recommendations for ATM monotherapy (up to 2 g q6h in patients with normal renal function), *in vitro* MIC distributions for ATM and AVI in combination against target pathogens and simulations of joint probability of target attainment (PTA). Dose adjustments for renal impairment were selected to match exposures to normal

renal function. Consideration was also made for regimens that reduce the frequency of ATM-associated transaminase rises during treatment.

During Phase I dose-finding, an observation of increased hepatic transaminases led to a reduction in dose of the ATM component from 2 g to 1.5 g IV q6h accompanied by an extension of the infusion duration to 3 hours to ensure the PK/PD target (PDT) was achieved. With the extended infusion, a loading dose of ATM-AVI was introduced to speed up reaching target concentrations. A simplified loading dose compared with that used in the clinical trials is proposed in the product information to mitigate the risk for dosing errors. The simplified loading dose and final dosing regimens for the respective renal function categories are used in the PTA analyses presented below.

Hollow fibre infection model

As is well described for beta-lactam antibacterials, the percentage of time the unbound fraction of the drug exceeds the minimum inhibitory concentration (%*f*T>MIC) is the PK/PD index that best correlates with ATM activity. This was confirmed in a hollow fibre infection model (HFIM) against one strain each of *E. coli* and *K. pneumoniae*.

The PK/PD index best correlated with AVI activity was the %*f*T> C_T (concentration threshold) of 2 and 2.5 mg/L, respectively or the AUC when evaluated in the same HFIM experiment as described above. In additional HFIM experiments the %*f*T>C_T was confirmed as the best correlated PK/PD index for AVI with a threshold of 2.5 mg/L.

The tables below show the respective PK/PD indices and magnitudes to achieve 1-$\log_{10}$ reduction in bacterial densities for ATM and AVI in the HFIM experiments. A magnitude of at least 50 to 55% of time the unbound ATM concentration remained above the MIC was needed for a 1-$\log_{10}$ reduction in bacterial load. For AVI a magnitude of 25 to 60% *f*T>C_T of 2-2.5 mg/L was needed to achieve 1-$\log_{10}$ reduction in bacterial load.

Table 24: Summary of PK/PD Indices and Magnitudes for Aztreonam-Avibactam against Enterobacteriaceae Clinical Isolates Expressing MBL and ESBLs

Clinical Isolates	Aztreonam (with 4 µg/mL constant infusion of avibactam)		Avibactam (with q6h dosing of aztreonam)	
K. pneumoniae ARC3802 (NDM-1, TEM-1, OXA-1, CTX-M15, SHV-2a, DHA-1) MIC=0.125 µg/mL	Index:	% free T>MIC	Index:	% free T>[Threshold =2][a]
	Stasis	49.3% (0.7% CV)[b]	Stasis	22.7% (11% CV)
	1 Log-kill	50.3% (0.9% CV)	1 Log-kill	24.5% (8% CV)
	2 Log-kill	51.4% (1% CV)	2 Log-kill	26.0% (11% CV)
E. coli ARC3600 (NDM-1, OXA-1, CMY-6) MIC=0.125 µg/mL	Index	% free T>MIC	Index	% free T>[Threshold =2.5][c]
	Stasis	45.3% (9% CV)	Stasis	28.5% (21% CV)
	1 Log-kill	55.1% (10% CV)	1 Log-kill	31.0% (18% CV)
	2 Log-kill	56.0% (7% CV)	2 Log-kill	33.7% (17% CV)

[a] With C_{max} 0.625 µg/mL administered q6h (100% Time>MIC).
[b] Coefficient of variation.
[c] With C_{max} 1.25 µg/mL administered q6h (100% Time>MIC).

Table 25: AVI %ƒT>Ct Required for Various Clinical Isolates

Clinical Isolate	% $fT>C_T$			
	24-Hour Endpoint	Estimate	SD	CV%
K. pneumoniae ARC3802 *f*T>2 mg/L	Stasis	34.0	3.6	10.5
	1-log-unit-kill	37.7	3.2	8.4
K. pneumoniae ARC3602 *f*T>2.5 mg/L	Stasis	39.3	3.6	9.2
	1-log-unit-kill	46.1	3.5	7.6
K. pneumoniae ARC3803 *f*T>2.5 mg/L	Stasis	41.8	2.2	5.3
	1-log-unit-kill	44.3	2.2	4.9
E. coli ARC3600 *f*T>2.5 mg/L	Stasis	36.1	2.8	7.8
	1-log-unit-kill	40.9	3.3	8.0
E. coli ARC3805 *f*T>2.5 mg/L	Stasis	56.4	1.3	2.3
	1-log-unit-kill	58.2	1.6	2.7
E. coli ARC3807 *f*T>2.5 mg/L	Stasis	43.2	3.7	8.6
	1-log-unit-kill	48.1	4.1	8.5

Murine thigh and lung models of infection

The PDT for AVI associated with 1-log_{10} reduction in bacterial burden or EC_{80} representing near maximal activity (if 1-log_{10} kill was not reached) was furthermore evaluated in murine neutropenic thigh and lung models of infection (NTM and NLM, respectively) against seven isolates of *K. pneumoniae* and *E. coli* (Table 26 below). ATM exposure was set at 50% *f*T>MIC. The exposures required to achieve these magnitudes were <40% *f*T>C_T of 2.5 mg/L and <30% *f*T>C_T of 2.5 mg/L in the NTM and NLM, respectively (Table 27 and Table 28).

Table 26: MICs of Aztreonam and Aztreonam-Avibactam against Isolates of Enterobacteriaceae Producing MBLs and ESBLs

Isolate	β-lactamase content	MIC (mg/L)	
		ATM	ATM-AVI
K. pneumoniae ARC3602	NDM-1, CMY-6, CTX-M15, SHV-11, TEM-1	256	0.5
K. pneumoniae ARC3803	NDM-1, CTX-M-15,OXA-1, SHV-11, TEM-1	256	0.25
K. pneumoniae ARC3802	0NDM-1, TEM-1, CTX-M-15, SHV-2a, SHV-11	128	0.125
E. coli ARC3805	NDM-1, OXA-2, CTX-15, CMY-4, TEM-208, OXA-1	>256	4
E. coli ARC3801	NDM-1, TEM-1, OXA-1, CTX-M-15, CMY-42	>256	8
E. coli ARC3600	NDM-1, OXA-1, CMY-6	16	0.125
E.coli ARC3807	NDM-1, TEM-1, SHV-12, OXA-9, CMY-42	>256	8

Table 27: Avibactam-Free % T>[Threshold] Associated with Efficacy of Aztreonam-Avibactam against MBL and ESBL-Producing Enterobacteriaceae in Neutropenic Mouse Thigh Model

Isolate	MIC	E_{max}	E_0	EC_{80}	Stasis	CV%	1-Log-kill	CV%
	mg/L	ΔCFU	ΔCFU	$\%T>C_T$	$\%T>C_T$		$\%T>C_T$	
ARC3602	0.5	+2.5	-0.46	14	11	44	--	--
ARC3803	0.25	+3.8	-1.0	35	17	20	--	--
ARC3802	0.125	+1.5	-0.34	15	13	110	--	--
ARC3805	4	+1.3	-2.0	29	4.0	32	25	20
ARC3600	0.125	+1.8	-2.3	34	26	4.8	29	3.9
ARC3801	8	+0.6	-1.5	35	0.54	198	15	83

Table 28: Avibactam-free % T>[Threshold] Associated with Efficacy of Aztreonam-Avibactam against MBL and ESBL-Producing Enterobacteriaceae in Neutropenic Mouse Lung Model

Isolate	MIC mg/L	E_{max} ΔCFU	E_0 ΔCFU	EC_{80} %T>C_T	Stasis %T>C_T	CV%	1-Log-kill %T>C_T	CV%
ARC3602	0.5	+0.92	-3.4	29	13	16	17	10
ARC3803	0.25	+0.82	-3.4	--	0.13	--	0.90	--
ARC3802	0.125	+1.1	-2.3	23	18	51	20	8.5
ARC3805	4	+3.1	-4.0	--	10	65	17	17
ARC3600	0.125	+1.4	-3.3	25	5.4	16	9.0	14
ARC3807	8	+1.6	-2.8	19	12	57	15	64

Summary of PDTs for PTA

Based on the results from the *in vitro* HFIM and *in vivo* mouse model studies, ATM-AVI dose regimens were designed to achieve the following PTDs:

- ATM: >60% *f*T>$MIC_{ATM\text{-}AVI}$ of 8 mg/L covering Enterobacterales, including MBL-producing strains.
- AVI: >50% *f*T>C_T of 2.5 mg/L
- Achieve these PDTs with a joint PTA ≥90%.

Probability of target attainment

The proposed ATM-AVI dose regimens across renal function groups are displayed in the table below. The same ATM-AVI dose regimen was used for all indications in the clinical studies. It has previously been demonstrated in the ceftazidime-avibactam development programme that AVI acceptably reaches the lung and that the PK profiles of AVI were comparable in patients with cIAI, cUTI and HAP/VAP using the same dosing regimen. The applicant states that the penetration of ATM into ELF and bronchial secretions has been reported to be approximately 40% in rats and humans which would be at the same level as for AVI. However, according the one of the references provided the penetration was variable (6 to 55% and averaged 17%) which warrants further discussion of the relevance of applying the same dose in lung infections as in other types of infections especially when the ATM dose in ATM-AVI is lower than the highest approved dose of ATM when used alone.

The final population PK model was used to simulate concentration-time profiles for patients with cIAI, HAP/VAP and cUTI to predict joint PTA for the dose regimens administered to patients in Phase 3 but utilising the simplified loading dose. The proposed dose for ESRD and augmented renal clearance (ARC; CrCL>150 mL/min) was evaluated separately. Joint PTA for adult patients were satisfactory (≥90% or very close to 90%) across indications and renal function groups (tables below).

Table 29: Joint PTA (%) for Adult cIAI Patients with Various Degrees of Renal Function Following the Recommended Doses of ATM-AVI as IV Infusion over 3 Hours in the First Dosing Interval and at Steady-State Based on Simulations

	First Dosing Interval: LD over 3 hours		Steady-State: MD over 3 hours		
	ATM/AVI Dose (mg)	Joint PTA (%)	ATM/AVI Dose (mg)	Frequency	Joint PTA (%)
ARC	2000/667	93.26	1500/500	q6h	90.24
Normal	2000/667	97.04	1500/500	q6h	96.74
Mild	2000/667	99.28	1500/500	q6h	99.32
Moderate	2000/667	99.80	750/250	q6h	95.04
Severe	1350/450	97.94	675/225	q8h	91.22
ESRD	1000/334	91.40	675/225	q12h	89.06

Repository artifact ID FI-42815963
[a]ARC (augmented): CRCL>150 mL/min: Normal: 80<CRCL≤150 mL/min; Mild:50<CRCL≤80 mL/min; Moderate: 30<CRCL≤50 mL/min; Severe: 15<CRCL≤30 mL/min; ESRD (end stage renal disease): CRCL≤15 mL/min; Values are percent of patients based on summary of 5000 simulated patients per renal function category.

Table 30: Joint PTA (%) for Adult NP (HAP/VAP) Patients with Various Degrees of Renal Function Following the Recommended Doses of ATM-AVI as IV Infusion over 3 Hours in the First Dosing Interval and at Steady-State Based on Simulations.

	First Dosing Interval: LD over 3 hours		Steady-State: MD over 3 hours		
	ATM/AVI Dose (mg)	Joint PTA (%)	ATM/AVI Dose (mg)	Frequency	Joint PTA (%)
ARC	2000/667	96.08	1500/500	q6h	95.88
Normal	2000/667	98.30	1500/500	q6h	98.36
Mild	2000/667	99.52	1500/500	q6h	99.86
Moderate	2000/667	99.88	750/250	q6h	98.92
Severe	1350/450	99.18	675/225	q8h	97.52
ESRD	1000/334	96.32	675/225	q12h	96.58

Repository artifact ID FI-42816613
[a]ARC (augmented): CRCL>150 mL/min: Normal: 80<CRCL≤150 mL/min; Mild:50<CRCL≤80 mL/min; Moderate: 30<CRCL≤50 mL/min; Severe: 15<CRCL≤30 mL/min; ESRD (end stage renal disease): CRCL≤15 mL/min; Values are percent of patients based on summary of 5000 simulated patients per renal function category.

Table 31: Joint PTA (%) for Adult UTI Patients with Various Degrees of Renal Function Following the Recommended Doses of ATM-AVI as IV Infusion over 3 Hours in the First Dosing Interval and at Steady-State Based on Simulations.

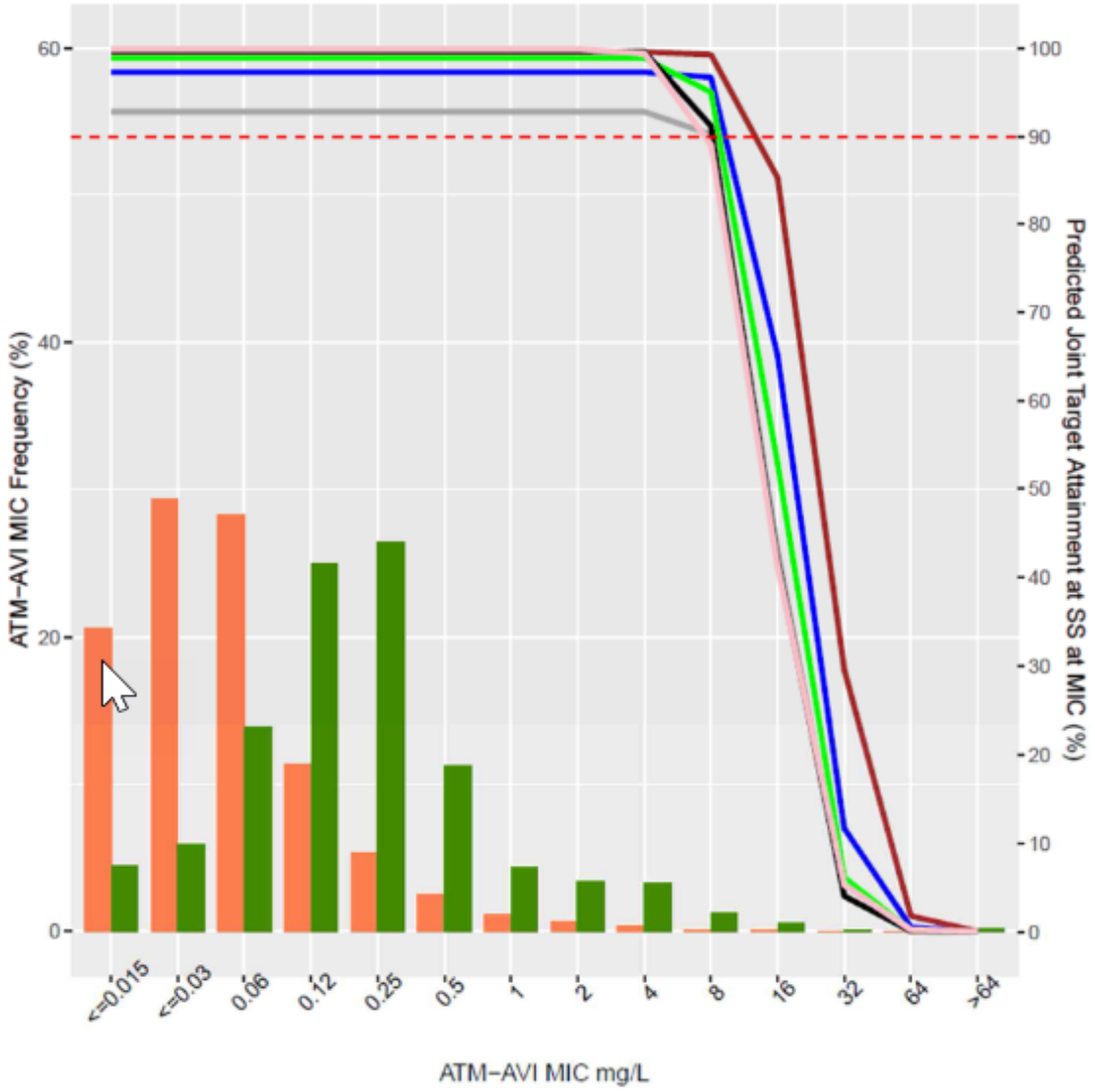
	First Dosing Interval: LD over 3 hours		Steady-State: MD over 3 hours		
	ATM/AVI Dose (mg)	Joint PTA (%)	ATM/AVI Dose (mg)	Frequency	Joint PTA (%)
ARC	2000/667	90.66	1500/500	q6h	89.50
Normal	2000/667	95.20	1500/500	q6h	95.78
Mild	2000/667	98.44	1500/500	q6h	99.32
Moderate	2000/667	99.64	750/250	q6h	98.00
Severe	1350/450	97.92	675/225	q8h	96.26
ESRD	1000/334	95.22	675/225	q12h	94.32

Repository artifact ID FI-42816628

[a]ARC (augmented): CRCL>150 mL/min: Normal: 80<CRCL≤150 mL/min; Mild:50<CRCL≤80 mL/min; Moderate: 30<CRCL≤50 mL/min; Severe: 15<CRCL≤30 mL/min; ESRD (end stage renal disease): CRCL≤15 mL/min; Values are percent of patients based on summary of 5000 simulated patients per renal function category.

The figure below depicts the joint PTA at steady state for cIAI patients across renal function groups including the MIC distributions for Enterobacterales +/- MBL-production demonstrating that the different dosing regimens across renal function groups appear satisfactory up to the proposed susceptibility breakpoint of 8 mg/L which would cover the vast majority of Enterobacterales including those producing MBL.

Figure 5: Predicted Joint PTA at Steady-State for cIAI Patients Across Renal Function Groups vs ATM-AVI MIC for Enterobacterales from 2017-2021



Repository artifact ID FI-42837209.
Coral bar represents Enterobacterales all strains and Darkgreen bar represents Enterobacterales MBL+
Solid darkgrey line = augmented renal function, solid blue line = normal renal function, solid brown line = mild renal impairment, solid green line = moderate renal impairment, solid black line = severe renal impairment, and solid pink line = end-stage of renal disease
Dash red line is 90% joint PTA

Susceptibility testing breakpoints

Susceptibility breakpoints are pending EUCAST interaction. The applicant proposes a susceptibility breakpoint for Enterobacterales ≤8 mg/L and resistance >8 mg/L.

Pharmacodynamic interactions

Fractional inhibitory concentrations (FIC) of ATM-AVI (avibactam tested at a constant concentration of 4 mg/L) in combination with 12 currently utilised antibiotics (amikacin, ceftazidime, ceftolozane/tazobactam, ciprofloxacin, colistin, daptomycin, gentamicin, linezolid, metronidazole, meropenem, tigecycline and vancomycin) were assessed in a checkerboard assay. The test isolates

included Gram-negatives (Enterobacterales [n=8], P. aeruginosa [n=2], A. baumannii [n=1]) and Gram-positives (Staphylococcus aureus [n=2], Enterococcus faecalis [n=1] and Streptococcus pneumoniae [n=1]). Determinations of synergy, antagonism, or indifference were based on growth observed in the checkerboard panels and corresponding FIC indices (FICI).

In summary, antagonism was overall not demonstrated in drug combinations studies with ATM-AVI and other antibacterial agents.

Relationship between plasma concentration and effect

Population PK estimated ATM and AVI exposures for Phase 3 participants confirmed the dose regimens used in the clinical trials achieved the PK/PD targets and were similar across renal function groups (dose regimens, based on renal function used in the clinical trial).

There were no trends observed in clinical and microbiological response across infection types, resistance to ATM, or other pathogen resistance/subgroups. Patients who did not achieve clinical cure or a favourable response had similar plasma exposures and target attainment to those who did respond across infection types.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Therapeutic window

The therapeutic window has not been extensively discussed by the applicant. Dosage adjustment is only proposed in patients with renal impairment, which is reasonable considering that both active substances are primarily eliminated renally as unchanged drug. Regarding efficacy, the proposed dose and the proposed dose adjustments in patients with renal impairment as well as the simplified loading dose compared to the phase 3 dosing regimen are supported by pop-PK and PTA analyses. From a safety perspective, regarding ATM the proposed daily dose is lower than that approved for ATM as mono-component. The proposed dose adjustment for Emblaveo also means a similar or larger decrease in total daily maintenance dose of ATM for subjects with various degrees of renal impairment compared to that of ATM as mono-component. Thus, a higher ATM exposure than that approved for ATM mono-component is not expected with Emblaveo. Regarding AVI, the proposed daily dose of AVI (2g) is somewhat higher than that approved for the fixed dose combination CAZ/AVI (1.5 g) but there is safety data with the proposed AVI dose from the phase 3 studies. The doses in patients with renal impairment are also higher than those approved for the fixed dose combination CAZ/AVI. This is further discussed in the *Impaired renal function* section.

Methods

Bioanalytical methods

The bioanalytical methods were adequately validated. Two issues were raised regarding the bioanalytical methods that might affect the population PK analysis; storage of samples outside demonstrated stability and cross-validation between two methods indicating a 20% difference in quantification of ATM. A popPK sensitivity analysis was performed by removing the small number of subjects affected from the analysis. The sensitivity analysis showed that parameters estimates were very similar which mitigates that these issues had a relevant effect on popPK analysis.

PopPK

Standard methods have been used.

Starting from the previous popPK model is generally considered a good approach. Parameters were generally estimated with good precision (RSE below 25% for most parameters).

Body weight based allometric scaling with fixed exponents was included a priori on Cl, Vc, Q and Vp. Time-varying body surface area-normalised creatinine clearance (nCRCL) effect on clearance was estimated. Calculating creatinine clearance includes body weight, normalising the creatinine clearance thus makes sense when having both allometric scaling and CRCL on clearance.

ESRD was estimated on Cl for AVI. It is unclear if this was needed as it was included in the base model. However, the estimate is similar to the base model and the RSE was low, so this is accepted.

Some of the previously identified covariates for AVI related to renal impairment, ESRD and dialysis on AVI CL, and Study NXL104/2002 effect on AVI CL and Vc were included in the initial base model. These covariates could have been retested but the strategy to include them in the base model is accepted. However, there is a concern that for ESRD only 3 patients (AVI) have been included.

The Goodness of fit plots support that the model is satisfactory. The applicant has provided pcVPCs with and without observed data points. The applicant discusses that overall, the figures support the adequacy of the model for both Avibactam and aztreonam. ATM and AVI concentrations over time after dose were adequately predicted across indications and renal function groups. It is generally agreed that the ATM and AVI concentrations are satisfactory predicted across studies, indications and renal function groups. However, the model is not considered satisfactory for AVI ESRD. The data is very sparse for AVI ESRD and thus, the dedicated RI study results are considered more appropriate.

The simulation settings are generally satisfactory. Keeping the covariate correlation is appropriate and supported.

ADME

Mass balance studies show that both aztreonam and avibactam are excreted mainly in urine as unchanged compound. Neither of the substances are extensively metabolised and no major metabolites are formed.

The potential for *in vivo*-isomerisation or inversion of avibactam was concluded to be low during the assessment of the fixed dose combination CAZ/AVI. Aztreonam has been approved for a long time and additional data or discussion regarding possible interconversion will not be requested.

Dose proportionality and time dependency

The results of study D4910C00001 indicate approximate dose-proportionality in the (rather limited) dose range studied, supporting the proposed SmPC statement that the pharmacokinetics of both aztreonam and avibactam are approximately linear across the dose range studied (1500 mg to 2000 mg aztreonam; 375 mg to 600 mg avibactam). AVI has previously been concluded to have approximately linear PK across the dose range studied (0.05 g to 2 g) for a single intravenous administration. Also for ATM, previous data indicate dose-proportionality.

There was little or no accumulation of ATM and AVI following repeated q6h dosing, which is consistent with the short half-lives of both substances (2-3 hours). There was no evidence of time-dependent kinetics for ATM or AVI following multiple dosing.

Pharmacokinetics in target population

The applicant has justified the simplified loading dose by providing simulations. The simulations support that the PTA is adequate and that the exposure is similar with a slightly higher Cmax. See further discussion in Clinical part regarding PTA analysis. Thus, the simplified loading dose is supported.

Special populations

Impaired renal function

As both ATM and AVI are mainly eliminated by renal excretion of unchanged drug, the exposure of both substances is significantly affected by renal impairment and dose adjustment based on renal function is thus needed. Information regarding exposure in subjects with renal impairment is available from a dedicated RI study with ATM-AVI, from dedicated RI studies with the mono-components as well as from popPK analysis.

The proposed dose adjustment in RI is based primarily on the ATM component. However, as AVI is almost exclusively eliminated by renal excretion of unchanged drug while ATM to a minor extent is eliminated by other routes, this means that AVI will be more affected by renal impairment than ATM and that, if adjusting the dose in order to match ATM exposure in patients with renal impairment compared to patients with normal renal function, the AVI exposure would be somewhat higher in patients with renal impairment compared to patients with normal renal function.

A dedicated multiple dose study was performed, investigating the effect of severe renal impairment (eGFR >15 - ≤30 mL/min, not on dialysis) on ATM-AVI. The doses administered in this study were those proposed in the current SmPC for subjects with severe RI and normal renal function respectively, except that the SmPC proposes a simplified loading dose administration but with the same total loading dose. This is not expected to affect any conclusions regarding the exposure at steady state. The proposed dosing regime in subjects with severe renal impairment resulted in a steady-state daily exposure of ATM that was approximately 21% lower and for AVI that was approximately 24% higher compared to subjects with normal renal function receiving the standard dose regimen.

The proposed dose adjustment is not the same as that approved for ATM as mono-component, but the proposed dose means a similar or larger decrease in total daily maintenance dose of ATM for subjects with various degrees of renal impairment compared to that of ATM as mono-component. The normal daily dose is also lower than the maximum approved daily dose of ATM. Thus, from a safety perspective, no concern is raised for ATM. From an efficacy perspective the provided PTA simulations support the adequacy of the proposed dosing for normal renal function and different RI groups as well as augmented renal clearance (see Pharmacodynamics).

Based on previous data with AVI (Study NXL104/1003), exposure (expressed by AUC_{inf}) increased with increasing level of renal impairment by approximately 2.6-, 3.8-, 7.0-, and 19.5-fold respectively when comparing subjects with mild to moderate RI (CrCL 50 to 79 mL/min), moderate RI (30 to 49 mL/min), severe RI (<30 mL/min) and ESRD to subjects with normal renal function (>80 mL/min). It is noted that the definitions used for renal function groups were not exactly those recommended in the current RI guideline.

For AVI, similarly to ATM, from an efficacy perspective the provided PTA simulations support the adequacy of the proposed dosing for normal renal function and different RI groups as well as augmented renal clearance.

The dose of AVI in patients with RI given Emblaveo will be higher than that approved for AVI given in combination with ceftazidime, especially in patients with CrCL below 30 ml/min. Thus, no support for safety in patients with low CrCL with the proposed AVI doses in Emblaveo is obtained from the fixed dose combination CAZ/AVI.

Based on the dedicated RI study performed during AVI development (Study NXL104/1003), the following increases in steady state exposure would be expected with the proposed doses compared to subjects with normal renal function (CrCL above 80 ml/min) receiving the standard dose regimen: 2.6-fold in patients with CrCL 50-80 ml/min; 1.9-fold in patients with CrCL 30-50 ml/min, 2.4-fold in patients with CrCL<30 mL/min and 4.4-fold in patients with ESRD. This is considerably different compared to the predicted exposure increases (40% in mild RI (defined as 50-80 ml/min), 14% in moderate RI (defined as 30-50 ml/min), 47% in severe RI) and also compared to the results from study C3601006 where subjects with severe RI given ATM/AVI with the proposed dosage adjustment only had 24% higher AUC compared to subjects with normal renal function receiving the standard dose regimen. The predicted exposure increase in mild RI appears low considering that AVI is almost exclusively eliminated renally as unchanged drug.

When looking at all available data there is uncertainty regarding the increases in AVI exposure expected when AVI is dose adjusted as recommended in patients with renal impairment. However, the increases in exposure expected (based on the results of study NXL104/1003) in patients with CrCL 30-50 ml/min or with severe renal impairment are not higher than the increase expected for patients with CrCL 50-80 ml/min. As discussed in the clinical safety part there were 69 patients with CrCL 50-80 ml/min included in the phase 2 and 3 studies and the incidence of side effects was comparable in this group compared to the group with normal renal function. Thus, these increases in AVI exposure are considered covered by available safety data.

At steady-state, AVI exposures are predicted to be approximately 2.4-fold higher for the ESRD dose regimen compared to normal renal function, while a 4.4-fold increase in exposure is expected based on the dedicated RI study. The popPK model is however based on very limited data for ESRD and a separate parameter was estimated for ESRD on clearance. It is not possible in this case to determine if the popPK model is satisfactory. Thus, the dedicated study is more appropriate to base a decision on. Based on the dedicated RI study, the AVI exposure expected at the proposed ESRD dose is higher than that for which clinical safety data have been generated in the Phase 2/3 programme. Further reduction in the ATM-AVI dose regimen is however not possible without compromising efficacious ATM exposure. This is further discussed under the section Discussion on Clinical Safety. In conclusion, the proposed dose in patients with ESRD, with the additional recommendation to limit treatment in ESRD to those patients on haemodialysis (or another form of RRT) as suggested by the applicant, was acceptable.

Regarding continuous renal replacement therapy (CRRT), a general text regarding dosing in CRRT has been included in the SmPC, which is adequate. In addition, the MAH is recommended to provide data describing the clearance of avibactam and aztreonam when treating individuals receiving continuous renal replacement therapy, in order to provide more specific dosing recommendations.

Impaired hepatic function

No hepatic impairment study has been performed for AVI or for ATM-AVI. As avibactam does not appear to undergo significant hepatic metabolism, the systemic clearance is not expected to be significantly altered by hepatic impairment and the SmPC of the fixed dose combination CAZ/AVI concludes that no dosage adjustment in patients with HI is required. Regarding ATM mono-component, the approved SmPC recommends a 20-25% dose reduction in case of long-term treatment of patients with chronic liver disease with cirrhosis, especially in cases of alcoholic cirrhosis and when renal function is also impaired. As long-term treatment is not indicated for ATM-AVI (maximum 14 days of

treatment), it is not considered necessary to include this statement in the SmPC for Emblaveo. Thus, no dose adjustment is needed in patients with HI.

Interactions

The applicant proposed to use C_{max} data from patients with mild RI for establishing relevance of *in vitro* findings, e.g. establishment of cut-offs for DDI potential *in vivo*. It is agreed that this can be considered a conservative approach as the exposure is higher in patients with mild RI than in patients with normal renal function.

Cmax values are for ATM a Cmax of 65.1 µg/mL and for AVI a Cmax of 13.8 µg/ml.

The concentrations used for investigating CYP inhibition of AVI were strictly speaking not high enough to exclude an *in vivo* relevant interaction but the conclusion regarding no significant CYP inhibition may be extrapolated from the fixed dose combination CAZ/AVI. Equally, the conclusion drawn regarding the fixed dose combination CAZ/AVI that AVI would not inhibit OAT1/3 in the clinically relevant exposure range may be extrapolated to Emblaveo.

In vitro studies indicate that ATM and AVI are substrates of human OAT1 and OAT3. In the population PK analysis, the potential impact of concomitant administration of OAT1 or OAT3 inhibitors on ATM and AVI exposure was evaluated. This type of analysis is limited by the absence of controlled doses and timing of administration of the inhibitors as well as by sparse sampling. Thus, no firm conclusions can be drawn. The conclusion regarding not recommended use with probenecid is however in line with what has been approved for the fixed dose combination CAZ/AVI and can be agreed.

The information in the SmPC section 4.5 regarding the potential for PK interactions with AVI is in accordance with the SmPC for the fixed dose combination CAZ/AVI and can be agreed.

Regarding ATM as perpetrator of drug interactions, the applicant refers to an EPAR for inhaled ATM stating that ATM is not an inhibitor or inducer of CYPs. It is however not clear that this conclusion can be extrapolated to IV use and the corresponding higher plasma concentrations. A warning regarding use with CYP substrates is not considered necessary, as the SmPC of IV aztreonam includes no information on interactions due to CYP inhibition or induction.

There is an *in vitro* signal for OAT1 inhibition and potentially also for OAT3 inhibition by ATM. No interaction was observed between ATM and AVI in the clinical study, which gives some support that this signal would not result in a clinically relevant interaction, although AVI is likely not a very sensitive OAT1/OAT3 substrate. Considering also that no warning regarding concomitant use with OAT1/3 substrates is included in the SmPC of IV ATM it is agreed not to include a warning for Emblaveo either.

SmPC

In the proposed SmPC, dose adjustments are only proposed in patients with renal impairment. As both active substances are primarily eliminated renally as unchanged drug, exposure is significantly affected by reduced renal function and dose adjustment is needed in these patients. See above on Renal impairment.

Pharmacodynamics

Mechanism of action

ATM is a monocyclic beta-lactam antibacterial agent (monobactam) that inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins (PBPs).

AVI is a non-β-lactam BLI with inhibitory activity against certain beta-lactamases which prevents the hydrolysis of ATM.

In vitro activity

ATM exerts clinically relevant antibacterial activity against aerobic gram-negative pathogens that mainly include Enterobacterales and to a lesser extent also *P. aeruginosa*. Although ATM is subject to hydrolysis by class A ESBLs and carbapenemases, class C (AmpC) beta-lactamases and class D oxacillinases and carbapenemases, it is generally stable to hydrolysis by class B carbapenemases (MBLs).

AVI inhibits class A ESBLs and carbapenemases, class C β-lactamases and some class D oxacillinases and carbapenemases. It has no inhibitory activity against the class B MBLs.

Because ATM-AVI is largely unaffected by beta-lactamases from various classes due to the substance's respective characteristics, the utility of the combination is anticipated in Enterobacterales that carry different types of beta-lactamases and most importantly those that are MBL-producing for which there are limited treatment options.

The combination of ATM-AVI has no advantage compared with ATM alone against *P. aeruginosa* regardless of MBL-production. Moreover, ATM-AVI at the proposed dose will not be sufficient for the full wild-type population (those without acquired resistance mechanisms). Therefore, the proposal from the applicant to include *P. aeruginosa* in the list of pathogens for which *in vitro* studies suggest would be susceptible to aztreonam-avibactam in the absence of acquired mechanisms of resistance is not appropriate. *P. aeruginosa* consequently should be removed from this list (SmPC-comment).

Due to some potentiation of ATM activity by AVI against *S. maltophilia* resulting in MIC_{90} values below 8 mg/L there may additionally be some value of ATM-AVI in infections caused by this pathogen.

Resistance

Mechanisms of resistance to ATM-AVI include production of beta-lactamases that can hydrolyse ATM and which are not inhibited by AVI, porin mutations which affect outer membrane permeability, overexpression of efflux pumps and mutations in the PBP genes.

Summary of support for dose selection

Dose regimen selection for ATM-AVI was guided by the approved dosing recommendations for ATM monotherapy, *in vitro* MIC distributions for ATM and AVI in combination against target pathogens and simulations of joint PTA. Dose adjustments for renal impairment were selected to match exposures to normal renal function. Consideration was also made for regimens that reduce the frequency of ATM-associated transaminase rises during treatment.

The proposed dosing regimen in patients with normal renal function consists of a slightly lower than maximum dose of ATM when used alone (1.5 g q6h) combined with 0.5 g AVI applying a loading dose and extended infusion duration.

The PK/PD index best correlated with ATM and AVI activity was initially evaluated in the HFIM. It was confirmed for ATM that, as with other beta-lactams, the percentage of time the unbound fraction of the drug exceeds the minimum inhibitory concentration (%*f*T>MIC) is the PK/PD index that best correlates with ATM activity. A magnitude of at least 50 to 55% of time the unbound ATM concentration remained above the MIC was needed for a 1-$\log_{10}$ reduction in bacterial load.

When AVI was combined with ceftazidime it was demonstrated that the PK/PD index best correlated with AVI activity was the %*f*T> C_T. In HFIM experiments the %*f*T>C_T was confirmed as the best correlated PK/PD index for AVI with a threshold of 2.5 mg/L although the AUC also were well correlated with AVI activity in some of the experiments. A magnitude of 25 to 60% *f*T>CT of 2-2.5 mg/L was needed to achieve 1-$\log_{10}$ reduction in bacterial load.

The PDT for AVI associated with 1-log_{10} reduction in bacterial burden or EC_{80} representing near maximal activity (if 1-log_{10} kill was not reached) was furthermore evaluated in murine neutropenic thigh and lung models of infection (NTM and NLM, respectively). The exposures required to achieve these magnitudes were <40% *f*T>C_T of 2.5 mg/L and <30% *f*T>CT of 2.5 mg/L in the NTM and NLM, respectively.

Based on the results from the *in vitro* HFIM and *in vivo* mouse model studies, ATM-AVI dose regimens were designed to achieve >60% *f*T>$MIC_{ATM\text{-}AVI}$ of 8 mg/L for ATM and >50% fT>C_T of 2.5 mg/L for AVI. Overall, the PDT chosen for AVI is acceptably conservative for the purpose of PTA. The PDT chosen for ATM was based on findings from the *in vitro* HFIM and is according to the applicant in the range for beta-lactams.

The joint PTA for the proposed dosing regimens including the simplified loading dose were satisfactorily above (or very close to) 90% using a joint target of >60% *f*T>MICATM-AVI for ATM and >50% *f*T>C_T of 2.5 mg/L for AVI for all renal function groups up to a MIC of 8 mg/L. The dosing regimens therefore would be sufficient to cover the vast majority of Enterobacterales regardless production of MBL or production of other beta-lactamases. However, based on data from the ATLAS surveillance studies the dosing regimens would not be sufficient for a significant proportion of *P. aeruginosa* especially those that are MBL-producing. Notably the applicant does only propose susceptibility breakpoints for Enterobacterales.

The PTA analyses support applying the same dosing regimens across infection types. Additionally, data from the CAZ-AVI development programme with regards lung penetration of AVI support the adequacy of the AVI dose regimens for the treatment of lung infections. For ATM, the applicant refers to historical data of approximately 40% ELF-penetration in rats and humans which would be at the same level as for AVI, for which no dose adjustments are warranted when used for the treatment of lung infections. Additional support for the adequacy of using the same ATM dose in the combination for the treatment of lung infections is that the PTA for ATM 1.5 g every 6 hours infused over 3 hours in the ATM-AVI regimen is comparable to the PTA for ATM 2 g every 6 hours infused over 0.5 hours.

2.6.4. Conclusions on clinical pharmacology

Regarding pharmacokinetics, all concerns were addressed and the SmPC adequately reflects the data.

Regarding pharmacodynamics, it is notable that the efficacy demonstration for ATM-AVI rests on preclinical PK/PD experiments and models, as the design of the pivotal trials does not allow for the isolation of the effect. This has been accepted for previous, analogous applications.

The applicant has provided relevant data that describe the *in vitro* activity of ATM-AVI, the potentiation of ATM activity by the addition of AVI and studies and analyses for dose selection of the single components of the fixed-dose-combination (FDC).

The MAH is recommended to provide data describing the clearance of ATM-AVI when treating individuals receiving continuous renal replacement therapy (CRRT), in order to provide more specific dosing recommendations.

2.6.5. Clinical efficacy

The clinical development programme for ATM-AVI relies partly on previous findings of safety and efficacy of ATM when used alone and PK of AVI when used in combination with CAZ. ATM, a monocyclic BL, was first authorised in Guatemala in 1984. Generics of ATM are, or have been, marketed by

different MAHs in the European Economic Area. Approved indications for ATM when used alone includes (among other indications) treatment of UTI/pyelonephritis, treatment of pneumonia (without a restriction to either community acquired pneumonia (CAP) or HAP/VAP and IAI.

AVI was centrally approved in the EU in combination with CAZ in 2016 for the treatment of cIAI, cUTI/pyelonephritis, HAP/VAP, bacteraemia that occurs in association with, or is suspected to be associated with, any of these infections and infections due to aerobic Gram-negative organisms in patients with limited treatment options.

The clinical programme for ATM-AVI included six clinical studies:

- D4910C00001, a Phase 1 study with single and multiple doses of aztreonam and avibactam alone and in combination in healthy male subjects.
- C3601006, a Phase 1 study of ATM-AVI in volunteers with normal renal function and severe renal impairment receiving multiple doses of ATM-AVI.
- C3601007, a Phase 1 study with single and multiple doses of ATM-AVI in healthy Chinese participants.
- C3601001, a Phase 2 study of ATM-AVI and metronidazole in hospitalised cIAI patients. One patient had impaired renal function (CrCL >30 – 50 mL/min).
- C3601002, a phase 3 study of ATM-AVI ± MTZ or meropenem ± colistin in patients with serious Gram-negative infections.
- C3601009, a phase 3 study of ATM-AVI ± MTZ or best available therapy in patients with serious MDR Gram-negative infections. The study was terminated early due to challenges with enrolment.

The clinical studies of main relevance to the applied indications are the two phase 3 studies C3601002 and C3601009, with the Phase 2 study C3601001 providing some support for the cIAI indication.

It should be noted that phase 3 studies evaluating a beta-lactam (BL) at its approved dose combined with a beta-lactamase inhibitor (BLI) are generally not designed to provide stand-alone efficacy data to support the dose regimen for the BLI, which is acceptable by precedent and by CHMP guidelines. Therefore, the PK/PD analyses incorporating the non-clinical PK/PD data and patient PK data are pivotal to support the efficacy and dose regimen of the BLI for the proposed indications.

2.6.5.1. Dose response studies

N/A

2.6.5.2. Main studies

Study C3601002 (D4910C00004)

Title: A Phase 3 Prospective, Randomized, Multicentre, Open Label, Central Assessor Blinded, Parallel Group, Comparative Study to Determine the Efficacy, Safety and Tolerability of Aztreonam Avibactam (ATM-AVI) ± Metronidazole (MTZ) Versus Meropenem ± Colistin (Mer ± Col) for the Treatment of Serious Infections due to Gram Negative Bacteria, Including Metallo β-Lactamase (MBL) Producing Multidrug Resistant Pathogens, for Which There are Limited or no Treatment Options

This was a phase 3, randomised, central assessor-blinded, open label, multicentre study comparing the efficacy of ATM-AVI with or without metronidazole to meropenem with or without colistin in hospitalised adults with cIAI or HAP/VAP.

Study C3601009

Title: A Prospective, Randomized, Open-Label, Comparative Study to Assess the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) and Best Available Therapy for the Treatment of Serious Infections due to Multi-Drug Resistant Gram-Negative Bacteria Producing Metallo β -Lactamase (MBL)

This was a phase 3, randomised, central assessor-blinded, open label, multicentre study comparing the efficacy of ATM-AVI with or without metronidazole to best available therapy (BAT) as defined locally based on epidemiology and practices, in adult patients with cIAI, cUTI, HAP/VAP, or BSI.

Studies C3601002 and C3601009

- **Participants**

Study C3601002 (D4910C00004)

Main inclusion criteria

- Subject must be ≥18 years of age.
- Confirmed diagnosis of HAP/VAP, or presumed diagnosis of cIAI requiring administration of IV antibacterial treatment.
    - Diagnosis of cIAI made either:
        - Intra-operatively or post-operatively with visual confirmation (presence of pus within the abdominal cavity) of an intra-abdominal infection associated with peritonitis, or
        - Pre-operatively (based on clinical criteria with confirmation of infection at time of surgical intervention within 24 hours [before or after] of randomization)
    - For HAP/VAP participants:
        - Onset of symptoms >48 hours after admission or <7 days after discharge from an inpatient care facility (for which the duration of admission was >3 days).
        - New or worsening infiltrate on chest X ray (or CT scan) obtained within 48 hours prior to randomization.
        - At least 1 of the following:
            - Documented fever (temperature ≥38°C) or hypothermia (rectal/core temperature ≤35°C);
            - WBC ≥10,000 cells/mm^3, leukopenia with total WBC ≤4500 cells/mm^3, or
            - 15% immature neutrophils (bands) noted on peripheral blood smear.

Main exclusion criteria:

- APACHE II score >30.
- Received more than one day (>24 hours) of any systemic antibiotic within 48 hours prior to randomization. This is inclusive of all doses of any systemic antibiotic initiated in this time period (but not counting overlapping periods of antibiotics).
    - Exception: failure of prior systemic antibiotic treatment as evident by either documented worsening of objective signs and symptoms of infection or lack of improvement in at least one objective sign or symptom of infection despite a minimum of 48 hours antibiotic treatment.
    - For cIAI subjects, who received less than one day (<24 hours) of any systemic antibiotic within 48 hours prior to randomization, one dose of antibiotic may be received postoperatively within 6 hours of the surgical procedure (defined as 6 hours from the time of skin closure or, if skin closure is not performed, 6 hours from the time the wound dressing is applied).
- Concurrent infection that may interfere with the evaluation of response to the study antibiotics.

A total of 422 participants were randomised at 81 sites in 20 countries in Asia, Europe, Latin America, North America and South Africa.

Study C3601009

Main inclusion criteria

- Subject must be ≥18 years of age.
- Subjects must have a confirmed diagnosis of serious bacterial infection, specifically cIAI, HAP/VAP, cUTI, or BSI requiring administration of IV antibacterial therapy.
- Subjects must have an MBL- positive Gram-negative bacteria (an Enterobacterales and/or *Stenotrophomonas maltophilia* for which the imipenem or MER MIC is ≥4 µg/mL), that was isolated from an appropriate specimen obtained within 7 days prior to screening (the study qualifying pathogen, which was determined to be the causative agent of entry infection, and which was available to be sent to the central laboratory). Prior to screening, genotypic confirmation of an MBL-positive pathogen at the local laboratory was required. If this was not possible then selected phenotypic tests may be acceptable with prior approval of the sponsor. In the case of mixed infection, the subject was allowed to participate in the study if the species were deemed susceptible to ATM-AVI or the investigator considered that the additional species were colonizers which did not warrant specific treatment.
- cIAI Subjects
    - must have a specimen obtained from an abdominal source during a surgical intervention within 7 days prior to screening from which a study-qualifying pathogen was isolated upon culture. Surgical intervention included open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery.
- HAP/VAP Subjects
    - Onset of symptoms >48 hours after admission or <7 days after discharge from an inpatient care facility (for which the duration of admission was >3 days).

- New or worsening infiltrate on chest X-ray (or CT scan) obtained within 48 hours prior to randomization.
- At least 1 of the following:
  - Documented fever (temperature ≥38°C) or hypothermia (rectal/core temperature ≤35°C);
  - WBC ≥10,000 cells/mm3, leukopenia with total WBC ≤4500 cells/mm^3, or >15% immature neutrophils (bands) noted on peripheral blood smear.

- cUTI Subjects
  - Subject had urine within 7 days prior to screening that cultured positive; containing ≥10^5 CFU/mL of at least 1 carbapenem-non-susceptible, MBL-positive Gram-negative bacteria, i.e., the isolate from the study-qualifying culture.
  - Subject had pyuria in the 7 days prior to screening as determined by a midstream clean catch or catheterised urine specimen with ≥10 WBCs per HPF on standard examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine.
  - Subject demonstrated either acute pyelonephritis or complicated lower UTI without pyelonephritis.
- • BSI Subjects
  - Subject had a confirmed diagnosis of primary BSI or C-BSI.
  - Signs and symptoms of systemic infection characterised by at least one of the following:
    - Chills, rigors, or fever (temperature of ≥38.0°C or ≥100.4°F);
    - Elevated white blood cell count (≥10,000/mm^3) or left shift (>15% immature PMNs).

Main Exclusion Criteria

- Subject had history of serious allergy such as anaphylaxis, angioedema and bronchospasm, hypersensitivity or any serious reactions to any systemic antibacterial which is allowed per protocol.
- Subject had a concurrent infection that may interfere with the evaluation of response to the study antibiotics.
- Subject had a need for effective concomitant systemic antibacterials in addition to those allowed per protocol for the diagnoses under study.
- Subject had an estimated CrCL ≤ 15 mL/min by Cockcroft-Gault formula (Cockcroft and Gault 1976), receiving or requirement for peritoneal dialysis, haemodialysis or haemofiltration.
- Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who were unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study treatment and for at least 7 days after the last infusion of investigational product.
- Subject had other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behaviour or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may

interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

- Treatments

Study C3601002 (D4910C00004)

Patients were randomised in a 2:1 ratio to receive either ATM-AVI, 1500 mg aztreonam plus 500 mg avibactam, q6h, i.v. (± metronidazole 500 mg q8h, i.v.) or 1000 mg meropenem plus optional colistimethate sodium:

- 500 mg aztreonam plus 167 mg avibactam as a first loading dose, i.v. infusion over 30 minutes, followed by an extended loading dose of 1500 mg aztreonam plus 500 mg avibactam immediately after the first loading dose, as a 3h infusion. Maintenance dose was started 3 hours after the end of the extended loading dose, as 3-hour infusions q6h. Patients with cIAI were also given 500 mg metronidazole, q8h, i.v. infusion over 60 minutes.
- 1000 mg meropenem q8h as a 30-minute infusion. If a meropenem-resistant pathogen was suspected, the dose was raised to 2000 mg meropenem q8h as a 3-hour infusion. Investigators were also allowed to add colistimethate sodium with a 9 million IU loading dose as a 30–60-minute infusion followed by a maintenance dose of 9 million IU daily in two or three doses.

Dose adjustments were made in patients with renal impairment. The protocol also allowed for concomitant use of aminoglycosides in case of *Pseudomonas aeruginosa* suspicion, and either vancomycin, linezolid or daptomycin for Gram-positive coverage, all at the investigator's discretion.

Study C3601009

Patients were randomised in a 2:1 ratio to receive either ATM-AVI, 1500 mg aztreonam plus 500 mg avibactam, q6h, i.v. (± metronidazole 500 mg q8h, i.v.) or best available therapy based on local conditions:

- 500 mg aztreonam plus 167 mg avibactam as a first loading dose, i.v. infusion over 30 minutes, followed by an extended loading dose of 1500 mg aztreonam plus 500 mg avibactam immediately after the first loading dose, as a 3h infusion. Maintenance dose was started 3 hours after the end of the extended loading dose, as 3-hour infusions q6h. Patients with cIAI were also given 500 mg metronidazole, q8h, i.v. infusion over 60 minutes to provide anaerobic coverage.
- Best available therapy (BAT) was determined based on local epidemiology and practices according to investigators' standard of care.

Dose adjustments were made in patients with renal impairment.

- **Objectives**

Study C3601002 (D4910C00004)

The objective of this study was to evaluate the efficacy of ATM-AVI ±MTZ and MER ±COL for the treatment of serious infections due to Gram-negative bacteria, including those due to MBL-producing MDR pathogens.

Secondary objectives of the study were:

- To assess the safety of ATM-AVI in in hospitalised patients with HAP/VAP or cIAI.
- To characterise the PK of ATM-AVI in in hospitalised patients with HAP/VAP or cIAI.

Study C3601009

The objective of this study was to evaluate the efficacy of aztreonam-avibactam (ATM-AVI) and best available therapy for the treatment of selected serious infections that are caused by MBL-producing Gram-negative bacteria.

Secondary objectives of the study were:

- To assess the safety of ATM-AVI in hospitalised patients with HAP/VAP or cIAI.
- To characterise the PK of ATM-AVI in hospitalised patients with HAP/VAP or cIAI.

- **Outcomes/endpoints**

Study C3601002 (D4910C00004)

The primary endpoint was the proportion of subjects with clinical cure at the TOC visit in the Intent-To-Treat (ITT) and Clinically Evaluable (CE) analysis sets. ITT and CE are considered co-primary analysis sets.

Secondary efficacy endpoints included:

- Proportion of subjects with clinical cure at the TOC visit in the micro-ITT and ME analysis sets.
- Proportion of subjects with clinical cure at the TOC visit by infection type in the ITT and CE analysis sets.
- Proportion of subjects with clinical cure at the TOC visit for subjects with MBL-positive pathogens in the micro-ITT and ME analysis sets.
- Proportion of subjects with a favourable per-subject microbiological response at the TOC visit in the micro-ITT and ME analysis sets.
- Proportion of subjects who died on or before 28 days from randomization in the ITT and micro-ITT analysis sets.

Tertiary efficacy outcomes include proportions of subjects with clinical cure and favourable response at EOT, based on subgroups like infection type and resistance type in the different analysis sets.

Clinical and microbiological outcome criteria were the following:

Table 32: Definition of Clinical Response Categories at the EOT and TOC visits

Clinical response	Definition
Cure	Baseline signs and symptoms have improved such that after study treatment, no further antimicrobial treatment for the index infection (ie, cIAI or HAP/VAP) is required.[a] In addition, none of the failure criteria listed below should be met. **Additionally for cIAI subjects:** No unplanned drainage or surgical intervention is necessary since the initial procedure.
Failure	Subjects who meet any of the following criteria will be considered a treatment failure: Death (after receiving at least 48 hours of study treatment). Subject who received treatment with further antibiotics for the index infectiona. This includes subjects prematurely discontinued from study treatment due to an AE who require further antibiotics for the index infection. **Additionally for cIAI subjects:** Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively in situation of adequate infection source control at the time of initial surgical procedure. Postsurgical wound infections (eg, signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or non-routine wound care).
Indeterminate	Death (after receiving less than 48 hours of study treatment). Subject lost to follow-up. **Additionally for cIAI subjects:** Inadequate infection source control at time of initial surgical procedure.

Abbreviations: AE=adverse event; cIAI=complicated intra-abdominal infection; EOT=end of treatment; HAP=hospital-acquired pneumonia; TOC=test of cure; VAP=ventilator-acquired pneumonia.

a. Further antibiotics for the index infection should only be initiated for ongoing or worsening signs and symptoms of the infection.

Table 33: Definition of Microbiological Response Categories at the EOT and TOC Visits, for Each Pathogen Identified at Initial/Pre Study (Study Qualifying) Culture

Microbiological response	Definition
Eradication	Absence of causative pathogen from an appropriately obtained specimen[a] at the site of infection.
Presumed eradication	Repeat culture of specimens were not performed/clinically indicated in a subject who had a clinical response of cure.
Persistence	Causative organism is still present from an appropriately obtained specimen at the site of infection. If the causative organism displays ≥4-fold higher MIC to study therapy after treatment with IV study therapy, the response will also be categorized as "Persistence with increasing MIC".
Presumed persistence	Subject was assessed as a clinical failure and repeat culture of specimens were not performed/clinically indicated.
Indeterminate microbiological response	Death (after receiving less than 48 hours of study treatment). Subject lost to follow-up. **Additionally for cIAI subjects:** Inadequate infection source control at time of initial surgical procedure.

Abbreviations: BAL=bronchoalveolar lavage; cIAI=complicated intra-abdominal infection; EOT=end of treatment; IV=intravenous(ly); MIC=minimum inhibitory concentration; PSB=protected-specimen brush; TOC=test of cure.

a. A definition of an appropriately obtained specimen for each infection site will be included in the study microbiology manual (see Appendix 6). For subjects with cIAI, an appropriately obtained specimen for determination of microbiological response is defined as a specimen obtained using an adequate technique (eg, surgical procedure (laparotomy or laproscopic), percutaneous drainage (where in place for less than 24 hours) or wounds where the subject has a superficial or deep surgical wound reported at any point during the follow-up period). From expectorated or induced sputum, an adequate specimen is one with ≤10 squamous epithelial cells and >25 polymorphonuclear neutrophils per Low Power Field (LPF) upon a Gram-stain; throat secretions are considered to be inadequate; other specimens such as endotracheal aspirate, BAL, mini-BAL, and PSB are considered to be adequate. For blood, two sets of blood cultures should be collected (ie, 4 bottles) from 2 different sites for aerobic and anaerobic incubation. One set of blood cultures must be obtained through a venipuncture. Collect samples, ideally over a period of 2 hours at least 10 to 20 minutes apart from separate sites.

The analysis sets used for statistical analysis and presentation were:

- Intent-To-Treat (ITT) Analysis Set: all randomised subjects regardless of receipt of study drug.
- Clinically Evaluable (CE) Analysis Set: all subjects who meet the definition of the ITT analyses, disease criteria for diagnosis of cIAI, or HAP/VAP, and did not have important protocol deviations such as concomitant antibiotics or were otherwise unevaluable.
- Microbiological Intent-To-Treat (micro-ITT) Analysis Set: all subjects in the ITT set that had at least 1 Gram-negative pathogen in an adequate initial or pre-study culture. Subjects with inherently resistant pathogens (monomicrobial infections due to any *Acinetobacter spp*.), and subjects with only Gram-positive pathogens were excluded from this set.
- Microbiologically Evaluable (ME) Analysis Set: all subjects that were included in both micro-ITT and CE analysis sets and had at least 1 Gram-negative pathogen.
- Modified Intent-To-Treat Analysis Set: all randomised subjects who receive any amount of study drug.
- Microbiological Modified Intent-To-Treat (micro-MITT) Analysis Set: all subjects that were included in the micro-ITT set and received any amount of study drug.

Study C3601009

The primary endpoint was the proportion of subjects with clinical cure at the TOC visit in the micro-ITT population.

Secondary efficacy endpoints included:

- Proportion of subjects with clinical cure at the TOC visit in the ME analysis set.
- Proportion of subjects with clinical cure at the EOT visit in the micro-ITT and ME analysis sets.

- Proportion of subjects with a favourable per-subject microbiological response at the EOT and TOC visits in the micro-ITT and ME analysis sets.
- Proportion of subjects with a favourable per-pathogen microbiological response at the EOT and TOC visits in the micro-ITT and ME analysis sets.

Proportion of subjects who died on or before 28 days from randomization in the ITT and micro-ITT analysis sets.

- **Sample size**

Since no formal hypothesis testing had been planned in any of the two phase 3 studies, no power calculations had been performed.

Study C3601002

According to the final protocol (dated 20 October 2017), the intention was to randomise approximately 300 subjects; 200 subjects to receive ATM-AVI±MTZ and 100 subjects to receive MER±COL. After the study had started, the sample size was increased twice (CSP amendment 1, 05 July 2018 and CSP amendment 2, 18 May 2022).

With amendment 1 the study was instead to randomise 375 (250/125) subjects estimating that approximately 25 and 12 subjects respectively were to be identified with MBL-producing Gram-negative pathogens in the ATM-AVI ±MTZ and the MER ±COL treatment arms.

With amendment 2, the sample size was increased to 425 subjects, 283 and 142 in each arm respectively. Here, a somewhat more conservative estimate for the prevalence of infections caused by pathogens producing MBLs was made (8-10%) and expected number of subjects in each arm to be identified with MBL-producing Gram-negative pathogens was deleted.

The increase in the sample size with amendment 2 (18 May 2022) is stated to have been in response to a slower than anticipated recruitment in study C3601009. The change was to help ensure that there was a minimum of patients on the ATM-AVI treatment arm across the programme for safety evaluation.

Study C3601009

For this study, the planned total sample size was approximately 60 subjects: 40 subjects in the ATM-AVI treatment arm and 20 subjects in the BAT treatment arm. Due to recruitment difficulties, the number of subjects was reduced to 15.

- **Randomisation and Blinding (masking)**

Both studies used an open-label design.

Clinical response outcome was to be assessed at EOT and TOC by an independent clinical adjudication committee (central assessor) in a blinded fashion with the aim of unbiased adjudication of the primary objective measure. Data was to be provided to the adjudication committee relating to the subject's clinical response without disclosing treatment arm. The adjudication committee was to be blinded to investigator assessments of clinical response.

In each study respectively, eligible subjects were to be randomised in a 2:1 ratio to the ATM-AVI treatment group or the comparator treatment group according to a central randomisation schedule and

using an IRT system (interactive response technology). Study treatment was to be administered as soon as possible after a subject had been randomised.

Study C3601002

In study C3601002 randomisation was stratified according to infectious disease type (cIAI versus HAP/VAP).

cIAI subjects were to be further stratified by APACHE II score category (≤10 versus >10).

HAP/VAP subjects were to be further stratified by mechanical ventilation status (yes versus no).

Study C3601009

In study C3601009 randomisation was stratified based on infectious disease type (cIAI, HAP/VAP, cUTI or BSI).

The number of subjects with cUTI were to be no more than approximately 75% of the study population.

BAT selection was to be based upon site practice and local epidemiology. The choice of BAT (monotherapy or combination) for each subject was to be recorded prior to randomisation.

- **Statistical methods**

Both studies were descriptive. No formal hypothesis testing was to be performed meaning that there was no adjustment for multiplicity. In case of missing efficacy data, there was to be no imputation.

The Statistical Analysis Plan (SAP) for study **C3601002** was based on protocol amendment 1 dated 05 July 2018. The submitted SAP is version 2, dated 25 June 2020. Main statistical analysis features are described below.

The submitted statistical analysis plan (SAP) for study **C3601009** is version 1.0 dated 21 April 2020. It was based on the study protocol dated 5 July 2018.

Given the limitations in the number of randomised subjects (N=15) in study C3601009, efficacy data have been presented by treatment arm, with no between treatment group comparisons.

Study C3601002

Co-primary efficacy analysis sets

The Intent-to-Treat (ITT) analysis set, and the Clinically Evaluable (CE) analysis set were considered co-primary analysis sets.

The ITT analysis set included all randomised subjects regardless of receipt of study drug. Subjects in the ITT analysis set were analysed according to the treatment to which they had been randomised.

The CE analysis set was defined as all subjects included in the ITT analysis set who met the disease criteria for diagnosis of cIAI, or HAP/VAP and who received at least 48 hours of study treatment or received <48 hours of study treatment before discontinuing study drug due to an AE. Further requirements were:

• Did not receive concomitant antibiotic treatment with potential activity against any baseline pathogens between the time of first dose of study treatment and the time of TOC. This did not include those participants who have received protocol allowed antibiotics or have failed study treatment and require additional antibiotics to treat their infection.

• Did not receive prior antibiotics other than as outlined as acceptable in the protocol.
• Had no important protocol deviations that may affect the assessment of efficacy.
• Did not have a clinical outcome of indeterminate at TOC.
• Did not have monomicrobial infections due to non-eligible pathogens and did not have only Gram-positive pathogens.

In addition, the following efficacy analysis sets had been predefined in the SAP: the microbiologically evaluable (ME) set, the modified intent-to-treat (MITT) set and the microbiological modified intent-to-treat (micro-MITT) set.

Primary endpoint analyses

The primary endpoint was the proportion of participants with clinical cure at the TOC visit as assessed by the Clinical Adjudication Committee.

The difference in clinical cure rate between treatment arms at the TOC visit (ATM-AVI ± MTZ minus MER ± COL) and the corresponding two-sided 95% CI were to be calculated for the ITT and CE analysis sets.

The two-sided 95% CI for the observed difference in the cure rates were to be computed using the method proposed for unstratified designs by Miettinen and Nurminen. An additional supporting descriptive analysis was planned to use the stratified Miettinen and Nurminen method (Miettinen and Nurminen 1985), if each stratum had at least 3 subjects per each treatment group.

Sensitivity/Robustness Analyses

An analysis of the Investigator's assessment of clinical response in the ITT and CE analysis sets at the TOC visit.

An analysis of clinical response at TOC (adjudicated response) using the MITT population.

An analysis of the primary endpoint (clinical response at TOC, adjudicated response) based on the ITT population considering all deaths prior to the TOC as clinical failures.

An analysis of the use of concomitant antibiotics (other than those allowed per the protocol – Gram positive coverage and aminoglycosides) on the primary endpoint (clinical response at TOC) in the ITT population. Subjects who received at least one dose of a restricted/prohibited concomitant medication were to be included in this analysis of the primary endpoint.

Subgroup analyses

Several subgroup analyses of the primary endpoint were predefined. Among them, analyses based on e.g.:

• Baseline renal function category: Severe renal impairment, Moderate renal impairment, Normal renal function, or Mild renal impairment, Augmented renal function.

• For cIAI subjects: APACHE II score category (≤10 or > 10) based on eCRF data.
• For cIAI subjects: Diagnosis of Appendicitis vs non appendicitis diagnosis.
• For HAP/VAP subjects: Mechanical Ventilation status at baseline (Yes/No), based on the eCRF data.

Secondary endpoint analyses

Secondary efficacy outcome measures were to be assessed and presented similar to the primary endpoint.

Interim Analysis

No formal interim analysis was to be conducted for this study. An external data monitoring committee (E-DMC) was to be responsible for ongoing monitoring of the safety of subjects in the study according to the E-DMC Charter.

Results

- **Participant flow**

Study C3601002 (D4910C00004)

Table 34 below summarises patient disposition by treatment for the ITT population. Out of 461 subjects screened, 38 were screening failures due to not fulfilling eligibility criteria. One subject was not randomised due to lack of drug at the investigation site.

Table 34: Study Disposition, All Participants – ITT Analysis Set

Number (%) of Participants	ATM-AVI (+/-MTZ) (N=282) n (%)	Meropenem (N=140) n (%)	Total (N=422) n (%)
Disposition phase: Treatment			
Discontinued	40 (14.2)	19 (13.6)	59 (14.0)
Adverse event	7 (2.5)	3 (2.1)	10 (2.4)
Death	4 (1.4)	2 (1.4)	6 (1.4)
Lack of efficacy	7 (2.5)	4 (2.9)	11 (2.6)
Lost to follow-Up	0	0	0
Physician's decision	4 (1.4)	3 (2.1)	7 (1.7)
Withdrawal by subject	16 (5.7)	4 (2.9)	20 (4.7)
Other	2 (0.7)	3 (2.1)	5 (1.2)
Completed	242 (85.8)	121 (86.4)	363 (86.0)
Disposition phase: Late Follow-up			
Discontinued	40 (14.2)	18 (12.9)	58 (13.7)
Adverse event	3 (1.1)	1 (0.7)	4 (0.9)
Death	17 (6.0)	11 (7.9)	28 (6.6)
Lack of efficacy	0	0	0
Lost to follow-Up	1 (0.4)	1 (0.7)	2 (0.5)
Physician's decision	1 (0.4)	0	1 (0.2)
Withdrawal by subject	16 (5.7)	3 (2.1)	19 (4.5)
Other	2 (0.7)	2 (1.4)	4 (0.9)

Number (%) of Participants	ATM-AVI (+/-MTZ) (N=282) n (%)	Meropenem (N=140) n (%)	Total (N=422) n (%)
Completed	242 (85.8)	122 (87.1)	364 (86.3)

The denominator to calculate percentages is N, the number of particpants in the Intent to Treat set within each treatment arm.
Note: MTZ therapy administered to participants with cIAI only.

PFIZER CONFIDENTIAL SDTM Creation: 02MAY2023 (10:46) Source Data: adds Table Generation: 06JUN2023 (14:51) (Cutoff date: not applicable, Snapshot Date: 18APR2023 (18:56)) Output File: ./csr_figaro/C3601002_CSR/adds_s001
Table 14.1.1.2 ATM-AVI is for Pfizer internal use.

Table 35 summarises the study participant numbers per analysis population:

Table 35: Participants Evaluation Groups – All Participants

	ATM-AVI (+/-MTZ) (N=282) n (%)	Meropenem (N=140) n (%)	Total (N=422) n (%)
Screened: 461			
Screened Failure: 38			
ATM-AVI (+/-MTZ) (N=282) n (%)	**Meropenem (N=140) n (%)**	**Total (N=422) n (%)**	
Not Screen Failure but not Randomized: 1			
Assigned to Treatment (ITT)	282 (100.0)	140 (100.0)	422 (100.0)
Treated (Safety)	275 (97.5)	137 (97.9)	412 (97.6)
Clinically Evaluable (CE)	213 (75.5)	105 (75.0)	318 (75.4)
Microbiological Intent to Treat (micro-ITT)	177 (62.8)	94 (67.1)	271 (64.2)
Microbiologically Evaluable (ME)	149 (52.8)	79 (56.4)	228 (54.0)
Modified Intent to Treat (MITT)	275 (97.5)	137 (97.9)	412 (97.6)
Microbiological Modified Intent-To-Treat (micro-MITT)	175 (62.1)	94 (67.1)	269 (63.7)
Not Treated	7 (2.5)	3 (2.1)	10 (2.4)

The denominator to calculate percentages is N, the number of participants in the Intent to Treat set within each treatment arm.
Note: MTZ therapy administered to participants with cIAI only.

PFIZER CONFIDENTIAL SDTM Creation: 02MAY2023 (10:46) Source Data: adsl adbase Table Generation: 06JUN2023 (15:32) (Cutoff date: not applicable, Snapshot Date: 18APR2023 (18:56)) Output File: ./csr_figaro/C3601002_CSR/adsl_s002_all
Table 14.1.1.1.a ATM-AVI is for Pfizer internal use.

In the ITT population, a total of 10 patients did not receive study drugs and were excluded. A total of 116 participants were not included in the micro-ITT population for not having pathogens identified in baseline cultures (n.b. culture positivity was not an inclusion criterion). A total of 104 subjects were not included in the CE population due to meeting at least one exclusion criterion.

Study C3601009

Table 36 below summarises patient disposition by treatment for all subjects. All screened subjects were also randomised.

Table 36: Participants Evaluation Groups – All Participants

	ATM-AVI (N=12) n (%)	BAT (N=3) n (%)	Total (N=15) n (%)
Screened: 15			
Screened Failure: 0			
Not Screen Failure but not Randomized: 0			
Assigned to Treatment (ITT)	12 (100.0)	3 (100.0)	15 (100.0)
Treated (Safety)	12 (100.0)	2 (66.7)	14 (93.3)
Microbiological Intent to Treat (micro-ITT)	12 (100.0)	3 (100.0)	15 (100.0)
Microbiologically Evaluable (ME)	9 (75.0)	1 (33.3)	10 (66.7)
Population Pharmacokinetic (popPK)	12 (100.0)	0	12 (80.0)
Not Treated	0	1 (33.3)	1 (6.7)

The denominator to calculate percentages is N, the number of participants in the Intent to Treat set within each treatment arm.

PFIZER CONFIDENTIAL SDTM Creation: 01APR2023 (05:12) Source Data: adsl adbase Table Generation: 02MAY2023 (20:43) (Cutoff date: not applicable, Snapshot Date: 24MAR2023 (21:27)) Output File: ./csr_figaro/C3601009_CSR/adsl_s002_all
Table 14.1.1.1 ATM-AVI is for Pfizer internal use.

Table 37 below summarises the study participant numbers per analysis population:

Table 37: Analysis Datasets Summary - All Participants

	ATM-AVI (N=12) n(%)	BAT (N=3) n(%)	Total (N=15) n(%)
Intent-to-Treat(ITT)	12 (100.0)	3 (100.0)	15 (100.0)
Safety (SAF)	12 (100.0)	2 (66.7)	14 (93.3)
Did not receive study treatment	0	1 (33.3)	1 (6.7)
Microbiological Intent-To-Treat (micro-ITT)	12 (100.0)	3 (100.0)	15 (100.0)
Microbiologically Evaluable (ME)	9 (75.0)	1 (33.3)	10 (66.7)
Exclusion for 1 or more criteria[a]	3 (25.0)	2 (66.7)	5 (33.3)
Not a member of the Micro-ITT analysis set	0	0	0
Did not receive at least 48 hours of study treatment[b]	1 (8.3)	2 (66.7)	3 (20.0)
Received concomitant antibiotic treatments with potential activity against any baseline pathogen between time of first dose of study treatment and time of test of cure[c]	0	0	0
Baseline entry organism(s) not genetically confirmed by central lab[d]	0	0	0
Indeterminate clinical outcome at TOC	2 (16.7)	2 (66.7)	4 (26.7)
Ineligible baseline pathogens	2 (16.7)	0	2 (13.3)

The denominator to calculate percentages is N, the number of participants in the analysis set within each treatment arm.
a. Meets at least 1 criteria for exclusion. Exclusion categories are not mutually exclusive.
b. Participants receiving < 48 hours of study treatment before discontinuing study drug due to an AE will not be excluded.
c. This does not include those subjects who have failed study therapy and require additional antibiotics to treat their infection.
d. A repeat adequate culture taken closer to study treatment start yielded no MBL-producing pathogen when an MBL-producing pathogen was isolated from an earlier adequate culture.

PFIZER CONFIDENTIAL SDTM Creation: 01APR2023 (05:12) Source Data: adsl adbase Table Generation: 15JUN2023 (18:59) (Cutoff date: not applicable, Snapshot Date: 24MAR2023 (21:27)) Output File: ./csr_figaro/C3601009_CSR/t14114
Table 14.1.1.4 ATM-AVI is for Pfizer internal use.

In the ITT population, a one patient in the BAT group did not receive study drugs and were excluded. All subjects were included in the micro-ITT population. A total of 5 subjects were not included in the ME population due to meeting at least one exclusion criterion.

- **Recruitment**

Study C3601002 (D4910C00004)

Initiation date: 05 April 2018

Completion date: 23 February 2023

Study C3601002

Initiation date: 25 December 2020

Completion date: 23 January 2023

- **Conduct of the studies**

Study C3601002 (D4910C00004)

The original Study protocol was dated 20 October 2017 and was amended twice, Amendment 1 on 05 July 2018 and Amendment 2 on 18 May 2022. Main changes in the protocol amendments were increases of the number of study participants.

The SAP used for the analysis is Version 2 (Amendment 1) dated 25 June 2020.

There were 306 subjects (208 vs. 98 in respective arm) with important protocol deviations in the study. The most frequently reported important protocol deviations occurred in the Laboratory (40.3%), Procedures/Tests (27.5%), Investigational Product (25.8%), and Inclusion/Exclusion (18.7%) categories. All other categories occurred in ≤7.1% of participants.

Study C3601009

The original Study protocol was dated 13 November 2017 and was amended twice, Amendment 1 on 05 July 2018 and Amendment 2 on 23 May 2022. Main changes in the protocol amendments were changes in the number of study sites and eligibility criteria.

The SAP used for the analysis is Version 1 dated 21 April 2020.

There were protocol deviations in Laboratory (8/15 subjects), Procedures/Tests (6/15 subjects), Concomitant Medications (5/15 subjects) and Informed Consent (5/15 subjects) categories.

The study was terminated early due to recruitment problems, after discussion with the CHMP. In order to expand the safety database to the minimum requirement of 300 subjects, the number or subjects in study C3601002 was increased correspondingly.

- **Baseline data**

Study C3601002 (D4910C00004)

Table 38: Demographic Characteristics – ITT Analysis Set

	cIAI			HAP/VAP			All Participants		
	ATM-AVI (+/- MTZ) (N=208)	Meropenem (N=104)	Total (N=312)	ATM-AVI (+/-MTZ) (N=74)	Meropenem (N=36)	Total (N=110)	ATM-AVI (+/- MTZ) (N=282)	Meropenem (N=140)	Total (N=422)
Age (years): n(%)									
<65	152 (73.1)	83 (79.8)	235 (75.3)	34 (45.9)	14 (38.9)	48 (43.6)	186 (66.0)	97 (69.3)	283 (67.1)
65-74	30 (14.4)	18 (17.3)	48 (15.4)	23 (31.1)	14 (38.9)	37 (33.6)	53 (18.8)	32 (22.9)	85 (20.1)
75-84	22 (10.6)	2 (1.9)	24 (7.7)	15 (20.3)	7 (19.4)	22 (20.0)	37 (13.1)	9 (6.4)	46 (10.9)
>=85	4 (1.9)	1 (1.0)	5 (1.6)	2 (2.7)	1 (2.8)	3 (2.7)	6 (2.1)	2 (1.4)	8 (1.9)
Mean (SD)	52.4 (17.65)	50.5 (15.76)	51.7 (17.04)	63.0 (16.02)	64.3 (13.37)	63.4 (15.15)	55.2 (17.84)	54.0 (16.30)	54.8 (17.33)
Median (range)	53.0 (18.0, 87.0)	53.0 (18.0, 87.0)	53.0 (18.0, 87.0)	66.5 (19.0, 85.0)	66.0 (22.0, 87.0)	66.0 (19.0, 87.0)	57.5 (18.0, 87.0)	57.0 (18.0, 87.0)	57.0 (18.0, 87.0)
Gender: n(%)									
Male	133 (63.9)	71 (68.3)	204 (65.4)	53 (71.6)	30 (83.3)	83 (75.5)	186 (66.0)	101 (72.1)	287 (68.0)
Female	75 (36.1)	33 (31.7)	108 (34.6)	21 (28.4)	6 (16.7)	27 (24.5)	96 (34.0)	39 (27.9)	135 (32.0)
Race: n(%)									
White	121 (58.2)	42 (40.4)	163 (52.2)	43 (58.1)	22 (61.1)	65 (59.1)	164 (58.2)	64 (45.7)	228 (54.0)
Black or African American	1 (0.5)	1 (1.0)	2 (0.6)	0	0	0	1 (0.4)	1 (0.7)	2 (0.5)
Asian	78 (37.5)	58 (55.8)	136 (43.6)	29 (39.2)	11 (30.6)	40 (36.4)	107 (37.9)	69 (49.3)	176 (41.7)
American Indian or Alaska Native	7 (3.4)	2 (1.9)	9 (2.9)	0	0	0	7 (2.5)	2 (1.4)	9 (2.1)
Mixed	1 (0.5)	0	1 (0.3)	1 (1.4)	1 (2.8)	2 (1.8)	2 (0.7)	1 (0.7)	3 (0.7)
Other	0	0	0	0	1 (2.8)	1 (0.9)	0	1 (0.7)	1 (0.2)
Not Reported	0	1 (1.0)	1 (0.3)	1 (1.4)	1 (2.8)	2 (1.8)	1 (0.4)	2 (1.4)	3 (0.7)
Ethnicity: n(%)									
Hispanic or Latino	51 (24.5)	15 (14.4)	66 (21.2)	7 (9.5)	6 (16.7)	13 (11.8)	58 (20.6)	21 (15.0)	79 (18.7)
Not Hispanic or Latino	150 (72.1)	84 (80.8)	234 (75.0)	63 (85.1)	29 (80.6)	92 (83.6)	213 (75.5)	113 (80.7)	326 (77.3)
Not Reported	7 (3.4)	5 (4.8)	12 (3.8)	4 (5.4)	1 (2.8)	5 (4.5)	11 (3.9)	6 (4.3)	17 (4.0)

The denominator to calculate percentages is N, the number of participants in the analysis set within each treatment arm.
Note: MTZ therapy administered to participants with cIAI only.

PFIZER CONFIDENTIAL SDTM Creation: 02MAY2023 (10:46) Source Data: adsl Table Generation: 21JUN2023 (10:26) (Cutoff date: not applicable, Snapshot Date: 18APR2023 (18:56)) Output File: ./csr_figaro/C3601002_CSR/t14121_itt
Table 14.1.2.1 ATM-AVI is for Pfizer internal use.

Table 39: Baseline Characteristics – ITT Analysis Set

	cIAI			HAP/VAP			All Participants		
	ATM-AVI (+/-MTZ) (N=208)	Meropenem (N=104)	Total (N=312)	ATM-AVI (+/-MTZ) (N=74)	Meropenem (N=36)	Total (N=110)	ATM-AVI (+/-MTZ) (N=282)	Meropenem (N=140)	Total (N=422)
Body Mass Index (kg/m**2)									
n	207	103	310	73	35	108	280	138	418
Mean (SD)	25.9 (5.46)	25.7 (5.73)	25.8 (5.54)	24.8 (5.06)	24.6 (6.61)	24.7 (5.57)	25.6 (5.37)	25.4 (5.96)	25.5 (5.57)
Median (range)	25.7 (14.2, 58.6)	24.5 (13.4, 41.8)	25.4 (13.4, 58.6)	24.3 (10.4, 41.5)	24.7 (10.9, 48.3)	24.5 (10.4, 48.3)	25.3 (10.4, 58.6)	24.5 (10.9, 48.3)	25.0 (10.4, 58.6)
Height (cm)									
n	207	103	310	73	35	108	280	138	418
Mean (SD)	168.2 (9.10)	167.3 (10.27)	167.9 (9.50)	169.0 (8.03)	170.3 (8.50)	169.4 (8.17)	168.4 (8.83)	168.1 (9.91)	168.3 (9.19)
Median (range)	168.8 (145.0, 195.0)	167.0 (134.6, 190.0)	168.0 (134.6, 195.0)	170.0 (150.0, 193.0)	171.0 (147.0, 185.0)	170.0 (147.0, 193.0)	169.0 (145.0, 195.0)	169.0 (134.6, 190.0)	169.0 (134.6, 195.0)
Weight (kg)									
n	207	103	310	73	35	108	280	138	418
Mean (SD)	73.2 (16.11)	72.2 (18.66)	72.9 (16.98)	70.6 (15.20)	71.8 (20.98)	71.0 (17.19)	72.6 (15.89)	72.1 (19.19)	72.4 (17.03)
Median (range)	72.0 (37.1, 130.0)	69.0 (44.5, 125.0)	70.0 (37.1, 130.0)	70.0 (32.9, 120.0)	75.0 (30.0, 130.0)	72.0 (30.0, 130.0)	71.4 (32.9, 130.0)	70.0 (30.0, 130.0)	70.0 (30.0, 130.0)
Creatinine Clearance (mL/min)									
n	206	104	310	74	35	109	280	139	419
Mean (SD)	104.8 (46.59)	101.9 (43.19)	103.8 (45.43)	102.7 (65.04)	106.3 (81.69)	103.9 (70.45)	104.2 (51.99)	103.0 (55.14)	103.8 (52.99)
Median (range)	102.0 (20.1, 337.0)	94.0 (29.0, 305.0)	99.5 (20.1, 337.0)	88.0 (19.0, 317.0)	88.0 (38.0, 404.0)	88.0 (19.0, 404.0)	100.0 (19.0, 337.0)	92.0 (29.0, 404.0)	97.0 (19.0, 404.0)
Renal Function Group, n (%)									
CrCl >15 to ≤ 30 mL/min	5 (2.4)	1 (1.0)	6 (1.9)	6 (8.1)	0	6 (5.5)	11 (3.9)	1 (0.7)	12 (2.8)
CrCl > 30 to ≤ 50 mL/min	18 (8.7)	7 (6.7)	25 (8.0)	10 (13.5)	7 (19.4)	17 (15.5)	28 (9.9)	14 (10.0)	42 (10.0)
CrCl > 50 to ≤ 150 mL/min	157 (75.5)	85 (81.7)	242 (77.6)	43 (58.1)	23 (63.9)	66 (60.0)	200 (70.9)	108 (77.1)	308 (73.0)
CrCl > 150 mL/min	26 (12.5)	11 (10.6)	37 (11.9)	15 (20.3)	5 (13.9)	20 (18.2)	41 (14.5)	16 (11.4)	57 (13.5)
APACHE II Score									
n	208	104	312	74	35	109	282	139	421
Mean (SD)	7.5 (5.17)	7.7 (5.06)	7.5 (5.13)	16.4 (5.06)	17.3 (5.54)	16.7 (5.21)	9.8 (6.48)	10.1 (6.65)	9.9 (6.53)
Median (range)	7.0 (0.0, 28.0)	7.0 (0.0, 23.0)	7.0 (0.0, 28.0)	15.0 (10.0, 30.0)	17.0 (10.0, 29.0)	15.0 (10.0, 30.0)	9.0 (0.0, 30.0)	10.0 (0.0, 29.0)	9.0 (0.0, 30.0)
APACHE II Score Category, n (%)									
≤ 10	162 (77.9)	80 (76.9)	242 (77.6)	8 (10.8)	4 (11.1)	12 (10.9)	170 (60.3)	84 (60.0)	254 (60.2)
> 10	46 (22.1)	24 (23.1)	70 (22.4)	66 (89.2)	31 (86.1)	97 (88.2)	112 (39.7)	55 (39.3)	167 (39.6)
Source of Acquired Pneumonia[a], n (%)									
Hospital	NA	NA	NA	41 (55.4)	18 (50.0)	59 (53.6)	41 (14.5)	18 (12.9)	59 (14.0)
Ventilator	NA	NA	NA	33 (44.6)	18 (50.0)	51 (46.4)	33 (11.7)	18 (12.9)	51 (12.1)
Mechanical Ventilation Status at Baseline[a], n (%)									
Yes	NA	NA	NA	38 (51.4)	19 (52.8)	57 (51.8)	38 (13.5)	19 (13.6)	57 (13.5)
No	NA	NA	NA	36 (48.6)	17 (47.2)	53 (48.2)	36 (12.8)	17 (12.1)	53 (12.6)
Previous Treatment Failure, n(%)									
Yes	25 (12.0)	10 (9.6)	35 (11.2)	50 (67.6)	20 (55.6)	70 (63.6)	75 (26.6)	30 (21.4)	105 (24.9)
No	183 (88.0)	94 (90.4)	277 (88.8)	24 (32.4)	16 (44.4)	40 (36.4)	207 (73.4)	110 (78.6)	317 (75.1)

a. Mechanical ventilation and souce of acquired pneumonia assessed only for HAP/VAP participants.
The denominator to calculate percentages is N, the number of participants within each treatment arm.
Note: MTZ therapy administered to participants with cIAI only.

PFIZER CONFIDENTIAL SDTM Creation: 14JUN2023 (10:36) Source Data: adsl Table Generation: 21JUN2023 (10:36) (Cutoff date: not applicable, Snapshot Date: 18APR2023 (18:56)) Output File: ./csr_figaro/C3601002_CSR/t14122_itt
Table 14.1.2.2 ATM-AVI is for Pfizer internal use.

Table 40: Microbiology Baseline Characteristics - ITT Analysis Set

	Number (%) of Participants								
	cIAI			HAP/VAP			Total		
	ATM-AVI (+/-MTZ) (N=208) n (%)	Meropenem (N=104) n (%)	Total (N=312) n (%)	ATM-AVI (+/-MTZ) (N=74) n (%)	Meropenem (N=36) n (%)	Total (N=110) n (%)	ATM-AVI (+/-MTZ) (N=282) n (%)	Meropenem (N=140) n (%)	Total (N=422) n (%)
No Pathogen	47 (22.6)	23 (22.1)	70 (22.4)	31 (41.9)	15 (41.7)	46 (41.8)	78 (27.7)	38 (27.1)	116 (27.5)
Monomicrobial	92 (44.2)	53 (51.0)	145 (46.5)	31 (41.9)	18 (50.0)	49 (44.5)	123 (43.6)	71 (50.7)	194 (46.0)
Polymicrobial	69 (33.2)	28 (26.9)	97 (31.1)	12 (16.2)	3 (8.3)	15 (13.6)	81 (28.7)	31 (22.1)	112 (26.5)
2	32 (15.4)	14 (13.5)	46 (14.7)	10 (13.5)	2 (5.6)	12 (10.9)	42 (14.9)	16 (11.4)	58 (13.7)
3	20 (9.6)	4 (3.8)	24 (7.7)	1 (1.4)	1 (2.8)	2 (1.8)	21 (7.4)	5 (3.6)	26 (6.2)
4	8 (3.8)	5 (4.8)	13 (4.2)	1 (1.4)	0	1 (0.9)	9 (3.2)	5 (3.6)	14 (3.3)
>=5	9 (4.3)	5 (4.8)	14 (4.5)	0	0	0	9 (3.2)	5 (3.6)	14 (3.3)
Monomicrobial infection[a]									
Gram-positive aerobe	11 (6.8)	3 (3.7)	14 (5.8)	0	1 (4.8)	1 (1.6)	11 (5.4)	4 (3.9)	15 (4.9)
Gram-negative aerobe	80 (49.7)	49 (60.5)	129 (53.3)	31 (72.1)	17 (81.0)	48 (75.0)	111 (54.4)	66 (64.7)	177 (57.8)
Anaerobe	1 (0.6)	1 (1.2)	2 (0.8)	0	0	0	1 (0.5)	1 (1.0)	2 (0.7)
Polymicrobial infection[a]									
Anaerobe	4 (2.5)	0	4 (1.7)	0	0	0	4 (2.0)	0	4 (1.3)
Gram-positive aerobe	1 (0.6)	1 (1.2)	2 (0.8)	0	0	0	1 (0.5)	1 (1.0)	2 (0.7)
Gram-negative aerobe	13 (8.1)	9 (11.1)	22 (9.1)	9 (20.9)	1 (4.8)	10 (15.6)	22 (10.8)	10 (9.8)	32 (10.5)
Anaerobe + Gram-positive aerobe	5 (3.1)	1 (1.2)	6 (2.5)	0	0	0	5 (2.5)	1 (1.0)	6 (2.0)
Anaerobe + Gram-negative aerobe	15 (9.3)	5 (6.2)	20 (8.3)	0	0	0	15 (7.4)	5 (4.9)	20 (6.5)

Gram-negative aerobe + Gram-positive aerobe	12 (7.5)	6 (7.4)	18 (7.4)	3 (7.0)	2 (9.5)	5 (7.8)	15 (7.4)	8 (7.8)	23 (7.5)
Gram-negative aerobe + Gram-positive aerobe + Anaerobe	19 (11.8)	6 (7.4)	25 (10.3)	0	0	0	19 (9.3)	6 (5.9)	25 (8.2)

The denominator to calculate percentages is N, the number of participants within each treatment arm of the analysis set.
a. Percentages based on the number of participants with at least one bacterial pathogen.
Multiple isolates of the same species from the same patient are counted only once, regardless of source (intra-abdominal, respiratory, or blood).
Note: MTZ therapy administered to participants with cIAI only.

PFIZER CONFIDENTIAL SDTM Creation: 02MAY2023 (10:46) Source Data: adsl adbase adms Table Generation: 08JUN2023 (13:29) (Cutoff date: not applicable, Snapshot Date: 18APR2023 (18:56)) Output File: ./csr_figaro/C3601002_CSR/t141332
Table 14.1.3.3.2 ATM-AVI is for Pfizer internal use.

In Vitro Susceptibility to ATM, Meropenem and Colistin (by EUCAST Criteria) Among Baseline Pathogens, All Participants - micro-ITT Analysis Set (Protocol C3601002_CSR)

	ATM-AVI (+/-MTZ) (N=177)				Meropenem (N=94)				Total (N=271)			
Pathogen Type Baseline Pathogen Study Drug	Number of Pathogens/ Number of Pathogens Tested	%S	%I	%R	Number of Pathogens/ Number of Pathogens Tested	%S	%I	%R	Number of Pathogens/ Number of Pathogens Tested	%S	%I	%R
Overall												
ATM	312/192	68.8	9.9	21.4	159/105	64.8	6.7	28.6	471/297	67.3	8.8	23.9
Meropenem	312/252	91.3	1.2	7.5	159/128	89.8	1.6	8.6	471/380	90.8	1.3	7.9
Colistin	312/195	91.3	0	8.7	159/104	90.4	0	9.6	471/299	91.0	0	9.0
Enterobacterales												
Overall Enterobacterales												
ATM	190/174	75.9	2.3	21.8	101/98	68.4	2.0	29.6	291/272	73.2	2.2	24.6
Meropenem	190/174	92.5	1.1	6.3	101/98	91.8	0	8.2	291/272	92.3	0.7	7.0
Colistin	190/174	91.4	0	8.6	101/98	89.8	0	10.2	291/272	90.8	0	9.2
Citrobacter farmeri												
ATM	1/1	100.0	0	0	0/0	NA	NA	NA	1/1	100.0	0	0
Meropenem	1/1	100.0	0	0	0/0	NA	NA	NA	1/1	100.0	0	0
Colistin	1/1	100.0	0	0	0/0	NA	NA	NA	1/1	100.0	0	0
Citrobacter freundii complex												
ATM	4/4	100.0	0	0	1/1	0	0	100.0	5/5	80.0	0	20.0

Percentages are based on the number of pathogens tested.
Multiple pathogens of the same species from the same patient are counted only once, regardless of source (intra-abdominal, respiratory, or blood), using the pathogen with the highest MIC to study drug received.
S=Susceptible, I=Intermediate, R=Resistant, NA=Not Applicable
Note: MTZ therapy administered to participants with cIAI only.

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Table 41: Demographic Characteristics - ITT Analysis Set

	ATM-AVI (N=12)	BAT (N=3)	Total (N=15)
Age (Years), n (%)			
<65	8 (66.7)	2 (66.7)	10 (66.7)
65-74	3 (25.0)	1 (33.3)	4 (26.7)
75-84	1 (8.3)	0	1 (6.7)
Mean (SD)	56.6 (17.14)	65.7 (6.66)	58.4 (15.85)
Median (Range)	61.0 (31.0, 83.0)	64.0 (60.0, 73.0)	62.0 (31.0, 83.0)
Gender, n (%)			
Male	8 (66.7)	1 (33.3)	9 (60.0)
Female	4 (33.3)	2 (66.7)	6 (40.0)
Race, n (%)			
White	5 (41.7)	2 (66.7)	7 (46.7)
Asian	6 (50.0)	1 (33.3)	7 (46.7)
American Indian or Alaska Native	1 (8.3)	0	1 (6.7)
Ethnicity, n (%)			
Hispanic or Latino	1 (8.3)	0	1 (6.7)
Not Hispanic or Latino	11 (91.7)	3 (100.0)	14 (93.3)

The denominator to calculate percentages is N, the number of participants in the analysis set within each treatment arm.

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Table 14.1.2.1 ATM-AVI is for Pfizer internal use.

Table 42: Demographic Characteristics - ITT Analysis Set

		ATM-AVI (N=12)	BAT (N=3)	Total (N=15)
Type of Infection, n (%)				
	cIAI	2(16.7)	0	2(13.3)
	HAP/VAP	3(25.0)	1(33.3)	4(26.7)
	cUTI	3(25.0)	1(33.3)	4(26.7)
	BSI	4(33.3)	1(33.3)	5(33.3)
Body Mass Index (kg/m**2)				
	n	12	3	15
	Mean (SD)	27.4 (6.1)	23.6 (2.7)	26.7 (5.7)
	Median (Range)	26.3 (18.8, 39.8)	25.1 (20.5, 25.1)	25.4 (18.8, 39.8)
Height (cm)				
	n	12	3	15
	Mean (SD)	167.5 (8.9)	165.0 (8.7)	167.0 (8.6)
	Median (Range)	168.0 (157.0, 185.0)	160.0 (160.0, 175.0)	168.0 (157.0, 185.0)
Weight (kg)				
	n	12	3	15
	Mean (SD)	76.9 (17.0)	64.6 (12.3)	74.5 (16.6)
	Median (Range)	77.5 (48.0, 107.0)	64.3 (52.5, 77.0)	75.0 (48.0, 107.0)
Creatinine Clearance (mL/min)				
	n	12	3	15
	Mean (SD)	100.8 (67.2)	149.0 (123.8)	110.5 (78.3)
	Median (Range)	73.5 (15.0, 238.0)	104.0 (54.0, 289.0)	80.0 (15.0, 289.0)
Renal Function Group, n (%)				
	CrCl > 15 to≤ 30 mL/min	1 (8.3)	0	1 (6.7)
	CrCl > 30 to≤ 50 mL/min	1 (8.3)	0	1 (6.7)
	CrCl > 50 to≤ 150 mL/min	7 (58.3)	2 (66.7)	9 (60.0)
	CrCl > 150 mL/min	3 (25.0)	1 (33.3)	4 (26.7)
APACHE II Score				
	n	12	3	15
	Mean (SD)	12.8 (7.9)	12.0 (8.7)	12.6 (7.8)
	Median (Range)	13.0 (0.0, 25.0)	8.0 (6.0, 22.0)	13.0 (0.0, 25.0)
APACHE II Score Category, n (%)				
	<= 10	4 (33.3)	2 (66.7)	6 (40.0)
	> 10	8 (66.7)	1 (33.3)	9 (60.0)
Source of Acquired Pneumonia[a], n (%)				
	Hospital	1 (8.3)	0	1 (6.7)
	Ventilator	2 (16.7)	1 (33.3)	3 (20.0)
Mechanical Ventilation Status at Baseline[a], n (%)				
	Yes	2 (16.7)	1 (33.3)	3 (20.0)
Previous Treatment Failure, n(%)				
	Yes	8 (66.7)	2 (66.7)	10 (66.7)
Monomicrobial/Polymicrobial Status, n(%)				
	Monomicrobial	6 (50.0)	3 (100.0)	9 (60.0)
	Polymicrobial	6 (50.0)	0	6 (40.0)
Number of microbes, n(%)				
	1	6 (50.0)	3 (100.0)	9 (60.0)
	2	6 (50.0)	0	6 (40.0)
Participants with Positive ESBL Pathogen, n(%)				
	Yes	9 (75.0)	3 (100.0)	12 (80.0)
	No	1 (8.3)	0	1 (6.7)

a. Mechanical ventilation and source of acquired pneumonia assessed only for HAP/VAP participants.
The denominator to calculate percentages is N, the number of participants within each treatment arm.

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Table 14.1.2.2 ATM-AVI is for Pfizer internal use.

Table 43: Microbiology Baseline Pathogen Resistance Characteristics-micro-ITT Analysis Set

Baseline Characteristics	All Participants ATM-AVI (N=12)	BAT (N=3)	Total (N=15)
Number of baseline pathogens	18	3	21
Number of baseline aerobic Gram-negative pathogens	17	3	20
Number of baseline Enterobacterales pathogens	12	3	15
Number of baseline aerobic Gram-negative non-Enterobacterales pathogens	5	0	5
ATM or Meropenem resistant[a]			
Number of pathogens/Number tested	14/14	3/3	17/17
ATM non-susceptible(CLSI)	11(78.6)	3(100.0)	14(82.4)
ATM non-susceptible(EUCAST)	13(92.9)	3(100.0)	16(94.1)
Meropenem non-susceptible(CLSI)	14(100.0)	3(100.0)	17(100.0)
Meropenem non-susceptible(EUCAST)	14(100.0)	3(100.0)	17(100.0)

a. Percentages are based on the number of baseline aerobic Gram-negative pathogens excluding Stenotrophomonas maltophilia.
b. Percentages are based on the number of baseline Enterobacterales pathogens.
c. Stenotrophomonas maltophilia is inherently MBL+, and therefore, though not tested, is included.
d. Percentages of MBL-positive subgroups are based on the number of MBL-positive pathogens.

PFIZER CONFIDENTIAL SDTM Creation: 01APR2023 (05:12) Source Data: adsl adbase Table Generation: 08JUN2023 (17:30) (Cutoff date: not applicable, Snapshot Date: 24MAR2023 (21:27)) Output File: ./csr_figaro/C3601009_CSR/t141333tst
Table 14.1.3.3.3 ATM-AVI is for Pfizer internal use.

Table 44: Microbiology Baseline Pathogen Resistance Characteristics-micro-ITT Analysis Set

Baseline Characteristics	All Participants ATM-AVI (N=12)	BAT (N=3)	Total (N=15)
ESBL[b]			
Number of pathogens/Number tested	12/12	3/3	15/15
ESBL positive	10(83.3)	3(100.0)	13(86.7)
Carbapenemase			
Number of pathogens/Number tested	18/17	3/3	21/20
Carbapenamase-positive	17(100.0)	3(100.0)	20(100.0)
Serine Carbapenemase			
Number of pathogens/Number tested	18/17	3/3	21/20
Serine Carbapenamase-positive	3(17.6)	0(0.0)	3(15.0)
Metallo Beta-Lactamase[a,c]			
Number of pathogens/Number tested	17/17	3/3	20/20
MBL-positive[d]	15(88.2)	3(100.0)	18(90.0)
VIM	2(13.3)	0(0.0)	2(11.1)
NDM	10(66.7)	3(100.0)	13(72.2)
L1	3(20.0)	0(0.0)	3(16.7)

a. Percentages are based on the number of baseline aerobic Gram-negative pathogens excluding Stenotrophomonas maltophilia.
b. Percentages are based on the number of baseline Enterobacterales pathogens.
c. Stenotrophomonas maltophilia is inherently MBL+, and therefore, though not tested, is included.
d. Percentages of MBL-positive subgroups are based on the number of MBL-positive pathogens.

PFIZER CONFIDENTIAL SDTM Creation: 01APR2023 (05:12) Source Data: adsl adbase Table Generation: 08JUN2023 (17:30) (Cutoff date: not applicable, Snapshot Date: 24MAR2023 (21:27)) Output File: ./csr_figaro/C3601009_CSR/t141333tst
Table 14.1.3.3.3 ATM-AVI is for Pfizer internal use.

- **Numbers analysed**

<u>Study C3601002 (D4910C00004)</u>

See Table 43 above.

<u>Study C3601009</u>

See Table 44 above.

- **Outcomes and estimation**

Study C3601002 (D4910C00004)

Primary endpoints

Numerically similar results in clinical response were seen between the treatment arms at TOC in both the ITT and CE analysis populations. In the ITT population, the difference in cure rate was 2.7% (193/282 subjects (68.4%) vs. 92/140 subjects (65.7%)) with 95% CI -11.4%, 17.8%. In the CE population the difference in cure rate was also low, 2.7% (164/213 subjects (77%) vs. 78/105 subjects (74.3%)) with 95% CI -11.9%, 19.2%.

Table 45: Adjudicated Clinical Response at the TOC Visit – ITT Analysis Set

Response	Number (%) of Participants, 95% CI		Difference[a] (95% CI[b])
	ATM-AVI (+/-MTZ) (N=282)	Meropenem (N=140)	
Cure	193 (68.4) (62.8, 73.7)	92 (65.7) (57.6, 73.2)	2.7 (-11.4, 17.8)
Failure	67 (23.8)	40 (28.6)	
Indeterminate	22 (7.8)	8 (5.7)	

Note: MTZ therapy administered to participants with cIAI only.
a. Difference = Difference in clinical cure rates (ATM-AVI treatment arm minus meropenem treatment arm).
b. The confidence interval (CI) for the difference is calculated using the unstratified Miettinen and Nurminen method.
Percentages are based on the total number of participants in the treatment arm (N).

PFIZER CONFIDENTIAL SDTM Creation: 02MAY2023 (14:00) Source Data: adfa Table Generation: 06JUN2023 (15:05) (Cutoff date: not applicable, Snapshot Date: 18APR2023 (18:56)) Output File: ./csr_figaro/C3601002_CSR/adfa_crtcv_itt
Table 14.2.1.1 ATM-AVI is for Pfizer internal use.

Table 46: Adjudicated Clinical Response at the TOC Visit – CE Analysis Set

Response	Number (%) of Participants, 95% CI		Difference[a] (95% CI[b])
	ATM-AVI (+/-MTZ) (N=213)	Meropenem (N=105)	
Cure	164 (77.0) (71.0, 82.3)	78 (74.3) (65.3, 81.9)	2.7 (-11.9, 19.2)
Failure	49 (23.0)	27 (25.7)	

Note: MTZ therapy administered to participants with cIAI only
a. Difference = Difference in clinical cure rates (ATM-AVI treatment group minus meropenem treatment group).
b. The confidence interval (CI) for the difference is calculated using the unstratified Miettinen and Nurminen method.
Percentages are based on the total number of participants in the treatment arm (N).

PFIZER CONFIDENTIAL SDTM Creation: 02MAY2023 (14:00) Source Data: Table Generation: 06JUN2023 (14:59) (Cutoff date: not applicable, Snapshot Date: 18APR2023 (18:56))) Output File: ./csr_figaro/C3601002_CSR/adfa_crtcv_ce
Table 14.2.1.1.1 ATM-AVI is for Pfizer internal use.

Secondary endpoints

Clinical responses stratified by infection type in the ITT and CE populations by infection type are presented in the tables below:

Table 47: Adjudicated Clinical Response at the TOC Visit by type of Infection – ITT Analysis Set

Type of Infectious Disease	Response	Number (%) of Participants, 95% CI ATM-AVI (+/-MTZ) (N=282)	Number (%) of Participants, 95% CI Meropenem (N=140)	Difference[a] (95% CI[b])
cIAI	n	208	104	
	Cure	159 (76.4) (70.3, 81.8)	77 (74.0) (65.0, 81.7)	2.4 (-12.4, 19.1)
	Failure	34 (16.3)	23 (22.1)	
	Indeterminate	15 (7.2)	4 (3.8)	
HAP/VAP	n	74	36	
	Cure	34 (45.9) (34.9, 57.3)	15 (41.7) (26.7, 57.9)	4.3 (-25.6, 32.2)
	Failure	33 (44.6)	17 (47.2)	
	Indeterminate	7 (9.5)	4 (11.1)	

Note: MTZ therapy administered to participants with cIAI only.
a. Difference = Difference in clinical cure rates (ATM-AVI treatment arm minus meropenem treatment arm).
b. The confidence interval (CI) for the difference is calculated using the unstratified Miettinen and Nurminen method. The 95% confidence interval (CI) for the proportion in each arm is calculated using Jeffrey's method.
Percentages are based on the total number of participants in the treatment arm (n).

Table 48: Adjudicated Clinical Response at the TOC Visit by Type of Infection – CE Analysis Set

Type of Infectious Disease	Response	Number (%) of Participants, 95% CI ATM-AVI (+/-MTZ) (N=213)	Number (%) of Participants, 95% CI Meropenem (N=105)	Difference[a] (95% CI[b])
cIAI	n	168	83	
	Cure	143 (85.1) (79.2, 89.9)	66 (79.5) (69.9, 87.1)	5.6 (-8.9, 23.1)
	Failure	25 (14.9)	17 (20.5)	
HAP/VAP	n	45	22	
	Cure	21 (46.7) (32.7, 61.1)	12 (54.5) (34.3, 73.7)	-7.9 (-42.8, 29.4)
	Failure	24 (53.3)	10 (45.5)	

Note: MTZ therapy administered to participants with cIAI only.
a. Difference = Difference in clinical cure rates (ATM-AVI treatment arm minus meropenem treatment arm).
b. The confidence interval (CI) for the difference is calculated using the unstratified Miettinen and Nurminen method. The 95% confidence interval (CI) for the proportion in each arm is calculated using Jeffrey's method.
Percentages are based on the total number of participants in the treatment arm (n).

In the micro-ITT and the ME populations, the clinical cure rates at TOC are numerically similar between the treatment groups in the respective populations and consistent with those in the primary analysis sets (ITT/CE). In the micro-ITT population, the clinical cure rates at TOC were 72.9% (95% CI 66.0%, 79.0%) in the ATM-AVI treatment group and 72.3% (95% CI 62.7%, 80.6%) in the MER ± COL treatment group. The difference is 0.5% (95% CI -15.7%, 18.6%). In the ME population, the clinical cure rates at TOC were 78.5% in the ATM-AVI treatment group and 75.9% in the MER ± COL treatment group. The treatment difference is 2.6% (95% CI -14.0%, 21.6%).

The micro-MITT population is a subset of the micro-ITT population including all subjects who received any amount of study drug. In the micro-MITT population, the clinical cure rates at TOC were 73.7% in the ATM-AVI treatment group and 72.3% in the MER ± COL treatment group. The treatment difference is 1.4% (95% CI, -14.9%, 19.4%).

The proportion of participants with MBL-positive pathogens was very low in the micro-ITT population, 7 subjects in the ATM-AVI group and 3 subjects in the MER ± COL group of which 2 subjects in each

group was cured. Corresponding numbers in the ME population were 4 and 1 subjects respectively, with two cures at TOC in the ATM-AVI group:

Table 49: Adjudicated Clinical Response at the TOC Visit for Participants by Metallo-β-Lactamase-Positive Status – ME Analysis Set

Metallo-ß-Lactamase Status	Response	Number (%) of Participants	
		ATM-AVI (+/-MTZ) (N=149)	Meropenem (N=79)
Positive	n	4	1
	Cure	2 (50.0)	0
	Failure	2 (50.0)	1 (100)
	Indeterminate	0	0
Negative	n	145	78
	Cure	115 (79.3)	60 (76.9)
	Failure	30 (20.7)	18 (23.1)
	Indeterminate	0	0

Percentages are based on the total number of participants in the treatment arm (n).

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Table 14.2.2.3.1 ATM-AVI is for Pfizer internal use.

Per-participant microbiological responses at TOC for all participants in both analysis populations were numerically similar between the ATM-AVI and MER ± COL treatment groups. In both analysis populations, higher favorable microbiological response rates were observed in participants with cIAI infection compared to the participants with HAP/VAP. Per-participant microbiological response at the TOC visit in the micro-ITT analysis set is presented in Table 50 below. Participants with an Indeterminate per-participant microbiological response are excluded from this analysis.

Table 50: Per-Participant microbiological response at the TOC Visit – micro-ITT Analysis Set

Type of Infectious Disease	Response	Number (%) of Participants ATM-AVI(+/-MTZ) (N=177)	Number (%) of Participants Meropenem (N=94)
All Participants	n	169	92
	Favorable	128(75.7)	68 (73.9)
	Eradication	2 (1.2)	1 (1.1)
	Presumed Eradication	126(74.6)	67 (72.8)
	Unfavorable	41 (24.3)	24 (26.1)
	Persistence	8 (4.7)	2 (2.2)
	Persistence with increasing MIC[a]	2 (1.2)	0
	Presumed Persistence	33 (19.5)	22 (23.9)
cIAI	n	133	73
	Favorable	111(83.5)	59 (80.8)
	Eradication	0	1 (1.4)
	Presumed Eradication	111(83.5)	58 (79.5)
	Unfavorable	22 (16.5)	14 (19.2)
	Persistence	1 (0.8)	0
	Persistence with increasing MIC[a]	0	0
	Presumed Persistence	21 (15.8)	14 (19.2)
HAP/VAP	n	36	19
	Favorable	17 (47.2)	9 (47.4)
	Eradication	2 (5.6)	0
	Presumed Eradication	15 (41.7)	9 (47.4)
	Unfavorable	19 (52.8)	10 (52.6)
	Persistence	7 (19.4)	2 (10.5)
	Persistence with increasing MIC[a]	2 (5.6)	0
	Presumed Persistence	12 (33.3)	8 (42.1)

a. >= 4-fold higher MIC to study therapy after treatment with IV study therapy.
Percentages are based on the total number of participants in the treatment group (n).
Note: MTZ therapy administered to participants with cIAI only.

PFIZER CONFIDENTIAL SDTM Creation: 14JUN2023 (10:37) Source Data: admb Table Generation: 21JUN2023 (11:58) (Cutoff date: not applicable, Snapshot Date: 18APR2023 (18:56)) Output File: ./csr_figaro/C3601002_CSR/per_part_mi_resp_2
Table 14.2.2.4 ATM-AVI is for Pfizer internal use.

Overall, the 28-day all causality mortality rate was low and numerically similar between treatment groups in both analysis populations, with a total of 22 fatal outcomes. In both populations, mortality rates were lower for the cIAI subjects compared to the HAP/VAP subjects. The proportion of participants who died within 28 days from randomization in the ITT population is provided in Table 51

Table 51: Proportion of Participants Who Died Within 28 Days from Randomization – ITT analysis set

		ATM-AVI (+/-MTZ) (N=282) n (%)	Meropenem (N=140) n (%)
All Participants	n	282	140
	Death Within 28 Days After Randomization	12 (4.3)	10 (7.1)
	Disease Under Study	3 (1.1)	1 (0.7)
	Unknown	0	1 (0.7)
	Other	9 (3.2)	8 (5.7)
cIAI	n	208	104
	Death Within 28 Days After Randomization	4 (1.9)	3 (2.9)
	Disease Under Study	0	0
	Unknown	0	1 (1.0)
	Other	4 (1.9)	2 (1.9)
HAP/VAP	n	74	36
	Death Within 28 Days After Randomization	8 (10.8)	7 (19.4)
	Disease Under Study	3 (4.1)	1 (2.8)
	Unknown	0	0
	Other	5 (6.8)	6 (16.7)

Note: MTZ therapy administered to participants with cIAI only.
Percentages are based on the total number of participants in the treatment arm (n).

PFIZER CONFIDENTIAL SDTM Creation: 02MAY2023 (10:46) Source Data: adsl Table Generation: 08JUN2023 (14:09) (Cutoff date: not applicable, Snapshot Date: 18APR2023 (18:56)) Output File: ./csr_figaro/C3601002_CSR/addd_prop_itt
Table 14.2.2.5 ATM-AVI is for Pfizer internal use.

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Primary endpoints

Due to the small number patients in the study, possible conclusions are limited. Primary outcomes are provided in Table 52 below:

Table 52: Adjudicated Clinical Response at the TOC Visit – micro-ITT Analysis Set

Type of Infection	Response	Number (%) of Participants, 95% CI	
		ATM-AVI (N=12)	BAT (N=3)
All Participants	n	12	3
	Cure	5 (41.7) (18.0, 68.8)	0
	Failure	5 (41.7)	1 (33.3)
	Indeterminate	2 (16.7)	2 (66.7)
cIAI	n	2	0
	Cure	0	0
	Failure	2 (100.0)	0
	Indeterminate	0	0
HAP/VAP	n	3	1
	Cure	0	0
	Failure	1 (33.3)	0
	Indeterminate	2 (66.7)	1 (100.0)
cUTI	n	3	1
	Cure	2 (66.7) (17.7, 96.1)	0
	Failure	1 (33.3)	0
	Indeterminate	0	1 (100.0)
BSI	n	4	1
	Cure	3 (75.0) (28.4, 97.2)	0
	Failure	1 (25.0)	1 (100.0)
	Indeterminate	0	0

The percentages are based on the total number of participants in the treatment arm (n).
The two-sided 95% CI are calculated using Jeffrey's method.

PFIZER CONFIDENTIAL SDTM Creation: 26APR2023 (11:30) Source Data: adfa Table Generation: 30MAY2023 (15:21) (Cutoff date: not applicable, Snapshot Date: 24MAR2023 (21:27)) Output File: ./csr_figaro/C3601009_CSR/adfa_crtcv_micitt
Table 14.2.1.1 ATM-AVI is for Pfizer internal use.

All-cause mortality at day 28 was 1/12 subjects in the ATM-AVI treatment group and 1/3 in the BAT treatment group. Both participants who died on or before 28 days from randomization were in the HAP/VAP subgroup. Both had died before day 14, according to exploratory endpoint analysis. The subject who died in the ATM-AVI group died due to the disease under study, whereas the subject who died in the BAT group died due to mixed encephalopathy.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 53: Summary of Efficacy for Trial C3601002

Title: A Phase 3 Prospective, Randomized, Multicenter, Open-Label, Central Assessor Blinded, Parallel Group, Comparative Study to Determine the Efficacy, Safety and Tolerability of Aztreonam Avibactam (ATM-AVI) ± Metronidazole (MTZ) Versus Meropenem ± Colistin (MER ± COL) for the Treatment of Serious Infections due to Gram Negative Bacteria, Including Metallo β-Lactamase (MBL) Producing Multidrug Resistant Pathogens, for Which There are Limited or no Treatment Options				
Study identifier	Protocol number: C3601002 (D4910C00004) EudraCT Number: 2017-002742-68			
Design	Prospective, Randomised, Multicenter, Open-Label, Central Assessor Blinded, Parallel Group, Comparative			
	Initiation date: Completion date:		05 April 2018 23 February 2023	
Hypothesis	No formal hypothesis, comparative			
Treatments groups	Aztreonam-Avibactam ± metronidazole (ATM-AVI)		1500 mg aztreonam plus 500 mg avibactam, q6h, i.v. (+ metronidazole 500 mg q8h, i.v. in patients with cIAI) for 14 days. 282 subjects randomised.	
	Meropenem ± Colistin (MER±COL)		1000 mg meropenem q8h as a 30-minute infusion plus optional colistimethate sodium with 9 million IU daily for 14 days. 140 subjects randomised.	
Endpoints and definitions	Primary endpoint		The primary endpoint was the proportion of subjects with clinical cure at the TOC visit in the Intent-To-Treat (ITT) and Clinically Evaluable (CE) analysis sets. ITT and CE are considered co-primary analysis sets.	
	Secondary endpoint		Proportion of subjects with clinical cure at the TOC visit by infection type in the ITT and CE analysis sets.	
	Secondary endpoint		Proportion of subjects who died on or before 28 days from randomization in the ITT and micro-ITT analysis sets	
Database lock	18 April 2023			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat, Clinically evaluable, Test of cure (day 28)			
Descriptive statistics and estimate variability	Treatment group	ATM-AVI	MER±COL	
	Number of subjects	282	140	
	Primary endpoint, proportion of subjects with clinical cure at the TOC visit in the Intent-To-Treat (ITT) population	193/282 68.4 %	92/140 65.7 %	Difference: 2.7 %
	2-sided 95% confidence interval	62.8, 73.7	57.6, 73.2	-11.4, 17.8

Title: A Phase 3 Prospective, Randomized, Multicenter, Open-Label, Central Assessor Blinded, Parallel Group, Comparative Study to Determine the Efficacy, Safety and Tolerability of Aztreonam Avibactam (ATM-AVI) ± Metronidazole (MTZ) Versus Meropenem ± Colistin (MER ± COL) for the Treatment of Serious Infections due to Gram Negative Bacteria, Including Metallo β-Lactamase (MBL) Producing Multidrug Resistant Pathogens, for Which There are Limited or no Treatment Options				
Study identifier	Protocol number: C3601002 (D4910C00004) EudraCT Number: 2017-002742-68			
	Primary endpoint, proportion of subjects with clinical cure at the TOC visit in the clinically evaluable (CE) population	164/213 77.0 %	78/105 74.3 %	2.7
	2-sided 95% confidence interval	71.0, 82.3	65.3, 81.9	-11.9, 19.2
	Secondary endpoint: Clinical cure at TOC by type of infection, ITT.	cIAI: 159/208 76.4 % HAP/VAP: 34/74 45.9 %	cIAI: 77/104 74.0 % HAP/VAP : 15/36 41.7 %	2.4 (-12.4, 19.1) 4.3 (-25.6, 32.2)
	Secondary endpoint: Clinical cure at TOC by type of infection, CE.	cIAI: 143/168 85.1 % HAP/VAP: 21/45 46.7 %	cIAI: 66/83 79.5 % HAP/VAP : 12/22 54.5 %	5.6 (-8.9, 23.1) -7.9 (-42.8, 29.4)
	Secondary endpoint: Proportion of subjects that died within 28 of randomisation, ITT.	All: 12/282 (4.3%) cIAI: 4/208 (1.9%) HAP/VAP: 8/74 (10.8%)	All: 10/140 (7.1%) cIAI: 3/104 (2.9%) HAP/VAP: 7/36 (19.4%)	

Table 54: Summary of Efficacy for Trial C3601009

Title: A Prospective, Randomized, Multicenter, Open-Label, Comparative Study to Assess the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) and Best Available Therapy for the Treatment of Serious Infections due to Multi-Drug Resistant Gram-Negative Bacteria Producing Metallo β -Lactamase (MBL)	
Study identifier	Protocol number: C3601009 EudraCT Number: 2017-004544-38
Design	Prospective, Randomised, Open-Label, Central Assessor Blinded, Parallel Group, Comparative

Title: A Prospective, Randomized, Multicenter, Open-Label, Comparative Study to Assess the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) and Best Available Therapy for the Treatment of Serious Infections due to Multi-Drug Resistant Gram-Negative Bacteria Producing Metallo β -Lactamase (MBL)				
Study identifier	Protocol number: C3601009 EudraCT Number: 2017-004544-38			
	Initiation date: Completion date:		25 December 2020 23 January 2023	
Hypothesis	No formal hypothesis, comparative			
Treatments groups	Aztreonam-Avibactam ± metronidazole (ATM-AVI)		1500 mg aztreonam plus 500 mg avibactam, q6h, i.v. (+ metronidazole 500 mg q8h, i.v. in patients with cIAI) for 5-14 days. 12 subjects randomised.	
	Best available therapy (BAT)		Determined based on local epidemiology and practices according to investigators' standard of care. 3 subjects randomised.	
Endpoints and definitions	Primary endpoint		The primary endpoint was the proportion of subjects with clinical cure at the TOC visit in the micro-ITT population	
	Secondary endpoint		Proportion of subjects with clinical cure at the TOC visit in the ME analysis set.	
	Secondary endpoint		Proportion of subjects with clinical cure at the EOT visit in the micro-ITT and ME analysis sets.	
	Secondary endpoint		Proportion of subjects with a favourable per-subject microbiological response at the EOT and TOC visits in the micro-ITT and ME analysis sets.	
	Secondary endpoint		Proportion of subjects with a favourable per-pathogen microbiological response at the EOT and TOC visits in the micro-ITT and ME analysis sets.	
	Secondary endpoint		Proportion of subjects who died on or before 28 days from randomization in the ITT and micro-ITT analysis sets.	
Database lock	24 March 2023			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Microbiological intent to treat at TOC (day 28)			
Descriptive statistics and estimate variability	Treatment group	ATM-AVI	BAT	
	Number of subjects	12	3	
	Proportion of subjects with clinical cure at TOC, micro-ITT	5/12 41.7 %	0/3 0 %	
	2-sided 95% confidence interval	18.0, 68.8		
	Secondary endpoint: Proportion of subjects that died within 28 of randomisation, ITT.	1/12 8.3%	1/3 33.3%	

2.6.5.3. Clinical studies in special populations

Table 55: Summary of Participants in Older Age Categories for Trials in the Phase 2/3 Safety Pool, Safety Analysis Set

Phase 2/3 Trial	Age 65-74		Age 75-84		Age ≥85	
	ATM-AVI ± MTZ n/N (%)	Comparator n/N (%)	ATM-AVI ± MTZ n/N (%)	Comparator n/N (%)	ATM-AVI ± MTZ n/N (%)	Comparator n/N (%)
Controlled Trials						
C3601002	52/275 (18.9)	31/137 (22.6)	37/275 (13.5)	9/137 (6.6)	5/275 (1.8)	1/137 (0.7)
C3601009	3/12 (25.0)	0/2 (0)	1/12 (8.3)	0/2 (0)	0/12 (0)	0/2 (0)
Non-Controlled Trials						
C3601001	5/18 (27.8)	N/A	0/18 (0)	N/A	0/18 (0)	N/A

Phase 2/3 pool includes Studies C3601001 (high dose cohort), C3601002, and C3601009.

2.6.5.4. Supportive studies

Study: C3601001 (D4910C00009)

Study title: A Phase 2a Prospective, Open-Label, Multicenter Study to Determine the Pharmacokinetics (PK) and Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) for the Treatment of Complicated Intra-Abdominal Infections (cIAIs) In Hospitalized Adults.

This was a prospective, open-label, non-comparative, dose-confirming multicentre Phase 2a study to determine the PK, safety and tolerability of ATM-AVI + metronidazole in the treatment of hospitalised patients with cIAI. Dosages are presented in Table 56 below.

Table 56: ATM – AVI Dosing Regimens

Cohort	Loading dose	Extended loading infusion	Maintenance infusion
Patients in Cohort 1 with normal renal function or mild renal impairment (CrCl >50 mL/min)	500 mg ATM plus 137 mg AVI by intravenous infusion over a 30 minute period	Not applicable*	1500 mg ATM plus 410 mg AVI over a 3 hour period (to be administered every 6 hours)
Patients in Cohort 2 and 3 with normal renal function or mild renal impairment (CrCl >50 mL/min)	500 mg ATM plus 167 mg AVI by intravenous infusion over a 30 minute period	Not applicable*	1500 mg ATM plus 500 mg AVI over a 3 hour period (to be administered every 6 hours)
Patients in Cohort 2 and 3 with moderate renal impairment (CrCl 31 - 50 mL/min)	500 mg ATM plus 167 mg AVI by intravenous infusion over a 30 minute period	Extended loading infusion of 1500 mg ATM plus 500 mg AVI over a 3 hour period	750 mg ATM plus 250 mg AVI over a 3 hour period (to be administered every 6 hours)

CrCl, creatinine clearance; ATM, aztreonam; AVI, avibactam
The first maintenance dose was started immediately following the loading dose.

Cohort 1 received a lower dose of avibactam in relation to aztreonam than cohorts 2 and 3. As efficacy evaluation, the investigator determined the clinical response at the end of treatment, test of cure and late follow up visit as either cure, failure or indeterminate.

Patient disposition is summarised in Table 57 below.

Table 57: Patient Disposition

Patient Population / Analysis Set	Lower AVI Dose (Cohort 1)	Higher AVI Dose (Cohorts 2+3)	Total
Number (%) of Patients	n (%)	n (%)	n (%)
Enrolled: 40			
Screened Failure: 4			
Assigned to Treatment	16 (100.0)	20 (100.0)	36 (100.0)
Treated (MITT)	16 (100.0)	18 (90.0)	34 (94.4)
mMITT Analysis Set	12 (75.0)	11 (55.0)	23 (63.9)
PK Analysis Set	16 (100.0)	18 (90.0)	34 (94.4)
Not Treated	0	2 (10.0)	2 (5.6)

MITT, modified intent to treat; mMTT, microbiologically modified intent-to-treat; PK, pharmacokinetic, AVI, avibactam; n, number of patients with an observation

Around 60% of the patients were assessed as being cured at TOC (58.8% in the MITT population and 60.9% in the mMITT population). The differences in the clinical response to study treatment was similar in the lower and the higher AVI dose groups. Responses in the MITT set are presented in Table 58.

Table 58: Clinical Response by Visit – MITT Analysis Set

		Lower AVI Dose (Cohort 1) (N=16)	Higher AVI Dose (Cohorts 2+3) (N=18)	Total (N=34)
Study Visit	Response	n (%)	n (%)	n (%)
End of Study Treatment	CURE	10 (62.5)	13 (72.2)	23 (67.6)
	FAILURE	3 (18.8)	4 (22.2)	7 (20.6)
	INDETERMINATE	2 (12.5)	0	2 (5.9)
Test of Cure	CURE	10 (62.5)	10 (55.6)	20 (58.8)
	Cure Rate 80% CI	[43.5, 79.0]	[38.0, 72.1]	-
	Cure Rate 95% CI	[35.4, 84.8]	[30.8, 78.5]	-
	FAILURE	3 (18.8)	5 (27.8)	8 (23.5)
	INDETERMINATE	3 (18.8)	3 (16.7)	6 (17.6)
Late Follow-up	CURE	9 (56.3)	11 (61.1)	20 (58.8)
	FAILURE	3 (18.8)	5 (27.8)	8 (23.5)
	INDETERMINATE	0	0	0

AVI, avibactam, N, number of patients enrolled; n, number of patients with an observation; MITT, modified intent to treat; CI, confidence interval
Some patients did not have a clinical response assessment at one or more visits.
Source: Tables 14.2.1.1, 14.2.1.4.

2.6.6. Discussion on clinical efficacy

The clinical development programme for ATM-AVI relies partly on previous findings of safety and efficacy of ATM when used alone and PK of AVI when used in combination with CAZ.

ATM, a monocyclic BL, is an established antibiotic first approved in 1984 in Guatemala and since marketed by different MAHs in the European Economic Area. Approved indications for ATM when used alone includes (among other indications) treatment of UTI/pyelonephritis, treatment of pneumonia (without a restriction to either community acquired pneumonia (CAP) or HAP/VAP and IAI.

AVI was centrally approved in the EU in combination with CAZ in 2016 for the treatment of cIAI, cUTI/pyelonephritis, HAP/VAP, bacteraemia that occurs in association with, or is suspected to be associated with, any of these infections and infections due to aerobic Gram-negative organisms in patients with limited treatment options.

The clinical studies of main relevance to the applied indications are the phase 3 studies C3601002 and C3601009 providing comparative data on efficacy and safety, with the Phase 2 study C3601001 providing support for the PK/PD modelling, safety and the indication for other serious bacterial infections.

It should be noted that phase 3 studies evaluating a beta-lactam (BL) at its approved dose combined with a beta-lactamase inhibitor (BLI) are generally not designed to provide stand-alone efficacy data to support the dose regimen for the BLI, which is acceptable by precedent and by CHMP guidelines. Therefore, the PK/PD analyses incorporating the non-clinical PK/PD data and patient PK data are pivotal to support the efficacy and dose regimen of the BLI for the proposed indications.

Overall, the clinical programme in combination with the PK/PD package was considered acceptable to support the proposed indications. The applicant has generally followed scientific advice from the CHMP and relevant CHMP guidance supporting the limited clinical programme.

Design and conduct of clinical studies

The main studies were phase 3, randomised, central assessor-blinded, open label, multi-center studies comparing the efficacy of ATM-AVI with or without metronidazole, with meropenem ± colistin (study C3601002) and best available therapy (Study C3601009).

Study C3601002 included adult patients with cIAI and HAP/VAP based on clinical diagnosis. Study C3601009 included patients with cIAI, HAP/VAP, cUTI or blood stream infections requiring intravenous therapy and with a microbiologically confirmed diagnosis of a Gram-negative, MBL-positive bacterium. The inclusion and exclusion criteria were in consistency with the recommendations laid out in CPMP/EWP/558/95 Rev 3.

Patients were randomised in a 2:1 ratio to receive either ATM-AVI, 1500 mg aztreonam plus 500 mg avibactam, q6h, i.v. (+ metronidazole 500 mg q8h, i.v. for patients with cIAI), or comparator ATM AVI was given with two loading doses, 500 mg aztreonam plus 167 mg avibactam as a first loading dose, i.v. infusion over 30 minutes, followed by an extended loading dose of 1500 mg aztreonam plus 500 mg avibactam immediately after the first loading dose, as a 3h infusion. The dose of ATM is lower than maximum recommended dose for ATM alone but is given as a longer infusion. Comparator in study C3601002 was 1000 mg meropenem plus optional colistimethate sodium in accordance with "Framework for optimization of the clinical use of colistin and polymyxin B". Comparator in study C3601009 was best available therapy based on local epidemiology and best practices. The choice of comparators are acceptable, and in the case of meropenem and colistin, the dosage regimens are in accordance with general recommendations.

In study C3601002, the co-primary endpoints were the proportions of subjects with clinical cure at TOC, in the ITT and clinically evaluable populations. Secondary endpoints also included clinical cure in micro-ITT and microbiologically evaluable populations, microbiological responses and all-cause mortality at day 28. In study C3601009, the primary endpoint was the proportion of subjects with

clinical cure at TOC, in the micro-ITT analysis set. Secondary endpoints also included clinical cure in micro-ITT and microbiologically evaluable populations, microbiological responses and all-cause mortality at day 28. The primary and secondary efficacy endpoints and outcome criteria are acceptable.

No hypothesis testing was planned for the phase III studies. Statistical analysis was done by comparison of difference in proportion of outcomes between the two study arms, and calculation of 2-sided 95% confidence intervals. The comparison was made separately for each endpoint and subgroup. No adjustments for multiplicity were made. The statistical analysis plan is acceptable.

Efficacy data and additional analyses

In Study C3601002, a total of 461 subjects were screened for the study and 422 were randomised, 282 in the ATM-AVI arm and 140 in the comparator. Randomisation was done in a 2:1 ratio, and despite losses due to negative baseline cultures, the ratio remained stable. Micro-ITT consisted of 64.2% of the ITT population, whereas 75.4% of the ITT population were clinically evaluable. 86% of subjects completed the treatment phase of the study.

In study C3601009, a total of 15 subjects were screened and randomised. The actualised randomisation ratio was 4:1 rather than 2:1. The ME population consisted of 9 subjects in the ATM-AVI group and only 1 subject in the BAT group. The study was terminated early due to recruitment difficulties.

Study C3601002 participants were mainly male (68%) and white (54%) or Asian (41.7%) with a mean age of 54.8 years. 74% of subjects had a cIAI. 27.5% of subjects had no pathogen at baseline, whereas 46% had a monomicrobial culture. Of the subjects with a positive culture, a single Gram-negative bacterium was found in 57.8%, and 32.7% of the subjects with a polymicrobial infection had a Gram-negative pathogen. The most common bacteria were Enterobacterales, isolated from 93% of all culture positive subjects.

The characteristics were roughly similar between treatment arms with the exceptions that the meropenem arm had somewhat more Gram-negative pathogens. Of the baseline pathogens approximately 90% were susceptible to meropenem and colistin, whereas 68% were susceptible to aztreonam.

Almost all subjects (99.3%) received non-antibiotic concomitant medications during the study. The proportion of participants who received concomitant antibiotic medication was comparable in both the treatment groups.

Overall, there were no major differences in baseline or disease characteristics between the two treatment groups.

Study C3601009 participants were mainly male in the ATM-AVI group, but mainly female in the BAT group. Infection types were relatively evenly distributed. 9 subjects had a monomicrobial culture. 20/21 isolated pathogens were Gram-negative aerobes, and all Gram-negatives were MBL-producers.

Overall in study C3601002, the proportion of clinical cure in the ITT and CE populations (primary outcome) was similar between groups with only small differences and overlapping confidence intervals. Treatment difference in the ITT population was 2.7% (68.4% vs. 65.7%) with 95% CI -11.4%, 17.8%. In the CE population the difference was, 2.7% (77% vs. 74.3%) with 95% CI -11.9%, 19.2%. Among the four (4/149) subjects in the ME set that had an MBL-positive infection, two were considered cured and two were considered failures. No formal hypothesis testing was planned for the study, so no assessment of non-inferiority or superiority can be made.

The results for the secondary endpoints follow a similar pattern, with small differences between treatment groups. Worth noting is that cure rates were consistently lower in the HAP/VAP group than in the cIAI group.

Microbiological response rates were consistent with the clinical response rates.

In study C3601009, out of 12 subjects in the ATM-AVI arm, 5 were cured, 5 were failures, and 2 were indeterminate. In the BAT group, 1 was a failure and two were indeterminate. The subjects achieving cure had cUTI or BSI. Two subjects, one in each treatment arm, died within 28 days: the subject treated with ATM-AVI died due to the underlying disease, whereas the subject in the BAT arm died due to unrelated causes. Due to the small number of subjects, definite conclusions are not possible to draw, however, the results support the claim that ATM-AVI is has efficacy against MBL-positive Gram-negative bacteria.

2.6.7. Conclusions on the clinical efficacy

The clinical development programme was not designed to demonstrate the added spectrum of efficacy when AVI is added to ATM. There was no formal hypothesis testing for non-inferiority or superiority, as agreed with the CHMP, and the statistical analysis is thereby purely descriptive with no adjustment for multiplicity.

The application is thereby mainly reliant on the PK/PD package that includes non-clinical PK/PD analyses and PTA simulations using clinical PK data, which is pivotal to support the efficacy of ATM-AVI.

2.6.8. Clinical safety

The main clinical safety data comprise an integrated Phase 2/3 safety pool (305 participants exposed to ATM-AVI) In practice, the bulk of the data in this pool come from Study C3601002. Three Phase 1 ATM-AVI studies are presented separately (88 participants exposed to ATM-AVI) as well as data from 212 Phase 1 participants (171 healthy and 41 elderly/renal impairment) who received AVI only and were included in the Phase 1 AVI-only Integrated Safety Pool. These latter two pools of safety information include very few patients who received the to-be-marketed dose of ATM-AVI in combination and thus they are of marginal value. The Phase 2/3 Integrated Safety Pool is, therefore, the primary dataset for the safety assessment.

Table 59: ATM-AVI Studies Included in the Phase 2/3 Integrated Safety Pool

Study Number and Title	ATM-AVI Dose Regimen	Safety Population Type and Number
C3601001 (REJUVENATE) A Phase 2a prospective, open-label, multicenter study to determine the PK, safety and tolerability of aztreonam-avibactam (ATM-AVI) for the treatment of complicated intra-abdominal infections (cIAIs) in hospitalised adults ± MTZ*	**Normal renal function or mild renal impairment (CrCL >50 mL/min):** LD=500/167 (30 mins), immediately MD=1500/500 (3 hours) q6h. [**Moderate renal impairment (CrCL >30 to 50 mL/min)** as in study C3601009.]	Total (Cohorts 2 and 3) N = 18 No comparator. [Cohort 1 (N = 16) used a lower dose of AVI and is excluded from the safety pool.]
C3601002 (REVISIT) A Phase 3 prospective, randomised, multicenter, open-label, central assessor blinded, parallel group, comparative study to determine the efficacy, safety and tolerability ATM-AVI ± MTZ* versus MER ± COL for the treatment of serious infections due to G- bacteria	**Normal renal function or mild renal impairment (CrCL >50 mL/min):** LD=500/167 (30 mins), immediately ELD=1500/500 (3 hours), after 3h MD=1500/500 (3 hours) q6h. **Moderate renal impairment (CrCL >30 to 50 mL/min):** LD = 500/167 (30 mins), immediately ELD=1500/500 (3 hours), after 3h MD=750/250 (3 hours) q6h. **Severe renal impairment (CrCL >15 to 30 mL/min):** LD=675/225 (30 mins), immediately ELD=675/225 (3 hours), after 5h MD=675/225 (3 hours) q8h.	Total N = 412 **ATM-AVI ± MTZ** N = 275 (203 cIAI; 72 HAP/VAP) **MER ± COL** N = 137 (103 cIAI; 34 HAP/VAP)
C3601009 (ASSEMBLE) A prospective, randomised, open-label, comparative study to assess the efficacy, safety and tolerability of ATM-AVI ± MTZ* and best available therapy for the treatment of serious infections due to multi-drug resistant Gram- negative bacteria producing metallo-β-lactamase (MBL)	**Dosing** as in study C3601009.	Total N = 14 **ATM-AVI ± MTZ** N = 12 (2 cIAI; 3 HAP/VAP; 3 cUTI; 4 BSI) **BAT** N = 2 (1 HAP/VAP; 1 BSI)

Recommended minimal duration of IV study treatment: 5 days for cIAI, cUTI and BSI and 7 days for HAP/VAP. Maximal duration of treatment: 14 days.

*MTZ 500 mg q8h 5-14 days' duration until clinical response was co-administered with ATM-AVI in all participants with cIAI provided coverage for anaerobic organisms such as the *Bacteroides fragilis* group. Sections below therefore refer to relevant ATM-AVI arms as ATM-AVI ± MTZ.

2.6.8.1. Patient exposure

Table 60: Summary of patient exposure

	Patients exposed	Patients with altered renal function	Patients exposed to proposed dose	Patients exposed <u>above</u> proposed dose	Duration of treatment, mean (SD), median (range)
Phase I AVI-only	212†	CrCl 15-30 mL/min = 7 CrCl 31-50 mL/min = 12 CrCl 51-80 mL/min = 20 CrCl >150 = 316	96†	61†	2.3 (2.22) 1.0 (1.0, 12.0)
Phase I ATM-AVI	88	CrCl 15-30 mL/min = 5	26	49 exposed to ATM >1500mg	
Open-label single arm (C3601001)	34	CrCl 31-50 mL/min = 1	18*		6.67 (2.99) 6.0 (1.0, 15.0)
Open-label active - controlled (C3601002)	275	CrCl 15-30 mL/min = 11 CrCl 31-50 mL/min = 27 CrCl >150 = 41	275**		8.5 (3.52) 8.0 (1.0, 15.0)
Open-label active - controlled (C3601009)	12	CrCl 15-30 mL/min = 1 CrCl 31-50 mL/min = 1 CrCl >150 = 3	12***		9.5 (5.09) 9.5 (1.0, 15.0)

† Only exposed to AVI.

* All of which received metronidazole for a diagnosis of cIAI.

** Of which 203 also received metronidazole for a diagnosis of cIAI.

*** Of which 2 also received metronidazole for a diagnosis of cIAI.

Duration of treatment

The mean duration of treatment in the Phase 2/3 Integrated Safety Pool was 8.4 days in the ATM-AVI ± MTZ treatment group and 8.9 days in the comparator treatment group. The majority of participants (65.1%) were on study treatment for 5 to <11 days (62.3% in the ATM-AVI ± MTZ treatment group and 71.2% in the comparator treatment group).

Patient characteristics

As a result of study inclusion criteria in the different Phase 2 and 3 studies, most of the participants had cIAI (73.4% overall; 73.1% in the ATM-AVI ± MTZ treatment group and 74.1% in the comparator treatment group). There were approximately 25% of participants with HAP/VAP across both treatment groups whilst the number of participants with cUTI or BSI was small (<10 in total).

Patients with a diagnosis of cIAI underwent surgical intervention within 24 hours before or after administration of the first dose of study drug.

In all studies, MTZ 500 mg q8h 5-14 days' duration was co-administered with ATM-AVI or BAT (when required) in all participants with cIAI provided coverage for anaerobic organisms such as the Bacteroides fragilis group.

For All Participants:

- The overall median age was 57 years for both treatment groups.
- The majority of participants were male (68.7% overall; 66.9% in the ATM-AVI ± MTZ treatment group and 72.7% in the comparator treatment).
- The majority of participants were either White (55.9%) or Asian (39.6%):
- The proportion of White participants was higher in the ATM-AVI ± MTZ treatment group (60.0%) compared to the comparator treatment group (46.8%).
- The proportion of Asian participants was lower in the ATM-AVI ± MTZ treatment group (35.7%) compared to the comparator treatment group (48.2%).
- Participants with HAP/VAP were generally older than participants with cIAI with a median age of 66 years for participants with HAP/VAP compared to 53 years for participants with cIAI.

Many patients had received prior systemic antibiotics as well as other prior medications, as might be expected in the given clinical context. In In Study 3601001, over half of patients received concomitant systemic antibiotics and almost all received other concomitant medications during the course of study treatment. In Study 3601002, 27.3% (75/275) participants in the ATM-AVI ± MTZ treatment group and 20.4% (28/137) participants in the MER ± COL treatment received concomitant systemic antibiotics, most commonly linezolid and vancomycin, and almost all received other concomitant medications during the course of study treatment. In Study 3601009, 5/12 participants in the ATM-AVI ± MTZ treatment group and no participant in the BAT treatment received concomitant systemic antibiotics, and almost all received other concomitant medications during the course of study treatment. The heterogeneity of comparator and wide use of varied concomitant medications, including antibiotics, means that numerical differences between ATM-AVI ± MTZ and comparator groups must be interpreted with caution.

In the Phase 2/3 Integrated Safety Pool, the proportion of participants in each of the renal function groups were similar between treatment groups for participants with cIAI. For HAP/VAP there were more participants with severely impaired or augmented renal function in the ATM-AVI ± MTZ treatment group.

2.6.8.2. Adverse events

Summary frequencies

The overall incidence of all causality TEAEs, including severe TEAEs, SAEs and TEAEs resulting in death, was lower in participants with cIAI (58.6%) than participants with HAP/VAP (81.8%), which is not unexpected. There were only the low numbers of participants with cUTI (3 participants) and BSI (5 participants) across the clinical studies, precluding meaningful comparison between these infection types.

Table 61: Summary of Treatment – Emergent Adverse Events (All Causalities), Phase 2/3 Pool – Integrated Safety Analysis Set – All Participants

Number (%) of Participants	ATM-AVI (+/-MTZ)* (N=305) n (%)	COMPARATOR (N=139) n (%)	Total (N=444) n (%)
Participants evaluable for adverse events	305	139	444
Number of adverse events	619	228	847
Participants with adverse events	200 (65.6)	89 (64.0)	289 (65.1)
Participants with medication error events	0	0	0
Participants with serious adverse events	63 (20.7)	27 (19.4)	90 (20.3)
Participants with severe adverse events	47 (15.4)	17 (12.2)	64 (14.4)
Participants with fatal adverse events	22 (7.2)	12 (8.6)	34 (7.7)
Participants discontinued from study due to adverse events[a]	21 (6.9)	13 (9.4)	34 (7.7)
Participants discontinued study drug due to AE[b]	13 (4.3)	7 (5.0)	20 (4.5)

Phase 2/3 ATM-AVI pool includes studies C3601001 (Cohorts 2+3), C3601002, and C3601009.
*MTZ therapy administered to participants with cIAI only.
The denominator to calculate percentages is N, the number of participants in the analysis set within each treatment arm.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn

Adverse Events by Preferred Term

Table 62: Treatment-Emergent Adverse Events by Decreasing Frequency (All Causalities) Occurring in ≥2% of Any Treatment Arm, Phase 2/3 Pool – Integrated Safety Analysis Set – All Participants)

Number of Participants Evaluable for AEs	ATM-AVI (+/-MTZ)* (N=305)	COMPARATOR (N=139)	Total (N=444)
Number (%) of Participants: By Preferred Term	n (%)	n (%)	n (%)
With any adverse event	200 (65.6)	89 (64.0)	289 (65.1)
Anaemia	21 (6.9)	7 (5.0)	28 (6.3)
Alanine aminotransferase increased	19 (6.2)	7 (5.0)	26 (5.9)
Diarrhoea	19 (6.2)	5 (3.6)	24 (5.4)
Hypokalaemia	18 (5.9)	4 (2.9)	22 (5.0)
Aspartate aminotransferase increased	16 (5.2)	5 (3.6)	21 (4.7)
Pyrexia	14 (4.6)	7 (5.0)	21 (4.7)
Hepatic function abnormal	12 (3.9)	4 (2.9)	16 (3.6)
Nausea	12 (3.9)	3 (2.2)	15 (3.4)
Vomiting	10 (3.3)	2 (1.4)	12 (2.7)
Abdominal pain	7 (2.3)	4 (2.9)	11 (2.5)
Constipation	8 (2.6)	2 (1.4)	10 (2.3)
Pneumonia	9 (3.0)	1 (0.7)	10 (2.3)
Hypertension	6 (2.0)	3 (2.2)	9 (2.0)
Abdominal distension	5 (1.6)	3 (2.2)	8 (1.8)
Decubitus ulcer	7 (2.3)	1 (0.7)	8 (1.8)
Hypertransaminasaemia	7 (2.3)	1 (0.7)	8 (1.8)
Pleural effusion	7 (2.3)	1 (0.7)	8 (1.8)
Respiratory failure	4 (1.3)	4 (2.9)	8 (1.8)
Acute kidney injury	4 (1.3)	3 (2.2)	7 (1.6)
Atrial fibrillation	6 (2.0)	1 (0.7)	7 (1.6)
Phlebitis	7 (2.3)	0	7 (1.6)
Rash	7 (2.3)	0	7 (1.6)
SARS-CoV-2 test positive	6 (2.0)	1 (0.7)	7 (1.6)
Septic shock	2 (0.7)	5 (3.6)	7 (1.6)
Urinary tract infection	4 (1.3)	3 (2.2)	7 (1.6)
Blood alkaline phosphatase increased	2 (0.7)	3 (2.2)	5 (1.1)
Cardiac arrest	2 (0.7)	3 (2.2)	5 (1.1)
Injection site reaction	1 (0.3)	4 (2.9)	5 (1.1)
Transaminases increased	2 (0.7)	3 (2.2)	5 (1.1)
Intra-abdominal fluid collection	0	3 (2.2)	3 (0.7)

Phase 2/3 ATM-AVI pool includes studies C3601001 (Cohorts 2+3), C3601002, and C3601009.
*MTZ therapy administered to participants with cIAI only.
The denominator to calculate percentages is N, the number of participants in the analysis set within each treatment group.
Participants are only counted once per treatment per event.

AEs reported across the Phase 2/3 studies are consistent with the known safety profiles of the individual components of ATM-ATM, the frequent and varied concomitant medications and the underlying conditions, all of which confound the assessment of causality.

Adverse Events by Severity

The incidences of mild, moderate, and severe TEAEs were similar in the ATM-AVI ± MTZ treatment group and the comparator treatment group (approximately 30%, 20% and 15%, respectively). The

most frequently reported (≥3 participants in either treatment group) severe all causality TEAEs in the ATM-AVI ± MTZ treatment group were pulmonary embolism, sepsis, pneumonia, abdominal abscess, cardiac arrest and septic shock.

Treatment-related Adverse Events

In the Phase 2/3 Integrated Safety Pool (all participants), the overall incidence of treatment-related TEAEs was considered low (<15%) and broadly similar across treatment groups.

Given that the active-controlled studies included in the Phase 2/3 integrated safety pool were open-label, the designation of treatment-related AEs was not fully blinded and must be interpreted with caution. Extensive comparison between treatment groups or at the PT level for treatment-relatedness is not considered helpful.

Adverse Events by Renal Function

The definitions applied to the renal function groups by the applicant differ from those used in EMA Guidance, however for the purposes of assessment in this report the terms augmented and normal RF, and mild, moderate and severe RI refer to the CrCl bands as defined by the applicant in the submission (see table below). Participants with altered renal function were in practice only enrolled in meaningful numbers in Study C3601002.

Table 63: Baseline Characteristics, Phase 2/3 Pool – Integrated Safety Analysis Set – All Participants

	ATM-AVI (+/-MTZ)* (N=305)	COMPARATOR (N=139)	Total (N=444)
Renal Function Group, n (%)			
CrCl <=30 mL/min	12 (3.9)	1 (0.7)	13 (2.9)
CrCl 31-50 mL/min	29 (9.5)	14 (10.1)	43 (9.7)
CrCl 51-80 mL/min	69 (22.6)	32 (23.0)	101 (22.7)
CrCl 81-150 mL/min	148 (48.5)	75 (54.0)	223 (50.2)
CrCl >= 151 mL/min	46 (15.1)	17 (12.2)	63 (14.2)

Phase 2/3 ATM-AVI pool includes studies C3601001 (Cohorts 2+3), C3601002, and C3601009.
*MTZ therapy administered to participants with cIAI only.
The denominator to calculate percentages is N, the number of participants in the analysis set within each treatment group.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 13JUN2023 (21:19)
Table 14.1.2.2.2 is for Pfizer internal use.

The frequency of TEAEs for the Phase 2/3 Integrated Safety Pool was also presented by baseline renal function subgroups as defined above (not shown here)**.**

The overall incidence of all causality TEAEs, SAEs, severe TEAEs, fatal TEAEs, and discontinuations from study drug or from study due to TEAEs, in the ATM-AVI ± MTZ treatment group was higher for participants with severe or moderate renal impairment and augmented renal function, than in participants with mild renal impairment or normal renal function. This is not unexpected.

AVI is predominantly eliminated unchanged by the renal route while approximately 30% of an ATM dose undergoes extra renal clearance. Thus, daily exposures to AVI in patients with mild, moderate or severe RI will by necessity be greater than AVI exposure in patients with normal renal function, to maintain adequate ATM levels. The incidence of all causality TEAEs, SAEs, severe TEAEs, fatal TEAEs, and discontinuations from study drug or from study due to TEAEs on ATM-AVI ± MTZ was comparable for participants with mild RI (69 patients across the clinical programme) and normal RF. Considering the projected increased exposure for AVI in mild RI is comparable to that for severe RI, and indeed greater than that for moderate RI, this suggests that the increased incidence of all types of AE in the moderate and several RI groups (and indeed the augmented RF group) is related to a more severe

clinical state rather than increased AVI exposure *per se*. Moreover, as the majority of liver and kidney toxic effects are thought to be mediated by ATM, the clinical impact of modestly increased AVI exposure is likely to be clinically tolerable provided that ATM exposure is not similarly increased in these patients.

Patients with ESRD (CrCL ≤15 mL/min) were not included at all in the ATM-AVI clinical trials. A dose regimen for ESRD is proposed for inclusion in dose recommendations based on simulations using the final population PK model. There are no clinical safety data from the Phase 2/3 programme to support the recommendation and this is further elaborated in the section Discussion on Clinical safety.

Serious Adverse Events

In the Phase 2/3 Integrated Safety Pool (all participants), the overall incidence of serious TEAEs was around 20% in both treatment groups. The majority of SAEs were reported by participants with HAP/VAP, which is not unexpected. SAEs by Preferred Term were also provided in summary tables (not shown here).

The most frequently reported all causality SAEs by PT (≥5 participants in total) for all participants were abdominal abscess (1.4%), cardiac arrest, pneumonia, sepsis, septic shock, respiratory failure (all reported by 1.1%).

The incidence of all causality TEAEs with a fatal outcome for all participants in the Phase 2/3 Integrated Safety Pool was 7.2% in the ATM-AVI ± MTZ treatment group and 8.6% in the comparator treatment group.

The frequency of serious and fatal AEs and the nature of reported PTs are consistent with the comorbidities, clinical state and clinical outcomes expected in cIAI and HAP/VAP.

Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for the ATM-AVI programme included hypersensitivity/ anaphylaxis, liver disorders, and *Clostridioides difficile*-associated diarrhoea.

Reports related to hypersensitivity reactions were more frequent amongst participants on ATM-AVI ± MTZ than comparator, however the vast majority were generalised/ non-specific signs and symptoms. The submitted safety data do not indicate any safety concern for ATM-AVI over and above what is already established in clinical practice with respect to beta-lactams antibiotics and the potential for cross-sensitivity.

All causality TEAEs pertaining to liver disorders were reported by 16.4% in the ATM-AVI ± MTZ treatment group and 14.4% in the comparator treatment group. The most frequently reported PTs were Alanine aminotransferase increased (6.2% vs 5.0%) and Aspartate aminotransferase increased (5.2% versus 3.6%).

Across the Phase 2/3 Integrated Safety Pool, increases in transaminase levels were comparable between ATM-AVI ± MTZ and comparator groups and as expected for ATM-AVI as part of the known safety profile. Derangement of laboratory parameters for alanine aminotransferase and aspartate aminotransferase were predominant and tended to be transient in nature. Mean changes from baseline over time for liver function parameters were generally small and similar between ATM-AVI ± and comparator treatment groups. No case was identified that met the criteria for Hy's law. Negative effects on liver enzymes as well as hepatitis and jaundice included as ADRs in the currently authorised ATM Product Information.

Patients with pre-existing hepatic impairment were not included in the clinical programme and did not contribute to the safety database. There is no reason to expect a different safety profile amongst

patients with hepatic impairment on the basis of altered systemic clearance of either component of ATM-AVI, which is described in SmPC 5.2. Hepatotoxicity is a known risk for aztreonam and the warning proposed in SmPC 4.4 regarding the need for close monitoring in patients with pre-existing hepatic impairment is appropriate and sufficient. The applicant referred also to a dose adjustment for patients with hepatic impairment in the authorised text for aztreonam, however this is recommended in case of long-term treatment with the product, which is not relevant to the proposed indication for ATM-AVI.

Diarrhoea, Clostridioides difficile-associated diarrhoea and pseudomembranous colitis are expected events for ATM-AVI according to the authorised Product Information for the individual components. The incidence across the clinical programme was low.

2.6.8.3. Laboratory findings

Participants who had elevations in ALT or AST (to levels up to 3-fold, between 3 and 5-fold, between 5 and 10-fold and ≥10-fold multiples of the ULN) concurrent with bilirubin levels less than 2-fold or ≥2-fold multiples of ULN were summarised. No case was identified that met the criteria for Hy's law.

Abnormal laboratory values reflecting >3x ULN for GGT were reported in 5 patients, although this appears to be with a denominator of just 18 patients with data available. The AE GGT increased was reported for 3 participants (of which 2 reported as treatment-related) in the ATM-AVI ± MTZ arm across the Phase 2/3 Integrated Safety Pool.

Although kidney is considered a target for ATM toxicity, no participant on ATM-AVI ± MTZ in the Phase 2/3 Integrated Safety Pool met the criteria for increase in creatinine >2x ULN and >100% from baseline. There were few reports (1.3% participants) of acute kidney injury as a TEAE for ATM-AVI ± MTZ, and one instance of this adverse event leading to discontinuation from ATM-AVI ± MTZ, across the Phase 2/3 Integrated Safety Pool.

The incidence of other potentially clinically significant laboratory test abnormalities was considered low and comparable between the treatment groups.

2.6.8.4. Other findings

Electrocardiogram

The applicant presented the results of a negative thorough QT/QTc study of avibactam doses up to 2000mg in combination with ceftazidime or ceftaroline fosamil. No specific ECG studies were conducted as part of the ATM-AVI clinical programme.

No clinically meaningful changes in ECG parameters were observed in the Phase 2/3 studies.

2.6.8.5. Safety in special populations

The overall incidence of all causality TEAEs was lowest in the <45 years age group (60.5%) and appeared to progressively increase with age, being highest in the ≥75 years age group (79.2%), which was similar between treatment arms and is not unexpected. A similar proportion of ATM-AVI and comparator-treated participants experienced TEAEs in the different age groups except for the ≥75 age group where the incidence of TEAEs was numerically higher in the comparator treatment group. The applicant completed the table of safety data by older age cohort as part of the response to the Day 120 LoQ. Very few patients 85+ years and older were included in the study. An overview of adverse event

frequency in the different age cohorts by MedDRA term did not reveal any particular patterns with regard to the types of TEAEs in older patients.

The overall incidence of all causality TEAEs was similar between males and females and between White and Asian participants, with too few participants in the other subgroups of race as to permit meaningful comparison.

The majority of participants were in the <25 and 25 to <30 kg/m2 baseline BMI subgroups. The overall incidence of all causality TEAEs was similar between the ATM-AVI ± MTZ and comparator treatment groups within each subgroup but was higher in the >30 kg/m2 baseline BMI subgroup than the lower baseline BMI subgroups. The incidence of SAEs, severe TEAEs, fatal TEAEs and discontinuations due to TEAEs was also higher with increasing BMI subgroup.

In the Phase 2/3 Safety Analysis Pool, the majority of participants were from Eastern Europe followed by China. The incidence of all causality TEAEs for Eastern Europe and China were:

- Eastern Europe (N=158): 53.8% (85 participants); 54.5% (61/112 participants) in the ATM-AVI ± MTZ treatment group and 52.2% (24/46 participants) in the comparator treatment group.
- China (N=116): 66.4% (77 participants); 71.2% (52/73 participants) in the ATM-AVI ± MTZ treatment group and 58.1% (25/43 participants) in the comparator treatment group.

While there were some SOC variations and some variations in the number of TEAEs by PT for some of these subgroups, meaningful comparisons were often limited by small numbers of participants in some of the groups. Given that the findings were generally similar across treatment groups, no clinically important safety signals were identified as a result of these analyses.

There were no clinical studies allowing enrolment of women during pregnancy and/or lactation. No cases of pregnancy were reported as SAEs through 14 June 2023.

2.6.8.6. Safety related to drug-drug interactions and other interactions

No formal studies of drug-interaction with ATM-AVI have been performed. Single dose PK studies have not shown any significant interaction between aztreonam and avibactam. No drug-food or drug-alcohol interactions are expected for ATM, and neither drug-food nor drug-alcohol interactions have been studied for AVI.

The incidence of all causality TEAEs for diuretics, NSAIDs and PPIs was generally balanced across treatment groups across the Phase 2/3 Integrated Safety Pool. Comparisons of SOCs and PTs are limited due to the low numbers of participants in the concomitant medication subgroups.

2.6.8.7. Discontinuation due to adverse events

Discontinuations

All causality TEAEs leading to permanent discontinuation from study were reported by 6.9% (21 participants) in the ATM-AVI ± MTZ treatment group and 9.4% (13 participants) in the comparator treatment group.

All causality TEAEs leading to discontinuation from study treatment were reported by 4.3% (13 participants) in the ATM-AVI ± MTZ treatment group and 5.0% (7 participants) in the comparator treatment group. Most PTs were single occurrences, with significant overlap with those reported as reasons for study discontinuation, as might be expected.

The complexity of clinical condition and heterogeneity of comparator and concomitant medications confounds and indeed essentially precludes the assessment of treatment-relatedness.

2.6.8.8. Medication errors

Major protocol deviations relating to an incorrect dose or incorrect preparation/administration of ATM-AVI were reported across all three Phase 2/3 studies. Interestingly, no medications errors were formally reported as TEAE across the Phase 2/3 Integrated Safety Pool.

Following feedback from Phase 3 clinical trial investigators, the combined LD/ELD regimen, necessitating a change in infusion rate after the first 30 minutes, was recognised to have high potential for dosing administration errors in clinical practice. Based on the simulation results (see section Pharmacokinetics above), a simplified LD (a constant rate infusion over 3 hours, equivalent to the sum of LD and ELD in Phase 3 regimens) is specified in the product information.

2.6.8.9. Post marketing experience

As of July 2023, ATM-AVI had not been marketed in combination anywhere in the world. Therefore, no post-marketing data are available for ATM-AVI as a combination product. No post-marketing data relating to the individual components were submitted by the applicant.

2.6.9. Discussion on clinical safety

The safety data presented in this application built on what is already known about the safety profile of the two individual components, to support a proposed dosing regimen of ATM-AVI that reflects the upper end of the range of doses currently authorised in the EU for ATM and a 30% higher total daily dose of AVI than has previously been authorised in the EU. Both ATM and AVI are predominantly eliminated by the kidney. ATM is well known to have liver side effects, usually asymptomatic serum transaminase elevations proportional to ATM compartment concentrations and appearing with some 5 to 6 days delay after first administration, that are self- limiting and resolve rapidly upon discontinuation.

The primary clinical safety data comprise an integrated Phase 2/3 safety pool (305 participants exposed to ATM-AVI). In practice, the bulk of the data in this pool come from Study C3601002. The approach of pooling data from the completed phase 2/3 studies in a single integrated safety pool is reasonable, although it should be noted that the pooled "comparator" arm consequently incorporates a heterogeneous mix of several different antibiotics that precludes meaningful comparison between arms. Additionally, a wide variety of systemic antibiotics and non-antibiotics medications were administered during the course of the clinical studies, making it difficult to attribute reported adverse events and other negative effects to ATM-AVI.

The size of the safety database is sufficient in the context of two known substances with safety profiles that are already characterised. Long-term data beyond 14 days use are not available, which was reasonable for the proposed clinical indication.

Adverse Events

Two-thirds of participants receiving ATM-AVI ± MTZ reported at least one AE, and 1 in 5 patients reported an SAE. The incidence of all causality TEAEs with a fatal outcome for all participants in the Phase 2/3 Integrated Safety Pool was 7.2% in the ATM-AVI ± MTZ treatment group and 8.6% in the comparator treatment group. Adverse events were more frequent and more often serious or fatal in

nature amongst HAP/VAP patients, which is not unexpected. The most frequently reported (≥5%) all causality TEAEs in the overall ATM-AVI ± MTZ treatment group were anaemia (6.9%), ALT increased (6.2%), diarrhoea (6.2%), hypokalaemia (5.9%), and AST increased (5.2%). The reported AEs were consistent with the known safety profiles of the individual components ATM and AVI, the frequent and varied concomitant medications and the underlying clinical conditions.

Following feedback from Phase 3 clinical trial investigators that the combined LD/ELD infusion requiring a change in infusion rate showed high potential for dosing administration errors in clinical practice, a simplified LD (a constant rate infusion over 3 hours, equivalent to the sum of LD and ELD in Phase 3 regimens) is proposed for the labelling.

Adverse Events of Special Interest

With regard to Adverse Events of Special Interest (hypersensitivity/ anaphylaxis, liver disorders, and *Clostridioides difficile*-associated diarrhoea):

The submitted safety data do not indicate any specific safety concern regarding hypersensitivity reactions or ATM-AVI over and above what is already established in clinical practice with respect to beta-lactams antibiotics and the potential for cross-sensitivity. Aztreonam shares an aminothiazole side chain with ceftazidime. In a prospective study in patients with confirmed IgE-mediated allergic reactions to cephalosporins, approximately 3 % had a positive skin test to aztreonam. Cross-reactivity can be higher between aztreonam and cephalosporins that have the same R1 side chain as aztreonam. Both aztreonam and ceftazidime have an aminothiazole side chain and cross-reactivity between ceftazidime and aztreonam has been reported. The text in section 4.3 of the SmPC is appropriate and acceptable.

Across the Phase 2/3 Integrated Safety Pool, increases in transaminase levels were comparable between ATM-AVI ± MTZ and comparator groups and as expected for ATM-AVI as part of the known safety profile. Derangement of laboratory parameters for alanine aminotransferase and aspartate aminotransferase were predominant and tended to be transient in nature. Mean changes from baseline over time for liver function parameters were generally small and similar between ATM-AVI ± and comparator treatment groups. No case was identified that met the criteria for Hy's law. Negative effects on liver enzymes as well as hepatitis and jaundice included as ADRs in the currently authorised ATM Product Information.

The incidence of diarrhoea, *Clostridioides difficile*-associated diarrhoea and pseudomembranous colitis across the clinical programme was low. Although kidney is considered a target for ATM toxicity, no participant on ATM-AVI ± MTZ in the Phase 2/3 Integrated Safety Pool met the criteria for increase in creatinine >2x ULN and >100% from baseline. There were few reports (1.3% participants) of acute kidney injury as a TEAE for ATM-AVI ± MTZ, of which one instance of this adverse event leading to discontinuation from ATM-AVI ± MTZ, across the Phase 2/3 Integrated Safety Pool.

Cardiac safety

A thorough QT/QTc study of avibactam doses up to 2000mg in combination with ceftazidime or ceftaroline fosamil was negative for changes meeting the threshold for concern as per ICH guideline E14. No specific ECG studies were conducted as part of the ATM-AVI clinical programme. There were no clinically significant effects on ECG observed in the Phase 2/3 clinical programme.

Renal impairment

Participants with mild RI (total 69 across the clinical programme, defined by the applicant as CrCl 51-80 mL/min), in whom the need to achieve adequate ATM exposure necessitates a roughly 40% higher AVI exposure, reported similar incidences of all types of AE as compared with participants with normal RF (CrCl 81-150 mL/min). This provides safety reassurances regarding the similarly increased

exposures to AVI projected for moderate and severe RI at their respective adjusted doses, and suggests that the increased incidence of all types of AE in moderate and severe RI, and in augmented RF, is related to the underlying clinical state rather than increased AVI exposure *per se*.

Patients with ESRD (CrCL ≤15 mL/min) were not included at all in the ATM-AVI clinical trials and the dose regimen proposed for ESRD is based on simulations. Based on the dedicated renal impairment study NXL104/1003, the proposed dosage in patients with ESRD is expected to result in 4.4-fold increases in exposure compared to subjects with normal renal function (CrCL above 80 ml/min) receiving the standard dose regimen. This increase is higher than the 2.6-fold increase in exposure expected in patients with CrCL 50-80 ml/min, for which clinical safety data are available from the clinical programme. Further reduction in the ATM-AVI dose regimen is not possible without compromising efficacious ATM exposure.

Clinical safety data from healthy volunteers are not informative either, being limited to single supratherapeutic dose data in 8 participants and likely not sufficiently representative of safety in patients with complex chronic conditions like ESRD.

Limiting treatment in ESRD to those patients on haemodialysis (or another form of RRT) would safeguard to some degree against the risk of AVI accumulation during the treatment course. The applicant therefore proposes to add further guidance for the prescriber in the SmPC, which is supported:

Patients with CrCl ≤ 15 mL/min should not receive Emblaveo unless haemodialysis or another form of renal replacement therapy is instituted. A 4-hour haemodialysis session has been shown to remove approximately 55% of an administered AVI dose (Study NXL104/1003).

Other special populations

The overall median age across the Phase 2/3 studies was 57 years. The higher incidence of TEAEs in the older age groups is not entirely unexpected, particularly given that participants with HAP/VAP were generally older than participants with cIAI. Very few patients 85+ years and older were included in the study. An overview of adverse event frequency in the different age cohorts by MedDRA term did not reveal any particular patterns with regard to the types of TEAEs in older patients.

Some other patient groups (hepatic disease, immunosuppression) were excluded from the clinical programme and as such are not represented within the safety database for ATM-AVI. There is no compelling reason to believe that the safety profile of ATM-Avi should significantly differ for immunosuppressed patients so long as coadministration with products with the potential for DDI is carefully avoided.

Patients with pre-existing hepatic impairment were not included in the clinical programme and did not contribute to the safety database. There is no reason to expect a different safety profile amongst patients with hepatic impairment on the basis of altered systemic clearance of either component of ATM-AVI, which is described in SmPC 5.2. Hepatotoxicity is a known risk for aztreonam and the warning proposed in SmPC 4.4 regarding the need for close monitoring in patients with pre-existing hepatic impairment is appropriate and sufficient.

Selection of adverse drug reactions

The safety profile of aztreonam is established and the applicant stated that ADRs for aztreonam are considered ADRs for ATM-AVI.

Newly reported events were included in the reference safety information if they were considered related to ATM-AVI and if they were reported by 3 or more participants. Events already referred to in the aztreonam reference labels, and which were reported in the Phase 2/3 Integrated Safety pool,

were updated with the highest reported frequency, where appropriate. Event terms representing the same medical concept or condition were grouped together. Overall, 19 PTs moved to a higher frequency category and there was 1 new PT added which was gamma-glutamyl transferase increased (Uncommon), which is supported with consideration to the mechanistic plausibility and reported safety data.

The size of the ATM-AVI clinical programme, specifically the total number of ATM-AVI participants included in the Phase 2/3 safety pool (305), constrains qualification of newly reported events with a frequency of Uncommon or higher. Given that the active-controlled studies included in the Phase 2/3 integrated safety pool were open-label, the designation of treatment-related AEs was not fully blinded and must be interpreted with caution. However, it is acknowledged that confounding of the reported safety data due to heterogeneity of comparator, concomitant antibiotics and concomitant non-antibiotic medications is significant and complicates the attribution of new ADRs to the ATM-AVI combination product. The approach is therefore supported.

Three occurrences of GGT increased were reported by participants on ATM-AVI in the Phase 2/3 pool. Insufficient details of these cases are available to establish a causal relationship. The underlying condition may be a confounding factor. It is not likely, mechanistically, that an ADR not previously associated with either substance would result directly from the combination of ATM and AVI, given that no synergy with respect to negative effects is expected. "GGT increased" is not currently a recognised ADR for either of the known active substances, however aztreonam is well known to have liver side effects and lists effects on other liver enzymes amongst its ADRs. Additionally, in both cases considered to be treatment-related by the investigator, there are noted to have been increases in ALP (and in one case also ALT and AST) reported at the same time, which might be in keeping with a hepatic source of increased GGT. As it remains therefore a reasonable possibility that GGT increased is causally associated with ATM-AVI, it is accepted to add "GGT increased" as an ADR.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety profile of ATM-AVI seems to support a positive benefit-risk balance for this drug combination in the treatment of patients with cIAI, HAP/VAP, cUTI including pyelonephritis, BSI, and patients with serious infections caused by susceptible Gram-negative bacteria for which there are limited or no treatment options.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 64: Table SVIII.1: Summary of safety concerns

Summary of safety concerns for Emblaveo®	
Important identified risks	None.
Important potential risks	None.
Missing information	None.

The two components ATM and AVI are known substances with established safety profiles, and the clinical safety data submitted in this application do not raise any new safety issues for the combination product. Thus, the applicant's proposal that no concerns are to be listed in the RMP is acceptable and in line both with similar products recently authorised and with GVP Module V.

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are appropriate.

It is noted that safety concerns agreed for the fixed dose combination CAZ/AVI were the following:

Summary of safety concerns for the fixed dose combination CAZ/AVI	
Important identified risks	*C. difficile*-associated diarrhoea Anaphylaxis and other hypersensitivity reactions
Important potential risks	Superinfection (bacterial or fungal) Bacterial resistance development
Missing information	Pregnancy exposure Lactation exposure Pre-existing significant hepatic impairment Pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy Immunocompromised population exposure

This was agreed at a time when items that were not going to be subject to specific PhV efforts were still placed in the table, which is not the case at the time of the Emblaveo approval, hence the difference in RMPs.

2.7.2. Pharmacovigilance plan

Routine signal detection activities for ATM-AVI will include routine and specific review of AEs consistent with the AESI.

The applicant stated that no safety concerns have been identified and accordingly no additional pharmacovigilance activities are necessary. To be noted that there was an additional PhV activity for the fixed dose avibactam/ceftazidime - Resistance surveillance programme to address important potential risk Bacterial resistance development, which was recently completed (last data provided in the latest PSUR for avibactam/ceftazidime, covering period 25-Feb-2022 through 24-Feb-2023). Based on the findings of 5-year microbiological surveillance study, there were no unexpected levels of resistance identified.

No additional PhV activities are ongoing for both the fixed dose avibactam/ceftazidime and (aztreonam). The PRAC supports applicant's position that no additional pharmacovigilance activities are necessary for Emblaveo.

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

2.7.3. Risk minimisation measures

The PRAC, having considered the data submitted was of the opinion that routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7.4. Conclusion

The CHMP and PRAC consider that the risk management plan version 1.0 dated 12 March 2024 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. Periodic Safety Update Reports submission requirements

Based on the fact that avibactam and aztreonam are not included in the EURD list as combination of active substances, the PRAC is of the opinion that a separate entry in the EURD list for Emblaveo is needed, as it cannot follow either of the already existing entries for Aztreonam or Avibactam. 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 new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The User Test was assessed and accepted.

The results 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.

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The group accepted the justification of the company that due to the small size of the vial (30 ml) only the minimum particulars can be accommodated.

The minimum particulars for the 30ml vial will apply for all markets.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Emblaveo is being approved to be indicated for the treatment of the following infections in adults:

Emblaveo is indicated for the treatment of the following infections in adult patients (see sections 4.4 and 5.1):

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

Emblaveo is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (see sections 4.2, 4.4, and 5.1).

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

3.1.2. Available therapies and unmet medical need

Treatment of cUTI/acute pyelonephritis, cIAI and HAP/VAP is in general initially empirically chosen based on the knowledge of the main causative pathogens and their likelihood of carrying resistance mechanisms. The selection of antibacterial agent(s) is further guided by results of pathogen identification and susceptibility testing.

Beta-lactam antibacterial agents are commonly used to manage 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 a limited selection of antibacterial agents such as colistin, tigecycline, cefiderocol and newer BL/BLI combinations. However, there are limitations also to these agents. Importantly, acquired resistance occurs also against these agents. Treatment emergent nephrotoxicity is of concern for colistin. Tigecycline is not active against *Pseudomonas* spp. Moreover, safety concerns of an increased risk of death with tigecycline have limited its use. The newer beta-lactam/beta-lactamase (BL/BLI) combinations such as ceftolozane/tazobactam (TOL/TAZ), ceftazidime/avibactam (CAZ/AVI), meropenem/vaborbactam (MEM/VAB) and imipenem/relebactam (IMI/REL) are possible options for the treatment of some carbapenem-resistant Gram-negative organisms but none of them are universal or active against class B (metallo-beta-lactamase) producers. Overall, there is still a high unmet medical need for additional antibacterial agents addressing carbapenem resistance in Gram-negative organisms especially those producing class B beta-lactamases.

3.1.3. Main clinical studies

The clinical development programme for ATM-AVI relies partly on previous findings of safety and efficacy of ATM when used alone and PK of AVI when used in combination with CAZ. ATM, a monocyclic

BL, was first authorised in Guatemala in 1984. Generics of ATM are, or has been, marketed by different MAHs in the European Economic Area.

Approved indications for ATM when used alone includes (among other indications) treatment of UTI/pyelonephritis, treatment of pneumonia (without a restriction to either community acquired pneumonia (CAP) or HAP/VAP and IAI. AVI was centrally approved in the EU in combination with CAZ in 2016 for the treatment of cIAI, cUTI/pyelonephritis, HAP/VAP, bacteraemia that occurs in association with, or is suspected to be associated with, any of these infections and infections due to aerobic Gram-negative organisms in patients with limited treatment options.

It should be noted that phase 3 studies evaluating a beta-lactam (BL) at its approved dose combined with a beta-lactamase inhibitor (BLI) are generally not designed to provide stand-alone efficacy data to support the dose regimen for the BLI, which is acceptable by precedent and by CHMP guidelines. Therefore, the PK/PD analyses incorporating the non-clinical PK/PD data and patient PK data are pivotal to support the efficacy and dose regimen of the BLI for the proposed indications.

The main clinical studies were two phase 3, randomised, central assessor-blinded, open label, multicentre studies comparing the efficacy of ATM-AVI with or without metronidazole, with meropenem ± colistin (study C3601002) and best available therapy (Study C3601009). Study C3601002 included adult patients with cIAI and HAP/VAP, and study C3601009 included adult patients with cIAI, HAP/VAP, cUTI and BSI with a confirmed diagnosis of a Gram-negative, MBL-positive bacterium. Patients were randomised in a 2:1 ratio to receive either ATM-AVI, 1500 mg aztreonam plus 500 mg avibactam, q6h, i.v. (± metronidazole 500 mg q8h, i.v.) or the comparator. Primary endpoints were proportion of patients in the ITT and CE populations achieving clinical cure at TOC.

3.2. Favourable effects

The efficacy of AVI to protect ATM from hydrolysis by relevant beta-lactamases was demonstrated in preclinical models, including the hollow-fibre infection model and neutropenic murine thigh and lung infection models. Conservative PK/PD targets (PDTs) for ATM and AVI was derived from these models testing the agents alone and in combination against relevant isolated of Enterobacterales. The joint probability of target attainment (PTA) for the proposed dosing regimens including the simplified loading dose were satisfactorily above (or very close to) 90% using a joint target of >60% *f*T>$MIC_{ATM\text{-}AVI}$ for ATM and >50% *f*T>C_T of 2.5 mg/L for AVI for all renal function groups up to a MIC of 8 mg/L. The dosing regimens therefore would be sufficient to cover the vast majority of Enterobacterales regardless production of MBL or production of other beta-lactamases. Based on plasma exposure, the PTA analyses support applying the same dosing regimens across infection types. Additionally, data from the CAZ-AVI development programme with regards lung penetration of AVI support the adequacy of the AVI dose regimens for the treatment of lung infections.

In study C3601002, clinical cure at TOC in both the ITT and CE populations was achieved in a similar proportion between ATM-AVI and the comparator MER±COL. In the ITT population, 193/282 (68.4%) subjects achieved clinical cure in the ATM-AVI group and 92/140 (65.7%) subjects in the MER±COL group. The difference in cure rate was 2.7% with 95% CI -11.4%, 17.8%. In the CE population, 164/213 (77.0%) subjects achieved clinical cure in the ATM-AVI group and 78/105 (74.3%) subjects in the MER±COL group. The difference in cure rate was low also in this population, 2.7% with 95% CI -11.9%, 19.2%. Stratified by indication, cure rates with ATM-AVI were 76.4% and 45.9% in cIAI and HAP/VAP respectively in the ITT population with similar cure rates for the comparator. Differences between ATM-AVI and comparator were numerically similar in all subpopulations analysed.

In study C3601009, clinical cure was achieved in 5/12 subjects in the ATM-AVI arm, and 0/3 in the BAT arm. Stratified by infection type, cure was achieved in patients with cUTI (2/3 subjects) and BSI (3/4 subjects).

3.3. Uncertainties and limitations about favourable effects

As this application relies on a clinical programme that was not designed to isolate the effects of AVI in combination with ATM, the PK/PD package, including *in vitro* data, determination of non-clinical pharmacokinetic/pharmacodynamic targets and PTA simulations using clinical PK data, is pivotal to the application.

3.4. Unfavourable effects

The main clinical safety data comprise an integrated Phase 2/3 safety pool (305 participants exposed to ATM-AVI). In practice, the bulk of the data in this pool come from Study C3601002.

The proposed dosing regimen of ATM-AVI in combination reflects the upper end of the range of doses currently authorised in the EU for ATM and a 30% higher total daily dose of AVI than has previously been authorised in the EU and does not present a significantly altered safety profile when compared with the clinical safety of the two individual components as previously established.

Both ATM and AVI are predominantly eliminated by the kidney. ATM is well known to have liver side effects, usually asymptomatic serum transaminase elevations proportional to ATM compartment concentrations and appearing with some 5 to 6 days delay after first administration, that are self-limiting and resolve rapidly upon discontinuation. Although kidney is considered a target for ATM toxicity, no notable renal toxicity was observed amongst ATM-AVI ± MTZ participants in the Phase 2/3 Integrated Safety Pool.

Two-thirds of participants receiving ATM-AVI ± MTZ in the clinical Phase 2/3 programme reported at least one AE, and 1 in 5 patients reported an SAE. The incidence of all causality TEAEs with a fatal outcome for all participants in the Phase 2/3 Integrated Safety Pool was 7.2% in the ATM-AVI ± MTZ treatment group and 8.6% in the comparator treatment group. Adverse events were more frequent and more often serious or fatal in nature amongst HAP/VAP patients, which is not unexpected. The reported AEs were consistent with the known safety profiles of the individual components ATM and AVI, the frequent and varied concomitant medications and the underlying clinical conditions.

With regard to Adverse Events of Special Interest, the submitted safety data do not indicate any specific safety concern regarding hypersensitivity reactions or *Clostridioides difficile*-associated diarrhoea and pseudomembranous colitis with ATM-AVI over and above what is already established in clinical practice and reflected in existing Product Information.

Across the Phase 2/3 Integrated Safety Pool, increases in transaminase levels were comparable between ATM-AVI ± MTZ and comparator groups and as expected for ATM-AVI as part of the known safety profile. Derangement of laboratory parameters for alanine aminotransferase and aspartate aminotransferase were predominant and tended to be transient in nature. Mean changes from baseline over time for liver function parameters were generally small and similar between ATM-AVI ± and comparator treatment groups. No case was identified that met the criteria for Hy's law.

Following feedback from Phase 3 clinical trial investigators that the combined LD/ELD infusion requiring a change in infusion rate showed high potential for dosing administration errors in clinical practice, a simplified LD (a constant rate infusion over 3 hours, equivalent to the sum of LD and ELD in Phase 3 regimens) is proposed for the labelling.

Participants with mild RI (defined by the applicant as CrCl 51-80 mL/min), in whom the need to achieve adequate ATM exposure necessitates a roughly 40% higher AVI exposure, reported similar incidences of all types of AE as compared with participants with normal RF (CrCl 81-150 mL/min). This also provides safety reassurances regarding the similarly increased exposures to AVI projected for moderate and severe RI at their respective adjusted doses, and suggests that the increased incidence of all types of AE in moderate and severe RI, and in augmented RF, is related to the underlying clinical state rather than increased AVI exposure *per se*.

Patients with pre-existing hepatic impairment were not included in the clinical programme and did not contribute to the safety database. There is no reason to expect a different safety profile amongst patients with hepatic impairment on the basis of altered systemic clearance of either component of ATM-AVI, which is described in SmPC 5.2. Hepatotoxicity is a known risk for aztreonam and the warning proposed in SmPC 4.4 regarding the need for close monitoring in patients with pre-existing hepatic impairment is appropriate and sufficient. Finally, "GGT increased" is added as a new ADR following 3 reports from the Phase 2/3 pool (of which 2 were considered treatment-related by the sponsor) and a reasonable possibility of causal association with ATM.

3.5. Uncertainties and limitations about unfavourable effects

The approach of pooling data from the completed phase 2/3 studies in a single integrated safety pool was considered reasonable, although it should be noted that the pooled "comparator" arm consequently incorporates a heterogeneous mix of several different antibiotics that precludes meaningful comparison between arms. Additionally, a wide variety of systemic antibiotics and non-antibiotics medications were administered during the course of the clinical studies, making it difficult to attribute reported adverse events and other negative effects to ATM-AVI. The size of the ATM-AVI clinical programme, specifically the total number of ATM-AVI participants included in the Phase 2/3 safety pool (305), constrains qualification of newly reported events with a frequency of Uncommon or higher. Finally, as the active-controlled studies included in the Phase 2/3 integrated safety pool were open-label, the designation of treatment-related AEs was not fully blinded and must be interpreted with caution.

Patients with ESRD (CrCL ≤15 mL/min) were not included at all in the ATM-AVI clinical trials and the dose regimen proposed for ESRD is based on simulations. Based on study NXL104/1003 the proposed dosage in patients with ESRD is expected to result in 4.4-fold increases in exposure compared to subjects with normal renal function (CrCL above 80 ml/min) receiving the standard dose regimen. This increase is higher than the 2.6-fold increase in exposure expected in patients with CrCL 50-80 ml/min, for which clinical safety data are available across the Phase 2/3 programme.

Newly reported events were added as ADRs if they were considered related to ATM-AVI and if they were reported by 3 or more participants in the Phase 2/3 safety pool.

3.6. Effects Table

Table 65: Effects Table for Emblaveo for the Intended Indication.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Dose justification	PTA of ATM and AVI against target pathogens at the proposed susceptibility breakpoint based on PTA simulations using non-clinical PDTs and clinical PK data				**SoE:** PTA for the proposed dosing regimens including the simplified loading dose were satisfactorily above (or very close to) 90% using a joint target of >60% *f*T>$MIC_{ATM-AVI}$ for ATM and >50% *f*T>C_T of 2.5 mg/L for AVI for all renal function groups up to a MIC of 8 mg/L.	Section of Clinical pharmacodynamics
Cure rate	Proportion with clinical cure at TOC, ITT population (primary endpoint)	n/N %	ATM-AVI ± MTZ 193/282 68.4	MER ± COL 92/140 65.7	**SoE:** Similar effect in both treatment groups, difference 2.7% (95% CI: -11.4%, 17.8%) **UoE:** Small study, no hypothesis testing	Study C3601002
Cure rate	Proportion with clinical cure at TOC, CE population (coprimary endpoint)	n/N %	ATM-AVI ± MTZ 164/213 77	MER ± COL 78/105 74.3	**SoE:** Similar effect in both treatment groups, difference 2.7% (95% CI: -11.9%, 19.2%) **UoE:** Small study, no hypothesis testing	Study C3601002
Cure rate	Proportion with favourable outcome at TOC, micro-ITT population, by infection (secondary endpoint)	n/N % n/N % n/N %	ATM-AVI ± MTZ *All participants* 128/169 75.7 *cIAI* 111/133 83.5 *HAP/VAP* 17/36 47.2	MER ± COL 68/92 73.9 59/73 80.8 9/19 47.4	**SoE:** Similar effect in both treatment groups **UoE:** Small study, no hypothesis testing	Study C3601002

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Cure rate	Proportion with clinical cure at TOC, micro-ITT (primary endpoint)	 n/N %	ATM-AVI ± MTZ 5/12 41.7	BAT 0/3 0	**SoE:** Study participants with confirmed MBL-harbouring bacteria. **UoE:** Very small study with a total of 3 subjects in control arm (2 with result "indeterminate"), no hypothesis testing	Study C3601009
Unfavourable Effects not already described for individual components ATM and AVI						
GGT increased (Uncommon) added as new ADR	Reported in 3 participants on ATM-AVI in Phase 2/3 pool, of which 2 considered treatment-related by sponsor.				- Causal relationship with ATM-AVI possible but not confirmed. - ATM known to have effects on other liver enzymes.	Overview: *Discussion on Clinical Safety*
19 existing ADRs moved to higher frequency category	Based on frequencies observed in Phase 2/3 safety pool.					Overview: *Discussion on Clinical Safety*

Abbreviations: ADR = Adverse Drug Reaction. AR = Assessment report. ATM = Aztreonam. AVI = Avibactam. GGT = Gamma-glutamyl transferase. HFIM = Hollow-fibre infection model. LoQ = List of Questions. PDT = Pharmacodynamic target. PTA = Probability of target attainment. SoE = Strength of evidence. UoE = Uncertainties of evidence.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite some recent approvals of antibacterial agents for multi-resistant pathogens, there is still an unmet need of antibacterial agents with an acceptable safety profile that are active against bacteria resistant to available agents. The microbiology data indicate that ATM in combination with AVI may have an important utility in infections caused by MBL-producing Enterobacterales and the combination could therefore address un unmet need.

Because the clinical development programme for a new combination of a beta-lactam and a beta-lactamase inhibitor is generally not designed to isolate the effect of the combination, a robust PK/PD package is paramount to support the inference that AVI at the selected dose protect ATM from hydrolysis by beta-lactamases within the inhibitory range of AVI.

The PTA analyses support that the dosing regimens proposed for ATM-AVI would be adequate for the treatment of the intended indications caused by Enterobacterales including those caused by pathogens MBL-production.

The combination of ATM-AVI has no advantage compared with ATM alone against *P. aeruginosa* regardless of MBL-production. Notably, the activity of ATM against *P. aeruginosa* is moderate and the

dosing regimens would not be sufficient for a significant proportion of *P. aeruginosa* especially those that are MBL-producing.

The safety profile of ATM-AVI at the proposed dose appears favourable and generally reflects what is known about individual components. The extensive and heterogeneous use of systemic antibiotics and non-antibiotics medications during the course of the clinical studies confounds comparisons. Notwithstanding this, the safety observations were generally comparable for the ATM-AVI ± MTZ group as compared with comparator across the Phase 2/3 pool.

Neither drug-drug interactions nor extensive synergy with respect to off-target effects are anticipated with combined administration of ATM and AVI. The size of the safety database is thus considered sufficient in the context of two known substances with safety profiles that are already characterised. Long-term data beyond 14 days' use are not available and that is reasonable for the proposed clinical indication.

The majority of systemic effects resulting from the combination are suspected to relate to the administration of ATM, the safety profile of which is well established in clinical practice. ATM is well known to have predominant liver side effects, usually asymptomatic serum transaminase elevations proportional to ATM compartment concentrations and appearing with some 5 to 6 days delay after first administration, that are self- limiting and resolve rapidly upon discontinuation, as was reflected in the Phase 2/3 safety pool. No notable renal toxicity of ATM-AVI was observed in the clinical programme. The observed safety profile is generally clinically acceptable in the context of the intended clinical indication.

Patients with ESRD were not included in the Phase 2/3 programme. The proposed dose in patients with ESRD may result in AVI exposure up to 2.6-fold higher than that for which clinical safety data are available. Preclinical studies identified no major systemic toxicity with AVI at human exposure margins up to 3x the maximum recommended human dose (MRHD) and the Phase 2/3 clinical programme identified no new safety concerns beyond what has previously been characterised for ATM. It is unlikely (though not an impossibility) that clinically important new systemic toxicity would suddenly manifest only at the higher AVI exposure expected in ESRD, without any previous safety signal at lower exposures. Considering this, and additionally the short treatment duration and limited alternative treatment options for patients with infections caused by MBL-producing organisms, the paucity of clinical safety data at the exposure expected in ESRD patients is acknowledged as an uncertainty but is not considered to preclude conclusion of a positive-benefit risk balance for ATM-AVI even in patients with ESRD. ATM-AVI will be not primarily be used as a first-line empirical treatment of infections caused by potentially fully sensitive organisms. Rather, it will be reserved for a more limited subset of difficult-to-treat infections. The subset of these patients that also have ESRD is even smaller. Thus, it is unlikely that it would be feasible to generate meaningful post-marketing clinical safety data in ESRD patients receiving ATM-AVI to fully address the knowledge gap. Furthermore, isolating any adverse effects attributable to an increased AVI exposure from those attributable to underlying ESRD would be essentially impossible.

3.7.2. Balance of benefits and risks

Overall, the PK/PD package and clinical programme are considered acceptable to support a pathogen-specific indication in patients with limited treatment option and also the indications which are already approved for ATM when used alone.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Emblaveo is positive, subject to the conditions stated in section 'Recommendations'.

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 Emblaveo is favourable in the following indications:

Emblaveo is indicated for the treatment of the following infections in adult patients (see sections 4.4 and 5.1):

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

Emblaveo is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (see sections 4.2, 4.4, and 5.1).

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 (see Annex I: Summary of Product Characteristics, section 4.2).

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 marketing authorisation holder (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.