25 July 2019
EMA/463294/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zerbaxa

International non-proprietary name: ceftolozane / tazobactam

Procedure No. EMEA/H/C/003772/II/0020

Note

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

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List of abbreviations

AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
ARC	Augmented renal clearance
AST (SGOT)	Aspartate aminotransferase
ATCC	American Type Culture Collection
ATS	American Thoracic Society
AUC0-8	Area under the plasma concentration-time curve in the dosing interval 0 to 8 hours
AUC(0-∞)	Area under the plasma concentration-time curve in the dosing interval 0 to infinity
BAL	Bronchoalveolar lavage
BCRP	Breast cancer resistance protein
BL	β-lactamase
BP	Bronchopulmonary (concentration)
BSEP	Bile salt export pump
CAZ/AVI	Ceftazidime/avibactam
CDAD	Clostridium difficile-associated diarrhoea
CDC	Centers for Disease Control and Prevention
CE	Clinically evaluable
CFU	Colony-forming unit
cIAI	Complicated intra-abdominal infections
CLSI	Clinical and Laboratory Standards Institute
COPD	Chronic obstructive pulmonary disease
CPIS	Clinical Pulmonary Infection Score
CRE	Carbapenem-resistant Enterobacteriaceae
CRF	Case report form
CSR	Clinical study report
CT/Ct	Threshold concentration
cUTI	Complicated urinary tract infections
DAO	Data-as-observed
DSMB	Data and Safety Monitoring Board
ELF	Epithelial lining fluid
EMA	Exponential Moving Average
EOT	End-of-therapy
ESBL	Extended spectrum β-lactamase
ESRD	End stage renal disease
ETA	Endotracheal aspirate
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GCV	Geometric coefficient of variation
GM	Geometric least-squares mean
GMR	Geometric least-squares mean ratio between last dose and first dose
HABP	Hospital-acquired bacterial pneumonia
HAP	Hospital-acquired pneumonia
HF	Hollow fiber
I	Intermediate
IC50	Half-maximal inhibitory concentration
ICU	Intensive Care Unit
ID	Identification
IDSA	Infectious Diseases Society of America
IHMA	International Health Management Associates
ITT	Intent-to-Treat
K1E	Rate constant for disposition from plasma to epithelial lining fluid
KE0	Rate constant for elimination from epithelial lining fluid
LFU	Late follow-up
LRT	Lower respiratory tract
MAOI	Monoamine oxidase inhibitor
MCS	Monte Carlo Simulation
MATE	Multidrug and toxin extrusion
MDR	Multidrug resistant
MDRD	Modification of diet in renal disease
ME	Microbiologically evaluable
MIC	Minimum inhibitory concentration
MIC50	Minimum inhibitory concentration required to inhibit the growth of 50% of organisms
MIC90	Minimum inhibitory concentration required to inhibit the growth of 90% of organisms
mini-BAL	Non-bronchoscopic bronchoalveolar lavage
mITT	Microbiological Intent-to-Treat
MRP2	Multidrug resistance-associated protein 2
NB	Note well
NE	Not estimated
No.	Number

NOAEL	No observed adverse effect level
NP	Nosocomial pneumonia
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OmpK	Outer membrane protein K
P-gp	P-glycoprotein
PACTS	Program to Assess Ceftolozane Tazobactam Susceptibility
PaO2/FiO2	Partial pressure of oxygen to the fraction of inspired oxygen
PBS	Protected brush specimen
PDC	*Pseudomonas*-derived cephalosporinase
PIHP	Pneumonia in hospitalized patients
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PN	Protocol number
PPB	Plasma protein binding
POPP	Population and outcome process plan
PSUR	Periodic Safety Update Report
PT	Preferred term
PTA	Probability of target attainment
PV	Pharmacovigilance
Q	Inter-compartmental clearance
q8h	Every 8 hours
q12h	Every 12 hours
QC	Quality control
QIDP	Qualified Infectious Disease Product
QTc	Corrected QT interval
QTcI	Corrected QT interval using an individual-specific interval correction for heart rate
R	Resistant
RHD	Recommended human dose
RT-PCR	Real-time polymerase chain reaction
RV	Residual variability
S	Susceptible
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMART	Study for Monitoring Antimicrobial Resistance Trends
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SOFA	Sepsis Organ failure Assessment
Spp	Several species
SS-ELF	Steady state epithelial lining fluid
t½	Elimination half-life
T>CT	Time above threshold concentration
T>MIC	Time above the minimum inhibitory concentration
TAZ	Tazobactam
TAZ M1	Tazobactam metabolite
TEAE	Treatment-emergent adverse event
TFA	Treatment Failure Approach
Tmax	Time of maximum plasma concentration
TOC	Test-of-cure
TOL	Ceftolozane
TOL/TAZ	Ceftolozane/tazobactam
CEF/TAZ	Ceftolozane/tazobactam
TQT	Thorough QT
VABP	Ventilator-associated bacterial pneumonia
VAP	Ventilator-associated pneumonia
Vc	Volume of distribution for central compartment
VNP	Ventilated nosocomial pneumonia
Vp	Volume of distribution for peripheral compartment
Vss	Volume of distribution at steady state
WBC	White Blood Cell
XDR	Extensively Drug Resistant

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 21 November 2018 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of Nosocomial pneumonia, including ventilator associated pneumonia for Zerbaxa, based on results from the randomised, double-blind, multicentre clinical trial CXA-NP-11-04 (PN008).

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance (sections 1, 2, 3, 4 and 6).

The applicant also took the opportunity to implement editorial changes in sections 5.2 of the SmPC and to bring Section 4.4 of the SmPC and section 2 of the PL in line with the latest Annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'.

Version 2.1 of the RMP was also submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0277/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0277/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did seek scientific advice regarding the clinical developmental program for the pivotal phase 3 trial PN008 at the SAWP/CHMP in 2011 (procedure no: EMEA/H/SA/2182/1/2011/II) with follow-up clinical advice in 2017 (EMEA/H/SA/2182/1/FU/1/2016/II). The main issues for discussion with SAWP/CHMP regarding the pivotal phase 3 study were study objectives/endpoint, primary analysis population, the proposed eligibility criteria, comparator, non-inferiority margin, dose selection and

adjunctive therapy. An additional scientific advice regarding the toxico-pharmacological development and the non-clinical safety data package was also discussed in 2017 (EMEA/H/SA/2182/2/2016/I).

1.1. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	21 November 2018
Start of procedure:	29 December 2018
CHMP Rapporteur Assessment Report	22 February 2019
CHMP Co-Rapporteur Assessment Report	22 February 2019
PRAC Rapporteur Assessment Report	1 March 2019
PRAC members comments	6 March 2019
Updated PRAC Rapporteur Assessment Report	7 March 2019
PRAC Outcome	14 March 2019
CHMP members comments	18 March 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 March 2019
Request for supplementary information (RSI)	28 March 2019
PRAC Rapporteur Assessment Report	6 May 2019
CHMP Rapporteur Assessment Report	15 May 2019
PRAC Outcome	16 May 2019
CHMP members comments	20 May 2019
Updated CHMP Rapporteur Assessment Report	23 May 2019
Request for supplementary information (RSI)	29 May 2019
CHMP Rapporteur Assessment Report	12 June 2019
CHMP members comments	17 June 2019
Updated CHMP Rapporteur Assessment Report	20 June 2019
Request for supplementary information (RSI)	27 June 2019
CHMP Rapporteur Assessment Report	18 July 2019
CHMP members comments	15 July 2019
Opinion	25 July 2019

Summary

Please refer to Scientific Discussion Zerbaxa-H-C-3772-II-20.

2. Scientific discussion

2.1. Introduction

This application summarises the results from three Phase 1 studies (**PN018**, **PN028**, **PN007**) and one pivotal Phase 3 study (**PN008**) supporting the use of ceftolozane/tazobactam (*i.e.* TOL/TAZ; also known as ZERBAXA™, MK-7625A, CXA-201) for the treatment of nosocomial pneumonia (NP), including both Hospital-acquired bacterial pneumonia (HABP, also known as HAP) and Ventilator-associated bacterial pneumonia (VABP, also known as VAP), in patients 18 years or older.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity / environmental risk assessment

Introduction

ZERBAXA is a fixed dose combination product of ceftolozane (a cephalosporin antibiotic) and tazobactam (a well-established β-lactamase inhibitor); ZERBAXA is currently approved in the EU for the treatment of complicated genitourinary tract infections (cUTI) and intra-abdominal infections (cIAI). This application concerns an extension of indication to include treatment of nosocomial pneumonia (NP) infections in adults.

The currently marketed formulation of ZERBAXA will be used, which contains a dose of 1.5 g (1 g ceftolozane/0.5 g tazobactam). The proposed 3 g dose (2 g TOL/1 g TAZ) to be used for the NP indication will be produced by using two vials. This injection will be required three times per day for a total daily dose of 6 g ceftolozane and 3 g tazobactam for a maximum duration of treatment of 14 days.

Phase I analysis

The log of the n-octanol/water partition coefficient (log Dow) of ceftolozane was determined to be -0.21 at pH 7.4, and for tazobactam -0.63 at pH 7.4. As these values are well below 4.5, an evaluation for persistence, bioaccumulation and toxicity was not conducted.

PEC calculations

For the calculation of the PECsw values, the default Fpen was used to account for all indications. The DOSEai (maximum daily dose of active substance consumed) is 6000 mg/day for ceftolozane and 3000 mg/day for tazobactam.

- The PECsw for ceftolozane was calculated to be 30.0 µg/L, which is above the threshold of 0.01 µg/L and therefore a phase II risk assessment is provided.
- The PECsw for tazobactam was calculated to be 15.0 µg/L, which is above the threshold of 0.01 µg/L and therefore a phase II risk assessment is provided.

Phase II

Phase II studies were conducted and assessed in the previous application in 2014.

PEC and RQ values have now been updated for surface water, groundwater and wastewater treatment facilities, based on a maximum daily dose of 6 g ceftolozane and 3 g tazobactam (see table). All RQs for Tazobactam are under the threshold of 1, indicating no risk to the environment. For Ceftolozane a risk for surface water is indicated, which is investigated further in Tier B.

Both ceftolozane and tazobactam are not readily biodegradable, however, tazobactam did not significantly shift to the sediment, and a Tier B assessment was not necessary. For ceftolozane a Tier B for sediment was conducted, by means of an OECD 218 study (sediment-water chrironomid toxicity using spiked sediment) which did not indicate a risk when the updated PEC values were used in the risk calculation.

Ceftolozane monosulfate			
Compartment	PEC (µg/L)	PNEC(µg/L)	RQ
Surface water	30.0	1.5	20.4
Ground water	7.5	740	1.0×10^{-2}
Wastewater treatment plant	30.0	43,000	7.0×10^{-4}
Sediment	5.5	33.5	0.2

Tazobactam sodium			
Compartment	PEC (µg/L)	PNEC(µg/L)	RQ
Surface water	15.0	39.9	0.4
Ground water	3.8	860	4.4×10^{-3}
Wastewater treatment plant	15.0	91,500	1.6×10^{-4}

In the Tier B the PECsurfacewater for ceftolozane was refined using consumption data for the period 19/03/2018-18/03/2019 in Europe. These consumption data were extrapolated to include the new indication and higher maximum dose:

- Consumption ceftolozane in 2018/2019: 2,359,004 g/yr.
- Extrapolated DDD (old indication) 3* 1 g/day = 7,077,012 g
- Extrapolated DDD (new indication) 3* 2 g/day = 14,154,024 g
- Projected consumption: 21,231,036 g/yr = 21,231,036,000 mg/yr
- DDD: 6000
- Inhabitants Europe: 5.03×10^8

$$refined\ Fpen = \frac{21231000000*100}{6000*5.03\ x\ 10^8*365} = 0.002$$

An Fpen of 0.002 results in a PECsurfacewater of 5.8 µg/L and a corresponding RQ of 3.9. This ratio indicates a potential risk to the environment.

Based on the currently available information, the SmPC for ZERBAXA includes the following statement:

One of the active ingredients, ceftolozane, may have harmful effects if it reaches the aquatic environment. Do not throw away any unused medicinal product or waste material via wastewater. Any unused medicinal product or waste material should be disposed in accordance with local requirements. These measures will help protect the environment.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application lead to a significant increase in environmental exposure further to the use of ceftolozane and tazobactam.

Considering the above data, ceftolozane and tazobactam should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

During the procedure the applicant confirmed that there have been no inspections during the study period for studies included in the submission (MK-7625A PN007, PN008 and PN018). Regarding inspections within the last year since finalization of the clinical study, the applicant confirmed that there were two FDA investigator site inspections for MK-7625A PN008, week beginning 08 April 2019. The applicant confirmed that there were no observations noted and a Form FDA 483 was not issued at either site.

Tabular overview of clinical studies

Study ID	Country /region	Study title	Study design	Dosing regimen	Study population	Participant exposure
CXA-ICU-14-01 **7625A-007** **PN007**	USA (including Puerto Rico), EU (Belgium, France, Germany, Italy, Spain)	A Phase 1, Prospective, Multicenter, Open-label Study to Assess the Plasma Pharmacokinetics and Lung Penetration of Intravenous (IV) Ceftolozane/tazobactam in Critically Ill Patients	Non-comparative, open label, prospective, multicenter, plasma PK and intrapulmonary penetration (epithelial lining fluid [ELF] concentrations)	Group 1: CrCL >50 mL/min: TOL/TAZ 3 g IV q8h, 4-6 doses CrCL 30-50 mL/min: TOL/TAZ 1.5 g IV q8h, 4-6 doses CrCL 15-29 mL/min: TOL/TAZ 750 mg IV q8h, 6 doses Group 2 : TOL/TAZ 3 g IV single dose	Males/female Group 1: Age 21-88 26 ventilated patients with pneumonia receiving concurrent antibiotic therapy Group 2: Age: 20-50 10 critically ill patients with CrCL ≥180 mL/min	Group 1: TOL/TAZ 3 g IV q8h: 21 patients TOL/TAZ 1.5 g IV q8h: 4 patients TOL/TAZ 0.75 g IV q8h: 1 patient Group 2: TOL/TAZ 3 g IV single dose: 10 patients
CXA-NP-11-04 **7625A-008** **PN008**	Global	A Prospective, Randomized, Double-Blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam Compared with Meropenem in Adult Patients with Ventilated Nosocomial Pneumonia	Phase 3 Randomized, double-blind, prospective, multicenter	TOL/TAZ 3000 mg q8h IV or Meropenem 1000 mg q8h IV administered for a minimum of 8 days up to maximum 14 days	Male/female Age: ≥18 Subjects with VNP, including VABP and ventilated HABP subjects stratified by diagnosis and by age (≥65 or <65) Planned enrollment: 726 subjects	TOL/TAZ 3000 mg: 361 patients Meropenem 1000 mg: 359 patients
CXA-EB-13-05 **7625A-018** **PN018**	USA	A Single-dose, Open-label, Parallel-group Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Ceftolozane/Tazobactam Administered Intravenously to Adult Japanese, Chinese and Caucasian Healthy Subjects	Phase 1 Open-label, parallel group	TOL/TAZ 1.5 g IV single dose on Day 1; and Ceftolozane/Tazobactam 3 g IV single dose on Day 4	Male/female Age: 20-50 Caucasian, Chinese, and Japanese healthy subjects	TOL/TAZ 1.5 g IV (Day 1): 29 (Caucasian: 10; Chinese: 9; Japanese: 10) TOL/TAZ 3g IV (Day 4): 27 (Caucasian: 10; Chinese: 8; Japanese: 9)

2.3.2. Pharmacokinetics

A comprehensive clinical pharmacology program was conducted to support the original application of TOL/TAZ for cUTI and cIAI indications at the TOL/TAZ 1.5 g q8h dose. Nine phase 1 studies evaluated the safety, PK, effect of intrinsic and extrinsic factors, tissue distribution (ELF PK), and effect on QTc interval of TOL/TAZ. The studies cover a dose range that included the proposed 3 g dose for the NP indication. Additional studies (**PN018**, **PN007**, **PN008**) have been completed since the original cIAI/cUTI application to provide data to support the new adult NP indication and dose regimen (3g q8h). Also, four popPK modelling and ER analysis reports have been submitted in the current application:

- popPK analysis for TOL/TAZ in adults with ventilated NP (**050zc7**),
- popPK analysis for TOL/TAZ for CXA-ICU-14-01 (**050w2j**),
- popPK modelling and simulation to support paediatric dose selection for TOL/TAZ (**04kb9q**), and
- ER analysis for TOL/TAZ in adult patients with ventilated NP (**050zc9**).

The current commercial formulation will be used for the NP indication by reconstituting two 1.5 g vials to make an infusion solution containing the intended 3 g dose of TOL/TAZ. Single agent or commercial TOL/TAZ formulations were used in the three new clinical studies. As the TOL and TAZ powder was

reconstituted into clear solution and infused intravenously, similar *in vivo* performance was anticipated for each component regardless of formulation. This enabled pooling of PK data across studies to fully characterise the PK profile and assess factors affecting TOL and TAZ PK using a population PK (popPK) modeling approach.

CHMP's comment

A paediatric indication for Zerbaxa is not pursued at this stage. Hence, the popPK model report concerning selection of paediatric dose in cUTI and cIAI has not been assessed.

Methods

Analytical methods

Validated analytical methods

LC-MS/MS methods validated in accordance with applicable regulatory guidance were used for the determination of TOL, TAZ, and TAZ M1 metabolite in biological matrices. Colorimetric methods were used to determine urea in plasma and ELF. Methods are listed in Table 1. The methods MN10131 (TOL) and MN14014 (TOL+TAZ, TAZM1) were developed and validated to support the studies in the original submission. New analytical LC methods were developed and validated for the determination of:

- TOL (MN09055) and TAZ/ TAZ M1 metabolite (MN08036) in urine (study **PN018)**,
- TOL (MN10120) and TAZ (MN14114) in epithelial lining fluid, ELF (study **PN007**),
- urea (MN14016) in plasma (study **PN007**), and
- urea (MN14017) in ELF (study **PN007**).

Primarily, isotopically labelled internal standards (TOL, TAZ M1) were used. Sulbactam was internal standard for TAZ in ELF and plasma. Satisfactory between- and within-run accuracy and precision were shown for LLOQ, low, medium and high QC sample concentrations. Dilution integrity was demonstrated. Stability in matrixes at room temperature, -20°C and -70°C, and over a number of freeze-thaw cycles have been determined.

Table 1. Methods used to support the nosocomial pneumonia clinical program

Method	Analyte	Lower Limit of Quantitation (LLOQ)	Nominal Linear Range	Matrix
MN14014	TOL	0.25 µg/mL	0.250 - 150 µg/mL	Plasma
MN14014	TAZ	0.100 µg/mL	0.100 - 60.0 µg/mL	Plasma
MN14014	TAZ M1	0.050 µg/mL	0.050 - 30.0 µg/mL	Plasma
MN14016	Urea	2.50 mg/dL	2.50 – 50.0 mg/dL	Plasma
MN14017	Urea	0.150 mg/dL	0.150 – 2.50 mg/dL	ELF
MN14017	Urea (high sensitivity assay)	0.0500 mg/dL	0.0500 – 1.00 mg/dL	ELF
MN10120	TOL	1.00 ng/mL	1.00 - 1000 ng/mL	ELF
MN14114	TAZ	1.00 ng/mL	1.00 - 250 ng/mL	ELF
MN10131	TOL	0.25 µg/mL	0.25 - 150 µg/mL	Plasma
MN09054	TAZ	0.100 µg/mL	0.100 - 50 µg/mL	Plasma
MN09054	TAZ M1	0.0500 g/mL	0.0500 – 25.0 µg/mL	Plasma
MN08036	TOL	5.00 µg/mL	5.00 – 5000 µg/mL	Urine
MN09055	TAZ	10.0 µg/mL	10.0 - 5000 µg/mL	Urine
MN09055	TAZ M1	5.0 µg/mL	5.0 - 2500 µg/mL	Urine

ELF = Epithelial lining fluid
TAZ = Tazobactam
TAZ M1 = Tazobactam metabolite 1
TOL = Ceftolozane

Source: [Ref. 5.3.1.4: 0505VP] [Ref. 5.3.1.4: 0506KD] [Ref. 5.3.1.4: 0506JH] [Ref. 5.3.1.4: 0506DP] [Ref. 5.3.1.4: 0506XY] [Ref. 5.3.1.4: 05075L] [Ref. 5.3.1.4: 050739]

Acceptance criteria of analytical runs

Bioanalysis were performed. Inter-run accuracy and precision data for each trial are given in Table 2. ISR assessments were conducted for plasma and urine analyses in studies **PN007**, **PN008**, and **PN018**. All ISR assessment met acceptance criteria. Most clinical samples were analysed within the established stability period of the analysis.

Table 2. Analytical methods used to support each clinical study together with study assay performance

Trial	Method	Analyte	Matrix	Inter-run % Accuracy[a,b]	Inter-run Precision %CV[a]	% ISR Overall Acceptance
MK-7625-007	MN14014	Ceftolozane	plasma	-0.833 – 4.27	6.20 – 8.57	84.1
MK-7625-007	MN14014	Tazobactam	plasma	-1.33 – 2.00	7.27 – 11.9	78.2
MK-7625-007	MN14014	Tazobactam M1	plasma	-3.33 – 3.00	5.19 – 7.86	88.6
MK-7625-007	MN14016	Urea	plasma	-3.05 – 5.60	5.95 – 12.6	NA
MK-7625-007	MN14017	Urea	ELF	-5.00 to -1.50	7.54 – 10.9	N/A
MK-7625-007	MN14017-high sensitivity	Urea	ELF	-4.00 to -1.13	2.24 – 8.30	N/A
MK-7625-007	MN10120	Ceftolozane	ELF	0.200 – 4.50	6.27 – 7.78	N/A
MK-7625-007	MN14114	Tazobactam	ELF	-5.50 – 0.333	5.37 – 10.1	N/A
MK-7625-008	MN14014	Ceftolozane	plasma	2.50 – 5.60	6.20 – 7.01	91.4
MK-7625-008	MN14014	Tazobactam	plasma	0.75 – 2.00	6.77 -8.57	88.1
MK-7625-008	MN14014	Tazobactam M1	plasma	-1.25 – 3.33	4.50 – 8.09	92.9
MK-7625-18	MN10131	Ceftolozane	plasma	-3.60 to -0.133	4.81 – 7.83	100.0
MK-7625-18	MN09054	Tazobactam	plasma	-9.50 to -0.333	4.79 – 7.68	78.8
MK-7625-18	MN09054	Tazobactam M1	plasma	-0.500 – 4.67	3.46 – 5.52	82.7
MK-7625-18	MN08036	Ceftolozane	urine	-6.67 to -1.00	4.14 – 5.63	79.4
MK-7625-18	MN09055	Tazobactam	urine	-9.00 to -5.00	6.54 – 9.33	88.2
MK-7625-18	MN09055	Tazobactam M1	urine	-8.00 to -7.33	5.40 – 14.3	93.9

Abbreviations: %CV= Percent coefficient of variation; ELF = Epithelial lining fluid; ISR= Incurred sample reanalysis; QC= Quality control

[a] Statistics based on mean assay performance of QC samples from all analytical batches meeting acceptance criteria.

[b] Expressed as [(mean observed concentration/(nominal concentration)] x 100

Source: [Ref. 5.3.1.4: 04STZS] [Ref. 5.3.1.4: 04SV0F] [Ref. 5.3.1.4: 04RMB9] [Ref. 5.3.5.1: P008MK7625A:16.1.9.5]

Pharmacokinetic data analysis

In general, the PK data analyses were performed using non-compartmental analysis (Phoenix WinNonlin software version 6.3 or later). Standard statistical methods were used, including ANOVA analysis for comparisons to assess potential ethnicity differences in PK in study 018.

050ZC7: All exploratory data analyses and presentations of data were performed using SAS Version 9.4 (SAS Institute, Cary, NC), KIWI Version 2 (Cognigen Corporation, Buffalo, NY), and PsN Version 4.4.0 (Uppsala University, Uppsala, Sweden). PopPK modeling was performed using the computer program NONMEM, Version 7, Level 3.0 (ICON Development Solutions, Hanover, MD). NONMEM analyses were performed on an Intel cluster with the Linux operating system. The first-order conditional estimation method with interaction (FOCE-I) was used for the model development.

Evaluation and qualification of models

popPK model 050zc7

Methodology

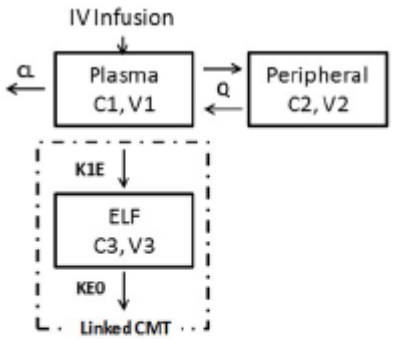
To evaluate the PK of TOL and TAZ in NP patients, the previously developed popPK models were refined by including PK data from studies **PN008** (ventilated NP patients), **PN013** (MK-7625A-013, Japanese cIAI patients) and **PN014** (MK-7625A-014, Japanese cUTI patients), whereas PK data from the paediatric study **CXA-PEDS-13-08** were excluded.

Prior modelling

Prior popPK modeling	Purpose / objectives	Data set	Comments
CUBI-PCS-100	Determine source of variability in PK parameters, identify intrinsic and extrinsic clinically relevant covariates, and compute model-based individual exposure measures of TOL/TAZ in special populations (renal impairment, subjects with bacterial infection).	Eight phase 1 and two phase 2 studies in healthy subjects and patients (renally impaired, cUTI, cIAI).	Main TOL and TAZ models submitted in support of the original MAA.

04dpz3[1]	Guide/support dose selection in phase 3 pivotal study (NP patients).	Nine phase 1 (incl. **CXA-ELF-10-03**, *i.e.* ELF PK in healthy subjects) and two phase 2 studies. Healthy subjects and patients (renally impaired, cUTI, cIAI).	Based on **CUBI-PCS-100**. The model report has not been submitted. Includes an ELF compartment analysis (healthy subjects).
04kb9q[2]	Support pediatric dose selection in cUTI and cIAI.	Eleven phase I (incl. **CXA-PEDS-13-08**, paediatric patients w/gram - infections) and two phase 2 studies. Healthy subjects and patients (renally impaired, cUTI, cIAI).	Based on previous model **04LJ74,** apparently identical to **CUBI-PCS-100**.
050w2j[3]	Develop and evaluate popPK models to characterise the plasma and ELF concentrations of TOL and TAZ in healthy subjects and in patients with pneumonia.	Twelve phase I and two phase 2 studies (incl. **PN007**, **CXA-PEDS-13-08**). Healthy subjects and patients (renally impaired, cUTI, cIAI, pneumonia).	Based on previous model **04kb9q**. Includes an ELF compartment analysis (healthy subjects and patients with pneumonia).

The current model is based on model **050w2j**; a 2-compartment model with first-order elimination, parameterised in terms of Vc, Vp, CL, and Q for both TOL and TAZ, and with a hypothetical ELF compartment linked to the plasma compartment (Figure 1). Significant covariates were body weight on Vc and Vp, CrCL on CL, and pneumonia on Vc. The TAZ model also included the covariate pneumonia on Vp.



$$\frac{dA1}{dt} = Q * C2 - (Q + CL) * C1$$
$$\frac{dA2}{dt} = Q * C1 - Q * C2$$
$$\frac{dA3}{dt} = K1E * A1 - KE0 * A3$$

Abbreviations: A = amount in compartment; C = concentration in compartment; CL = clearance from plasma compartment; CMT = compartment; ELF = epithelial lining fluid; IV = intravenous; K1E = rate constant for hypothetical mass transfer from plasma compartment to ELF compartment; KE0 = elimination rate constant from ELF

1 Xiao *et al*. Ceftolozane/tazobactam pharmacokinetic/pharmacodynamic-derived dose justification for phase 3 studies in patients with nosocomial pneumonia. J Clin Pharmacol. 2016 Jan;56(1):56-66 2016 (04dpz3).
[2] Willavize *et al*. Report for population pharmacokinetic modeling and simulation to support pediatric dose selection for ceftolozane/tazobactam (MK-7625A). Buffalo (NY): Cognigen Corp; January 25, 2017.
[3] Patel Y, Fiedler-Kelly J. Final technical report for the population pharmacokinetic analysis of ceftolozane and tazobactam (MK-7625A) for CXA-ICU-14-01 (MK7625A-007). Buffalo (NY): Cognigen Corp; September 28, 2018.

compartment; Q = intercompartmental clearance for peripheral compartment; V1 = plasma volume of distribution; t = time; V2 = peripheral volume of distribution; V3 =, volume of distribution for ELF compartment.

Figure 1. PopPK base structural model for plasma and epithelial lining fluid (ELF) data (050w2j)

Objectives (**050zc7**)

- Refine the popPK models for TOL and TAZ using data from **PN008**, **PN013** and **PN014**,
- evaluate the effect of pneumonia/other infections on the plasma PK parameters of TOL&TAZ,
- perform stochastic simulations to estimate individual plasma and ELF exposures and calculate the probability of target attainment (PTA) for TOL&TAZ in patients with NP, and
- support TOL/TAZ dose regimen justification in adult patients with NP.

Model development process

2-compartment model with zero-order input and first-order elimination was selected as a starting point for the base model development. Forward selection, backward elimination was used in the covariate analysis. An exponential variance model was used for IIV and a proportional variance model was used for RV. The IIV error model was further refined by estimating an additive plus constant coefficient of variation form. During model refinement, the TOL and TAZ models were evaluated for the effect of ESRD on CL and Vc, model sensitivity to identified outliers, and the effect of sparse data on the estimation of IIV in Vp (for TOL only).

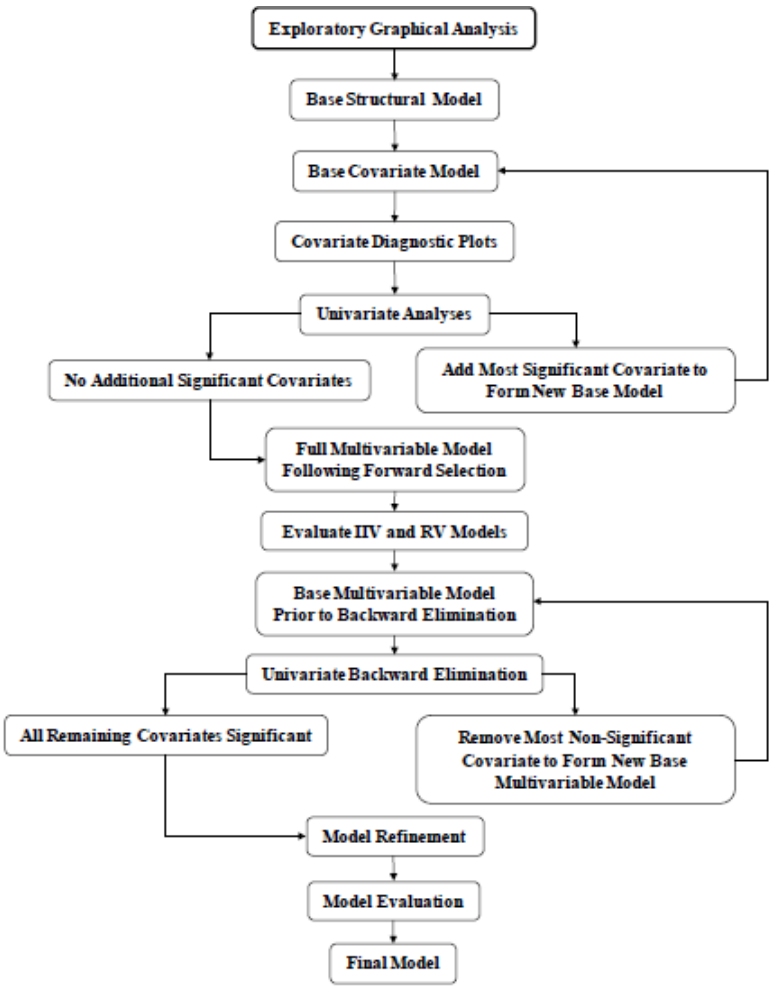


Figure 2. Flow chart of the popPK model development process (Model report 050zc7, Figure 1)

Dataset

Two single agent (TOL) phase 1 studies (**CXA-101-01**, **-101-02**), nine Phase 1 trials (**CXA-201-01**, **-201- 02**, **-MD-1107**, **-QT-10-02**, -**ELF-10-03**, -**REN-11-01** (incl. six patients receiving HD), **-DDI-12- 10**, **-EB-13-05**, and **PN007**), two Phase 2 studies (**CXA-IAI-10-01**, **-101-03**, the latter TOL single agent), and three Phase 3 trials (**PN013**, **PN014** and **PN008**).

TOL: Presumably a total of 8680 plasma concentrations from 987 subjects. Following data cleaning, 8330 (96%) observations from 968 (98%) subjects remained, including 1481 sparse observations from 305 NP patients (**PN008**). The final dataset also consisted of 47 ELF concentrations from 47 subjects.

TAZ: Presumably a total of 6144 plasma concentrations from 854 subjects. Following data cleaning 5679 (92.4%) observations and 835 (97.8%) subjects remained, including 1455 sparse PK samples from 305 NP patients (**PN008**). The final dataset also consisted of 42 ELF concentrations from 42 subjects.

In the overall pooled final dataset for TOL, median (range) for age, weight, and baseline CrCL was 56 years (18-98), 73.35 kg (33.5-173) and 102.9 mL/min (6.30 to 531.3). In study **PN008**, the median (range) for age, weight, and baseline CrCL was 62.0 years (18 to 98), 80 kg (42 to 150.1), and 110.4 mL/min (14.9 to 531.3), respectively, and the majority (84.6%) were whites. Demographics for the TAZ population were similar.

TOL/TAZ was administered as a 60 minute infusion in all studies. TOL (0.25-3 g) and TAZ (0.25-1.5g) were given either alone or as a TOL/TAZ combination. Single or combined agents were given as a single dose or as multiple doses (q6h, q8h, q12h, or QD). In **PN008** TOL/TAZ was administered according to renal function (≥30 mL/min) using the dose regimen proposed in the SmPC. A combination of rich (eleven phase 1 studies) and sparse (all phase 2 and 3 studies) PK sampling were performed. In study **PN008** sampling was performed at four time points on Day 4: end of infusion, 0.5-1.5, 2.5-3.5 and 5.0-6.0 hours post infusion.

Data missingness: BLQ data were excluded: 5.21% and 23.25% of TOL and TAZ observations, respectively, were BLQ. The majority of BLQs were 15 hours (5.09%, TOL) or 5 hours (22.93%, TAZ) post-dose.

Outliers: Outliers were defined as $[TOL]_{plasma}$ > 450 µg/mL, $[TAZ]_{plasma}$ >130 µg/mL, |CWRESI|≥6 for both TOL and TAZ, and were retained in the datasets but excluded during the model development process in the NONMEM control streams (*i.e.* N=23, N=23, N=33, N=12 observations excluded, respectively). Outliers were considered included in the final model dataset.

Assumptions

Baseline covariates were assumed to be constant. Other assumptions were not explicitly stated.

Co-variate considerations

Covariates evaluated were body weight (BW, kg), race (white, Japanese, and other), infection type (cIAI, cUTI, pneumonia, other infection and healthy), CrCL (Cockcroft and Gault formula, mL/min). Critically ill adult patients in Group 2 from study **PN007** were included in the other infection category. Covariate correlation (|r|>0.6) was examined prior to covariate analysis.

Diagnostics/GoF evaluation

Objective function value (forward inclusion ΔOFV ≥ 6.64 [α=0.01, df1], backward elimination ΔOFV ≥ 10.83 [α=0.01, df1]), convergence, adequate precision (%RSE), DV vs. PRED/IPRED, CWRES vs. PRED, IWRES vs. IPRED, IIV (Δ%IIV ≥5%), and RV for specified vs. comparator model, pcVPC (1000 simulations), unexplained IIV vs. all covariates, delta plots etc.

Simulations to support dose recommendations in special populations and for PTA analysis

Individual model-based empiric Bayesian parameter estimates (EBE) were used to simulate individual PK profiles for subjects included in the analysis datasets (**PN008**). The relevant parameters from the previously developed PK models for lung penetration of TOL/TAZ (**050w2j**) were combined with the simulated plasma concentrations (using model **050cz7**) to stochastically simulate ELF concentration-time profiles in patients with NP. Lung penetration of TOL/TAZ was described using a hypothetical linked compartment model, where drug disposition between the central and ELF compartments was described using K_{1E} and K_{E0} (Figure 1). The linked model assumes that the amount of drug transferred to the ELF compartment is negligible and does not affect plasma disposition.

Using a virtual demographic dataset, stochastic simulations of plasma and ELF concentrations were performed to support dose justification for patients with NP and varying degrees of renal function, based on CrCL (N=1000 for each subgroup): accelerated renal clearance (ARC) (≥ 210 mL/min, 180 mL/min to < 210 mL/min and 150 mL/min to < 180 mL/min), normal renal function (80 mL/min to <150 mL/min), mild, moderate and severe renal impairment (50 mL/min to < 80 mL/min, 30 mL/min to ≤ 50 mL/min and 15 mL/min to ≤ 29 mL/min, respectively), and ESRD (<15 mL/min or on HD). Correlation between CrCL and body weight in the pooled demographic dataset was graphically compared with that in study **PN008**, and was found generally comparable. Unexplained IIV and residual error components of the final model were retained in the simulations performed.

A sensitivity analysis was performed to evaluate the effect of varying magnitudes of IIV in K_{1E} on ELF PTA by: 1) assuming the estimated value, 2) restricting the distribution of eta in K_{1E} to the estimated range and 3) fixing IIV in K_{1E} to zero.

The effect of haemodialysis (HD) on CL, V_c, IIV in CL, and IIV in V_c, determined in a separate analysis (**CXA-POPPK-002**, **04DDG4**) was included in the current simulations by applying these effects during a 4-hour HD treatment (performed on Days 1, 3, 5, 8, 10, and 12). Three 14 days dosing schedules were investigated in ESRD (dose given immediately after HD):

- Scenario 1. single loading dose of 1.0/0.5 g, maintenance dose of 0.2/0.1 g q8h,
- Scenario 2. single loading dose of 1.5/0.75 g, maintenance dose of 0.3/0.15 g q8h, and
- Scenario 3. single loading dose of 2.0/1.0 g, maintenance dose of 0.4/0.2 g.

Results

Final model

A 2-compartment model with first-order elimination best described the plasma concentration time profile of TOL. The plasma PPK model was parameterised in terms of Vc, Vp, CL, and Q. The significant covariates relevant to the NP population included: body weight on Vc, and Vp; CrCL on CL; and pneumonia on Vc. The popPK model of TAZ had the same structure and parameterisation as that for TOL, but with one additional covariate *i.e.* pneumonia on Vp. PK parameter estimates are given in Table 3 and Table 4. Considering the substantial effect of outliers on many of the final fixed and random effect parameter estimates, outliers were not included in the final TOL and TAZ models.

Table 3. Parameter estimates and standard errors from the final popPK model for ceftolozane (Model report 050zc7, Table 16)

Parameter	Final Parameter Estimate		Interindividual Variability[a] / Residual Variability	
	Typical Value	%RSE	Magnitude	%RSE
CL: Systemic Clearance (L/h)	4.84	1.66	36.1 %CV	8.19
CL: Exponent of (CrCL/100) for CL	0.701	4.32		
CL: Fold-Change in CL for cUTI	1.18	2.99		
CL: Fold-Change in CL for cIAI	1.43	2.99		
CL: Fold-change in CL for ESRD	0.320	10.9		
V_c: Volume of Distribution of the Central Compartment (L)	9.23	1.83	42.9 %CV	16.5
V_c: Fold-Change in V_c for cUTI	1.25	3.52		
V_c: Fold-Change in V_c for cIAI	1.59	4.97		
V_c: Fold-Change in V_c for Pneumonia	2.00	3.29		
V_c: Fold-Change in V_c for Other Infections	2.14	14.8		
V_c: Exponent of (WTKG/70) for V_c	0.684	9.69		
V_c: Fold-change in V_c for ESRD	1.30	11.7		
Q: Intercompartmental Clearance (L/h)	3.13[b]	6.93	NE	NA
V_p: Volume of Distribution of the Peripheral Compartment (L)	4.78[b]	3.24	15.1 %CV	57.8
V_p: Exponent of (WTKG/70) for V_p	0.484	16.3		
cov(IIV in V_c, IIV in CL)[c]	0.0733	17.1	NA	NA
Residual Variability Proportional	0.0248	7.20	15.7 %CV[d]	NA
Residual Variability Additive	0.00984	17.8	0.0992 SD[d]	NA
Minimum Value of the Objective Function = 32902.322				

Parameter-covariate relationships were described as:

$$CL = 4.84 \times \left(\frac{CrCL}{100}\right)^{0.701} \times 1.18^{cUTI} \times 1.43^{cIAI} \times 0.32^{ESRD}$$

$$V_c = 9.23 \times \left(\frac{WTKG}{70}\right)^{0.684} \times 1.25^{cUTI} \times 1.59^{cIAI} \times 2.00^{Pneumonia} \times 2.14^{OINF} \times 1.30^{ESRD}$$

$$V_p = 4.78 \times \left(\frac{WTKG}{70}\right)^{0.484}$$

Abbreviations: cIAI, complicated intra-abdominal infection; CL, clearance; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; %CV, coefficient of variation expressed as a percent; ESRD, end-stage renal disease; IIV, interindividual variability; NA, not applicable; NE, not estimated; OINF, other infection types; %RSE, relative standard error expressed as a percent; SD, standard deviation (µg/mL); V_c, volume of distribution of the central compartment; V_p, volume of distribution of the peripheral compartment; WTKG, body weight (kg).

[a] Eta shrinkage: eta_CL: 1.76%, eta_V_c: 9.27%, eta_V_p: 55.8%.

[b] The following parameter estimates were found to be highly correlated ($r \geq 0.924$): (V_p: volume of distribution of the peripheral compartment (L), Q: intercompartmental clearance (L/h)).

[c] The calculated correlation coefficient (r) of the off-diagonal omegas was 0.474 for cov(IIV in V_c, IIV in CL).

[d] The magnitude of residual variability ranged from 100 %CV to 15.7 %CV over the range of 0.1 to 200 µg/mL in individual predicted ceftolozane concentrations.

Note: Other infections includes critically ill adult patients from Group 2 in Study MK-7625A-007.

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Table 4. Parameter estimates and standard errors from the final popPK model for tazobactam (Model report 050zc7, Table 17)

Parameter	Final Parameter Estimate		Interindividual Variability[a] / Residual Variability	
	Typical Value	%RSE	Magnitude	%RSE
CL: Systemic Clearance (L/h)	16.6	1.80	53.1 %CV	11.0
CL: Exponent of (CrCL/100) for CL	0.623	6.42		
CL: Fold-Change in CL for ESRD	0.626	14.6		
V_c: Volume of Distribution of the Central Compartment (L)	13.1	1.96	38.7 %CV	19.1
V_c: Fold-Change in V_c for cIAI	1.49	3.70		
V_c: Fold-Change in V_c for Pneumonia	2.17	4.46		
V_c: Fold-Change in V_c for Other Infections	2.49	16.5		
V_c: Exponent of (WTKG/70) for V_c	0.629	10.7		
V_c: Fold-Change in V_c for ESRD	0.749	11.0		
Q: Intercompartmental Clearance (L/h)	4.05	3.81	NE	NA
V_p: Volume of Distribution of the Peripheral Compartment (L)	4.89	2.59	19.4 %CV	54.7
V_p: Fold-Change in V_p for cUTI	1.25	4.27		
V_p: Fold-Change in V_p for cIAI	1.34	4.57		
V_p: Fold-Change in V_p for Pneumonia	2.06	8.89		
V_p: Exponent of (WTKG/70) for V_p	0.530	14.4		
cov(IIV in V_c, IIV in CL)[b]	0.0705	33.3	NA	NA
Residual Variability Proportional	0.0813	7.09	28.5 %CV	NA
Minimum Value of the Objective Function = 11256.828				

Parameter-covariate relationships were described as:

$$CL = 16.6 \times \left(\frac{CrCL}{100}\right)^{0.623} \times 0.626^{ESRD}$$

$$V_c = 13.1 \times \left(\frac{WTKG}{70}\right)^{0.629} \times 1.49^{cIAI} \times 2.17^{Pneumonia} \times 2.49^{OINF} \times 0.749^{ESRD}$$

$$V_p = 4.89 \times \left(\frac{WTKG}{70}\right)^{0.530} \times 1.25^{cUTI} \times 1.34^{cIAI} \times 2.06^{Pneumonia}$$

Abbreviations: cIAI, complicated intra-abdominal infection; CL, clearance; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; %CV, coefficient of variation expressed as a percent; ESRD, end-stage renal disease; IIV, interindividual variability; NA, not applicable; NE, not estimated; OINF, other infection types; %RSE, relative standard error expressed as a percent; V_c, volume of distribution of the central compartment; V_p, volume of distribution of the peripheral compartment; WTKG, body weight (kg).

[a] Eta shrinkage: eta_CL: 2.23%, eta_V_c: 23.2%, eta_V_p: 34.7%.

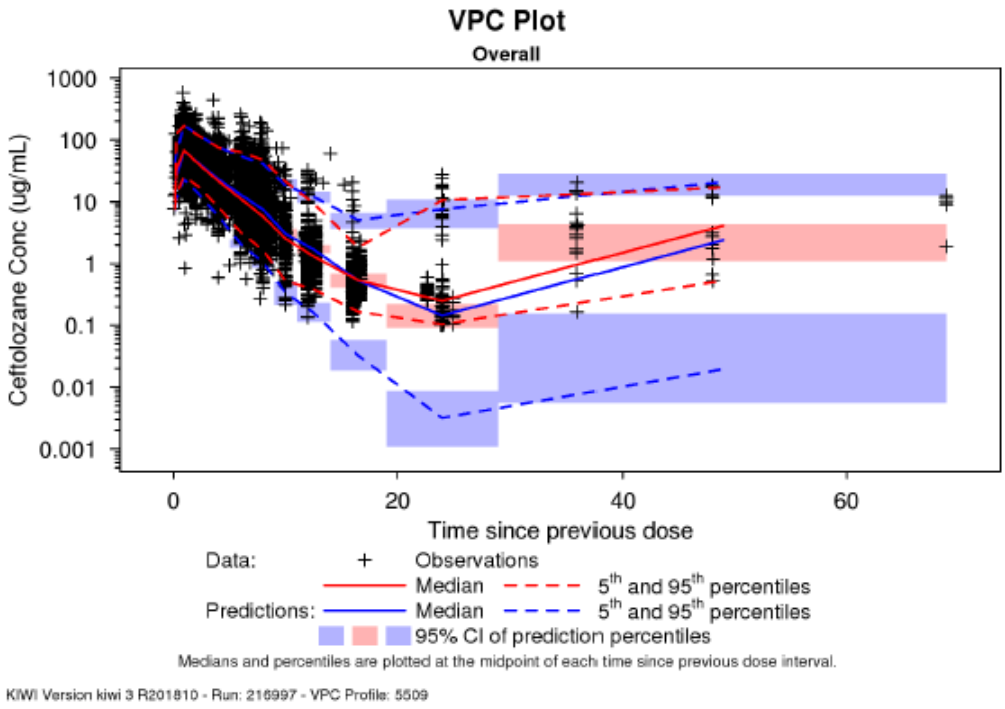
[b] The calculated correlation coefficient (r) of the off-diagonal omegas was 0.344 for cov(IIV in V_c, IIV in CL).

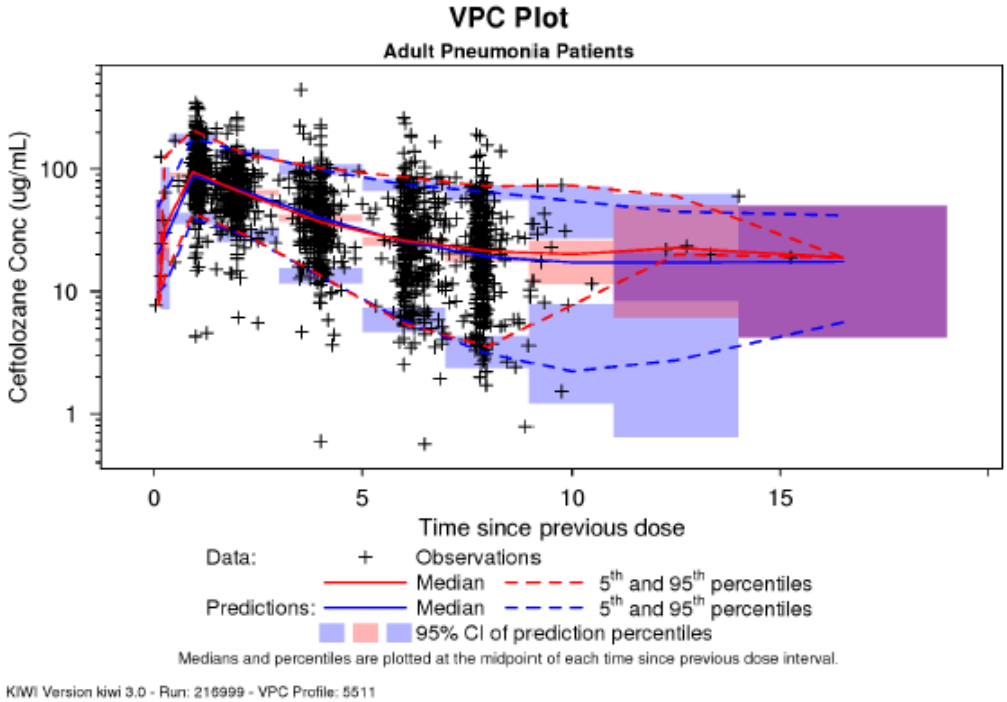
Note: Other infections includes critically ill adult patients from Study MK-7625A-007.

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Model diagnostics

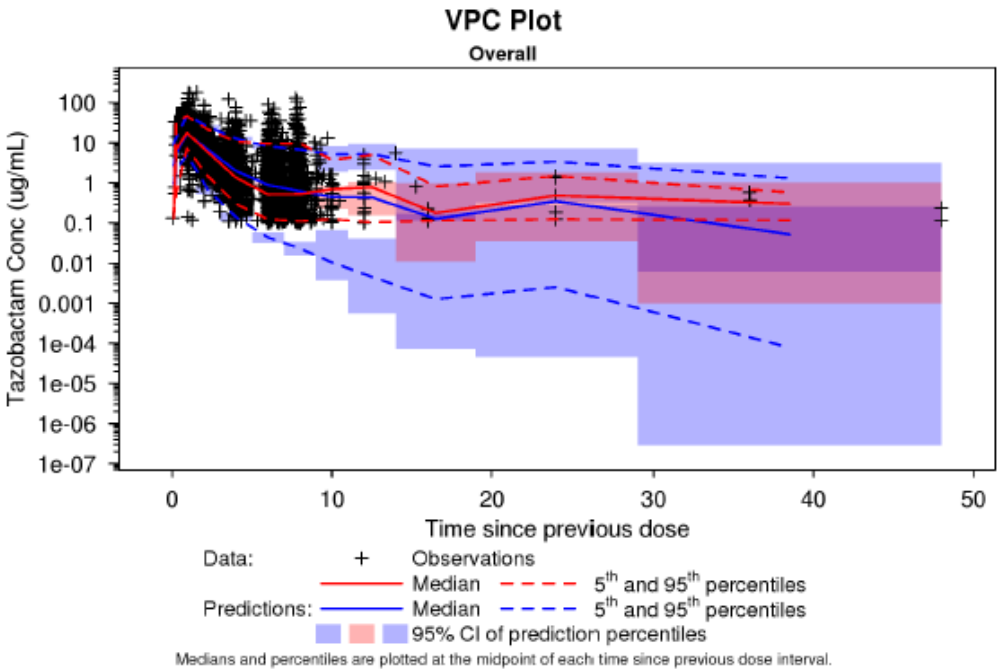
VPCs in overall and the pneumonia population are given below. For TOL, the percent of data below and above the 90% prediction interval was 2.5% and 4.27%, respectively, for the overall population and 5.06% and 7.5%, respectively, for the NP population. For TAZ, the percent of data below and above the 90% prediction interval was 1.71% and 3.94%, respectively, for the overall population and 3.52% and 8.65%, respectively, for the NP population.

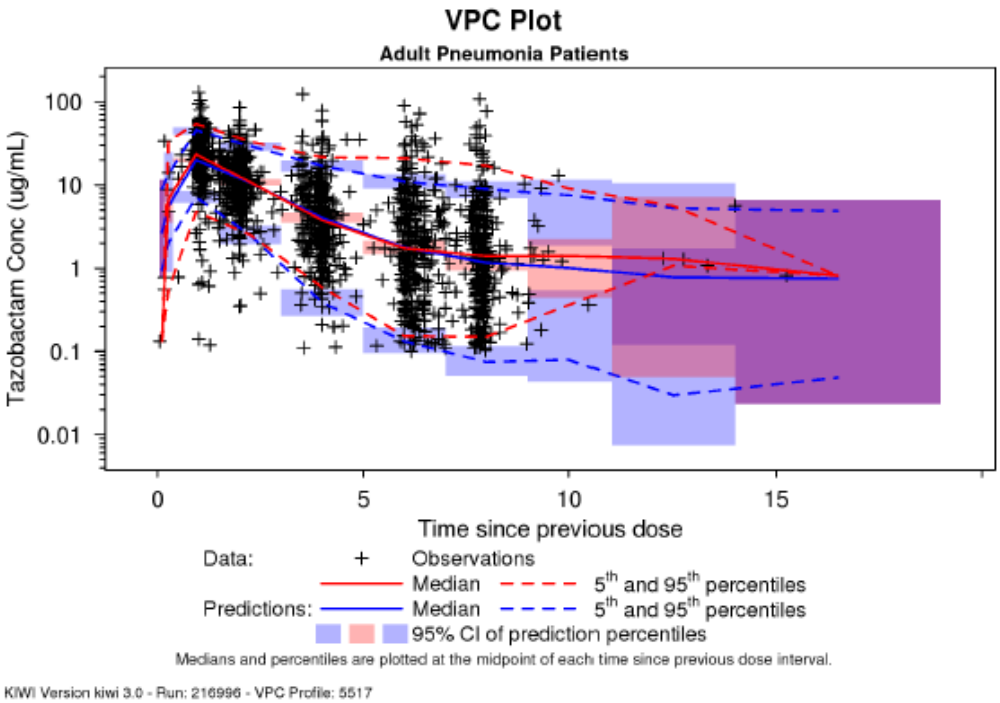




Abbreviations: CI, confidence interval; Conc, concentration; VPC, visual predictive check.
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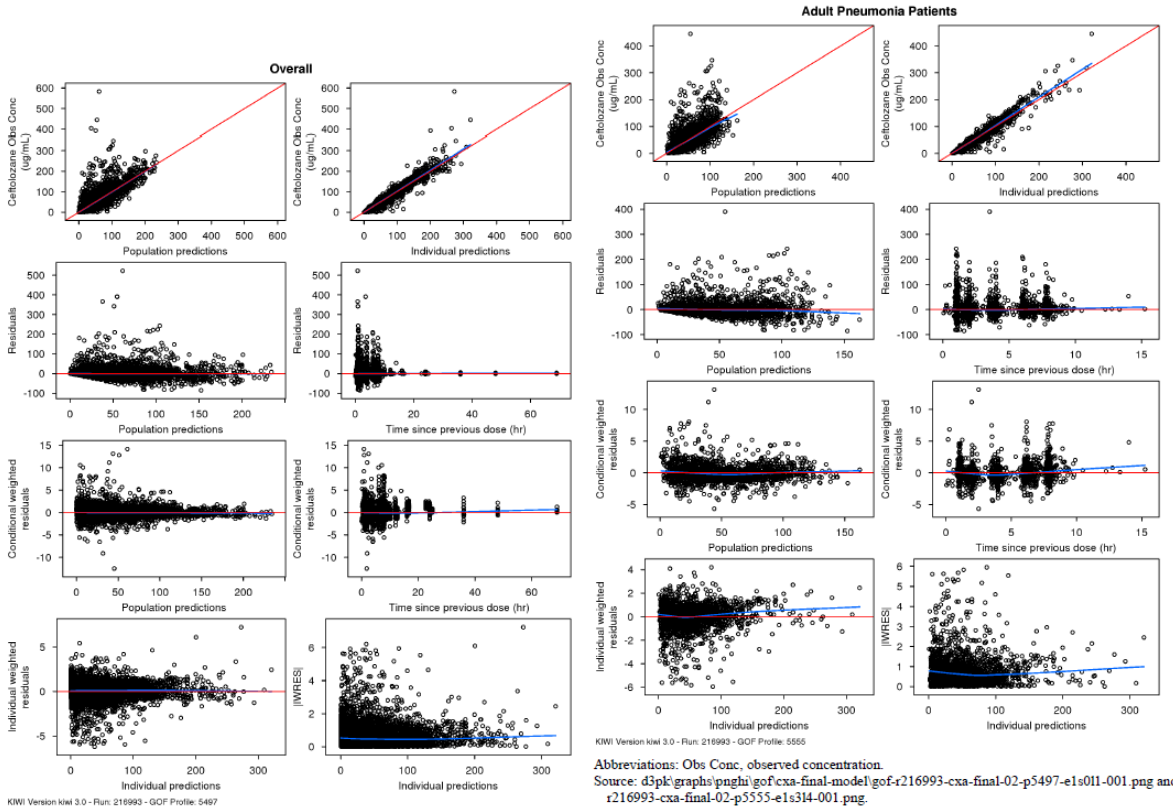
Figure 3. VPC for the final population plasma PK model for ceftolozane - overall and adult patients with nosocomial pneumonia (Model report 050zc7, Figure 7)





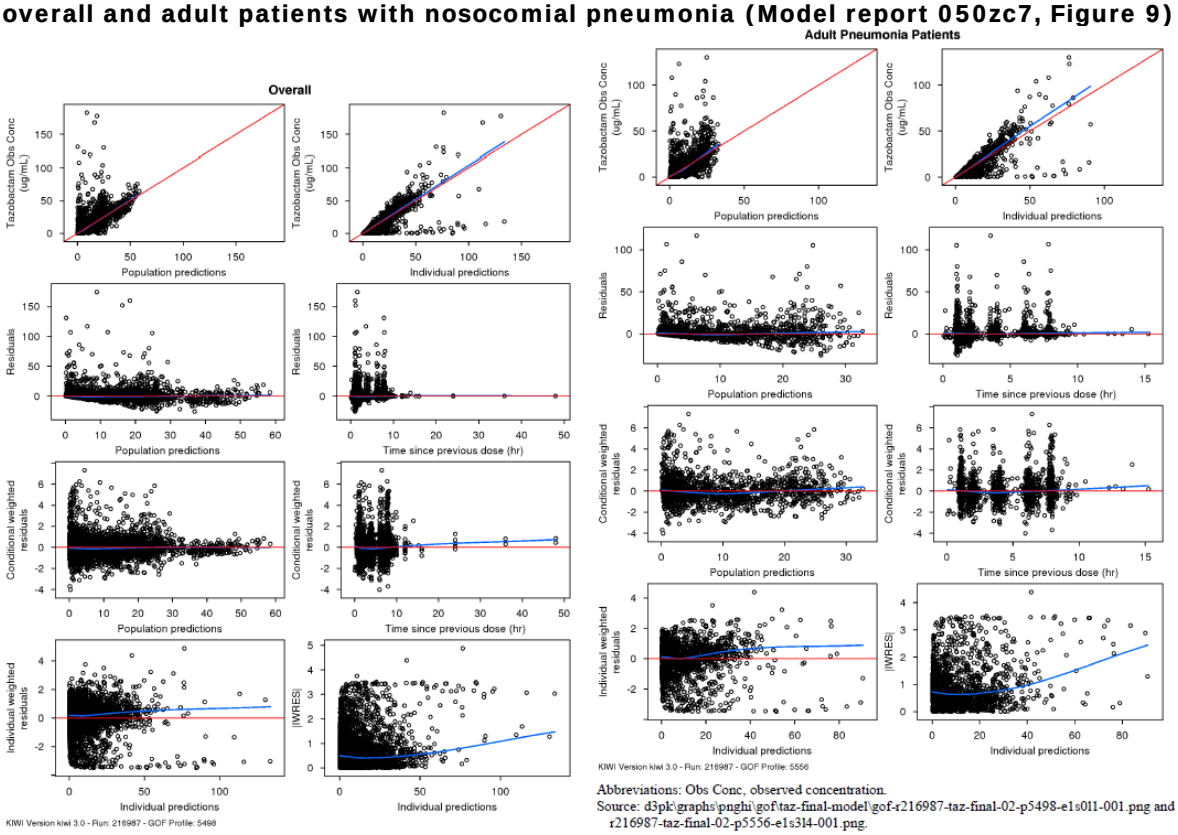
Abbreviations: CI, confidence interval; Conc, concentration; VPC, visual predictive check.
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Figure 4. VPC for the final population plasma PK model for tazobactam - overall and adult patients with nosocomial pneumonia (Model report 050zc7, Figure 8)



Abbreviations: Obs Conc, observed concentration.
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Figure 5. Goodness-of-fit plots for the final population plasma PK model for ceftolozane - overall and adult patients with nosocomial pneumonia (Model report 050zc7, Figure 9)



Abbreviations: Obs Conc, observed concentration.
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Figure 6. GoF plots for the final population plasma PK model for tazobactam - overall and adult patients with nosocomial pneumonia (Model report 050zc7, Figure 10)

Simulations

Simulation results are described in sections 5.3.2 (Target population and Special populations) and 5.3.3 (Pharmacodynamics).

In the sensitivity analysis to evaluate the influence of the magnitude of IIV in K1E on TOL and TAZ PTA (ELF model), TAZ PTA in ELF decreased when the magnitude of IIV in K1E increased. Ceftolozane PTA in ELF at an MIC = 4 µg/mL was > 90% for all K1E scenarios.

Distribution

Lung penetration - study **PN007**

Intrapulmonary penetration of TOL/TAZ was assessed in a phase 1, prospective, multi-centre, open-label lung penetration PK and safety trial of TOL/TAZ in two groups of patients: (1) mechanically ventilated patients with proven or suspected pneumonia and (2) critically ill patients with CrCL ≥180 mL/min (ARC). Twenty-six (26) mechanically ventilated (≥24 hours prior to enrolment) patients with proven or suspected pneumonia receiving concurrent standard antibiotic therapy, of whom eight patients had CrCL ≥150 mL/min (Cockcroft-Gault equation), were included in group 1. At least one clinical symptom (documented fever, hypothermia, elevated WBC count, radiological finding suggestive of bacterial pneumonia) were required.

Patients received 4-6 IV doses of TOL/TAZ q8h according to renal function using the proposed posology. Plasma PK sampling occurred at pre-dose, 1, 2, 4, 6, and 8 hours after the start of the first and last infusions. A BAL procedure was performed at either 1, 2, 4, 6 or 8 hours post-dose, with only one BAL sampling per patient.

The composite ELF profile showed delayed TOL and TAZ T_{max}, at 6 and 2 h, respectively, compared to 1 hour in plasma (Table 5). TOL ELF concentration was >8 µg/mL and TAZ ELF concentration was >1 µg/mL 100% of the dosing interval. The ELF penetration ratios (ELF AUC / unbound plasma AUC) were ~50% and 62% for TOL and TAZ, respectively. The tmax and elimination were slower in ELF than in plasma for both TOL and TAZ whereas the PK profiles for ELF and plasma were parallel in healthy subjects (not shown). The exposure profiles of TOL/TAZ in plasma and ELF from patients appear to be similar to those in healthy subjects (study **CXA-ELF-10-03**, Table 6).

Table 5. Plasma and ELF PK parameter values of TOL and TAZ after the last of multiple TOL/TAZ doses in ventilated patients with confirmed or suspected pneumonia (PN007 CSR)

Parameter	TOL			TAZ		
	N	Plasma† GM (95% CI)	ELF	N	Plasma† GM (95% CI)	ELF
AUC0-8 (h*µg/mL)	23	394 (323 – 481)	154	23	61.9 (49.6 – 77.2)	27.5
Cmax (µg/mL)	24	100 (84.2 – 120)	27.4	24	26.1 (21.8 – 31.3)	5.37
Tmax (h)‡	24	1.00 (0.917 – 2.17)	6.00	24	1.00 (0.917 – 2.17)	2.00
$t_{1/2}$ (h)	23	4.86 (61.5)	NA	23	2.33 (49.7)	NA
CL (L/h)	23	4.52 (67.7)	NA	23	14.1 (75.6)	NA
Vss (L)	23	29.4 (45.5)	NA	23	40.4 (38.8)	NA

Doses administered were adjusted based on baseline CrCL: >50 mL/min, 3-g TOL/TAZ; 30 mL/min ≤ CrCL ≤50 mL/min, 1.5-g TOL/TAZ; 15 mL/min ≤ CrCL ≤ 29 mL/min, 750-mg TOL/TAZ.

Total of 4 to 6 doses were administered depending on when BAL procedure was scheduled.

†Total plasma AUC and Cmax

‡Tmax reported as median (min, max); $t_{1/2}$, CL and Vss reported as GM (%GCV)

Source: [Ref. 5.3.3.2: P007MK7625A: Table 11-1] [Ref. 5.3.3.2: P007MK7625A: Table 11-3]

Table 6. Summary of PK parameters in plasma (top) and ELF (bottom) (Study CXA-ELF-10-03 in healthy subjects)

Treatment Group Analyte	T_{max}[1] (hr)	C_{max} (µg/mL) Mean (SD)	C_{max} (µg/mL) Median (min, max)	T_{last} (hr) Mean (SD)	C_{last} (µg/mL) Mean (SD)	C_{last} µg/mL Median (min, max)	$AUC_{0-\tau}$ (µg*hr/mL) Mean (SD)
CXA-201							
CXA-101	1.0	67.2 (12.1)	65.1 (47.8, 90.1)	8 (0.0)	3.3 (1.1)	3.1 (1.7, 5.8)	158.5 (24.1)
Tazobactam	1.0	14.9 (2.4)	15.6 (10.5, 18.4)	5.8 (1.1)	0.2 (0.1)	0.2 (0.1, 0.4)	19.3 (2.9)

-

Treatment Group Analyte	T_{max}[1] (hr)	C_{max} (µg/mL) Mean	C_{max} (µg/mL) Median (min, max)	T_{last} (hr) Mean	C_{last} (µg/mL) Mean	C_{last} µg/mL Median (min, max)	$AUC_{0-\tau}$ (µg*hr/mL) Mean
CXA-201							
CXA-101	1.0	21.8	22.6 (13.6, 29.6)	8.0	4.2	2.7 (1.7, 7.3)	75.1
Tazobactam	1.0	4.5	4.5 (3.3, 6.3)	8.0	0.3	0.3 (0.2, 0.4)	8.5

Elimination

Dose proportionality and time dependencies

- **Dose proportionality**

The dose proportionality of TOL/TAZ for single doses up to 4.5 g and multiple doses up to 3 g daily was assessed in the original application (studies **CXA-101-01, CXA-QT-10-02**). Exposures (Cmax and AUC) were found to be approximately dose proportional.

- **Time dependency**

Following multiple-dose administration in mechanically ventilated patients with proven or suspected pneumonia (**PN007**), plasma accumulation of ~1.6- and 1.2-fold was observed in AUC_{0-8h} for TOL and

TAZ, respectively. No accumulation in plasma of TOL and TAZ was observed in the PK trials of healthy subjects submitted in the original application (**CXA-101-01, CXA-201-01, CXA-MD-11-02**), with dosing up to 4 g q8h for 10 days.

Intra- and inter-individual variability

Target population

Model-based exposures and PK parameter estimates are shown for healthy individuals vs. pneumonia patients below.

Table 7. Summary of steady-state ceftolozane plasma exposures for patients with nosocomial pneumonia receiving a 2.0/1.0 g TOL/TAZ dosing regimen from study PN008 and healthy subjects receiving a 2.0/1.0 g TOL/TAZ dosing regimen from the analysis dataset (Model report 050zc7, Table 18)

Patient Characteristic	Statistic	Healthy Subjects	Pneumonia Patients	Overall
Clearance (L/h)	Mean (SD)	6.55 (0.813)	6.68 (3.90)	6.66 (3.66)
	Median	6.59	5.96	6.19
	Geometric mean (geometric %CV)	6.50 (13.1)	5.85 (55.5)	5.92 (51.8)
	%CV	12.4	58.4	54.9
	Min, Max	4.62, 8.07	1.09, 35.2	1.09, 35.2
	5th, 95th	4.71, 7.73	2.55, 12.6	2.66, 11.9
	n	35	247	282
V_{ss} (L)	Mean (SD)	15.1 (2.21)	28.4 (17.2)	26.7 (16.7)
	Median	14.4	25.3	24.2
	Geometric mean (geometric %CV)	15.0 (13.9)	25.8 (42.1)	24.1 (44.1)
	%CV	14.7	60.6	62.5
	Min, Max	11.4, 22.1	9.36, 215	9.36, 215
	5th, 95th	12.8, 19.4	14.0, 51.9	13.0, 48.3
	n	35	247	282
$AUC_{0\text{-}8}$ (µg × h/mL)	Mean (SD)	310 (42.8)	392 (236)	382 (223)
	Median	303	330	322
	Geometric mean (geometric %CV)	307 (13.1)	341 (55.2)	337 (51.6)
	%CV	13.8	60.2	58.4
	Min, Max	248, 433	54.4, 1860	54.4, 1860
	5th, 95th	258, 424	159, 783	168, 752
	n	35	247	282
C_{max} (µg/mL)	Mean (SD)	136 (17.0)	105 (46.2)	108 (44.9)
	Median	134	94.5	102
	Geometric mean (geometric %CV)	135 (12.8)	96.1 (43.3)	100 (42.3)
	%CV	12.5	44.2	41.4
	Min, Max	92.6, 187	11.4, 311	11.4, 311
	5th, 95th	104, 159	51.8, 193	52.8, 186
	n	35	247	282
T_{max} (h)	Mean (SD)	0.996 (0.000)	0.998 (0.047)	0.998 (0.044)
	Median	0.996	0.996	0.996
	Geometric mean (geometric %CV)	0.996 (0.000)	0.997 (4.61)	0.997 (4.32)
	%CV	0.000	4.71	4.40
	Min, Max	0.996, 0.996	0.830, 1.33	0.830, 1.33
	5th, 95th	0.996, 0.996	0.913, 1.08	0.913, 1.08
	n	35	247	282
Terminal Half-Life (h)	Mean (SD)	2.14 (0.265)	3.86 (1.92)	3.64 (1.89)
	Median	2.13	3.38	3.03
	Geometric mean (geometric %CV)	2.12 (12.2)	3.48 (46.2)	3.27 (46.8)
	%CV	12.4	49.9	51.9
	Min, Max	1.75, 2.92	1.52, 11.7	1.52, 11.7
	5th, 95th	1.78, 2.54	1.84, 7.37	1.82, 7.24
	n	35	247	282
Accumulation Ratio, Plasma	Mean (SD)	1.07 (0.026)	1.34 (0.343)	1.30 (0.334)
	Median	1.06	1.23	1.19
	Geometric mean (geometric %CV)	1.07 (2.37)	1.30 (21.7)	1.27 (21.4)
	%CV	2.40	25.7	25.6
	Min, Max	1.03, 1.15	1.01, 3.46	1.01, 3.46
	5th, 95th	1.03, 1.10	1.04, 1.96	1.04, 1.90
	n	35	247	282

Abbreviations: $AUC_{0\text{-}8}$, area under the concentration-time curve from time 0 to 8 hours after start of infusion; C_{max}, maximum drug concentration; %CV, coefficient of variation expressed as a percent; Max, maximum; Min, minimum; n, number of patients; SD, standard deviation; T_{max}, time of the maximum drug concentration; V_{ss}, steady-state volume of distribution.

Source: d3pk\tables\rtf\cxa-sumstat-exp-bypatient.rtf.

Table 8. Summary of steady-state tazobactam exposures for patients with nosocomial pneumonia receiving a 2.0 / 1.0 g ceftolozane / tazobactam dosing regimen from study PN008 and healthy subjects receiving a 2.0 / 1.0 g ceftolozane / tazobactam dosing regimen from the analysis dataset (Model report 050zc7, Table 19)

Patient Characteristic	Statistic	Healthy Subjects	Pneumonia Patients	Overall
Clearance (L/h)	Mean (SD)	24.1 (3.59)	21.4 (12.1)	21.7 (11.4)
	Median	23.6	19.4	20.5
	Geometric mean (geometric %CV)	23.9 (14.7)	17.8 (73.9)	18.5 (69.5)
	%CV	14.9	56.5	52.6
	Min, Max	17.3, 33.3	1.67, 81.8	1.67, 81.8
	5th, 95th	19.4, 31.5	5.72, 44.5	5.86, 40.8
	n	35	247	282
V_{ss} (L)	Mean (SD)	19.6 (2.66)	43.9 (13.7)	40.9 (15.1)
	Median	19.6	41.5	39.8
	Geometric mean (geometric %CV)	19.4 (13.5)	42.0 (30.9)	38.2 (39.8)
	%CV	13.6	31.1	37.0
	Min, Max	13.9, 25.5	17.4, 102	13.9, 102
	5th, 95th	16.4, 25.4	26.7, 70.0	18.3, 64.6
	n	35	247	282
AUC_{0-8} (µg × h/mL)	Mean (SD)	42.3 (6.13)	73.3 (76.4)	69.4 (72.3)
	Median	42.3	51.6	48.9
	Geometric mean (geometric %CV)	41.8 (14.7)	56.1 (73.7)	54.1 (69.3)
	%CV	14.5	104	104
	Min, Max	30.0, 57.7	12.3, 599	12.3, 599
	5th, 95th	31.7, 51.5	22.4, 178	24.5, 172
	n	35	247	282
C_{max} (µg/mL)	Mean (SD)	31.5 (3.64)	26.4 (12.9)	27.1 (12.2)
	Median	31.6	23.7	25.0
	Geometric mean (geometric %CV)	31.3 (11.6)	24.2 (41.6)	25.0 (40.0)
	%CV	11.5	48.8	45.3
	Min, Max	24.5, 40.1	10.4, 93.1	10.4, 93.1
	5th, 95th	25.7, 38.5	12.9, 46.6	13.5, 45.5
	n	35	247	282
T_{max} (h)	Mean (SD)	0.996 (0.000)	0.994 (0.044)	0.994 (0.041)
	Median	0.996	0.996	0.996
	Geometric mean (geometric %CV)	0.996 (0.000)	0.993 (4.41)	0.993 (4.13)
	%CV	0.000	4.39	4.10
	Min, Max	0.996, 0.996	0.830, 1.25	0.830, 1.25
	5th, 95th	0.996, 0.996	0.913, 1.08	0.913, 1.08
	n	35	247	282
Terminal Half-Life (h)	Mean (SD)	1.10 (0.125)	3.18 (1.93)	2.92 (1.93)
	Median	1.08	2.63	2.51
	Geometric mean (geometric %CV)	1.09 (11.2)	2.89 (40.0)	2.56 (51.5)
	%CV	11.4	60.6	66.1
	Min, Max	0.900, 1.38	1.64, 19.3	0.900, 19.3
	5th, 95th	0.920, 1.32	2.02, 6.42	1.03, 6.12
	n	35	247	282
Accumulation Ratio, Plasma	Mean (SD)	1.00 (0.004)	1.16 (0.319)	1.14 (0.303)
	Median	1.00	1.05	1.05
	Geometric mean (geometric %CV)	1.00 (0.353)	1.14 (19.7)	1.12 (18.9)
	%CV	0.355	27.4	26.5
	Min, Max	1.00, 1.01	1.00, 3.70	1.00, 3.70
	5th, 95th	1.00, 1.01	1.01, 1.81	1.00, 1.68
	n	35	247	282

Abbreviations: AUC_{0-8}, area under the concentration-time curve from time 0 to 8 hours after start of infusion; C_{max}, maximum drug concentration; %CV, coefficient of variation expressed as a percent; Max, maximum; Min, minimum; n, number of patients; SD, standard deviation; T_{max}, time of maximum drug concentration; V_{ss}, steady-state volume of distribution.

Source: d3pk\tables\rtf\taz-sumstat-exp-bypatient.rtf.

Special populations

- **Impaired renal function**

Renal impairment

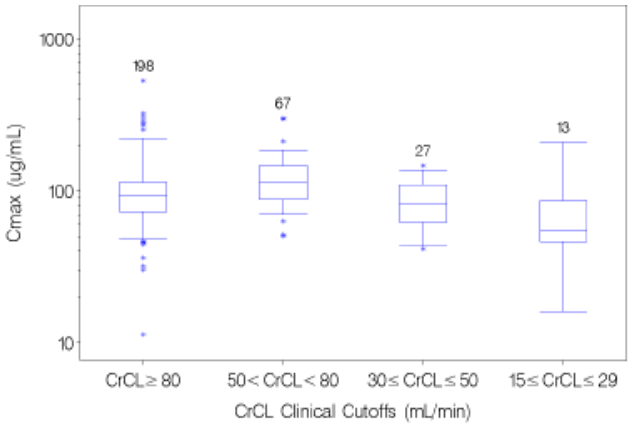
Model-based exposures in patients with different renal function from **PN008** are shown below (Table 9 and Figure 7).

Table 9. Summary of TOL and TAZ AUC0-8h,ss and Cmax,ss in Phase 3 NP subjects receiving adjusted TOL/TAZ dose based on CrCL categories (Module 2.7.2, Table 6)

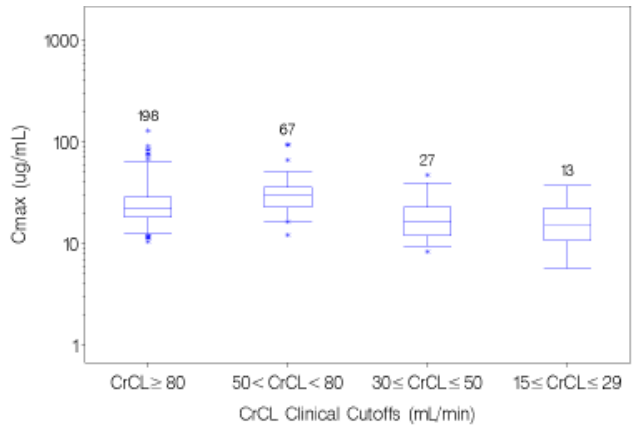
	TOL			TAZ		
	N	AUC_{0-8} GM (%GCV)	Cmax GM (%GCV)	N	AUC_{0-8} GM (%GCV)	Cmax GM (%GCV)
CrCL≥210 mL/min	20	201 (67.2)	65.3 (63.0)	20	34.8 (85.6)	18.6 (48.8)
180 mL/min ≤ CrCL < 210 mL/min	16	248 (59.7)	78.0 (52.7)	16	42.0 (90.7)	19.6 (43.6)
150 mL/min ≤ CrCL < 180 mL/min	24	276 (52.6)	88.6 (40.2)	24	42.1 (56.2)	21.0 (34.3)
80 mL/min ≤ CrCL < 150 mL/min	138	371 (55.3)	103 (42.6)	138	61.9 (80.1)	25.8 (45.0)
50 mL/min < CrCL < 80 mL/min	67	489 (46.7)	117 (36.4)	67	80.8 (67.1)	29.4 (39.7)
30 mL/min ≤ CrCL ≤ 50 mL/min	27	430 (42.5)	82.0 (37.5)	27	63.3 (71.9)	17.5 (48.3)
15 mL/min ≤ CrCL ≤ 29 mL/min	13	343 (78.7)	58.9 (69.3)	13	63.0 (93.3)	14.6 (58.7)
Steady-state TOL and TAZ AUC and Cmax were calculated at the following dosing regimens: for subjects with CrCL > 50 mL/min, 3 g TOL/TAZ; subjects with CrCL 30 to 50 mL/min, 1.5 g TOL/TAZ; subjects with CrCL 15 to 29 mL/min, 750 mg TOL/TAZ						

Source: [Ref. 5.3.5.3: 050ZC7]

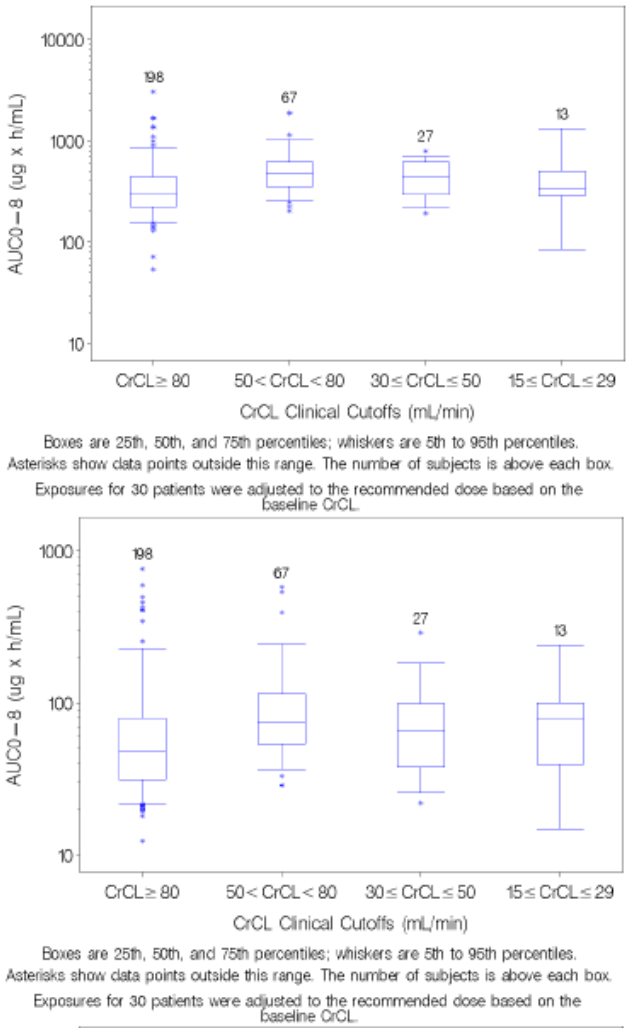
For TOL, relative ratios of geometric mean AUC0-8h,ss in NP patients with mild, moderate and severe renal impairment to that of NP patients with CrCL ≥ 80 mL/min were 1.50 (90%CI 1.33, 1.70), 1.32 (90%CI 1.10, 1.59) and 1.05 (90%CI 0.80, 1.38). Corresponding values for TAZ were 1.50 (90%CI 1.27, 1.76), 1.17 (90%CI 0.92, 1.49) and 1.17 (90%CI 0.83, 1.65).



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of subjects is above each box.
Exposures for 30 patients were adjusted to the recommended dose based on the baseline CrCL.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of subjects is above each box.
Exposures for 30 patients were adjusted to the recommended dose based on the baseline CrCL.

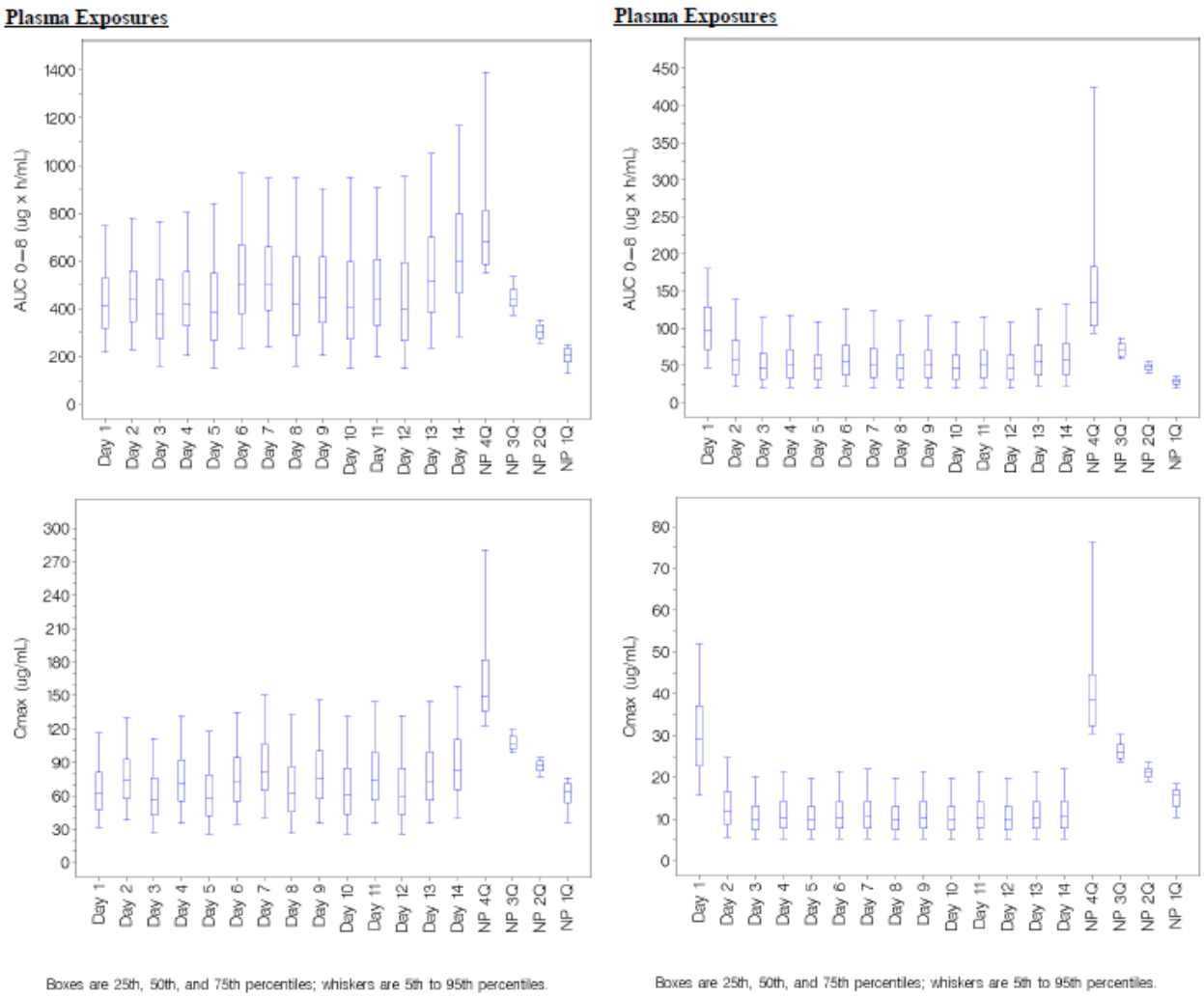


Abbreviations: AUC0-8, area under the concentration-time curve from time 0 to 8 hours after start of infusion; CrCL, creatinine clearance; FDA, United States Food and Drug Administration.
Note: Patients with nosocomial pneumonia were categorized based on the baseline CrCL values from the local laboratory.
Note: Exposures were adjusted to the recommended dose based on the baseline CrCL values from the local laboratory.
Note: Ceftolozane/tazobactam dosing regimens: 2.0/1.0 g for CrCL > 50 mL/min, 1.0/0.5 g for CrCL 30 to 50 mL/min, and 0.5/0.25 g for CrCL 15 to 29 mL/min.
Source: d3pk\graphs\pnghi\eda\rpt-cxa-b-log-aauc0t-crclct1.png and rpt-cxa-b-log-aauc0t-crclct2.png.

Figure 7. Comparison of ceftolozane (left) and tazobactam (right) plasma Cmax,ss and AUC0-8h,ss in patients with nosocomial pneumonia receiving dose-adjusted TOL/TAZ based on CrCL (Model report 050zc7, Figures 11 and 12 & Appendices 29 and 30)

Patients with ESRD requiring HD

Three different dosing regimens were simulated, taking into account the effect of a four-hour HD on CL, Vc, IIV in CL and IIV in Vc (Xiao *et al*. 2013). Simulation results from the final proposed dose of 2.25g loading dose and 450 mg maintenance dose q8h are shown below.



Abbreviations: AUC_{0-8}, area under the concentration-time curve from time 0 to 8 hours after start of infusion; C_{max}, maximum drug concentration; NP, nosocomial pneumonia.
Note: NP Q1 to NP Q4 represent quartiles of exposure observed in patients with nosocomial pneumonia.
HD was performed on day 1, 3, 5, 8, 10 and 12.

Figure 8. Boxplot of TOL (left) and TAZ (right) plasma AUC0-8 and Cmax, by treatment day, in NP patients with ESRD receiving hemodialysis using a 2.25 g ceftolozane/tazobactam loading dose and 0.45 g maintenance dose every 8 hours compared to exposures observed in NP patients (study PN008) (Model report 050zc7, Figure 16 and 17)

Augmented renal clearance (ARC)

PK parameters after a single IV dose of 3 g TOL/TAZ were assessed in plasma in ten critically ill patients with ARC (CrCL ≥ 180 mL/min; study **PN007**). Compared with patients without ARC, these patients had reduced exposures (AUC 223/34 vs. 394/61 h*µg/min) and shorter plasma half-lives (4.86/2.33 hours vs. 2.59/1.47 hours) of ceftolozane and tazobactam (Table 10). Free TOL plasma concentration was over the PK/PD target of 8 µg for approximately 70% of the dosing interval, and above the threshold of 1 µg/ml for approximately 60% of the dosing interval (not shown).

Model-based exposures in patients with different renal function, including ARC, from **PN008** are shown in Table 9 above.

Table 10. Ceftolozane and tazobactam total plasma PK in critically ill patients with augmented renal clearance after a single IV infusion of 3 g dose (PN007 CSR, Table 11-6)

Parameters	TOL		TAZ	
	N	GM (95% CI)	N	GM (95% CI)
AUC0-∞ (h*µg/mL)	10	223 (152 – 327)	9	34.8 (21.7 – 55.9)
Cmax (µg/mL)	10	68.9 (55.0 – 86.5)	10	17.4 (13.5 – 22.5)
Tmax (h)[T]	10	1.02 (0.983 – 1.07)	10	1.02 (0.983 – 1.07)
CL (L/h)	10	8.98 (57.6)	9	28.7 (67.9)
Vss (L)	10	30.2 (41.1)	9	51.6 (41.1)
$t_{1/2}$ (h)	10	2.59 (51.1)	9	1.47 (43.5)
[T]Tmax reported as median (min, max); $t_{1/2}$, CL and Vss reported as GM (%GCV)				

Source: [Ref. 5.3.3.2: P007MK7625A: Table 11-6]

- **Race**

A single-dose, open-label, parallel-group study was conducted to evaluate the effects of ethnicity on the PK of TOL/TAZ administered in Japanese, Chinese and Caucasian healthy subjects (study **PN018**). Ten Japanese, nine Chinese and ten Caucasian healthy subjects were administered IV single doses of 1.5 g and 3 g TOL/TAZ as 60 minute infusions. Blood and urine were sampled at predose, 0.5, 1, 2, 4, 8, 12, 24 and 36 hours postdose (*i.e.* start of infusion) and at 0-2, 2-4, 4-8, 8-12, 12-24 and 24-36 hours postdose, respectively. The mean values for most of the PK parameters are similar across ethnic groups for all the analytes (Table 11). Dose normalisation resulted in comparable PK parameters between doses for each ethnic group, suggesting dose proportional PK. Weight normalisation yielded comparable parameters between groups at both doses. A trend towards higher exposure (Cmax and AUC) levels for TAZ M1 in Caucasians compared to Japanese and Chinese subjects.

Table 11. Summary of ceftolozane, tazobactam and tazobactam M1 plasma PK parameters (PN018, PK population)

	1.5g						3.0g					
	Caucasian		Chinese		Japanese		Caucasian		Chinese		Japanese	
n	10		9		10		10		8		9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Ceftolozane												
Cmax (µg/mL)	68.3	9.47	67.2	5.47	71.8	10.8	135	15.6	133	7.35	132	10.6
tmax (h)	1.01	0.02	1.00	0.01	1.00	0.00	1.00	0.00	1.01	0.01	1.00	0.00
AUC(0-t) (h*µg/mL)	171	28.3	153	17.1	153	19.4	335	53.1	293	32.3	291	32.7
AUC(0-∞) (h*µg/mL)	175	30.0	155	17.9	155	19.8	340	52.7	296	33.6	294	33.8
Tazobactam												
Cmax (µg/mL)	16.4	3.36	14.9	2.13	17.0	2.32	32.6	5.13	29.6	3.43	32.9	3.69
tmax (h)	1.01	0.02	1.00	0.01	1.00	0.00	1.00	0.00	1.01	0.01	1.00	0.00
AUC(0-t) (h*µg/mL)	22.0	4.52	18.8	2.90	22.2	4.72	44.1	8.34	38.2	6.12	41.3	5.12
AUC(0-∞) (h*µg/mL)	22.5	4.72	19.2[%]	3.20[%]	22.5	4.83	44.6	8.12	38.6	6.02	41.9	5.23
Tazobactam M1												
Cmax (µg/mL)	0.845	0.220	0.712	0.135	0.627	0.171	1.84	0.492	1.44	0.302	1.41	0.354
tmax (h)	4.00	0.00	4.00	0.00	4.00	0.00	4.00	0.00	4.00	0.00	4.00	0.00
AUC(0-t) (h*µg/mL)	6.90	2.57	5.20	0.943	4.53	1.16	15.3	5.35	10.2	1.60	10.1	3.33
AUC(0-∞) (h*µg/mL)	11.2[‡]	3.64[‡]	NC	--	NC	--	18.4[§]	7.30[§]	NC	--	18.6[†]	--

NC = Not Calculated. As there were insufficient samples post Cmax on the terminal phase, lambda_z was not calculated and AUC0-inf was not reportable.
[†]N = 1; [‡]N = 2 ; [§]N = 4 ; [%]N = 8

Source: Table 14.2.1.3a, Table 14.2.1.3b, Table 14.2.1.3c

- **Weight**

In the NP popPK analyses (**050zc7**), body weight was a statistically significant covariate on volume parameters for both TOL and TAZ. TOL and TAZ AUC in NP subjects in the lowest weight tertiles (43 to <75 kg) with normal renal function (CrCL ≥80 mL/min) receiving the same 3-g TOL/TAZ dose throughout the treatment duration was estimated to be ~ 20% higher than those in the middle body weight tertile (75 to <88 kg). There was no significant difference in TOL and TAZ PK in the highest body weight tertile (88 to ~ 150 kg) compared to those in the middle body weight tertile. The small increases in the lowest body weight tertile were not considered clinically meaningful, and no dose adjustment based on body weight is recommended.

Pharmacokinetic interaction studies

Based on the predominant renal elimination as unchanged parent drug and minimal CYP450 mediated metabolism of TOL and TAZ, plasma levels are not expected to be altered in a clinically relevant manner by other CYP450 inhibitors or inducers. Co-administration of TOL/TAZ with drugs that inhibit OAT1 and/or OAT3 may increase TAZ plasma concentrations.

Co-administration of TAZ with probenecid has been shown to prolong the TAZ t1/2 by 71% (prescribing information for the FDA approved Zosyn [piperacillin/tazobactam]). In a clinical study (**CXA-DDI-12-10**) evaluating the potential of TOL/TAZ 1.5-g dose to alter the PK of substrates of CYP1A2, CYP3A4 and OAT1/3, the results showed minimal potential for a clinically relevant inhibition of CYP3A4, CYP1A2 enzymes or OAT1/OAT3 transporters by TOL/TAZ, as evidenced by no increase in exposure of the respective probe substrates. Similar results are expected after the 3 g TOL/TAZ dose given that the exposures observed are well below concentrations tested *in vitro*, which did not show any potential to alter activity of any major enzyme or transporter to a clinically meaningful extent.

Pharmacokinetics using human biomaterials

Findings from *in vitro* metabolism and transporter studies conducted in support of the original 1.5-g TOL/TAZ dose regimen can be extended to the 3-g TOL/TAZ dose regimen proposed in this application, based on the concentrations tested. Therefore, no new *in vitro* human biomaterial studies were conducted specifically to support the NP indication. Key *in vitro* data for TOL/TAZ from the original submission are summarised below; and the applicability of the data to the 3-g dose for NP is indicated where relevant.

Metabolism

TOL undergoes minimal metabolism and is not a substrate for hepatic CYP450 enzymes. TAZ, like TOL, appears not to be a substrate for hepatic CYP450 enzymes. The M1 metabolite of TAZ is formed by the hydrolysis of the tazobactam β-lactam ring and lacks pharmacological activity.

Transporters

TOL is not a substrate for the P-gp or BCRP human transporters at concentrations up to 1000 µg/mL. TOL produced no clinically relevant inhibition of any transporter at concentrations up to 1000 µg/mL (MRP2) to 2500 µg/mL (**OAT1**, OAT3, **OCT1**, **OCT2**, OATP1B1, **OATP1B3**, P-gp, BCRP, BSEP, MATE1, MATE2). The highest concentrations tested, 1000 and 2500 µg/mL, are approximately 10- and 26-fold greater, respectively, than the geom. mean Cmax,ss after 3 g TOL/TAZ dosing (96.1 µg/mL, **PN008**).

TAZ is not a substrate for the P-gp, BCRP, or OCT2 human transporters at 5-500 µg/mL, but is a substrate for the human OAT1 and OAT3 transporters. TAZ produced no clinically relevant inhibition of human OCT1, OCT2, OATP1B1, OATP1B3, Pgp, BCRP, and BSEP transporters at concentrations ≤900 µg/mL, *i.e.* 37-fold greater than geom. mean Cmax,ss after 3 g TOL/TAZ dosing (24.2 µg/mL, **PN008**). TAZ inhibited the human OAT1 and OAT3 transporters (IC50 ~118 and 147 µg/mL, respectively). These concentrations are ~ 5- to 6-fold greater than the geom. mean Cmax,ss after 3 g TOL/TAZ dosing (24.2 µg/mL, **PN008**).

TAZ M1 metabolite did not produce clinically relevant inhibition at concentrations ≤ 75 µg/mL, *i.e.* ~26-fold greater than the geom. mean TAZ M1 Cmax at a 3-g dose (2.84 µg/mL, **PN007**).

Induction/inhibition potential:

TOL showed no clinically relevant reversible or time-dependent inhibition of any major CYP450 isoform (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A) at concentrations up to 6000 µg/mL or induction of isoforms (1A2, 3A4, and 2B6) up to 1000 µg/mL, *i.e.* 62- and 10-fold, respectively, greater than the geom.mean Cmax,ss at the 3 g TOL/TAZ dose (96.1 µg/mL, **PN008**).

TAZ did not produce clinically relevant inhibition of any major CYP450 enzymes (1A2, 2B6, 2C8, 2C9, 2C19, and 2D6) at concentrations up to 2000 µg/mL or induction of enzymes (1A2, 2B6 and 3A4) up to 1250 µg/mL, *i.e.* 83- and 52-fold, respectively, greater than the geom.mean Cmax,ss at the 3 g TOL/TAZ dose (24.2 µg/mL, **PN008**). TAZ inhibited CYP3A4 with an estimated IC50 >500 µg/mL (estimated Ki > 250 µg/mL).

TAZ M1 metabolite did not produce clinically relevant inhibition of any major CYP450 enzyme (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) at concentrations up to 150 µg/mL or induction of enzymes (1A2, 2B6 and 3A4) up to 75 µg/mL (53- and 26-fold, respectively, greater than the geom. mean Cmax at the 3 g TOL/TAZ dose (2.84 µg/mL, **PN007**).

2.3.3. Pharmacodynamics

Primary pharmacology

Susceptibility (*In vitro* spectrum activity) - Methodology

TOL/TAZ is a β-lactam/β-lactamase inhibitor combination with activity against *P. aeruginosa*, including drug-resistant strains, and other common gram-negative pathogens. TOL belongs to the cephalosporin class of antibacterial drugs, but is less susceptible to hydrolysis by AmpC β-lactamases than other antibiotics in this class. The combination of TOL with β-lactamase inhibitor TAZ, which is a potent inhibitor of most class A and some class C β-lactamases, improves the coverage of TOL to include ESBL-producing Enterobacteriaceae.

The spectrum of activity for ceftolozane includes many clinically relevant gram-negative respiratory pathogens, including Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae* as well as *Pseudomonas aeruginosa* and *Haemophilus influenzae.*

Surveillance studies

In vitro activity of TOL/TAZ has been tested against respiratory tract isolates from hospitalized patients in a combined surveillance study for the US and Europe during 2015-2017. Results for the European isolates are summarised below.

TOL/TAZ (MIC50, 0.25 mg/L and MIC_{90}, 2 mg/L) inhibited 88.6% of 11,390 European Enterobacteriaceae from all infection types at the EUCAST susceptible breakpoint of ≤1 mg/L. Of the 2,456 isolates with an ESBL-phenotype, TOL/TAZ inhibited 64.0% ($MIC_{50/90}$ 0.5/>32 mg/L). When excluding CRE, 2,080 Enterobacteriaceae isolates were ESBL, non-CRE; 75.3% were inhibited by TOL/TAZ ($MIC_{50/90}$ 0.5/8 mg/L); and 99.9% of non-ESBL isolates were susceptible.

For 2,679 *P. aeruginosa* isolates from all infection types in European hospitals, 89.1% were susceptible (EUCAST, 2018) to TOL/TAZ ($MIC_{50/90}$, 0.5/16 mg/L). For 1,257 *P. aeruginosa* isolates from European PIHP, 87.6% were susceptible (EUCAST) with $MIC_{50/90}$ values of 0.5/32 mg/L.

For 852 *Acinetobacter* spp. isolates from all infection types in European hospitals, the $MIC_{50/90}$ values were 32/>32 mg/L.

For 171 *H. influenzae* isolates from all infection types in European hospitals, the TOL/TAZ $MIC_{50/90}$ values were 0.12/0.25 mg/L.

Susceptibility testing

MICs of TOL were determined using broth microdilution and agar dilution at a fixed 4 µg/mL concentration of TAZ, using CLSI methodology. Disk diffusion susceptibility testing was performed with a disk containing 30 µg TOL and 10 µg TAZ.

***In vitro* studies**

Hollow-fiber experiment

Twenty-one clinical isolates (8 *P. aeruginosa*, 9 *K. pneumoniae*, and 4 *E. coli*) were tested for efficacy in the HF model using a concentration-time profile simulating the steady-state exposures of TOL and TAZ in the lung ELF of pneumonia patients receiving the 3 g dosing regimen evaluated in the Phase 3 NP study (PN008). Clinical isolates were selected based on their resistance mechanisms and TOL/TAZ MICs ranged from 2 to 256 µg/mL for the Enterobacteriaceae isolates, and 4 to 8 µg/mL for the *P. aeruginosa* isolates.

Efficacy was defined as a ~ 3-log drop in CFU/mL from the starting inoculum, with no re-growth within 69 hours. Efficacy was observed in 4 of 4 *P. aeruginosa* isolates with a TOL/TAZ MIC of 4 µg/mL, as well

as in 3 of 4 isolates with a TOL/TAZ MIC of 8 µg/mL. Of the 9 *K. pneumoniae* isolates, efficacy was observed only in 3 of 4 isolates with a TOL/TAZ MIC of 4 µg/mL. Of the 4 *E. coli* isolates, efficacy was observed in 1 of 1 isolate with a TOL/TAZ MIC of 16 µg/ml.

Overall, these data demonstrate bactericidal activity of 3-g TOL/TAZ at simulated PK exposures corresponding to human SS-ELF in patients with confirmed or suspected pneumonia, supporting the current breakpoints of 4/4 µg/mL for *P. aeruginosa* isolates and a breakpoint of 2/4 µg/mL for Enterobacteriaceae (i.e. combined with PN008 clinical data hollow fiber results suggest a 1 dilution increase in the EUCAST breakpoint from 1 mg/L to 2 mg/L for the latter).

Animal model studies

Neutropenic Mouse Lung Infection Model

The *in vivo* efficacy of TOL/TAZ was evaluated in a delayed treatment neutropenic mouse lung infection model at doses that approximate the human TOL and TAZ concentrations in SS-ELF in ventilated patients with suspected or confirmed pneumonia receiving the 3 g TOL/TAZ dose evaluated in the Phase 1 NP study (PN007). Isolates (n=5) were chosen based on their various resistance mechanisms (with MIC up to 4 µg/mL) to represent isolates in patients with disease.

Efficacy in these studies was defined as a $\geqslant$1 log CFU/g decrease in lung bacterial burden 26 hours post infectious challenge relative to pre-treatment. Treatment with the humanized TOL/TAZ dose of 125/62.5 mg/kg was efficacious in all *K. pneumoniae* isolates (including one with a TOL/TAZ MIC of 256 µg/mL), except one isolate with a TOL/TAZ MIC of 2 µg/mL. A 2-fold lower TOL/TAZ dose did not show comparable efficacy, indicating that the humanized TOL/TAZ dose of 125/62.5 mg/kg was required to provide significant efficacy in this model.

Relationship between plasma concentration and effect

The currently approved dose regimen for TOL/TAZ in treatment of cUTI and cIAI in adults is 1.5 g q8h administered as a 1-hour IV infusion. The proposed TOL/TAZ dose regimen for the indication NP, including VAP is 2 g/1 g every 8 hours (i.e. 3 g q8h) administered in 1-hour IV infusion for a duration of 8-14 days. This dose regimen was selected based on probability of target attainment (PTA) analyses and Monte Carlo simulations (MCS), using the nonclinical PD targets,

Non-clinical PD targets

The non-clinical PD targets for ceftolozane and tazobactam were determined based on neutropenic mouse thigh infection models and are the same as those employed in MCS/PTA analyses in the initial Dossier.

For **ceftolozane**, the antimicrobial effect is correlated best with %fT>MIC (the time that free-drug concentrations are above the MIC). In neutropenic mouse thigh infection model using 4 *P. aeruginosa* and 4 Enterobacteriaceae strains, the mean (median) %T>MIC based on total drug concentration associated with bacteriostasis and 1-log kill were 31.5 (32.2), respectively (Craig and Andes 2013). As TOL plasma protein binding in mice is <10% and as no notable impact of serum on MIC was observed in *in vitro* studies, only total drug TOL was applied to these PD targets. Based on these results, the %fT>MIC of 30% was selected as the TOL PD target for PTA analysis.

For **tazobactam**, %fT>threshold concentration (CT), which is the time above the threshold free-drug concentration needed to effectively neutralize the beta-lactamase enzymes produced by bacteria, was previously identified as the PD parameter of importance based on hollow-fiber and animal model experiments. In neutropenic mouse thigh infection model (**04D9N8**), using 8 bacterial strains (4 *K. pneumoniae* and 4 *E. coli*), infected mice were treated with TOL doses that achieved 30% fT>MIC, in conjunction with different TAZ q2h or q8h dosing regimens in order to determine the PD target of TAZ. The applicant stated that the average TAZ %fT>1 µg/mL across bacterial strains was ~20% (for a static

effect, i.e. to obtain static effects of ceftolozane). Therefore, 20% fT>CT was selected as the TAZ PD target for PTA analysis. However, in the submitted study report (**04D9N8**) it is stated that "*Full exposure-response relationships (n=8, R2 0.51-0.90) for TOL/TAZ indicate that TAZ q2h was more efficacious than q8h, reducing the TAZ daily dose by a factor 4.1 to 117 to obtain a static effect of the TOL/TAZ combination, the reduction dependent on strain and resistance mechanism. This corresponds to a mean %fT>CT 1 mg/L of 32% (range 14.5-51.9)*".

Selection of Phase 3 dose based on PTA analysis

Population PK modeling and MCS were conducted to determine PTA based on the nonclinical PD targets for TOL and TAZ (Xiao *et al*. 2015). The objective was to achieve PTA >90% for the selected PD targets for TOL and TAZ both in plasma and ELF against pathogens with an MIC of ≤ 8 µg/mL.

On the basis of the 2012 US/European Union PACTS surveillance data selected from hospitalized patients with pneumonia, the most commonly isolated pathogens of interest were Enterobacteriaceae (n=1530; 51.5%) and *P. aeruginosa* (n=1019; 34.3%). The MIC distributions for these pathogens are illustrated in Figure 9 and Figure 10. The ceftolozane/tazobactam MIC_{50} and MIC_{90} against Enterobacteriaceae were 0.25 and 4 mg/L, respectively, and against *P. aeruginosa* were 0.5 and 4 mg/L, respectively.

The popPK model used for MCS included 2 parts, one for plasma PK and the other for plasma-to-ELF PK. The plasma PK model was developed with the plasma data from 8 Phase 1 studies and 2 Phase 2 studies in cUTI and cIAI patients. Thus, the PK model used for simulation was a mixed PK model, combining the plasma PK for cIAI patients and the plasma-to-ELF PK data from healthy subjects (**04D3Y0**). The individual TOL and TAZ concentration–time profiles in both plasma and ELF were simulated for different dosing regimens, including the 1.5 and 3 g TOL/TAZ doses through a 1 hr IV infusion every 8 hours for patients with normal renal function. The goal was to determine the dosing regimen that achieved a PTA >90% for the 1-log kill target. An unbound fraction of 0.79 was used for ceftolozane to calculate the %fT>MIC. In the simulation for tazobactam, an unbound fraction of 0.70 was used to calculate %fT>CT.

The generated PK profiles were then used to assess TOL and TAZ PTA for both ELF and plasma, using nonclinical PD targets as follows:

- For TOL, targets of 24.8% and 32.2% fT>MIC to achieve bacteriostasis and 1-log kill, respectively, and targets of 40% and 50% fT>MIC associated with greater killing (i.e. 2-log kill for Enterobacteriaceae and *P. aeruginosa*) effect were examined.
- For TAZ, 20% and 30% fT>CT to achieve bacteriostasis and 1-log kill, respectively, and targets of 40% and 50% fT>CT were examined.

As shown in Figure 9 and 10, the PTA for TOL was consistently higher for all the % fT>MIC targets with the 3 g dose relative to the 1.5-g dose at the targeted MIC of 8 mg/L in ELF for NP. Of note, the PTA for TOL was 98% against pathogens with an MIC up to 8 mg/L in ELF and 97.1% against pathogens with an MIC up to 16 mg/L in plasma for the 1-log kill target with the 3 g TOL/TAZ dose (Figure 5). The PTA was 95% for the 40% fT>MIC target up to 8 mg/L in ELF. Comparatively, at the 1.5 g dose, the PTA for 1-log kill was ~ 85% and 74% for pathogens with an MIC up to 8 mg/L in ELF or 16 mg/L in plasma, respectively (Figure 6), whereas the PTA was approximately 75% for the 40% fT>MIC target up to 8 mg/L in ELF. When using the target of 50%fT>MIC for the 3-g TOL/TAZ dose, the PTA reached 87.7% against pathogens with an MIC up to 8 mg/L in ELF. The 1.5 g dose of TOL/TAZ, however, achieved only 59% PTA for pathogens with an MIC up to 8 mg/L in ELF for NP.

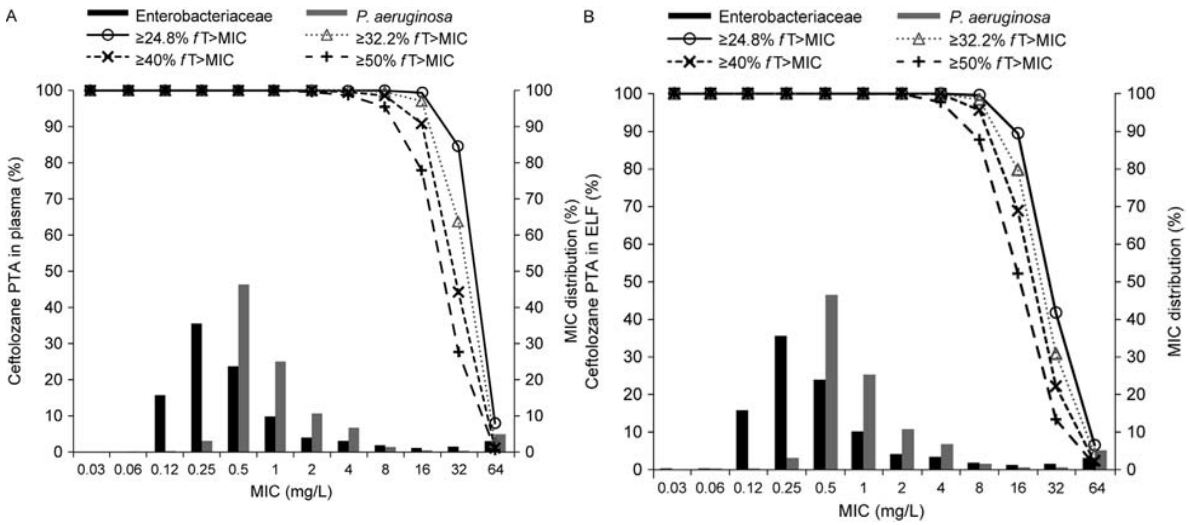


Figure 9. MIC distribution of Enterobacteriaceae and *P. aeruginosa* isolates from hospitalized patients with pneumonia from 2012 US/ European Union surveillance data and simulated PTA of ceftolozane in plasma (A) and ELF (B) in patients with normal renal function following 3 g ceftolozane/tazobactam administered as a 60-minute intravenous infusion every 8 hours.

Source: Xiao *et al* 2015

At the dose level of 3 g TOL/TAZ, the PTA for TAZ was comparable for all targets in plasma and ELF (Figure 11) and was higher than the PTA achieved in plasma at the 1.5-g dose. According to Xiao *et al* (2015), it was aimed that the target attainment in ELF of the 3-g dose of TOL/TAZ in nosocomial pneumonia patients with normal renal function would not be lower than that of the 1.5-g dose in plasma for cUTI/cIAI patients. The authors stated further that "*the MEC coverage achieved in plasma with the current dose of 1.5 g for treatment of cUTIs and cIAIs was confirmed to be sufficient against ESBL-producing pathogens in the ceftolozane/tazobactam clinical trial programs*".

Therefore, the applicant considered the 3-g dose of ceftolozane/ tazobactam as appropriate to be evaluated in patients with nosocomial pneumonia and normal renal function, which is double the dose that is approved for use in patients with cUTIs and cIAIs.

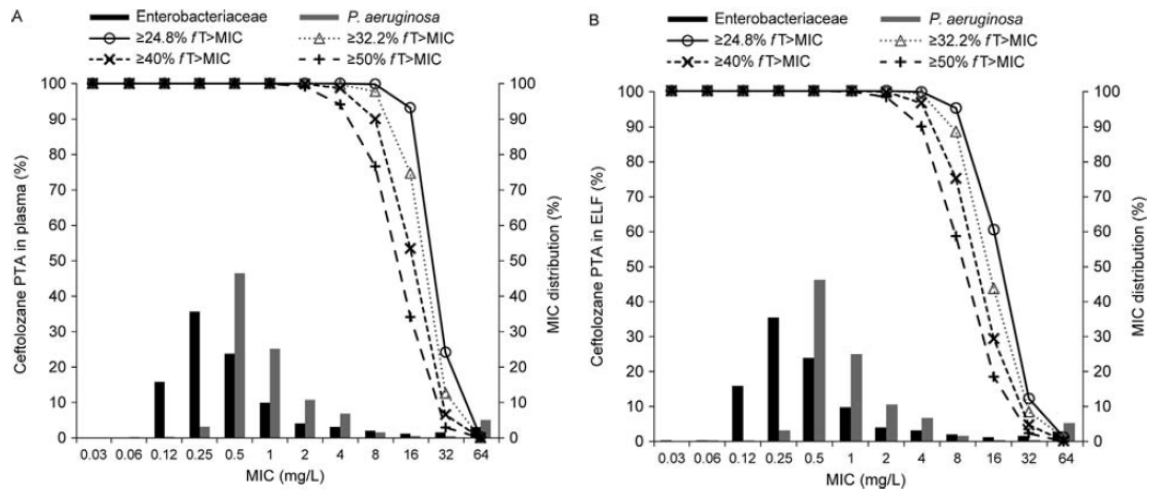


Figure 10. MIC distribution of Enterobacteriaceae and *P. aeruginosa* isolates from hospitalized patients with pneumonia from 2012 US/ European Union surveillance data and simulated PTA of ceftolozane in plasma (A) and ELF (B) in patients with normal renal function following 1.5 g ceftolozane/tazobactam administered as a 60-minute intravenous infusion every 8 hours.

Source: Xiao *et al* 2015

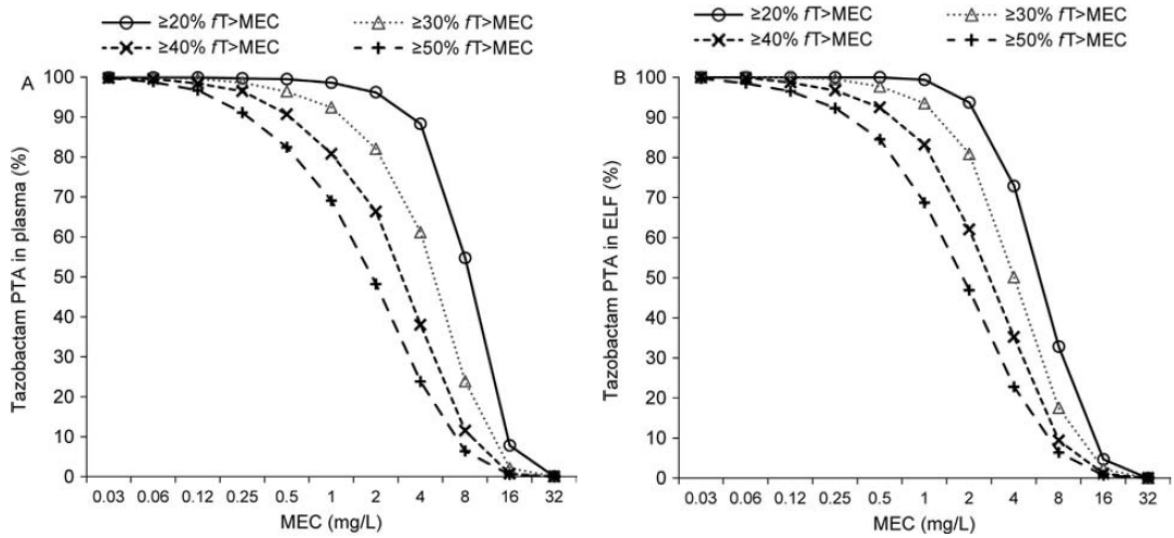


Figure 11. Simulated PTA of tazobactam in plasma (A) and ELF (B) in patients with normal renal function following 3 g ceftolozane/ tazobactam administered as a 60-minute intravenous infusion every 8 hours.

Source: Xiao *et al* 2015

Simulation of exposure and PTA analyses following Phase 3 study

The MCSs that employed the updated NP popPK models (**050ZC7)** for both TOL and TAZ following the Phase 3 study were used to justify the dose selection for the treatment of ventilated patients with NP, and to support the proposed susceptibility testing interpretive criteria by assessing the PTA.

The previously developed two separate popPK models for TOL and TAZ were refined by including PK data collected from 3 Phase 3 trials (**PN013**, **PN014** and **PN008**) in the analysis datasets. The TOL ELF data in healthy and critically ill ventilated patients with proven or suspected pneumonia were incorporated in previous TOL popPK models (**04D3Y0** and **050w2j**, respectively). The structure of the ELF compartment from the previous popPK model was directly transferred to the NP popPK model **050ZC7** with fixed parameter estimates. For TOL, a total of 8330 (including 1481 sparse PK samples from NP patients in PN008) plasma concentrations from 968 subjects (305 NP patients in PN008) and 47 ELF concentrations from 47 subjects were used for the popPK analysis. For TAZ, a total of 5679 plasma concentrations (including 1455 sparse PK samples from NP patients in PN008) from 835 subjects (305 NP subjects in PN008) and 42 ELF concentrations from 42 subjects were used. A 2-compartment model with first-order elimination best described the plasma concentration-time profile of both TOL and TAZ. The significant covariates relevant to the NP population in the model included: body weight on Vc, and Vp; CrCL on CL; and pneumonia on Vc. The updated popPK models were then used for stochastic simulations to generate plasma and ELF exposures and PTAs to justify the dose selection for the treatment of ventilated patients with NP.

MCSs were performed in NONMEM (version 7.3.0) using the final popPK models to generate individual ELF and plasma concentration-time profiles. These analyses were based on virtual subjects randomly selected from a virtual population dataset containing a distribution of demographic covariates (weight) and CrCL that is representative of the intended patient population. A total of 1000 virtual individuals were generated in each of the renal function categories. TOL/TAZ doses of 3 g (*i.e.* 2/1 g), 1.5 g (*i.e.* 1/0.5 g), and 0.750 g (*i.e.* 0.5/0.25 g) administered as 1-hour IV infusion were used to generate PK profiles in subjects with normal and mild, moderate, and severe renal impairment, respectively. The 3 g dose was also evaluated in subjects with augmented renal clearance (ARC).

The generated PK profiles were then used to assess TOL and TAZ PTA for both ELF and plasma, using non-clinical PD targets as follows:

- For TOL: 30% fT>MIC to achieve 1-log kill.
- For TAZ: 20%fT>Ct of 1 µg/mL to achieve 1-log kill.

PTA was defined as the percent of patients who achieved PD targets of %fT>MIC ≥ 30% for ceftolozane at MIC of 8 µg/ml and/or %fT>CT ≥ 20% for tazobactam at the CT of 1 µg/ml.

Further, the steady-state exposures in the patients with NP from **PN008** receiving adjusted dosing regimens based on CrCL were estimated using the Bayesian parameter estimates from the final models for ceftolozane and tazobactam. Results of steady-state exposures between different renal function groups are presented in the boxplots (Figure 7).

PTA simulations using estimated steady-state exposures in the patients with NP/VAP from PN008

A summary of target attainment parameters in plasma and ELF is provided in Table 12 and Table 13 for ceftolozane and tazobactam by CrCL groups, respectively. These PTA analyses were performed only at a TOL/TAZ MIC of 8 µg/mL.

Table 12. Summary of PTA for ceftolozane and tazobactam steady-state estimated plasma exposures in NP patients from PN008 receiving a dose-adjusted regimen based on CrCL

	15 ≤ CrCL ≤ 29	**30 ≤ CrCL ≤ 50**	**50 < CrCL < 80**	**80 ≤ CrCL < 150**	**150 ≤ CrCL < 180**	**180 ≤ CrCL < 210**	**CrCL ≥ 210**
%fT>MIC Mean (CD) %CV	99.0 (0.00) 0	81.3 (36.6) 45.1	91.3 (23.7) 25.9	83.1 (33.8) 40.6	90.5 (25.8) 28.5	76.8 (40.8) 53.1	95.4 (7.54) 7.91
PTA 30% fT>MIC, n (%)	11/11 (**100**)	16/19 (**84.2**)	44/46 (**95.7**)	95/109 (**87.2**)	17/18 (**94.4**)	12/15 (**80.0**)	13/13 (**100**)
%fT>CT Mean (CD) %CV	90.8 (20.0) 22.0	91.4 (14.8) 16.2	89.1 (17.0) 19.1	76.7 (23.1) 30.1	62.3 (24.4) 39.2	60.6 (27.5) 45.3	53.6 (23.5) 43.9
PTA 20% T>CT, n (%)	13/13 (**100**)	27/27 (**100**)	67/67 (**100**)	138/138 **100**)	24/24 (**100**)	16/16 (**100**)	20/20 (**100**)

Table 13. Summary of PTA for ceftolozane and tazobactam steady-state estimated ELF exposures in NP patients from PN008 receiving a dose-adjusted regimen based on CrCL

	15 ≤ CrCL ≤ 29	**30 ≤ CrCL ≤ 50**	**50 < CrCL < 80**	**80 ≤ CrCL < 150**	**150 ≤ CrCL < 180**	**180 ≤ CrCL < 210**	**CrCL ≥ 210**
%fT>MIC Mean (CD) %CV	99.0 (0.00) 0	78.2 (41.5) 53.1	86.1 (33.7) 39.2	83.6 (36.1) 43.2	93.2 (23.3) 25	79.2 (41.0) 51.8	91.4 (27.5) 30
PTA 30% fT>MIC, n (%)	11/11 (**100**)	15/19 (**78.9**)	40/46 (**87.0**)	92/109 (**84.4**)	17/18 (**94.4**)	12/15 (**80.0**)	12/13 (**92.3**)
%fT>CT Mean (CD) %CV	82.8 (32.5) 39.2	89.9 (24.2) 26.9	95.6 (11.7) 12.2	86.3 (21.9) 25.4	74.6 (25.5) 34.1	75.3 (21.6) 28.7	69.8 (26.3) 37.8
PTA 20% T>CT, n (%)	12/13 (**92.3**)	26/27 (**96.3**)	67/67 (**100**)	134/138 (**97.1**)	23/24 (**95.8**)	16/16 (**100**)	1 8/20 (**90.0**)

PTA simulations in virtual patients with NP/VAP

For virtual **NP patients with normal renal function** (80 mL/min≤CrCL <150 mL/min) receiving 3-g TOL/TAZ, the TOL ELF PTA was 98% at a TOL/TAZ MIC of 8 µg/mL (Table 14), and the TOL plasma PTA was >90% at a TOL/TAZ MIC of 16 µg/mL. The TAZ ELF PTA was 98% at a TAZ CT of 1 µg/mL for the PD target 20% of fT>CT (Table 15), and the TAZ plasma PTA was >90% at a TAZ CT of 2 µg/mL.

For patients with **mild renal impairment** (50 mL/min≤CrCL <80 mL/min), similar exposure levels and PTA were attained as the patients with normal renal function. Therefore, no dose adjustment is required.

For virtual NP patients with **moderate renal impairment** (30 mL/min ≤ CrCL≤50 mL/min) receiving CrCL-adjusted TOL/TAZ doses of 1.5 g which is 2-fold the recommended CrCL-adjusted doses for cIAI/cUTI patients with moderate renal impairment, the TOL ELF PTA was >90% at a TOL/TAZ MIC of up to 8 µg/mL (Table14), and the TOL plasma PTA was >90% at a TOL/TAZ MICs of up to 16 µg/mL. The TAZ ELF PTA was >90% at a TAZ CT of 1 µg/mL (Table 15), and the TAZ plasma PTA was >90% at a CT of 2 µg/mL.

For virtual NP patients with **severe renal impairment** (15 mL/min ≤ CrCL ≤29 mL/min) receiving CrCL-adjusted doses of 0.75 g, which is 2-fold the recommended CrCL-adjusted doses for cIAI/cUTI patients, the TOL ELF PTA was >90% at a TOL/TAZ MIC of up to 8 µg/mL (Table 14), and the TOL plasma PTA was >90% at a TOL/TAZ MIC of up to 16 µg/mL. The TAZ ELF PTA was 87.2% at a TAZ CT of 1 µg/mL (Table 15), and the TAZ plasma PTA was >90% at a CT of 2 µg/mL.

For virtual **NP patients with ARC** (CrCL ≥150 mL/min) at the 3 g dose, the TOL ELF PTA was >90% at a TOL/TAZ MICs of up to 4 µg/mL (Table 14), and the TOL plasma PTA was >90% at a TOL/TAZ MIC up to 16 µg/mL. The TAZ ELF PTA was >90% at a CT of 1 µg/mL (Table 15), and the TAZ plasma PTA was >90% at a TAZ CT of 2 µg/ml.

Table 14. Percentage of nosocomial pneumonia patients with different creatinine clearance values achieving 30 % of fT>MIC for TOL in ELF at steady state

Renal Function	Percentage of Patients Achieving 30 % of *f*T>MIC for TOL in ELF											
MIC (µg/mL)	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
15 mL/min ≤ CrCL ≤ 29 mL/min	100	100	100	100	100	100	100	99.7	95.3	60.9	16.8	1.2
30 mL/min ≤ CrCL ≤ 50 mL/min	100	100	100	100	100	100	100	100	97.4	80.7	34.7	5.2
50 mL/min < CrCL < 80 mL/min	100	100	100	100	100	100	100	100	99.6	93.4	56.9	15.6
80 mL/min ≤ CrCL < 150 mL/min	100	100	100	100	100	100	100	100	98.1	79.6	33.8	5.7
150 mL/min ≤ CrCL < 180 mL/min	100	100	100	100	100	100	100	99.9	95.4	64.7	19.3	1.3
180 mL/min ≤ CrCL < 210 mL/min	100	100	100	100	100	100	100	99.4	92.6	56.7	12.5	0.8
CrCL ≥210 mL/min	100	100	100	100	100	100	100	99.2	88.3	49.5	9.9	0.5

Dosing regimens based on CrCL: >50 mL/min, 3 g TOL/TAZ; 30 mL/min ≤ CrCL ≤50 mL/min, 1.5 g TOL/TAZ; 15 mL/min ≤ CrCL ≤ 29 mL/min, 750 mg TOL/TAZ.

Source: [Ref. 5.3.5.3: 050ZC7]

Table 15. Percentage of nosocomial pneumonia patients with different creatinine clearance values achieving 20 % of fT>CT for TAZ in ELF at steady state

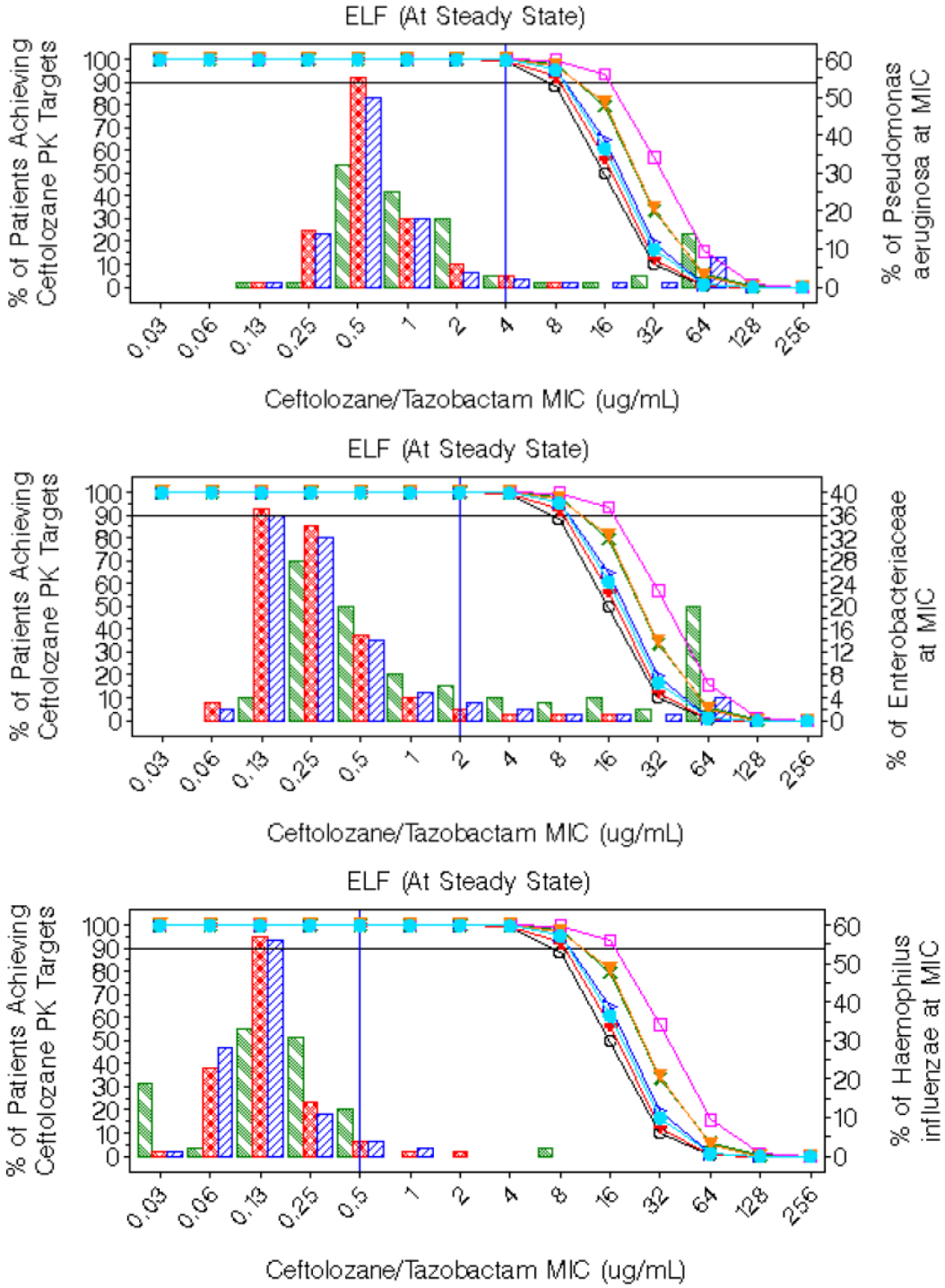
Renal Function	Percentage of Patients Achieving 20 % of fT>C_T for TAZ in ELF											
C_T (µg/mL)	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
15 mL/min ≤ CrCL ≤ 29 mL/min	100	100	100	100	98.5	87.2	53.4	18.4	2.6	0.2	0	0
30 mL/min ≤ CrCL ≤ 50 mL/min	100	100	100	100	99.8	96	73.1	31.7	5.3	0.5	0	0
50 mL/min < CrCL < 80 mL/min	100	100	100	100	100	99	89.8	57.5	19.8	2.7	0.5	0
80 mL/min ≤ CrCL < 150 mL/min	100	100	100	100	99.9	98.2	81.5	42.7	9	0.6	0	0
150 mL/min ≤ CrCL < 180 mL/min	100	100	100	100	99.5	94.3	70.6	27.4	4.9	0.3	0	0
180 mL/min ≤ CrCL < 210 mL/min	100	100	100	100	99.6	92.1	65	24.4	3.8	0	0	0
CrCL ≥210 mL/min	100	100	100	100	99.3	92.3	62.1	20.5	1.9	0	0	0

Dosing regimens based on CrCL: >50 mL/min, 3 g TOL/TAZ; 30 mL/min ≤ CrCL ≤50 mL/min, 1.5 g TOL/TAZ; 15 mL/min ≤ CrCL ≤ 29 mL/min, 750 mg TOL/TAZ.

Source: [Ref. 5.3.5.3: 050ZC7]

For virtual NP patients with **ESRD** using a 1.5/0.75 g loading dose and 0.3/0.15 g maintenance dose q8h, the TOL ELF PTA was >99% for 30%t>MIC target at a TOL/TAZ MICs of up to 4 µg/mL. This held true for each day during the simulated treatment duration of 14 days. The TAZ ELF PTA was also >90% for 20%T>CT target at the CT of 1 µg/mL during 14 days of simulation.

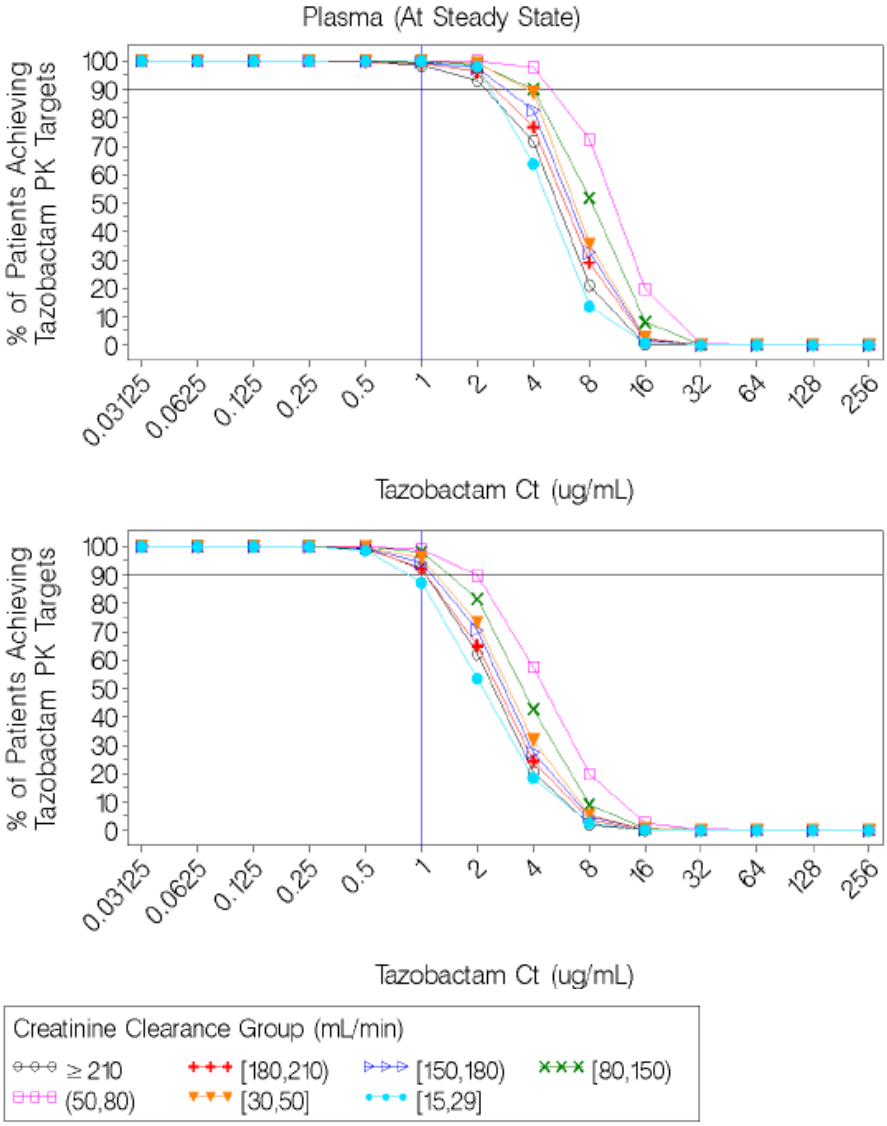
The figures below show the results of simulations in ELF for those with normal renal function as well as for those with different categories of renal impairment and ARC. At the 1-log kill target the 3 g q8h ceftolozane dose is supported for *P. aeruginosa* strains with MICs up to 4 µg/mL, for Enterobacteriaceae strains with MICs up to 2 µg/mL, and for *H. influenzae* strains with MICs up to 0.5 µg/mL.



Solid vertical line represents MIC of 4 µg/mL for *P. aeruginosa*, 2 µg/mL for Enterobacteriaceae, and 0.5 µg/mL for *H. influenzae*

Source: [Ref. 5.3.5.3: 050ZC7]

Figure 12: Percentage of patients achieving 30 % fT>MIC for TOL in ELF at steady state with *P. aeruginosa*, Enterobacteriaceae, and *H. influenzae* MIC distributions amongst isolates from PN008 and surveillance data



The solid vertical lines represent CT of 1 µg/ml. The solid horizontal line represents 90% PTA.

Figure 13: Individual probability of target attainment in plasma and epithelial lining fluid for tazobactam (using %fT>CT, 20% target) for virtual adult patients with nosocomial pneumonia, by creatinine clearance groups

Clinical exposure-response relationship

Exposure-response (E/R) analysis was conducted to assess the potential relationship between TOL and TAZ plasma PK and the two primary efficacy endpoints evaluated in study PN008: Day 28 all-cause mortality and clinical response at TOC visit. However, no interpretable trend between either efficacy endpoint and TAZ %fT> CT (1 µg/mL) was identified.

Of the 231 subjects in the E/R analysis dataset, the highest baseline TOL/TAZ MIC from relevant pathogens for the 177 subjects was ≤4 µg/mL. The TOL plasma %fT>MIC was >30% for all 177 subjects. Notably, TOL plasma %fT>MIC was 99% for 173 of the 177 subjects, and the lowest %fT>MIC in the remaining 4 subjects was 73.7%. The all-cause mortality rate and clinical cure rate in these 177 subjects were 13.3% and 70%, respectively.

A total of 65.4% patients (151 out of 231) were considered a clinical cure at the TOC visit in the E-R-efficacy population (Table 16). The occurrence of clinical cure at the TOC visit was 70.6% (125 patients out of 177) in patients with an MIC ≤ 4 µg/mL as compared to 48% (26 patients out of 54) in patients with MIC > 4 µg/mL. Of the 177 with an MIC ≤ 4 µg/mL, the clinical cure rate for the 173 patients with %fT>MIC of 99% was 70% versus 100% in the remaining 4 patients, suggesting a lack of an E-R relationship with ceftolozane exposures.

In the final E/R report, it was stated that: "*In patients with an MIC below the breakpoint, the mean %fT>MIC was higher in patients (98.6%) as compared to patients above the breakpoint (47.7%); the all-cause mortality rate on Day 28 was 13% in the 177 patients with an MIC below the breakpoint as compared to 24% in the 54 patients with an MIC above the breakpoint, respectively*".

As no AEs met the pre-defined criteria for in the E-R safety analysis, no safety E-R modeling was conducted.

The applicant concluded that there was no E-R relationship trend with both TOL and TAZ in patients with an MIC ≤ 4 µg/mL as all patients achieving exposures above the PD targets.

Table 16. Summary statistics of exposure measurements and efficacy response, by MIC group

Variable	Statistic	MIC ≤ 4	MIC > 4	Overall
Percent Free Time > 1 µg/mL for Tazobactam	Mean (SD)	74.436 (24.685)	85.257 (21.599)	76.965 (24.390)
	Median	78.900	99.000	89.200
	Min, Max	22.80, 99.00	36.30, 99.00	22.80, 99.00
	n	177	54	231
Percent Free Time > MIC for Ceftolozane	Mean (SD)	98.644 (2.506)	47.676 (43.349)	86.729 (30.086)
	Median	99.000	45.150	99.000
	Min, Max	73.70, 99.00	0.00, 99.00	0.00, 99.00
	n	177	54	231
MIC Ceftolozane/Tazobactam (µg/mL)	Mean (SD)	0.9608 (1.1024)	87.2593 (94.0079)	21.1345 (58.1134)
	Median	0.5000	32.0000	1.0000
	Min, Max	0.064, 4.000	8.000, 256.000	0.064, 256.000
	n	177	54	231
All-Cause Mortality on Day 28, n (%)	Alive	154 (87.0)	41 (75.9)	195 (84.4)
	Death	23 (13.0)	13 (24.1)	36 (15.6)
Clinical Response at TOC Visit, n (%)	Failure	52 (29.4)	28 (51.9)	80 (34.6)
	Cure	125 (70.6)	26 (48.1)	151 (65.4)

Abbreviations: Max, maximum; MIC, minimum inhibitory concentration; Min, minimum; n, number of patients; SD, standard deviation; TOC, test-of-cure.

Clinical trials

In the pivotal study **PN008**, microbiological cure rates at TOC were in general comparable between the study arms, slightly favoring TOL/TAZ in ME population. No correlation was observed between MIC and outcome in either treatment group.

In patients with *P. aeruginosa* isolates, higher microbiological eradication rates were observed in the TOL/TAZ arm compared to the meropenem arm in the mITT population [i.e. 74% (47/63) vs 63% (41/55), respectively]. Microbiological response rate against AmpC overexpressing *P. aeruginosa* isolates was (6/9) 66% vs. (1/6) 16% in the TOL/TAZ arm vs. the meropenem arm, respectively.

For ESBL-Enterobacteriaceae isolates, slightly lower microbiological cure rates were observed for the TOL/TAZ arm compared to the meropenem arm (mITT); 66% (56/84) vs. 71% (52/73), respectively.

Regarding the ESBL-*K. pneumoniae*, lower microbiological cure rates were observed in the TOL/TAZ arm compared to the meropenem arm (mITT); 62% (33/53) vs. 73% (38/52), respectively.

For *H. influenzae*, microbiological eradication rates were higher in the TOL/TAZ arm than in the meropenem arm [90% (20/22) vs. 73% (11/16) in mITT population, respectively].

The number of isolates with MIC ≥8 µg/mL encountered in the study **PN008** were in general limited, especially with *P. aeruginosa* isolates (n=5). For Enterobacteriaceae and *K. pneumoniae*, a total of 41 and 34 isolates had higher MIC values of ≥ 8 µg /mL. For these isolates, no correlation was observed between MIC and outcome, and compared isolates with MIC < 8 µg /mL.

Resistance development

Incidences of emergence of non-susceptibility (i.e. >1 dilution change in MIC) were comparable between the study arms in PN008; 29 (12.7%) subjects in the TOL/TAZ arm vs. 28 (12.0%) subjects in the meropenem arm by the TOC visit. In the TOL/TAZ treatment arm, the most common pathogens to develop non-susceptibility were 11 *K. pneumoniae* and 8 *A. baumannii* isolates; among *P. aeruginosa* isolates, 3 developed non-susceptibility. A lower percentage of subjects with *P. aeruginosa* isolates in the TOL/TAZ treatment arm (3/63, 4.8%) developed non-susceptibility compared to the meropenem treatment arm (17/65, 26.2%). Among 29 subjects in whom non-susceptibility emerged in the TOL/TAZ treatment arm, 17 (59%) and 17 (59%) subjects had clinical and microbiological cure at the TOC visit, respectively.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

The current application concerns the extension of indication to include treatment of adult patients with nosocomial pneumonia (NP) at a 3g q8h dose. Single dose and multiple dose PK data have been obtained for TOL/TAZ at doses up to 4.5 g and 3 g daily up to ten days, respectively (original MAA). Additional studies (**PN018**, **PN007**, **PN008**) as well as popPK and ER modelling have been performed since the original cIAI/cUTI application to provide data to support the present application.

Validated LC/MS/MS bioanalytical methods (in accordance with the EMA bioanalytical guideline (EMEA/CHMP/EWP/192217/2009 Rev. 1) were used for analysis of TOL, TAZ and TAZ M1 in plasma, urine, dialysate and epithelial lining fluid samples from the clinical studies.

Several popPK models have been developed throughout Zerbaxa product development, with separate models for each active substance. The preceding models are overall similar to the most recent ones with respect to base structure and co-variates. The main model (**050zc7**) includes phase I ELF PK data from healthy subjects and pneumonia patients, and sparse phase 3 plasma PK data from ventilated NP patients (**PN008**). The model is used to estimate probability of target attainment to further justify the proposed dosing regimen in NP patients with normal, augmented or impaired renal function, and is considered to be of low to moderate regulatory impact.

Overall, the methodology is considered appropriate. The final models for TOL and TAZ were 2-compartment models with first-order elimination. For TOL and TAZ (pneumonia population), significant covariates were BW on Vc and Vp, CrCL on CL and pneumonia on Vc. In addition, pneumonia was a covariate on Vp in the TOL model. Diagnostic plots are overall adequate for the TOL and TAZ model,

although they indicate that the TAZ model does not fully capture the observed. The VPC plots for the overall and NP populations look acceptable. The popPK models need to be sufficiently robust for simulations and subsequent PK/PD analyses to evaluate PTA. Additional VPC plots provided in the RSI response demonstrated that the model adequately captures the observed PK concentrations in patients from study **PN008** and in patients within the different renal function categories.

Results from study **PN007** indicate that TOL and TAZ distributes into the lung of ventilated patients with suspected pneumonia. Total ELF to free plasma AUC ratios for TOL and TAZ in ventilated patients with suspected pneumonia were 50% and 62%, respectively, overall similar to penetration ratios seen in healthy subjects (61% and 63%, respectively). The observed penetration ratio supports the use of TOL/TAZ in pneumonia.

The proposed dose is within the established linearity range. The slight accumulation noted for both TOL and TAZ following multiple doses of 3 g q8h in patients with suspected or proven pneumonia (**PN007**) was likely attributed to the high variability in CrCL of included patients. In the popPK analysis, IIV for TOL and TAZ were found to be moderate.

Based on model-predictions, TOL and TAZ $AUC_{0\text{-}8h}$ in pneumonia patients is comparable to that of healthy subjects, while Cmax is lower (25-30%), attributed to the larger volume of distribution in NP patients (~2-fold higher). Variability is markedly higher in patients compared to healthy subjects. Estimated exposures (AUC) appear to be ~2-fold of those estimated for the cUTI and cIAI populations receiving 1.5 g q8h.

Only sparse PK data in plasma were collected in study **PN008** and the applicant relies on plasma from **PN007** to characterise PK in NP patients. It is not clear in what extent these patients had a similar degree of infection-associated systemic disturbances as patients with confirmed nosocomial pneumonia in the pivotal study. Reassuringly, observed concentrations in **PN008** were adequately captured by the popPK models.

TOL and TAZ are eliminated by the kidney, and dosage adjustments according to renal function are warranted. The same percent reduction in dose as recommended for cUTI and cIAI patients with *moderate and severe renal impairment* are proposed (*i.e.* a 50% and 25% reduction in TOL/TAZ, respectively). TOL and TAZ model-predicted exposures in NP patients with renal impairment using the proposed posology are overall comparable to those of NP patients with normal renal function. Updated PTA analysis, taking variability into account, support the proposed doses of TOL and TAZ in patients with mild and moderate renal impairment.

All subjects with moderate/severe renal impairment at baseline received the per-protocol reduced dose within the treatment period. 52 (14,4%) patients with moderate/severe renal impairment were treated with TOL/TAZ, 47 (12.9%) were treated with meropenem. In 32 (61.5%) and 26 (55.3%) patients treated with TOL/TAZ and meropenem, respectively, the treatment failed. Analysis of underlying cause of the disease revealed that in patients suffering from VABP, treatment failure rates reached 65.2% (15 patients) and 58.3% (14 patients) in patients treated with TOL/TAZ and meropenem respectively. In patients with ventilated HABP, the failure rates were 58.6% (17 patients) and 52.2% (12) in patients treated with TOL/TAZ and meropenem respectively.

In *ESRD patients requiring HD* a loading dose of 2.25 g followed by maintenance dose of 450 mg q8h (*i.e.* reduction by 75% and 15% compared to the dose in NP patients with normal renal function), is proposed. The maintenance dose is suggested to be given at the earliest possible time following end of haemodialysis. Simulated TOL and TAZ exposures (AUC0-8h, Cmax) were overall within the range of model-predicted exposures in NP patients from study **PN008**. The proposed dose adjustments for patients with ESRD is considered appropriate based on the updated PTA analysis provided in the RSI response.

No dose adjustment is currently proposed for NP patients with augmented renal clearance (ARC; ≥150 mL/min). Model-predicted $AUC_{0\text{-}8h,ss}$ (**PN008**) decline with increasing CrCL within the three ARC categories compared to NP patients with normal renal function. The lack of dose recommendations in patients with ARC was adequately justified in the response to the 2nd RSI.

Based on the popPK analysis, race or body weight had no significant impact on TOL or TAZ PK.

Findings from *in vitro* metabolism and transporter studies conducted in support of the original 1.5 g TOL/TAZ dose regimen can be extended to the proposed 3 g TOL/TAZ dose regimen. The potential for DDIs to occur is considered to be relatively low.

Pharmacodynamics

The currently approved dose regimen for TOL/TAZ in treatment of cUTI and cIAI in adults is 1.5 g q8h administered as a 1-hour IV infusion. The proposed TOL/TAZ dose regimen for the indication NP, including VAP is 2 g/1 g every 8 hours (i.e. 3 g q8h) administered in 1-hour IV infusion for a duration of 8-14 days.

Although the dose is increased to 3 g for patients with NP/VAP, the TOL/TAZ exposure at the infection site (i.e. in ELF) will likely be comparable to plasma exposures achieved in patients with cIAI and cUTI as only 50% and 60% of these drugs penetrates to ELF, respectively.

Non-clinical PD targets

The non-clinical PD targets for ceftolozane and tazobactam were determined based on neutropenic mouse thigh infection models (i.e. plasma-derived) and are the same as those employed in MCS/PTA analyses in the initial Dossier.

For ceftolozane, the antimicrobial effect is correlated best with %fT>MIC. Based on neutropenic mouse thigh infection model using *P. aeruginosa* and Enterobacteriaceae strains, 30% fT>MIC (for 1 log kill), was selected as the TOL PD target for PTA analysis. In addition, 40% fT>MIC and 50% fT>MIC targets were employed to obtain 2 log-kill for Enterobacteriaceae *and P. aeruginosa*, respectively.

For tazobactam, %fT>threshold concentration needed to protect ceftolozane from the beta-lactamase enzymes produced by bacteria is the important factor for efficacy. Based on the neutropenic mouse thigh infection model, 20% fT>CT (stasis) and 35% fT>CT (1-log-kill) were selected as the TAZ PD target for PTA analysis. This would provide sufficient tazobactam exposures to protect ceftolozane from hydrolysis (i.e. as long as ceftolozane is required for activity to obtain at least 1 log-kill). This protection is particularly important against ESBL- producing Enterobacteriaceae isolates.

Selection of dose

For the selection of Phase 3 dose regimen, popPK modelling (including Phase 1 and 2 data, and ELF data from healthy subjects) and MCS were conducted using the non-clinical PD targets. For both TOL and TAZ, both the targets of 20% and ~30% fT>MIC/T>CT to achieve bacteriostasis and 1-log kill, respectively, were examined, in addition to 40% and 50% fT>MIC/fT>CT targets for greater killing effect against key respiratory pathogens (i.e. *P. aeruginosa* and Enterobacteriaceae, respectively). The objective was to achieve PTA >90% for the selected PD targets for TOL and TAZ both in plasma and ELF against pathogens with an MIC of ≤ 8 µg/mL.

PTA simulations suggested a high target achievement of >95% in ELF for ceftolozane with 3-g dose for the 1-log kill and 40% targets against pathogens with an MIC up to 8 mg/L while PTA was ~87% for the target of 50%fT>MIC. For tazobactam, the PTA was comparable for all targets in plasma and ELF following the 3-g dose. While >90% PTA was achieved for 20% and 30% fT>CT both in plasma and ELF at CT of 1 µg/ml, much lower PTAs of 85% and 65% were achieved in ELF for 40% and 50% fT>CT targets, respectively.

Of note, no simulations have been conducted to investigate prolongation of the infusion time, which might have led to higher target attainments (i.e. better coverage with pathogens with high MIC values) for both ceftolozane and tazobactam.

Simulations following Phase 3 study

Once the Phase 3 data from patients with NP/VAP were available, the popPK model was updated to justify the selected dose regimen, including also data from cIAI and cUTI studies as well as ELF data from critically-ill patients.

In general, target attainments were much higher in plasma than ELF for TOL, as expected. At a TOL/TAZ MIC of 8 µg/mL, 98% PTA was achieved in ELF based on the PD target of 30%T>MIC for TOL, according to the MCSs in virtual patients with normal renal function. Additional PTA data using more conservative targets of 40% and 50% T>MIC for TOL showed that >99% target attainments are achieved in ELF for MIC up to 4 µg/ml in all renal function categories (including patients with ESRD with a PTA >97%). Further, >95% target attainments achieved in ELF for MIC up to 8 µg/ml in all renal categories except for ARC categories of 180 mL/min≤CrCL>210 mL/min and CrCL≥210 mL/min (for these PTAs were ~92% and 87%, respectively). For plasma, even better results were obtained. These results are reassuring with regards to adequacy of TOL dose for treatment of patients with NP/VAP.

For tazobactam, PTA data using the PD target of 35% fT>CT=1 µg/mL revealed that patients with renal function categories between 30 to 150 ml/min achieved >95% target attainment in the ELF while 84% of patients with severe renal impairment and 86-90% of patients with ARC with a CrCL ≥150 ml/min achieved target attainment. For both subgroups of ARC patients and patients with severe renal impairment, available clinical data from **PN008** showed that clinical success rate and mortality rates were comparable to patients with normal renal function as well as to patients in the meropenem arm. In addition, very high PTA achieved in plasma is reassuring regarding the patients with severe renal impairment. Although extrapolation of clinical outcome data to a larger population is hampered by the TAZ PTA <90% for patient with ARC and uncertainties about the magnitude of the PTA estimate due to sparse PK data from this subpopulation, available clinical data support that efficacy was comparable between patients with and without ARC. Overall, the TAZ dose can be considered sufficient for restoring antibacterial TOL activity in all renal categories, including patients with extremes of ARC as well as severe renal impairment.

Additional joint PTA data in ELF and plasma using the PD target of 40% and 50%T>MIC for TOL and the PD target of 35% fT>CT=1 µg/mL for TAZ were provided. These data revealed that patients with renal function categories between 30 to 150 ml/min achieved >94% target attainment in the ELF while 84% of patients with severe renal impairment and 85-90% of patients with ARC with a CrCL ≥150 ml/min achieved target attainment at MIC ≤4 mg/L. These results revealed that TAZ dose is the limiting factor for achieving higher target attainments.

Separate simulations for patients with ESRD using the above mentioned TAZ target showed that daily ELF PTA is >90% on non-dialysis days and >88% on dialysis days of the 14-day treatment period at CT=1 µg/mL while daily plasma PTA is 99% for the entire treatment period. These target attainments hold true in the joint PTA analyses at MIC=4 µg/mL for both ELF and plasma. Although there is drop in concentration in dialysis days, generally higher PTAs achieved in ELF. Further, it is reassuring that plasma PTA was constantly >99% during the entire treatment period. The proposed dose adjustment for patients with ESRD is considered appropriate although a PTA of >95% on non-dialysis days could have been preferable.

Although no E-R relationship trend could be found with TOL or TAZ in patients with an MIC ≤4 µg/mL as all patients achieved exposures above the PD targets, Efficacy Response comparisons by MIC Group reveal that a higher proportion of subjects with an MIC ≤ 4 µg/mL achieved clinical cure at the TOC visit

compared to patients with MIC > 4 µg/mL (i.e. 70% vs. 48%). In addition, all-cause mortality on Day 28 was higher in patients with MIC > 8 µg/mL compared to those with MIC ≤4 µg/mL [i.e. 24.1% (13/54) vs. 13% (23/177)]. It is noted that patients with MIC ≤ 4 µg/mL achieved more than twice the ceftolozane exposures using the 30% T>MIC target (*i.e.* 98% vs. 47%) while TAZ exposures were similar. These results indicate a trend of better clinical outcomes and lower mortality in patients with an MIC ≤ 4 µg/mL. Whereas, these findings do not provide reassurance that the proposed dose will sufficiently cover bacteria with MIC > 4 µg/mL (i.e. up to 8 µg/mL or higher).

Clinical and microbiological success rates in the TOL/TAZ arm seem to be comparable to those in the meropenem arm for *P. aeruginosa* and Enterobacteriaceae isolates with baseline MIC values of ≤4 µg/mL and ≤2 µg /mL, respectively. Overall, MIC-based clinical outcomes data do not provide sufficient evidence in support of the adequacy of the dose regimen (especially the tazobactam dose) to cover bacteria with MIC up to 8 µg/mL and higher, as vast majority of the treated isolated had MIC ≤4 µg/mL in **PN008**.

2.3.5. Conclusions on clinical pharmacology

All issues regarding pharmacokinetics and pharmacodynamics have been satisfactorily addressed. In general, proposed ceftolozane-tazobactam dose of 3 g q8h and the proposed dose adjustments for some renal function categories, including ESRD, is considered appropriate.

2.4. Clinical efficacy

The indication applied for are:

“Nosocomial pneumonia, including ventilator-associated pneumonia.”

The clinical support for this indication mainly include one pivotal Phase 3 study. In addition, supportive data for administration of ceftolozane/tazobactam (TOL/TAZ) at a dose of 3 g q8h were obtained from three Phase 1 studies (PN007, PN018, PN028). Study PN007 provided PK data in a population intended to be comparable to the study population for the NP indication. Study PN018 studied impact of race in PK.

PN028 were assessed in the original marketing application and provided PK data in healthy subjects.

An overview of the pivotal clinical study supporting the variation application of ceftolozane/tazobactam in NP, including ventilator-associated pneumonia is provided in the table below.

Table 17. Overview of the pivotal clinical study included in the variation application

Study ID Number of study centres; locations	Study start; Enrolment status, date	Design; Control type	Study and control drugs dose; route &regime	Study objective	Subjects/ pt by arm; Randomised /completed	Treatment duration	Sex; Median age (range)	Diagnosis; Inclusion criteria
PN008 119 centres in 29 countries	First subject, first visit 16-jan 15 Last subj last visit 06-jun 18 Database lock 27-jul 18	Phase 3, R, DB, active comparator, multi-center	TOL/TAZ 3g iv q8h Meropenem 1g q8h	Non-inferiority to meropenem in adults with ventilated HAP or VAP	TOL/TAZ 362/245 Meropenem 364/250	8-14 days	71.2% M 60 y	Ventilated patients with HAP or patients with VAP

R=Randomized; DB= double blind; HAP= Hospital-acquired pneumonia; VAP=ventilator-associated pneumonia; TOL/TAZ= ceftolozane/tazobactam

2.4.1. Dose response study(ies)

A higher dose of 3 g ceftolozane/tazobactam (comprising 2 g ceftolozane and 1 g tazobactam), compared with the currently approved dose of 1.5 g for patients with cUTI and cIAI, was selected based on popPK modelling and Monte Carlo simulations. The modelling approach and adequacy of the proposed dose are discussed in sections 5.3.2 and 5.3.3.

2.4.2. Main study

Study **PN008** was a Phase 3, randomized, double-blind, multicenter study of ceftolozane/tazobactam in the treatment of adult subjects with ventilated nosocomial pneumonia (including VAP and ventilated HAP subjects), compared with meropenem. Approximately 726 subjects were planned to be randomized 1:1 to receive either ceftolozane/tazobactam or meropenem. The number of subjects enrolled with VAP was planned to be at least 50% of the randomized population. The overall study design is shown in the table below.

Table 18. Study design PN008

Screening	Treatment	EOT	D 14[a]	TOC	D 28[a]	LFU
Day -1 to 1	Days 1 to 14	Within 24 hours after last dose of study drug	Day 14	7 to 14 days after the EOT	Day 28	28 to 35 days after the EOT
Assess eligibility Collect LRT specimen Randomize to treatment	Infuse blinded IV study therapy (ceftolozane/tazobactam 3000 mg q8h or meropenem 1000 mg q8h) Total duration of study drug administration is a minimum of 8 days (24 doses) and up to a maximum of 14 days (42 doses)[b]	Evaluation for assessment of microbiological response, clinical response, and safety	Assess for all-cause mortality	Subjects return to study center for primary assessment of microbiological response, clinical response, and safety	Assess for all-cause mortality	Evaluation for final assessment of clinical response and safety

Abbreviations: D = day; EOT = end-of-therapy visit; IV=intravenous; LFU = late follow-up visit; LRT= lower respiratory tract; mg = milligram; q8h=every 8 hours; TOC = test-of-cure visit.

[a] If TOC visit and LFU visit are not on Day 14 and Day 28, respectively, an assessment of all-cause mortality must be conducted independently.

[b] The total number of infusions may increase if a dose adjustment is required based on renal function due to the addition of dummy infusions.

Methods

Study assessments at baseline, during study drug therapy and at scheduled study visits included components of the APACHE II score as an inclusion criterion (until 15 Mar 2016, protocol amendment 5.0), Clinical Pulmonary Infection Scores (CPIS), Sepsis Organ Failure Assessment (SOFA) scores, procalcitonin, C-reactive protein (CRP) measurements and safety labs. Quantitative LRT cultures were required in intubated patients at specified time points during study therapy.

Local (i.e. site laboratory) or regional laboratory results were used to determine patient eligibility for study enrolment as well as for the ongoing management of the patient during the treatment period.

The lower respiratory tract culture specimen could be obtained by any one of the techniques mentioned in inclusion criteria number 4 (refer to the table below). However, at sites where bronchoscopic or mini-BAL or PBS were available, these modalities were strongly recommended, instead of an ETA, for obtaining the baseline LRT specimen. Whenever possible, it was recommended that the same method used to obtain the baseline LRT specimen be used consistently throughout the study for obtaining post-baseline LRT specimens.

All patients had to have a chest radiograph for inclusion into the study. The Investigator's interpretation (or that of a qualified designee at the site) of the chest x-ray was used to make the enrolment decision. However, in addition to the local reading of chest-x-rays, a centralized independent second evaluation of the baseline and day 8 chest x-ray was conducted on all patients enrolled in the study.

Patients were hospitalized throughout the treatment period and completed all study treatment intravenously. No oral switch was permitted in this study.

The LFU visit could be conducted in person or via a telephone call. A telephonic LFU assessment was only permitted to assess the patient's wellbeing if the patient had no known adverse events or laboratory abnormalities that required an in-person follow-up assessment.

Analysis of susceptibility was based on data from the central microbiology lab when available. For subjects without central lab susceptibility data at baseline local lab data was used.

Study participants

Males or females (not pregnant or nursing) 18 years or older, intubated and on mechanical ventilation with a confirmed diagnosis of VABP or ventilated HABP.

Table 19. Key inclusion- and exclusion criteria

Inclusion criteria
1. Intubated (via endotracheal tube, including tracheostomy patients) and on mechanical ventilation at the time of randomization: For ventilated HABP: At least 1 of the following signs and/or symptoms must be present within the 24 hours prior to intubation OR within the 48 hours after intubation in a patient who has been either hospitalized for ⩾48 hours or who has been discharged from a hospital within the prior 7 days (includes patients institutionalized in skilled nursing or other long-term care facility): - A new onset of cough (or worsening of baseline cough) - Dyspnea, tachypnea, or respiratory rate greater than 30 per minute, particularly if any or all of these signs or symptoms are progressive in nature - Hypoxemia defined as an arterial blood gas partial pressure of oxygen less than 60 mmHg while the subject is breathing room air, OR a pulse oximetry oxygen saturation less than 90% while the subject is breathing room air, OR worsening of the ratio of PaO2/FiO2 For VABP: Receiving mechanical ventilation ⩾48 hours and at least 1 of the following: - Acute changes made in the ventilator support system to enhance oxygenation, as determined by worsening partial pressure of oxygen on arterial blood gas, or worsening PaO2/FiO2 - Hypoxemia defined as an arterial blood gas partial pressure of oxygen less than 60 mmHg while the subject is breathing room air (or FiO2 equivalent), OR a pulse oximetry oxygen saturation less than 90% while the subject is breathing room air (or FiO2 equivalent), OR worsening PaO2/FiO2.
2. Chest radiograph (or CT scan) obtained within the 24 hours prior to the first dose of study drug shows the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia.
3. Have the following clinical criteria within the 24 hours prior to the first dose of study drug: - Purulent tracheal secretions - And at least 1 of the following: - Documented fever (body temperature ⩾38° C) - Hypothermia (body temperature ⩽35° C) - WBC count ⩾10,000 cells/mm^3 - WBC count ⩽4,500 cells/mm^3 - ⩾15% immature neutrophils.
4. Have a baseline lower respiratory tract specimen obtained for Gram stain and quantitative culture within 36 hours prior to the first dose of study drug. This specimen can be obtained by a BAL, mini-BAL, PBS, or an ETA; 5. Willing and able to comply with all study procedure and restrictions.

Exclusion criteria
1. Any of the following diagnoses or conditions that interfere with the assessment or interpretation of outcome: - Atypical, viral, or fungal (including Pneumocystis jiroveci), known or suspected community-acquired bacterial pneumonia - Tracheobronchitis (without documented pneumonia), chemical pneumonitis, or postobstructive pneumonia - Active primary or metastatic lung cancer - Pleural effusions (or empyema) requiring therapeutic drainage, lung abscess, or bronchiectasis - Cystic fibrosis, acute exacerbation of chronic bronchitis, or active pulmonary tuberculosis - NYHA Stage IV Congestive Heart Failure or Cirrhotic Liver Disease - Full thickness burns (greater than 15% of total body surface area) - Severe confounding respiratory condition due to penetrating chest trauma (ie, chest trauma with paradoxical respiration)
2. Has a documented history of any moderate or severe hypersensitivity (or allergic) reaction to any β-lactam antibacterial;
3. Received systemic or inhaled antibiotic therapy effective against gram-negative pathogens that cause VNP, for >24 hours in the 72 hours prior to the first dose of study drug. Exceptions: - Persistent/worsening signs and/or symptoms of VNP are still present despite ≥48 hours of antibiotic therapy for the treatment of the current VNP, and (a) a LRT culture obtained while the subject is on the failing antibiotic therapy for this episode of VNP showed growth of a gram-negative pathogen and (b) the isolated pathogen is not known to be resistant to one of the study drugs. - Signs and/or symptoms of VNP develop after receiving ≥48 hours of antibacterial therapy for treatment of an infection other than the current VNP. NOTE: Subjects on ≥48 hours of antibiotics for infection prophylaxis (rather than treatment of a documented or suspected infection) are not eligible for enrollment under this exception. - Treatment with a non-absorbed antibiotic used for gut decontamination (*e.g.*, low dose erythromycin) or to eradicate *C. difficile*.
4. Baseline Gram stain shows the presence of only gram-positive bacteria. Exception: If the subject has a lower respiratory tract culture growing a gram-negative pathogen obtained within 72 hours prior to the first dose of study drug, these results will supersede baseline Gram stain results of only gram-positive bacteria.
5. Active immunosuppression;
6. Receipt of >24 hours of a carbapenem within 7 days prior to the first dose of study drug;
7. Growth of a meropenem-resistant or ceftolozane/tazobactam-resistant, gram-negative pathogen from a respiratory or blood culture, within 15 days prior to the first dose of study drug;
8. Development of end-stage renal disease defined as a CrCL <15 mL/min, OR requirement for peritoneal or hemo-dialysis or hemofiltration, OR a urine output <20 mL/hour over a 24-hour period;
9. The presence of any of the following: • ALT or AST >3 × ULN • Total bilirubin >2 × ULN • Alkaline phosphatase >4 × ULN.
10. Hematocrit <21% or hemoglobin <7 gm/dL;
11. Neutropenia with absolute neutrophil count <500/mm^3;
12. Platelet count <50,000/mm^3 ;
13. Expected survival <72 hours;

Treatments

The study treatments are outlined in the table below. Treatment duration was 8-14 days.

Table 20. Study drug treatment

	Investigational Product	**Active Comparator**
Product Name	Ceftolozane/tazobactam	Meropenem
Dosage Form	IV infusion over 60 (±10) minutes	IV infusion over 60 (±10) minutes
Unit Dose	3000 mg (2000 mg ceftolozane and 1000 mg tazobactam) q8h	1000 mg q8h
Route of Administration	Intravenous	Intravenous

Dose adjustment criteria for the study drugs

Dose adjustment for TOL/TAZ and meropenem was made for subjects with moderate or severe renal insufficiency. Please refer to the tables below.

Dose adjustments for renal insufficiency were performed by the un-blinded pharmacist following notification from the PI, including the subject's CrCL value.

Table 21. Recommended intravenous dose regimens for ceftolozane / tazobactam according to renal function

Renal Function	Dose	Infusion Frequency
CL_{CR} >50 mL/min	3000 mg IV	q8(±2)h
CL_{CR} 30 - 50 mL/min	1500 mg IV	q8(±2)h
CL_{CR} 26 - 29 mL/min	750 mg IV	q8(±2)h
CL_{CR} 15 - 25 mL/min	750 mg IV	q8(±2)h
CL_{CR} <15 mL/min	Discontinue study drug	

CL_{CR}=creatinine clearance; IV=intravenous;q8h=every 8 hours

Table 22. Recommended intravenous dose regimens for meropenem according to renal function

Renal Function	Dose	Infusion Frequency
CL_{CR} >50 mL/min	1000 mg IV	q8(±2)h
CL_{CR} 30 - 50 mL/min	1000 mg IV	q12(±2)h
CL_{CR} 26 - 29 mL/min	1000 mg IV	q12(±2)h
CL_{CR} 15 - 25 mL/min	500 mg IV	q12(±2)h
CL_{CR} <15 mL/min	Discontinue study drug	

CLCR=creatinine clearance; IV=intravenous;q12h=every 12 hours

The total number of infusions may increase if a dose adjustment is required based on renal function due to the addition of dummy infusions.

In cases where dosing every 8 hours is used for both ceftolozane/tazobactam and meropenem, the use of a dummy infusion is not required.

Conversely, to maintain blinding of the dosing regimens when meropenem is required to be dosed every 12 hours, the subjects' treatment schedule must be adjusted to 4 infusions per day. These 4 infusions are to accommodate the 3 every 8 hours infusions for ceftolozane/tazobactam and the 2 every 12 hours infusions for meropenem (the first infusion for active drug and dummy infusions should be administered simultaneously at time zero, therefore, leading to a total of 4 total infusions per day).

Subjects who develop a CrCL <15 mL/minute or who were placed on dialysis or hemofiltration were withdrawn from study drug because dose recommendations of ceftolozane/tazobactam for such subjects have not yet been determined.

Non-study antibiotic use

In the 72 hours preceding the first dose of study drug for treatment of the current VNP, subjects may not receive more than 24 hours (i.e. >1 dose of a once daily antibiotic, >2 doses of a twice daily antibiotic, etc.) of antibiotic therapy active against gram-negative pathogens known to cause VNP. Exceptions to this prior antibiotic rule are noted under Exclusion criteria #3.

After randomization, non-study antibiotics for the treatment of VNP are not permitted except in the following circumstances:

- Allowed empiric adjunctive therapy (as described below) administered at baseline for potential resistant pathogens, OR
- For treatment of documented clinical and/or microbiologic failure.

If non-study antibiotics for the treatment of VNP are required after randomization, the subject must be discontinued from study treatment.

Empiric therapy at baseline

Empiric gram-positive adjunctive therapy

Subjects were required to receive empiric gram-positive adjunctive therapy (linezolid) at baseline. Alternatives to linezolid could be permitted (if these were standard of care or the patient did not tolerate linezolid) but only after discussion and prior approval from the Medical Monitor. At sites with a low incidence of MRSA pneumonia (e.g., MRSA prevalence <5% as determined by the local antibiogram), the investigator could request, from the Medical Monitor, substitution of linezolid with a semisynthetic penicillin. If *S. aureus* (MRSA or MSSA) was not isolated from baseline LRT culture, the investigator was recommended to discontinue linezolid and complete treatment with assigned study drug alone. Patients whose baseline LRT culture grew both a gram-negative pathogen and *S. aureus* (MRSA or MSSA) should complete treatment with study drug and with linezolid.

Empiric gram-negative adjunctive therapy

Subjects were permitted to receive adjunctive gram-negative (aminoglycoside-amikacin) therapy for ≤72 hours started at baseline (at sites with >15% carbapenem resistant *P. aeruginosa*) pending baseline culture results. Aminoglycosides other than amikacin may be permitted if standard of care at the site, but only after discussion and prior approval from the Medical Monitor. Upon receipt of the baseline LRT microbiology results (including study drug susceptibility), if the isolate(s) were susceptible to both study drugs, empiric amikacin had to be discontinued immediately and study drug alone continued for the remainder of the treatment duration. Concomitant therapy with study drug and amikacin (or other approved gram-negative adjunctive therapy) was not permitted after day 3.

From the protocol:

Upon availability of the baseline LRT culture and pathogen susceptibility results:

Management of study drug and empiric gram-negative adjunctive therapy:

- If all gram-negative isolates are resistant to both study drugs: study drug must be discontinued, appropriate non-study antibiotics started, and the subject followed for safety through the LFU visit.
- If gram-negative isolate(s) with varying susceptibility results is/are present: the Investigator is strongly encouraged to base decisions regarding continuation or discontinuation of study therapy on the clinical presentation of the patient and the totality of the available clinical and laboratory data, including the baseline LRT culture susceptibility testing results. Empiric gram-negative adjunctive therapy, if started at baseline, must be discontinued after 72 hours.
- If no growth of any gram-negative organism: study drug should be continued based on the discretion of the Investigator and guided by the subject's clinical response. Empiric gram-negative adjunctive therapy, if started at baseline, must be discontinued after 72 hours.

Management of empiric gram-positive adjunctive therapy:

- If *S. aureus* (MSSA or MRSA) is present [with or without a gram-negative pathogen]: linezolid should be continued for a minimum of 8 days. If MSSA is the only LRT pathogen isolated, the Investigator may switch the gram-positive adjunctive therapy to an anti-staphylococcal semisynthetic penicillin (with gram-positive coverage only) and complete treatment with the semisynthetic penicillin.
- If *S. aureus* (MRSA or MSSA) does not grow: empiric gram-positive coverage should be discontinued, unless in the opinion of the Investigator, continuation provides expected benefit for the patient. If gram-positive adjunctive therapy is discontinued and then a subsequent, post-baseline LRT culture shows presence of S. aureus, the appropriate gram-positive adjunctive therapy may be reinitiated (i.e., linezolid if MRSA or anti-staphylococcal semisynthetic penicillin for MSSA).

Objectives

Primary objective

To demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in adult subjects with ventilator-associated nosocomial pneumonia based on the difference in clinical response rates in the Intent-to-treat (ITT) population at the TOC visit (7 to 14 days after the EOT visit), using a non-inferiority margin of 12.5%.

Key secondary objective

- To compare the Day 28 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms in the ITT population.

For other secondary objectives, please see under “Secondary efficacy endpoints” below.

Outcomes/endpoints

Primary endpoint

Clinical response at the TOC visit in the ITT population

Key secondary endpoint

- Day 28 all-cause mortality in the ITT population

Secondary efficacy endpoints

- Clinical response at the TOC visit in the CE population
- Clinical response for subjects at the TOC visit in the subset of subjects who had *P. aeruginosa* isolated from the baseline LRT culture in the mITT population
- Clinical response for subjects at the TOC visit in the subset of subjects who had Enterobacteriaceae isolated from the baseline LRT culture in the mITT population
- Per-subject microbiological response at TOC in the ME population
- Per-pathogen microbiological response for *P. aeruginosa* at TOC in the ME population
- Per-pathogen microbiological response for Enterobacteriaceae at TOC in the ME population
- Per-pathogen microbiological response at TOC in the ME population
- Day 28 all-cause mortality in the mITT population
- Day 14 all-cause mortality in the ITT population
- Clinical response at EOT in the ITT and CE populations
- Clinical response at the LFU visit in the CE population
- Per-subject microbiological response at EOT in ME population

- Per-pathogen microbiological response at EOT in the ME population
- Per-pathogen clinical response at TOC by baseline MIC in the mITT and ME populations

Definition of clinical outcomes at TOC, EOT and LFU visit

Clinical response at the TOC visit will be classified as cure, failure, or indeterminate. A favourable clinical response is "clinical cure."

Table 23. Clinical Response Categories at the TOC and EOT visit

Outcome	Definition
Cure	• Complete resolution of all or most of the clinical signs and symptoms of VNP which were present at baseline, AND • No new signs, symptoms or complications attributable to VNP, AND • No additional antibiotic therapy administered for VNP*, except for the approved adjunctive therapy, AND • Patient is alive *Subjects receiving potentially effective concomitant antibiotic therapy for an indication other than VNP may still be considered a clinical cure provided they meet all other Cure criteria.
Failure	• Progression, relapse, or recurrence of new symptoms or complications attributable to VNP, OR • Lack of resolution (persistence), insufficient improvement in signs and symptoms of VNP which were present at baseline, study drug discontinuation due to resistant LRT pathogens, or need for alternative or prolonged antibiotic therapy for treatment of VNP, OR • Patient died of VNP
Indeterminate	• Subject **prematurely discontinued** study drug due to No Growth or only *S. aureus* isolated from the baseline LRT culture, OR • Study data are not available for the evaluation of efficacy for any reason including: o Lost to follow-up o Withdrawal of consent o Subject died from cause other than VNP o Randomized not treated

Clinical response at the LFU visit will be classified as sustained cure, relapse, or indeterminate only in patients deemed a clinical cure at the TOC visit. A favourable clinical response is "sustained clinical cure."

Table 24. Clinical Response Categories at the LFU visit

Outcome	Definition
Sustained Cure	No recurrence of signs or symptoms of pneumonia and, in addition, did not receive any antibiotics for the treatment of VNP* since the TOC visit. *Subjects receiving potentially effective concomitant antibiotic therapy for an indication other than VNP may still be considered a clinical cure provided they meet all other Cure criteria.
Relapse	Recurrence of signs or symptoms of pneumonia or new radiologic evidence of pneumonia or received antibiotic after the TOC for treatment of pneumonia.
Indeterminate	• Subject **prematurely discontinued** study drug due to No Growth or only *S. aureus* isolated from the baseline LRT culture, OR • Study data are not available for the evaluation of efficacy for any reason including: – Lost to follow-up – Withdrawal of consent – Subject died from cause other than VNP – Randomized not treated

Definition of microbiological outcome at TOC and EOT visit

Table 25. Per-Pathogen Microbiologic Outcome Categories at the EOT and TOC visits

Outcome	Definition
Eradication	Absence defined as a ≥1- log reduction in bacterial burden of the original baseline LRT pathogen AND a per pathogen count of $\leq 10^4$ CFU/mL for ETA or sputum specimens, $\leq 10^3$ CFU/mL for a BAL specimen, and $\leq 10^2$ CFU/mL for a PBS specimen) from a follow-up LRT culture.
Presumed eradication	Absence of material to culture (eg, inability to obtain a culture in an extubated subject) in a subject deemed a clinical cure.
Persistence	Continued presence of the original causative baseline pathogen(s) from a LRT culture obtained at or after EOT. Presence is defined as <1-log reduction in bacterial burden of the baseline pathogen OR $>10^4$ CFU/mL for ETA or sputum specimens, $>10^3$ CFU/mL for a BAL specimen, and $>10^2$ CFU/mL for a PBS specimen OR baseline organism is still present, but no quantitative culture count was determined.
Presumed persistence	Absence of material to culture in a subject deemed a clinical failure.
Indeterminate	Absence of respiratory material to culture at the EOT or TOC in a subject with Indeterminate clinical response
Recurrence (at the TOC visit)[a]	Isolation of the original causative bacterial baseline pathogen(s) at the appropriate diagnostic threshold (ie, $\geq 10^5$ CFU/mL for ETA or sputum specimens, $\geq 10^4$ CFU/mL for a BAL specimen, and $\geq 10^3$ CFU/mL for a PBS specimen) from a LRT culture in a subject with documented eradication at the EOT visit

[a]Relatedness will be determined by Genus, species and antibiogram at the discretion of the Sponsor, the pathogen from the TOC visit will be further tested by pulsed field gel electrophoresis to confirm relatedness to the baseline pathogen.

Table 26. Per-Patient Microbiologic Outcome Categories at the EOT and TOC visits

Outcome	Definition
Microbiologic cure or presumed cure	All baseline pathogens are deemed eradicated/presumed eradicated or absence of respiratory material to culture at the EOT or TOC in a subject deemed a clinical cure.
Microbiologic failure or presumed failure	Any baseline pathogen is deemed persistent/presumed persistent or absence of material to culture in a subject deemed a clinical failure.
Indeterminate	Absence of respiratory material to culture at the EOT or TOC in a subject with Indeterminate clinical response

Definition of emergent infections

Qualifying pathogens other than the causative baseline pathogen isolated after baseline assessment will be assessed as a superinfection or new infection. A qualifying emergent pathogen is defined as one meeting the threshold of $\geq 10^5$ CFU/mL (for an ETA specimen), $\geq 10^4$ CFU/mL (for a BAL or mini-BAL specimen), or $\geq 10^3$ CFU/mL (for a specimen obtained by PBS).

Table 27. New pathogens

Outcome	Definition
Superinfection	Isolation of a pathogen, other than the causative baseline pathogen, from a post baseline LRT specimen obtained while the subject is still on study therapy.
New infection	Isolation of a pathogen other than the causative baseline pathogen from an LRT culture obtained after completion of study therapy.

Analysis populations

ITT Population

The ITT population consisted of all randomized subjects with documented informed consent, regardless of whether or not they received study drug. Subjects in the ITT population were categorized based on the treatment arm to which they were randomized. No subjects were excluded from the ITT population due to important deviations or premature un-blinding of study treatment.

mITT Population

The mITT population was a subset of the ITT population that included any subject who received any amount of study drug and had at least 1 bacterial respiratory pathogen isolated from the baseline LRT culture that was susceptible to at least 1 of the study drugs. Subjects with a non-streptococcal gram-positive pathogen as their only baseline LRT pathogen were excluded from the mITT population. No subjects were excluded from the mITT population due to important deviations or premature un-blinding of study treatment.

CE Population

The CE population was a subset of the ITT population that included any subject who received study drug, adhered to the study protocol through the TOC visit, and had an evaluable clinical outcome (either Cure or Failure) at the TOC visit (or were classified as a clinical failure prior to the TOC visit).

ME Population

The ME population was a subset of the mITT population that included any subject who adhered to the study protocol through the TOC visit, had an evaluable clinical outcome (Cure or Failure) at the TOC visit (or were classified as clinical failure prior to the TOC visit), and had at least 1 bacterial respiratory pathogen (at the appropriate CFU/mL threshold) isolated from the baseline LRT culture. To be eligible for the ME population, the following quantitative bacterial counts were required: $\geq 10^5$ CFU/mL for ETA, $\geq 10^4$ CFU/mL for BAL/mini-BAL, and $\geq 10^3$ CFU/mL for PBS.

Safety Analysis Population

All safety analyses were based on a subset of the ITT population (the Safety Population), who received any amount (i.e., full or partial dose) of study drug. All subjects received their randomly assigned treatments, and no subjects with important deviations were excluded from the safety population.

Sample size

This population comprised totally 726 subjects (i.e., 362 in the ceftolozane/tazobactam arm vs. 364 in the meropenem arm). The study was designed to have at least 85.3% power to meet non-inferiority for the primary endpoint, assuming a cure rate of 58.4% in both arms. It was initially powered at 88%, but power decreased due to the planned futility look by DSMB when approximately 30% of patients had been enrolled.

Randomisation

Randomisation was stratified by diagnosis (HABP or VABP) and by age (≥65 or <65 years) to balance distribution of 726 subjects between the 2 double-blind treatment arms. Three pre-specified sensitivity analyses for the primary efficacy endpoints were conducted to confirm the overall robustness of the study results: 1) unadjusted for the stratification factors, 2) based on randomized stratification from IRT to evaluate the impact from mis-stratifications, and 3) stratified and un-stratified approaches based on a subset of subjects that were not forced randomized. Additional analyses were conducted in the mITT, CE, and ME populations across applicable time points, including Day 14, EOT, TOC (7 to 14 days after EOT), and LFU (28 to 35 days after EOT) for each primary efficacy endpoint. Subgroup analyses based on various demographic and baseline disease characteristics were also conducted for the primary efficacy endpoints.

Blinding (masking)

This is a double-blinded study. The subject, site personnel (with the exception of the un-blinded pharmacist), Sponsor personnel (with the exception of the un-blinded drug supply and quality assurance teams, as appropriate) and Sponsor designees (with the exception of the un-blinded monitoring team) will have no knowledge of treatment assignment. A treatment assignment was only un-blinded in a situation of urgent medical necessity when the identity of the study medication needed to be known in order to select appropriate continuing therapy for the disease under study or to manage an AE.

To maintain blinding of the study staff, an independent statistical reporting group will provide data to the DSMB.

The recommended dose of meropenem in this indication is 1000 mg q8h administered over 30 minutes. To facilitate blinding of the study, meropenem was administered as a one-hour infusion in this study to match the duration of infusion of ceftolozane/tazobactam. The efficacy of meropenem was not affected by administration in this way, as it is a β-lactam antibiotic whose efficacy depends on time the drug

concentration is greater than minimum-inhibitory concentration (MIC), see also Assessor's comment under "Treatments".

In the protocol, it is stated that if gram-negative isolate(s) with varying susceptibility results were present, the Investigator was strongly encouraged to base decisions regarding continuation or discontinuation of study therapy on the clinical presentation of the patient and the totality of the available clinical and laboratory data, including the baseline LRT culture susceptibility testing results.

The handling of patients with resistant pathogens was therefore guided by clinical outcome in order to decide whether to continue or discontinue study therapy.

Statistical methods

Primary and key secondary objectives

The primary and key secondary efficacy analyses were conducted in the ITT population, defined as all randomized subjects, regardless of whether or not they received study drug. Subjects in the ITT population were categorized based on the treatment arm to which they were randomized.

The primary objective was to demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in adult subjects with VNP based on the difference in clinical response rates in the ITT population at the TOC visit (7 to 14 days after the EOT visit), using a non-inferiority margin of 12.5%.

The secondary key objective was to compare the Day 28 all-cause mortality rates of subjects in the ceftolozane/tazobactam versus meropenem arms in the ITT population using a non-inferiority margin of 12.5%.

For both primary and key secondary objectives, a 2-sided 97.5% CI was constructed instead of 95% CIs. A sequential testing approach was used in order to maintain a 1-sided 0.0125 overall type I error rate across the primary and key secondary efficacy endpoints in the ITT population.

For categorical data, descriptive statistics (frequency and percentage) were provided for each category; 95% CIs were constructed around the percentage, when appropriate.

Changes to the planned analysis

There were five versions of the statistical analysis plan (SAP). All revisions to the final SAP (version 2.0) occurred before database lock and un-blinding.

The following additional changes to the planned analyses were performed *post-hoc* after study un-blinding:

- To evaluate the impact of miss-stratification within each stratum for primary efficacy endpoints, the following sensitivity analyses were performed:
    - Clinical response at TOC visit by randomized stratum per EMA analysis (ITT Population)
- To evaluate the magnitude of treatment difference in TEAE rates in the safety population, treatment differences and associated 95% CIs for the key TEAE summary categories were provided. The magnitude of treatment differences in serious TEAE rates and associated 95% CIs for various serious TEAEs (≥1% of subjects in either treatment group) were also provided.
- To evaluate the proportions of subjects who received concomitant non-study antibiotic medications in the ITT population during the study treatment period, the non-study concomitant antibiotic medications between first and last dose of study drug by ATC class and preferred term were summarized.
- To evaluate the enrollment status of ICU patients on study, the number of subjects randomized while in the ICU was summarized.
- To evaluate the magnitude of treatment difference in clinical response on a pathogen level, per-pathogen clinical cure rates with associated unstratified 95% CIs were summarized for the mITT and ME populations.

Handling of missing data

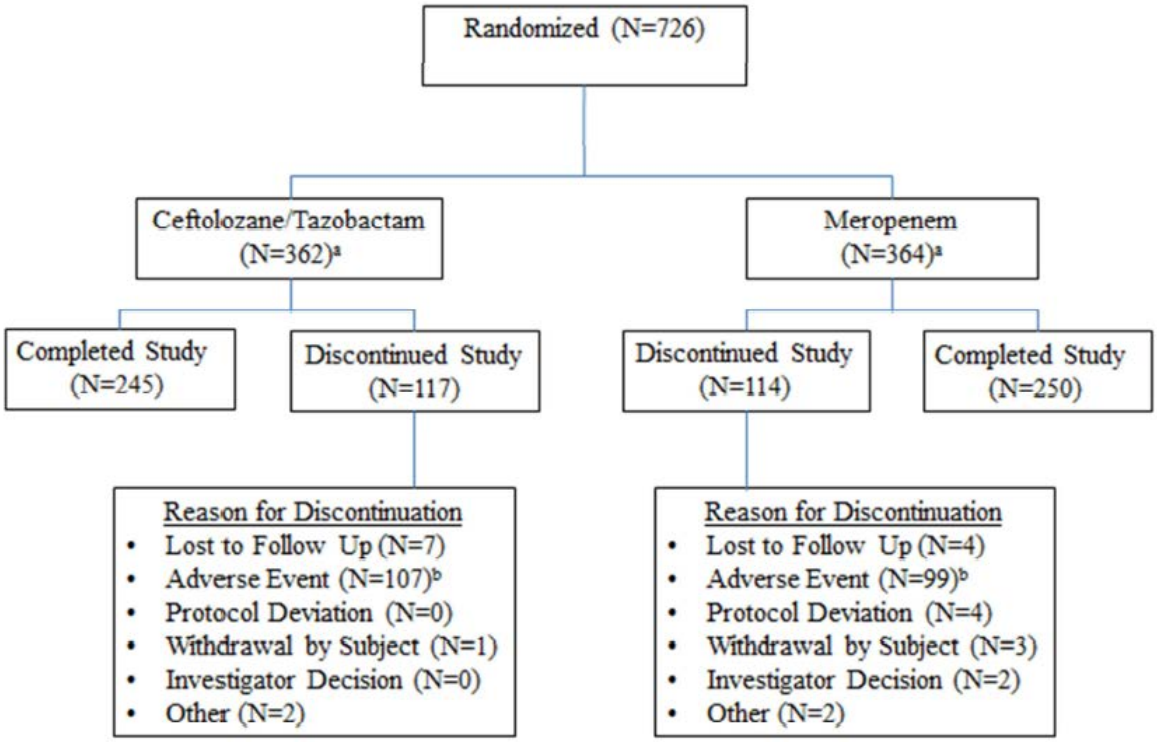
For all-cause mortality at Day 14 and Day 28, subjects with missing or unknown mortality outcomes were categorized as deceased. For time to all-cause mortality from randomization through LFU visit, subjects with a missing or unknown all-cause mortality status were analyzed using the following two approaches: 1) assumed missingness as death at the time of last study contact, and 2) assumed missingness as alive and censored at the time of last study contact.

For clinical response, missing data were handled using a TFA for the ITT and mITT populations and with a DAO approach for the CE and ME populations. In the TFA, subjects with a missing (including indeterminate) efficacy endpoint were categorized as treatment failures. In the DAO approach, all subjects with missing outcomes including indeterminate were excluded from the analysis.

Results

Participant flow

The figure below displays the distribution of all randomised subjects.



[a] 1 subject in the ceftolozane/tazobactam group and 5 subjects in the meropenem group were randomized but did not receive study drug.
[b] Reason for discontinuation due to adverse event includes death.

Figure 14. Participant flow

Subject disposition

Table 28. Study disposition (ITT population)

	Ceftolozane/Tazobactam (N=362)	Meropenem (N=364)	Total (N=726)
Number of Subjects Randomized but Did Not Receive Study Drug [1]	1 (0.3)	5 (1.4)	6 (0.8)
Number of Subjects Completing Study Drug [1]	263 (72.7)	271 (74.5)	534 (73.6)
Number of Subjects Prematurely Discontinuing Study Drug, N1 [1]	98 (27.1)	88 (24.2)	186 (25.6)
Reasons for Premature Discontinuation of Study Drug [2]			
All baseline LRT pathogens resistant to both study drugs	13 (13.3)	11 (12.5)	24 (12.9)
Gram-negative adjunctive therapy continued/started beyond 72 h or study treatment regimen changed	4 (4.1)	2 (2.3)	6 (3.2)
Investigator decision based on no growth or only S. aureus isolated on baseline LRT culture	4 (4.1)	4 (4.5)	8 (4.3)
Development of ESRD [CLCR <15 mL/min], oliguria [<20 mL/h urine output over 24 hours], or requirement for dialysis or hemofiltration	3 (3.1)	0	3 (1.6)
Adverse event	36 (36.7)	42 (47.7)	78 (41.9)
Suspected or confirmed pregnancy or nursing	0	0	0
Insufficient therapeutic effect	23 (23.5)	15 (17.0)	38 (20.4)
Lost to follow-up	1 (1.0)	0	1 (0.5)
Withdrawal by subject	2 (2.0)	1 (1.1)	3 (1.6)
Investigator decision	8 (8.2)	7 (8.0)	15 (8.1)
Protocol deviation	2 (2.0)	1 (1.1)	3 (1.6)
Other	2 (2.0)	5 (5.7)	7 (3.8)
Number of Subjects Completing Study [1]	245 (67.7)	250 (68.7)	495 (68.2)
Number of Subjects Prematurely Withdrawing from Study, N2 [1]	117 (32.3)	114 (31.3)	231 (31.8)
Reasons for Premature Withdrawal from Study [3]			
Lost to Follow Up	7 (6.0)	4 (3.5)	11 (4.8)
Adverse Event	107 (91.5)	99 (86.8)	206 (89.2)
Protocol Deviation	0	4 (3.5)	4 (1.7)
Withdrawal by Subject, Decline Follow up	1 (0.9)	3 (2.6)	4 (1.7)
Investigator Decision	0	2 (1.8)	2 (0.9)
Other	2 (1.7)	2 (1.8)	4 (1.7)

Notes: n=Number of subjects in specific category. N=Number of subjects in ITT population. N1=Number of subjects prematurely discontinuing study drug in ITT population. N2=Number of subjects prematurely withdrawing from study in ITT population.
ESRD: end stage renal disease. Premature discontinuation or withdrawal due to adverse event includes death.
[1] Percents are calculated as 100 x (n/N).
[2] Percents are calculated as 100 x (n/N1).
[3] Percents are calculated as 100 x (n/N2).

Source: [P008MK7625A: analysis-adsl]

Recruitment

A total of 263 sites were opened for enrollment, of which 119 randomized at least 1 subject (whereof around 40 sites appear to have included only 1 patient). The majority of subjects was recruited from sites in Europe (in total 36.3% whereof 21.8% from the eastern part and 14.5% from the western part), Russia (in total 24.2%), Ukraine (in total 9.6%) and Georgia (in total 8.0%). Contributions from other continents were distributed as follows: Latin America (5.8%), North America (4.3%), Asia/Pacific (7.9%) and Rest of the World (3.9%).

A total of 726 subjects were randomized: 362 subjects to ceftolozane/tazobactam and 364 subjects to meropenem.

The first subject's first visit was 16 January 2015. The last subject's last visit was 06 June 2018. The date of the study report was 17 October 2018.

Conduct of the study

There were 10 protocol amendments to the original protocol dated 11 May 2012 (6 global amendments and 4 country-specific amendments, resulting in 7 versions of the protocol). The last global protocol was dated 27 Aug 2017.

The table below summarises the key changes instituted with each of the amendments.

Table 29. Summary of key changes to the conduct of the study implemented by protocol amendments

Amendment Number: MK-7625A-008-01 (Protocol Version 2.0)	**Date:** 06-FEB-2013	**Number of Subjects Enrolled in Protocol Version:** 0
Rationale and Key Changes	• Acinetobacter was removed as a target pathogen given new in vitro data demonstrating ceftolozane/tazobactam has poor antimicrobial activity against Acinetobacter strains. • Criteria for CL_{CR} was adjusted from <30 mL/min to <15 mL/min based on new clinical data (CXA-REN-11-01). Key changes to the protocol included updates to the dosing regimen for subjects with renal impairment, the exclusion criteria, and the criteria for withdrawal. • Additional secondary and exploratory objectives were added with corresponding endpoints. • Statistical methods were revised to include: the final analysis CI for endpoints reviewed at the interim analysis and a detailed description of the hierarchical gatekeeping procedure to preserve overall type I error. • Program level definitions for clinical response outcomes for EOT, TOC and LFU milestones were further clarified and incorporated.	
Amendment Number: MK-7625A-008-02 (Protocol Version 3.0)	**Date:** 27-NOV-2013	**Number of Subjects Enrolled in Protocol Version:** 0
Rationale and Key Changes	• The comparator, imipenem, was revised to meropenem, widely used for the treatment of a variety of serious bacterial infections, including NP. The recommended dose in this indication, which was used in this study, was 1000 mg every 8 hours. To facilitate blinding, meropenem was administered as a 1-hour infusion in this study to match the duration of infusion of ceftolozane/tazobactam. A summary of risks and benefits for meropenem was added. • The FDA primary objective was revised from the mITT to ITT population. Statistical comparisons were updated. cITT and clinical mITT were considered subsets of the ITT. CE was considered a subset of the cITT, and ME a subset of the mITT. The primary objective for all other regulatory jurisdictions was updated to the cITT, and the non-inferiority margin was reduced from 15% to 12.5% for other regulatory jurisdictions. • Randomization stratification was updated to accommodate a reduced sample size with the addition of ventilated HABP subjects to the study population. • A window for the duration of study drug administration was added, along with dose adjustment criteria for meropenem. • PK sampling was added to the study assessments. • Several criteria were added, clarified, modified, or removed: criteria for contraception were clarified, diagnostic criteria for subjects with ventilated HABP were added, standalone criteria for PaO_2/FiO_2 ratio were removed, exclusion criteria for acute respiratory distress syndrome were removed, allowance of prior non-study antibiotic use for subjects who failed prior therapy was clarified, Gram-stain criteria were added, prohibited duration for prior receipt of meropenem was updated, hematocrit/hemoglobin criteria to exclude subjects based on critical care publications that lowered transfusion recommendation thresholds was modified, allowed window of baseline lower respiratory specimens for quantitative culture and procalcitonin samples was added, criterion to discontinue study drug if the LRT culture came back negative was removed, language for expected events was added, clinical and laboratory criteria for the definition of cure for the clinical outcomes at the EOT and LFU visits were updated, and language specifying that a subject who received concomitant nonstudy antibiotic for infection other than pneumonia should be assigned an indeterminate outcome was added. • Definitions of populations for analysis were updated.	

Amendment Number: MK-7625A-008-03 (Protocol Version 4.0)	**Date:** 14-MAR-2014	**Number of Subjects Enrolled in Protocol Version:** 9

Rationale and Key Changes

- In order to avoid selection bias in the PK/PD analyses, PK sample collection was changed from Day 3 to Day 4 to ensure that all subjects received at least 72 hours of therapy and reached steady state concentrations.
- Stratification factor APACHE II score was changed to age in order to better facilitate equal distribution of severity.
- The requirement for CL_{CR} was updated from <50 to ≤50 to be consistent with the dosing recommendation for ceftolozane/tazobactam in renal impairment.
- Inclusion criteria describing the clinical criteria requirements were updated to be more consistent with FDA Guidance on Developing Drugs for treatment of HABP/VABP.
- Language was added to help clarify the following: the required for prior antibiotic therapy, use of alternatives to linezolid if it was standard of care at that site after prior approval from the medical monitor, use of imipenem or doripenem data as a surrogate for meropenem susceptibility at sites that did not include meropenem on the antiobiogram, use of alternatives to amikacin if standard of care at that site and prior approval from the medical monitor, and disclosures detailing the potential personnel that may become unblinded during the trial to assure quality of investigational drug product.
- Statistical methods were revised as follows: confidence intervals for analysis of dichotomous endpoints were changed from 2-sided of 95.034% to 95.002%, multiplicity analyses were only to be performed for the newly defined key secondary endpoints, all populations specific to EOT, TOC, and LFU were removed and a single CE population and a single ME population was used after removing the cITT population, study endpoints were reassigned and reprioritized based on the planned statistical analysis with consideration to the hierarchy of endpoints and multiplicity analyses and objectives corresponding to the updates in endpoints were updated, the primary population for EMA was changed from cITT to CE population, and ITT replaced the cITT analysis and was considered a key secondary endpoint, and a Data Monitoring Committee was to perform an interim review after 30% (~218 subjects) of enrollment was completed in order to evaluate potential safety signals.

Amendment Number: MK-7625A-008-04 (Protocol Version 5.0)	**Date:** 22-OCT-2014	**Number of Subjects Enrolled in Protocol Version:** 199

Rationale and Key Changes

- The minimum proportion of subjects with VABP as the baseline diagnosis was increased to 50% (from 30%) to align with the updated FDA draft guidance on drug development for treatment of HABP/VABP.
- Clinical response at the TOC visit in the mITT population was added as a key secondary endpoint in order to evaluate clinical response in the overall population prior to constructing the subgroup analysis in the subset with *P. aeruginosa*.
- Additional information regarding the co-administration of meropenem and valproic acid/sodium valproate/valpromide was added, consistent with the information provided in the product information and summary of product characteristics for meropenem.
- Information was provided regarding the selection of the 1 hour infusion duration.
- Additional method for collection of LRT specimens was permitted for post-baseline specimens only in order to perform cultures if a subject was no longer on a ventilator.
- Additional detail was added to Exclusion Criterion #3 (prior antibiotics) to further clarify the allowance for prior antibiotics administered for indication other than VNP.
- Alternative gram-positive adjunctive therapy was permitted in subjects who were contraindicated to linezolid. Alternative gram-negative adjunctive therapy was permitted in subjects who were contraindicated to amikacin.

	• Clarification was provided for making study drug treatment decisions, including adjunctive therapy, following the results of the baseline LRT culture. • Based on the results of the baseline respiratory culture, the investigator had discretion for continuing or discontinuing study drug and the applicable adjunctive therapy based on the subject's clinical presentation. • If unblinding occurred and the baseline LRT isolates were susceptible to the study drug received, open-label therapy was permitted regardless of study drug received. • Language was added regarding the role of unblinded sponsor (or designee) and processes in place to ensure unblinding information was not divulged. • Clarified that clinical failures, including the following, were NOT AEs: progression, relapse, or recurrence of new symptoms or complications attributable to VNP, as well as lack of resolution (persistence) or insufficient improvement in signs and symptoms of VNP which were present at baseline that required new or prolonged antibiotic therapy. • The DSMB charter was amended to include only a futility look during the interim analysis. Therefore, it was no longer necessary to adjust the type I error rate in this study.
Amendment Number: MK-7625A-008-05 (Protocol Version 6.0) MK-7625A-008-06 (Protocol Version 6.0 – SS1 Japan) MK-7625A-008-07 (Protocol Version 6.0 – SS2 Czech Republic)	**Date:** 15-MAR-2016 15-MAR-2016 11-JUL-2016
Rationale and Key Changes	• Removed APACHE II score as an inclusion criterion since it was no longer required as an entry criterion in regulatory guidance documents. • Changed treatment duration of study drug from a fixed duration of 8 days (with extension to 14 days only when Pseudomonas is isolated from baseline culture) to a treatment duration range of 8 to 14 days. • If a prior LRT culture taken within 72 hours prior to the first dose of study drug produced a gram-negative pathogen, this confirmed a case of gram-negative bacterial pneumonia and took precedence over the results of a baseline Gram stain that showed only gram-positive bacteria. • Exclusion Criterion #6 was modified to allow for the entry of subjects who had ≤24 hours of a carbapenem within the 7 days prior to the first dose of study drug. Previously, any carbapenem use within the prior 15 days was excluded. • Excluded medications were added that were contraindicated for the use of meropenem or linezolid. • Guidance of patient management was modified following receipt of the baseline LRT susceptibility results. The requirement to discontinue a subject from study therapy if all baseline LRT gram-negative pathogens were resistant to both study drugs was maintained. The ability to unblind subjects and keep them on unblinded study drug based on presence of a resistant pathogen was removed. • Replaced text referring specifically to the Etest device with language generally indicating that gradient test strips as well as other standard/validated antibiotic susceptibility testing methods may be used for testing susceptibility to ceftolozane/tazobactam and meropenem.

Amendment Number: MK-7625A-008-08 (Protocol Version 7.0)	**Date:** 25-AUG-2017	**Number of Subjects Enrolled in Protocol Version:** 85
MK-7625A-008-09 (Protocol Version 7.0 – SS1 Japan)	19-SEP-2017	
Rationale and Key Changes	• The analysis population for the primary EMA endpoint (clinical response at TOC) was changed to ITT since it was a larger, more uniformly defined, all-inclusive population. The CE population was moved to a secondary endpoint. • Key secondary endpoints were established for both EMA and FDA (Day 28 all-cause mortality and clinical response at TOC, respectively) to prioritize secondary analyses. The SAP was updated to align with these changes. • Inclusion/exclusion criteria were clarified for prestudy chest radiograph, gram-negative VABP diagnosis, and antibiotic prophylaxis.	

Protocol deviations

Table 30. Summary of important protocol deviations (ITT population)

Deviation Category Protocol Deviation Description	Ceftolozane/Tazobactam (N=362) n (%)	Meropenem (N=364) n (%)	Total (N=726) n (%)
Subjects with at Least one Important Protocol Deviation Reported	105 (29.0)	124 (34.1)	229 (31.5)
Inclusion/Exclusion Criteria	29 (8.0)	35 (9.6)	64 (8.8)
Participants who do not meet inclusion criterion # 1	0	1 (0.3)	1 (0.1)
Participants who do not meet inclusion criterion # 2	1 (0.3)	0	1 (0.1)
Participants who do not meet inclusion criterion # 3	3 (0.8)	3 (0.8)	6 (0.8)
Participants who do not meet inclusion criterion # 4	9 (2.5)	6 (1.6)	15 (2.1)
Participants who do not meet inclusion criterion # 5	4 (1.1)	0	4 (0.6)
Participants who do not meet inclusion criterion # 6 (protocol version 6.0)	6 (1.7)	11 (3.0)	17 (2.3)
Participants who do not meet inclusion criterion # 7 (protocol version 4.0)	0	1 (0.3)	1 (0.1)
Participants who do not meet inclusion criterion # 7 (protocol version 5.0)	1 (0.3)	1 (0.3)	2 (0.3)
Participants who meet exclusion criterion # 1	1 (0.3)	1 (0.3)	2 (0.3)
Participants who meet exclusion criterion # 18 (protocol version 6.0)	1 (0.3)	2 (0.5)	3 (0.4)
Participants who meet exclusion criterion # 3	7 (1.9)	11 (3.0)	18 (2.5)
Participants who meet exclusion criterion # 7	1 (0.3)	0	1 (0.1)
Participants who meet exclusion criterion # 8	0	1 (0.3)	1 (0.1)
Informed Consent	7 (1.9)	3 (0.8)	10 (1.4)
Participants (or LARs on behalf of the participants) who provided written informed consent on an incorrect version of the ICF.	5 (1.4)	2 (0.5)	7 (1.0)
Participants who provided consent through a LAR come to consciousness while still in the study and are able to make their own decision to participate in the trial are not re-consented. (The consent by the subject must be obtained at the time the PI/site d	1 (0.3)	0	1 (0.1)
Participants with no documented initial consent to enter the trial.	1 (0.3)	1 (0.3)	2 (0.3)
Prohibited Medications	2 (0.6)	6 (1.6)	8 (1.1)
Participants who received serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, and/or buspirone concomitantly with linezolid.	0	6 (1.6)	6 (0.8)
Participants who received valproic acid or divalproex sodium concomitantly with study treatment.	2 (0.6)	0	2 (0.3)
Safety Reporting	9 (2.5)	9 (2.5)	18 (2.5)
Participants with reportable Safety Events and/or follow up Safety Event information that were not reported per the timelines outlined in the protocol.	9 (2.5)	9 (2.5)	18 (2.5)
Study Intervention	47 (13.0)	48 (13.2)	95 (13.1)
Participants who did not receive the protocol required, empiric Gram-positive adjunctive therapy at baseline.	8 (2.2)	7 (1.9)	15 (2.1)

Participants who have their blinded study therapy inadvertently unblinded during the trial.	6 (1.7)	5 (1.4)	11 (1.5)
Participants who missed 2 consecutive doses of study treatment OR 3 non-consecutive doses during the treatment period.	0	1 (0.3)	1 (0.1)
Participants who received Gram-negative adjunctive therapy that exceeds the maximum duration specified by the protocol.	1 (0.3)	1 (0.3)	2 (0.3)
Participants who received additional, Gram-negative antibiotics for treatment of VNP while on study treatment. This excludes the protocol-allowed Gram-negative adjunctive therapy.	8 (2.2)	8 (2.2)	16 (2.2)
Participants who received dose(s) of study medication that are not consistent with the protocol-specified dose for their renal function.	5 (1.4)	4 (1.1)	9 (1.2)
Participants who received incorrect study treatment and/or were administered improperly stored study treatment.	5 (1.4)	6 (1.6)	11 (1.5)
Participants who received study treatment that was exposed to a temperature excursion while in the vial (unprepared product) that has not been first approved by the Sponsor that it was okay to use.	1 (0.3)	3 (0.8)	4 (0.6)
Participants who received study treatment that was stored for greater than 1.5 hours at ambient conditions (15°C to 25°C) or greater than 15.5 hours under refrigeration (2°C to 8°C) prior to start of infusion.	2 (0.6)	7 (1.9)	9 (1.2)
Participants with renal impairment who received a study treatment dosing schedule that is not consistent with the protocol specified dosing schedule for their renal function.	19 (5.2)	17 (4.7)	36 (5.0)
Trial Procedures	41 (11.3)	54 (14.8)	95 (13.1)
Participants who are mis-stratified in Bracket (IXRS System)	26 (7.2)	32 (8.8)	58 (8.0)
Participants who are still in the study at or beyond Day 28 who have a missing assessment of mortality for Day 28.	0	1 (0.3)	1 (0.1)
Participants who are still in the study during the period in which the TOC visit should be completed who do not have an assessment of clinical response at the TOC visit performed	8 (2.2)	17 (4.7)	25 (3.4)
Participants who have a TOC assessment of clinical response performed out of the protocol specific window (i.e. 7-14 days following EOT visit)	9 (2.5)	9 (2.5)	18 (2.5)
Participants who remain intubated through Study Day 8 who do not have at least one post-baseline LRT sample collected on Days 1, 2, 3, or 8.	0	1 (0.3)	1 (0.1)

Notes: n=Number of subjects in specific category. N=Number of subjects in ITT population. Percents are calculated as 100 x (n/N).

P008MK7625A: [P008MK7625A: analysis-adsl; addv]

Approximately 40% of important protocol deviations led to exclusion of subject data from the CE and ME analysis populations. These important deviations included: subjects who did not meet inclusion criterion #3, #4, or #5; subjects who met exclusion criterion #1 or #3; subjects who were un-blinded; receipt of >72 hours of gram-negative adjunctive therapy; receipt of non-study gram-negative antibiotics for the treatment of VNP; and subjects with a missing or out of window TOC visit.

Baseline data

Table 31. Key demographic and Baseline Characteristics (ITT Population)

Characteristic	Statistic	Ceftolozane/Tazobactam (N=362)	Meropenem (N=364)	Total (N=726)
Primary Diagnosis				
VABP	n (%)	263 (72.7)	256 (70.3)	519 (71.5)
Ventilated HABP	n (%)	99 (27.3)	108 (29.7)	207 (28.5)
Age Groups				
>= 65 years	n (%)	160 (44.2)	160 (44.0)	320 (44.1)
>= 75 years	n (%)	83 (22.9)	76 (20.9)	159 (21.9)
Age (years)				
	Mean (SD)	60.5 (16.7)	59.5 (17.2)	60.0 (16.9)
Sex				
Male	n (%)	262 (72.4)	255 (70.1)	517 (71.2)
Race				
White	n (%)	301 (83.1)	300 (82.4)	601 (82.8)
APACHE II Score				
	Mean (SD)	17.5 (5.2)	17.4 (5.7)	17.5 (5.5)
Creatinine Clearance (CLCR) (mL/min)				
CLCR >= 80 mL/min (normal)	n (%)	227 (62.7)	236 (64.8)	463 (63.8)
CLCR > 50 - < 80 mL/min (mild impairment)	n (%)	82 (22.7)	77 (21.2)	159 (21.9)
CLCR >= 30 - <= 50 mL/min (moderate impairment)	n (%)	35 (9.7)	26 (7.1)	61 (8.4)
CLCR >= 15 - < 30 mL/min (severe impairment)	n (%)	17 (4.7)	21 (5.8)	38 (5.2)
CLCR < 15 mL/min (ESRD)	n (%)	0	1 (0.3)	1 (0.1)
CLCR >= 150 mL/min (hyperclearance)	n (%)	67 (18.5)	64 (17.6)	131 (18.0)
Failed Prior Antibiotic Therapy for VNP				
Yes	n (%)	53 (14.6)	40 (11.0)	93 (12.8)
Bacteremic at Baseline (Any Pathogen)				
Yes	n (%)	64 (17.7)	41 (11.3)	105 (14.5)
Duration of Mechanical Ventilation Prior to Randomization				
>= 5 days	n (%)	182 (50.3)	176 (48.4)	358 (49.3)
Randomized while in ICU	n (%)	334 (92.3)	334 (91.8)	668 (92.0)

Notes: n=Number of subjects in specific category. N=Number of subjects in ITT population. Percents are calculated as 100 x (n/N).
ESRD: end stage renal disease.

Source: [P008MK7625A: analysis-adsl]

Baseline microbiology

Baseline lower respiratory tract pathogens and blood pathogens

The incidence and distribution of baseline LRT infecting pathogens in PN008 were generally comparable between the ceftolozane/tazobactam and meropenem groups in the mITT and ME populations.

The table below summarises the most frequently occurring baseline respiratory tract pathogens in the mITT population.

Table 32. Baseline LRT Microbiological Assessment (>= 10 Isolates) (mITT Population)

Characteristic	Ceftolozane/Tazobactam (N=264)	Meropenem (N=247)	Total (N=511)
Number of Baseline LRT Pathogens			
Monomicrobial	164 (62.1)	158 (64.0)	322 (63.0)
Polymicrobial	100 (37.9)	89 (36.0)	189 (37.0)
Baseline LRT Pathogen(s) [1]			
Gram-Negative Pathogens	259 (98.1)	240 (97.2)	499 (97.7)
Pseudomonas aeruginosa	63 (23.9)	65 (26.3)	128 (25.0)
AmpC Overexpressing Pseudomonas aeruginosa	9 (3.4)	6 (2.4)	15 (2.9)
Enterobacteriaceae	195 (73.9)	185 (74.9)	380 (74.4)
ESBL+ Enterobacteriaceae	84 (31.8)	73 (29.6)	157 (30.7)
Enterobacter cloacae	17 (6.4)	16 (6.5)	33 (6.5)
ESBL+ Enterobacter cloacae	1 (0.4)	1 (0.4)	2 (0.4)
Escherichia coli	51 (19.3)	42 (17.0)	93 (18.2)
ESBL+ Escherichia coli	20 (7.6)	10 (4.0)	30 (5.9)
Klebsiella oxytoca	14 (5.3)	12 (4.9)	26 (5.1)
ESBL+ Klebsiella oxytoca	0	3 (1.2)	3 (0.6)
Klebsiella pneumoniae	86 (32.6)	91 (36.8)	177 (34.6)
ESBL+ Klebsiella pneumoniae	53 (20.1)	52 (21.1)	105 (20.5)
Proteus mirabilis	24 (9.1)	20 (8.1)	44 (8.6)
ESBL+ Proteus mirabilis	10 (3.8)	11 (4.5)	21 (4.1)
Serratia marcescens	18 (6.8)	12 (4.9)	30 (5.9)
ESBL+ Serratia marcescens	6 (2.3)	2 (0.8)	8 (1.6)
Acinetobacter baumannii	24 (9.1)	14 (5.7)	38 (7.4)
Haemophilus influenzae	22 (8.3)	16 (6.5)	38 (7.4)
Relative Frequency of Different Methods of Baseline LRT Specimen Collection			
ETA	134 (50.8)	130 (52.6)	264 (51.7)
BAL	89 (33.7)	73 (29.6)	162 (31.7)
mini-BAL	39 (14.8)	40 (16.2)	79 (15.5)
PBS	3 (1.1)	4 (1.6)	7 (1.4)
Number of Infecting LRT Pathogen(s) Identified at Baseline			
1	164 (62.1)	158 (64.0)	322 (63.0)
2	84 (31.8)	68 (27.5)	152 (29.7)
3	14 (5.3)	18 (7.3)	32 (6.3)
>3	2 (0.8)	3 (1.2)	5 (1.0)

Notes: n=Number of subjects in specific category. N=Number of subjects in mITT population. Percents are calculated as 100 x (n/N).

LRT=Lower Respiratory Tract, BAL=Bronchoalveolar Lavage, PBS=Protected Brush Specimen, ETA=Endotracheal Aspirate.

ESBL+ includes any ESBL enzyme.

[1] Subjects with more than 1 pathogen isolated at baseline are counted only once within each pathogen category (i,e, Gram-negative or Gram-positive), once within organism/group (e.g. Enterobacteriaceae) and once for each pathogen (e.g. Escherichia coli).

P008MK7625A: [P008MK7625A: analysis-adsl; admb]

Table 33. Susceptibility Interpretation of Baseline LRT Pathogens (>= 10 Isolates) to ceftolozane/tazobactam and meropenem (mITT Population)

Pathogen Category	Ceftolozane/Tazobactam (N=264)			Meropenem (N=247)		
Organism/Group Pathogen	Susceptible n/N1 (%)	Intermediate n/N1 (%)	Resistant n/N1 (%)	Susceptible n/N1 (%)	Intermediate n/N1 (%)	Resistant n/N1 (%)
Gram-Negative	608/699 (87.0)	17/699 (2.4)	74/699 (10.6)	650/697 (93.3)	5/697 (0.7)	42/697 (6.0)
Pseudomonas aeruginosa	123/127 (96.9)	0/127	4/127 (3.1)	106/127 (83.5)	5/127 (3.9)	16/127 (12.6)
AmpC Overexpressing Pseudomonas aeruginosa	15/15 (100)	0/15	0/15	6/15 (40.0)	1/15 (6.7)	8/15 (53.3)
Enterobacteriaceae	381/456 (83.6)	17/456 (3.7)	58/456 (12.7)	456/457 (99.8)	0/457	1/457 (0.2)
ESBL+ Enterobacteriaceae	106/171 (62.0)	11/171 (6.4)	54/171 (31.6)	171/171 (100)	0/171	0/171
Enterobacter cloacae	29/33 (87.9)	4/33 (12.1)	0/33	33/33 (100)	0/33	0/33
ESBL+ Enterobacter cloacae	1/2 (50.0)	1/2 (50.0)	0/2	2/2 (100)	0/2	0/2
Escherichia coli	92/93 (98.9)	0/93	1/93 (1.1)	93/93 (100)	0/93	0/93
ESBL+ Escherichia coli	29/30 (96.7)	0/30	1/30 (3.3)	30/30 (100)	0/30	0/30
Klebsiella oxytoca	26/26 (100)	0/26	0/26	26/26 (100)	0/26	0/26
ESBL+ Klebsiella oxytoca	3/3 (100)	0/3	0/3	3/3 (100)	0/3	0/3
Klebsiella pneumoniae	114/175 (65.1)	7/175 (4.0)	54/175 (30.9)	175/176 (99.4)	0/176	1/176 (0.6)
ESBL+ Klebsiella pneumoniae	46/105 (43.8)	7/105 (6.7)	52/105 (49.5)	105/105 (100)	0/105	0/105
Proteus mirabilis	40/43 (93.0)	3/43 (7.0)	0/43	43/43 (100)	0/43	0/43
ESBL+ Proteus mirabilis	19/21 (90.5)	2/21 (9.5)	0/21	21/21 (100)	0/21	0/21
Serratia marcescens	26/29 (89.7)	2/29 (6.9)	1/29 (3.4)	29/29 (100)	0/29	0/29
ESBL+ Serratia marcescens	6/8 (75.0)	1/8 (12.5)	1/8 (12.5)	8/8 (100)	0/8	0/8
Acinetobacter baumannii	32/38 (84.2)	0/38	6/38 (15.8)	25/38 (65.8)	0/38	13/38 (34.2)
Haemophilus influenzae	37/37 (100)	0/37	0/37	35/35 (100)	0/35	0/35

Notes: n=Number of pathogens within a specific category. N=Number of subjects in mITT population. N1=Number of pathogens with baseline susceptibility data available.
Percents are calculated as 100 x (n/N1). LRT=Lower Respiratory Tract.
Susceptibility interpretation by broth microdilution testing for ceftolozane/tazobactam was based on provisional interpretive breakpoints for nosocomial pneumonia from PN008.
Susceptibility interpretation by broth microdilution testing for meropenem was based on the 28th Edition of M100 Institute Performance Standards for Antimicrobial Susceptibility Testing, CLSI.
All ESBL+ includes any ESBL enzyme.

P008MK7625A: [P008MK7625A: analysis-adsl; adms]

Table 34. Baseline LRT Pathogens (>= 10 Isolates) and their MIC Summary Statistics (mITT Population)

Pathogen category	Statistic	Ceftolozane/tazobactam N=264	Meropenem N=247
Klebsiella pneumoniae	N1 MIC range MIC50 MIC90	175 0.125 - > =256 2 128	176 <0.064 – 16 <0.064 1
ESBL+ *K. pneumoniae*	N1 MIC range MIC50 MIC90	105 0.25 - >256 8 128	105 <0.064 – 1 <0.064 1
E. coli	N1 MIC range MIC50 MIC90	93 0.125-64 0.25 1	93 <0.064 – 0.125 <0.064 <0.064
ESBL+ *E. coli*	N1 MIC range MIC50 MIC90	30 0.25-64 0.5 1	30 <0.064-<0.064 <0.064 <0.064
Pseudomonas aeruginosa	N1 MIC range MIC50 MIC90	127 0.125 - > =256 1 2	127 <0.064 – 128 0.5 8
AmpC Overexpressing *Pseudomonas aeruginosa*	N1 MIC range MIC50 MIC90	15 1-8 2 4	15 0.25-32 8 32

Notes: N=Number of subjects in mITT population. N1=Number of pathogens with baseline MIC data available. MIC=Minimum inhibitory concentration in ug/mL. MIC50=Minimum inhibitory concentration required to inhibit the growth of 50% of organisms. MIC90=Minimum inhibitory concentration required to inhibit the growth of 90% of organisms. The MIC ranges are for the respective drugs. LRT=Lower Respiratory Tract. Each pathogen is counted once per subject and where there are multiple values, the pathogen with highest MIC is used for summaries. ESBL+ includes any ESBL enzyme. Data from Table 10-6, Study report. Source: [P008MK7625A: analysis-adsl; adms]

Baseline blood pathogens

Overall, the proportion of subjects with bacteremia at baseline (16.3% versus 10.5%, respectively) and the distribution of baseline blood pathogens were comparable between the ceftolozane/tazobactam and meropenem groups in the mITT population, and similar results were observed in the ME population. The most common blood pathogen in the mITT population was *Staphylococcus epidermidis* 17/511 (3.3%), and the most common gram-negative blood pathogen was *K. pneumoniae* 13/511 (2.5%).

The MIC_{50} and MIC_{90} values for gram-negative baseline blood pathogens were 2 and ≥256 µg/mL, respectively, for ceftolozane/tazobactam and 0.25 and 64 µg/mL, respectively, for meropenem in the mITT population with high MICs for both *Staphylococcus epidermidis* and *K. pneumoniae*. Similar results were observed in the ME population.

Non-study concomitant medication

Table 35. Non-Study Concomitant Antibiotic Medication by ATC Class and Preferred Term (>= 10% subjects) (ITT Population)

ATC Class Preferred Term	Ceftolozane/Tazobactam (N=362) n (%)	Meropenem (N=364) n (%)	Total (N=726) n (%)
Number of Subjects with Any Non-Study Concomitant Antibiotic Medication	218 (60.2)	205 (56.3)	423 (58.3)
CARBAPENEMS	77 (21.3)	54 (14.8)	131 (18.0)
MEROPENEM	63 (17.4)	34 (9.3)	97 (13.4)
GLYCOPEPTIDE ANTIBACTERIALS	40 (11.0)	54 (14.8)	94 (12.9)
VANCOMYCIN	38 (10.5)	52 (14.3)	90 (12.4)
OTHER AMINOGLYCOSIDES	55 (15.2)	45 (12.4)	100 (13.8)
AMIKACIN	43 (11.9)	37 (10.2)	80 (11.0)

Notes: n=Number of subjects in specific category. N=Number of subjects in ITT population. Percents are calculated as 100 x (n/N).
Non-study concomitant antibiotic medications are those that were received anytime from on or after the first dose of study drug to on or before the late follow-up visit.
Medications are coded using WHO Drug Dictionary March 2014 version. For each ATC class and preferred term, subjects are counted only once. ATC = Anatomic Therapeutic Chemical.

Source: [P008MK7625A: analysis-adsl; adcm]

Extent of exposure to study medication

Table 36. Study Drug Exposure (Safety Population)

Category	Statistic	Ceftolozane/Tazobactam (N=361)	Meropenem (N=359)	Total (N=720)
Duration of Exposure: Study Days [1]	n	361	359	720
	Mean (SD)	8.00 (3.532)	8.23 (3.609)	8.12 (3.570)
	Median	7.70	7.70	7.70
	Q1, Q3	7.30, 9.70	7.50, 10.70	7.40, 9.70
	Min, Max	0.3, 13.8	0.0, 13.8	0.0, 13.8
Duration of Exposure: Categorized by Calendar Day [2]				
1 day	n (%)	1 (0.3)	4 (1.1)	5 (0.7)
2 days	n (%)	9 (2.5)	14 (3.9)	23 (3.2)
3 days	n (%)	20 (5.5)	10 (2.8)	30 (4.2)
4 days	n (%)	19 (5.3)	10 (2.8)	29 (4.0)
5 days	n (%)	7 (1.9)	17 (4.7)	24 (3.3)
6 days	n (%)	11 (3.0)	4 (1.1)	15 (2.1)
7 days	n (%)	11 (3.0)	12 (3.3)	23 (3.2)
8 days	n (%)	13 (3.6)	15 (4.2)	28 (3.9)
9 days	n (%)	163 (45.2)	156 (43.5)	319 (44.3)
10 - 13 days	n (%)	39 (10.8)	41 (11.4)	80 (11.1)
14 days	n (%)	12 (3.3)	15 (4.2)	27 (3.8)
15 days	n (%)	56 (15.5)	61 (17.0)	117 (16.3)
> 15 Days	n (%)	0	0	0
Number of Doses Received	n	361	359	720
	Mean (SD)	25.8 (11.20)	26.5 (11.40)	26.1 (11.30)
	Median	24.0	24.0	24.0
	Q1, Q3	23.0, 32.0	24.0, 33.0	23.5, 32.0
	Min, Max	2, 56	1, 56	1, 56

Numbers analysed

The Intent-To-Treat (ITT) population used for efficacy analyses was defined as all subjects randomized, whether or not they received treatment.

Table 37. Reason for Exclusion from Analysis Population (All Randomized Subjects)

Population Reason for Exclusion	Ceftolozane/ Tazobactam (N=362)	Meropenem (N=364)	Total (N=726)
Intent-to-Treat (ITT)	362 (100)	364 (100)	726 (100)
Subject not randomized	0	0	0
Subject never signed the ICF	0	0	0
Other	0	0	0
Safety	361 (99.7)	359 (98.6)	720 (99.2)
Not in Safety	1 (0.3)	5 (1.4)	6 (0.8)
Subject not randomized	0	0	0
Subject did not take any study medication	1 (0.3)	5 (1.4)	6 (0.8)
Subject never signed the ICF	0	0	0
Subject not in the ITT Population	0	0	0
Other	0	0	0
Microbiological Intent-to-Treat (mITT)	264 (72.9)	247 (67.9)	511 (70.4)
Not in mITT	98 (27.1)	117 (32.1)	215 (29.6)
Subject not randomized	0	0	0
Subject did not take any study medication	1 (0.3)	5 (1.4)	6 (0.8)
Subject never signed the ICF	0	0	0
No baseline pathogen identified	30 (8.3)	44 (12.1)	74 (10.2)
Non-streptococcal species Gram-positive organism is the only baseline pathogen	13 (3.6)	13 (3.6)	26 (3.6)
All baseline pathogens are non-susceptible to both study drugs	53 (14.6)	48 (13.2)	101 (13.9)
Subject not in the ITT Population	0	0	0
No susceptibility data available for baseline pathogens	2 (0.6)	9 (2.5)	11 (1.5)
Other	2 (0.6)	9 (2.5)	11 (1.5)
Clinically Evaluable (CE)	218 (60.2)	221 (60.7)	439 (60.5)
Not in CE	144 (39.8)	143 (39.3)	287 (39.5)
Subject not in the ITT Population	0	0	0
Subject was unblinded	6 (1.7)	6 (1.6)	12 (1.7)
Clinical diagnosis unconfirmed	18 (5.0)	20 (5.5)	38 (5.2)
Subject received <= 48 hours of study therapy	27 (7.5)	23 (6.3)	50 (6.9)
Course too long (>120%) for cure	0	0	0
Course too short (<80%) for cure	3 (0.8)	4 (1.1)	7 (1.0)
Receipt of effective concomitant therapy before the TOC visit and is a Non-Failure	48 (13.3)	51 (14.0)	99 (13.6)
Gram-negative adjunctive therapy is initiated post-baseline or continued inappropriately	0	0	0
No evaluable clinical response at TOC	63 (17.4)	73 (20.1)	136 (18.7)
TOC visit out of window	4 (1.1)	5 (1.4)	9 (1.2)
Investigator outcome not acceptable for TOC	2 (0.6)	1 (0.3)	3 (0.4)
Subject never signed the ICF	0	0	0
Subject did not take any study medication	1 (0.3)	5 (1.4)	6 (0.8)
Other protocol violation	0	0	0
Subject discontinued study drug due to all resistant baseline pathogens	13 (3.6)	12 (3.3)	25 (3.4)
Other	13 (3.6)	12 (3.3)	25 (3.4)
Microbiologically Evaluable (ME)	115 (31.8)	118 (32.4)	233 (32.1)
Not in ME	247 (68.2)	246 (67.6)	493 (67.9)
Not in CE population	107 (29.6)	113 (31.0)	220 (30.3)
Not in mITT population	98 (27.1)	117 (32.1)	215 (29.6)
Insufficient bacterial pathogen load	85 (23.5)	71 (19.5)	156 (21.5)
All baseline pathogens are non-susceptible to both study drugs	43 (11.9)	40 (11.0)	83 (11.4)
Receipt of effective concomitant therapy before the TOC active against any of the subject's specific pathogens in a Non-Failure subject	34 (9.4)	27 (7.4)	61 (8.4)
Receipt of effective concomitant therapy before the TOC active against any of the subject's specific pathogens in a Micro Cure and Clinical Failure subject	8 (2.2)	9 (2.5)	17 (2.3)
Other	43 (11.9)	41 (11.3)	84 (11.6)

Notes: n=Number of subjects in specific category. N=Number of subjects in the ITT population. Percents are calculated as 100 x (n/N).
Subjects can be excluded from a given population due to multiple reasons and is only counted once for each reason.
LRT=Lower Respiratory Tract. EOT=End of Therapy. TOC=Test of Cure. LFU=Late Follow-up. ICF=Informed Consent Form.

Source: [P008MK7625A: analysis-adsl]

Outcomes and estimation

Primary and key secondary endpoint

Table 38. Primary and Key Secondary Efficacy Endpoints – EMA Analysis (ITT Population)

Endpoint	Statistic	Ceftolozane/ Tazobactam	Meropenem	% Difference
Primary Efficacy Endpoint				
Clinical Response at TOC Visit				
Cure	n/N (%) [1]	197/362 (54.4)	194/364 (53.3)	1.1
	Stratified 97.5% CI [2]	(48.74, 60.30)	(47.72, 59.25)	(-7.20, 9.31)
Failure	n/N (%)	165/362 (45.6)	170/364 (46.7)	
Key Secondary Efficacy Endpoint				
Day 28 All-cause Mortality	n/N (%) [1]	87/362 (24.0)	92/364 (25.3)	1.1
	Stratified 97.5% CI [2]	(18.31, 28.09)	(19.43, 29.08)	(-6.03, 8.28)

Notes: n=Number of subjects in specific category. N=Number of subjects in specific population. Percents are calculated as 100 x (n/N). Subjects whose Day 28 mortality outcomes are missing or unknown are analysed as deceased. Subjects with missing clinical responses are considered failures.

[1] The % difference is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >= 65) categories. The % difference is Meropenem minus Ceftolozane/Tazobactam for Day 28 all-cause mortality and Ceftolozane/Tazobactam minus Meropenem for clinical cure rate.

[2] The 97.5% CIs of % difference are stratified Newcombe CIs. The 97.5% CIs of each treatment are stratified Wilson CIs.

Source: [P008MK7625A: analysis-adsl; adef1]

Table 39. Clinical Response at Test of Cure (TOC) Visit by Stratum – EMA Analysis (ITT Population)

Stratum Population Clinical Outcome	Statistic	Ceftolozane/Tazobactam	Meropenem	% Difference (Ceftolozane/Tazobactam minus Meropenem)
Overall				
ITT - TFA	N	362	364	
Cure	n (%) [1]	197 (54.4)	194 (53.3)	1.1
	Stratified 97.5% CI [2]	(48.74, 60.30)	(47.72, 59.25)	(-7.20, 9.31)
	Unstratified 97.5% CI [3]	(48.53, 60.19)	(47.43, 59.07)	(-7.13, 9.35)
Failure	n (%)	165 (45.6)	170 (46.7)	
Observed Failure	n (%)	19 (5.2)	23 (6.3)	
Failure Carried Forward from EOT	n (%)	86 (23.8)	74 (20.3)	
Observed Indeterminate	n (%)	28 (7.7)	36 (9.9)	
Imputed Indeterminate [4]	n (%)	32 (8.8)	37 (10.2)	
Diagnosis: VABP				
ITT - TFA	N	263	256	
Cure	n (%)	147 (55.9)	146 (57.0)	-1.1
	Unstratified 97.5% CI [3]	(48.98, 62.58)	(50.03, 63.76)	(-10.79, 8.55)
Failure	n (%)	116 (44.1)	110 (43.0)	
Observed Failure	n (%)	15 (5.7)	20 (7.8)	
Failure Carried Forward from EOT	n (%)	56 (21.3)	54 (21.1)	
Observed Indeterminate	n (%)	22 (8.4)	18 (7.0)	
Imputed Indeterminate [4]	n (%)	23 (8.7)	18 (7.0)	
Diagnosis: Ventilated HABP				
ITT - TFA	N	99	108	
Cure	n (%)	50 (50.5)	48 (44.4)	6.1
	Unstratified 97.5% CI [3]	(39.49, 61.47)	(34.21, 55.17)	(-9.31, 21.06)
Failure	n (%)	49 (49.5)	60 (55.6)	
Observed Failure	n (%)	4 (4.0)	3 (2.8)	
Failure Carried Forward from EOT	n (%)	30 (30.3)	20 (18.5)	
Observed Indeterminate	n (%)	6 (6.1)	18 (16.7)	
Imputed Indeterminate [4]	n (%)	9 (9.1)	19 (17.6)	
Age Category: < 65 Years				
ITT - TFA	N	202	204	
Cure	n (%)	121 (59.9)	118 (57.8)	2.1
	Unstratified 97.5% CI [3]	(52.02, 67.30)	(50.00, 65.31)	(-8.80, 12.84)
Failure	n (%)	81 (40.1)	86 (42.2)	
Observed Failure	n (%)	10 (5.0)	12 (5.9)	
Failure Carried Forward from EOT	n (%)	40 (19.8)	33 (16.2)	
Observed Indeterminate	n (%)	10 (5.0)	20 (9.8)	
Imputed Indeterminate [4]	n (%)	21 (10.4)	21 (10.3)	
Age Category: >= 65 Years				
ITT - TFA	N	160	160	
Cure	n (%)	76 (47.5)	76 (47.5)	0.0
	Unstratified 97.5% CI [3]	(38.86, 56.29)	(38.86, 56.29)	(-12.32, 12.32)
Failure	n (%)	84 (52.5)	84 (52.5)	
Observed Failure	n (%)	9 (5.6)	11 (6.9)	
Failure Carried Forward from EOT	n (%)	46 (28.8)	41 (25.6)	
Observed Indeterminate	n (%)	18 (11.3)	16 (10.0)	
Imputed Indeterminate [4]	n (%)	11 (6.9)	16 (10.0)	

Notes: n=Number of subjects in specific category. N=Number of subjects in specific population of each stratum. Percents are calculated as 100 x (n/N).
For subjects with clinical failure response at EOT, they are counted in failure category at TOC.
TFA (Treatment Failure Approach): Subjects with missing clinical responses are considered failures.
[1] The % difference is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >=65) categories.
[2] The 97.5% CIs of % difference are stratified Newcombe CIs. The 97.5% CIs of each treatment are stratified Wilson CIs.
[3] The 97.5% CIs of % difference are unstratified Newcombe CIs. The 97.5% CIs of each treatment are unstratified Wilson CIs.
[4] Overall imputed indeterminate clinical response includes subjects that were a clinical cure or indeterminate at EOT and had missing clinical response at TOC.

Source: [P008MK7625A: analysis-adsl; adefl]

Table 40. Day 28 All-cause mortality rate by stratum - EMA analysis (ITT population)

Stratum	Statistic	Ceftolozane/ Tazobactam	Meropenem	% Difference (Meropenem minus Ceftolozane/ Tazobactam)
Overall				
	n/N (%) [1]	87/362 (24.0)	92/364 (25.3)	1.1
	Stratified 97.5% CI [2]	(18.31, 28.09)	(19.43, 29.08)	(-6.03, 8.28)
	Unstratified 97.5% CI [3]	(19.38, 29.40)	(20.53, 30.69)	(-5.92, 8.39)
Diagnosis				
VABP	n/N (%)	63/263 (24.0)	52/256 (20.3)	-3.6
	Unstratified 97.5% CI [3]	(18.58, 30.31)	(15.27, 26.49)	(-11.75, 4.55)
Ventilated HABP	n/N (%)	24/99 (24.2)	40/108 (37.0)	12.8
	Unstratified 97.5% CI [3]	(15.99, 34.99)	(27.42, 47.81)	(-1.63, 26.37)
Age Category				
< 65 Years	n/N (%)	37/202 (18.3)	38/204 (18.6)	0.3
	Unstratified 97.5% CI [3]	(13.01, 25.16)	(13.30, 25.46)	(-8.36, 8.96)
>= 65 Years	n/N (%)	50/160 (31.3)	54/160 (33.8)	2.5
	Unstratified 97.5% CI [3]	(23.71, 39.93)	(25.98, 42.51)	(-9.15, 14.06)

Notes: n=Number of deaths at Day 28 in specific category. N=Number of subjects in specific population of each stratum. Percents are calculated as 100 x (n/N). Subjects whose Day 28 mortality outcomes are missing or unknown are analysed as deceased.

[1] The % difference is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >=65) categories.

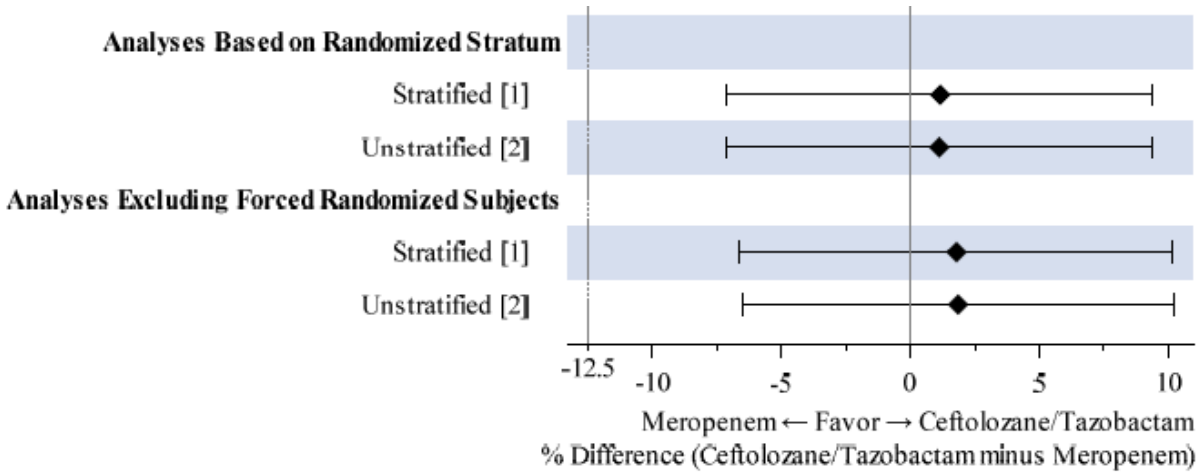
[2]The 97.5% CIs of % difference are stratified Newcombe CIs. The 97.5% CIs of each treatment are stratified Wilson CIs.

[3]The 97.5% CIs of % difference are unstratified Newcombe CIs. The 97.5% CIs of each treatment are unstratified Wilson CIs.

Source: [P008MK7625A: analysis-adsl; adef1]

Sensitivity analyses

Various sensitivity analyses of the primary and key secondary efficacy endpoints were performed. Results for each sensitivity analysis are displayed in the Forest plot below.



Notes: For stratified, the adjusted proportions are a weighted average across strata of diagnosis (VABP, ventilated HABP) and age (< 65, >=65) categories constructed using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights. Forced assignment of subjects to a treatment arm was permitted and implemented in a blinded fashion when subjects were randomized to a study drug which was temporarily unavailable at the site.

[1] The 97.5% CIs are stratified Newcombe CIs for diagnosis and age factors using MRc stratum weights.
[2] The 97.5% CIs are unstratified Newcombe CIs.

Figure 15. Additional Sensitivity Analyses for Difference in Clinical Response at Test of Cure (TOC) Visit – EMA Analysis (ITT Population)

Additional secondary endpoints – clinical response

Table 41. Clinical Response at Test of Cure (TOC) Visit (CE Population)

Stratum Population Clinical Outcome	Statistic	Ceftolozane/Tazobactam	Meropenem	% Difference (Ceftolozane/Tazobactam minus Meropenem)
Overall				
CE - DAO Approach	N	218	221	
Cure	n (%) [1]	139 (63.8)	143 (64.7)	-1.3
	Stratified 95% CI [2]	(57.50, 70.11)	(58.83, 71.19)	(-10.21, 7.67)
	Unstratified 95% CI [3]	(57.19, 69.85)	(58.20, 70.71)	(-9.84, 7.97)
Failure	n (%)	79 (36.2)	78 (35.3)	

Notes: n=Number of subjects in specific category. N=Number of subjects in specific population of each stratum. Percents are calculated as 100 x (n/N).
For subjects with clinical failure response at EOT, they are counted in failure category at TOC.
DAO (Data-as-Observed) Approach: Subjects with missing clinical responses, including indeterminate outcomes, are excluded from the analysis population.
[1] The % difference is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >=65) categories.
[2] The 95% CIs of % difference are stratified Newcombe CIs. The 95% CIs of each treatment are stratified Wilson CIs.
[3] The 95% CIs of % difference are unstratified Newcombe CIs. The 95% CIs of each treatment are unstratified Wilson CIs.

Source: [P008MK7625A: analysis-adsl; adef1]

Clinical response at the Test-of-Cure visit in the mITT and ME population

Table 42. Clinical Response at Test of Cure (TOC) Visit by Population (mITT and ME)

Population Clinical Outcome	Statistic	Ceftolozane/Tazobactam	Meropenem	% Difference (Ceftolozane/Tazobactam minus Meropenem)
mITT - TFA	N	264	247	
Cure	n (%) [1]	160 (60.6)	140 (56.7)	2.7
	Stratified 95% CI [2]	(54.40, 66.01)	(51.50, 63.62)	(-5.85, 11.23)
Failure	n (%)	104 (39.4)	107 (43.3)	
ME - DAO Approach	N	115	118	
Cure	n (%) [1]	87 (75.7)	78 (66.1)	9.0
	Stratified 95% CI [2]	(66.61, 81.96)	(57.29, 74.05)	(-2.79, 20.39)
Failure	n (%)	28 (24.3)	40 (33.9)	

Notes: n=Number of subjects in specific category. N=Number of subjects in specific population. Percents are calculated as 100 x (n/N).
For subjects with clinical failure response at EOT, they are counted in failure category at TOC.
TFA (Treatment Failure Approach): Subjects with missing clinical responses are considered failures.
DAO (Data-as-Observed) Approach: Subjects with missing clinical responses, including indeterminate outcomes, are excluded from the analysis population.
[1] The % difference is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >=65) categories.
[2] The 95% CIs of % difference are stratified Newcombe CIs. The 95% CIs of each treatment are stratified Wilson CIs.

Source: [P008MK7625A: analysis-adsl; adef1]

Secondary endpoints – microbiological results

Table 43. Per-Subject Microbiological Response at Test of Cure (TOC) Visit by Population (mITT and ME)

Population Per-Subject Microbiological Response	Statistic	Ceftolozane/ Tazobactam	Meropenem	% Difference (Ceftolozane/Tazobactam minus Meropenem)
mITT - TFA	N	264	247	
Cure or Presumed Cure	n (%) [1]	193 (73.1)	168 (68.0)	4.5
	Stratified 95% CI [2]	(67.73, 78.27)	(62.87, 74.32)	(-3.39, 12.45)
Failure or Presumed Failure	n (%)	71 (26.9)	79 (32.0)	
ME - DAO Approach	N	115	118	
Cure or Presumed Cure	n (%) [1]	81 (70.4)	74 (62.7)	7.0
	Stratified 95% CI [2]	(61.37, 77.55)	(54.12, 71.24)	(-5.11, 18.93)
Failure or Presumed Failure	n (%)	34 (29.6)	44 (37.3)	

Notes: n=Number of subjects in specific category. N=Number of subjects in specific population. Percents are calculated as 100 x (n/N).
TFA (Treatment Failure Approach): Subjects with missing culture and clinical responses that were failure (including clinical failure at EOT and was carried forward to TOC), indeterminate, or missing, are considered presumed failures.
DAO (Data-as-Observed) Approach: Subjects with missing culture and clinical responses that were failure, including clinical failure at EOT and was carried forward to TOC, are considered presumed failures.
[1] The % difference is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >=65) categories.
[2]The 95% CIs of % difference are stratified Newcombe CIs. The 95% CIs of each treatment are stratified Wilson CIs.

Source: [P008MK7625A: analysis-adsl; adef2]

Table 44. Per-Pathogen (>= 10 Isolates at baseline) Microbiological Response at Test of Cure (TOC) Visit (mITT population)

Baseline Pathogen Category Baseline Pathogen	Per-Pathogen Microbiological Response	Statistic	Ceftolozane/ Tazobactam (N=264)	Meropenem (N=247)	% Difference (Ceftolozane/Tazobactam minus Meropenem)
Gram-Negative		N1	259	240	
	Eradication or Presumed Eradication	n (%)	189 (73.0)	163 (67.9)	5.1
		Unstratified 95% CI [1]	(67.26, 78.02)	(61.77, 73.50)	(-2.93, 13.01)
	Persistence or Presumed Persistence	n (%)	70 (27.0)	77 (32.1)	
Pseudomonas aeruginosa		N1	63	65	
	Eradication or Presumed Eradication	n (%)	47 (74.6)	41 (63.1)	11.5
		Unstratified 95% CI [1]	(62.66, 83.72)	(50.92, 73.77)	(-4.51, 26.72)
	Persistence or Presumed Persistence	n (%)	16 (25.4)	24 (36.9)	
AmpC Overexpressing Pseudomonas aeruginosa		N1	9	6	
	Eradication or Presumed Eradication	n (%)	6 (66.7)	1 (16.7)	50.0
		Unstratified 95% CI [1]	(35.42, 87.94)	(3.01, 56.35)	(-0.51, 75.28)
	Persistence or Presumed Persistence	n (%)	3 (33.3)	5 (83.3)	
Enterobacteriaceae		N1	195	185	
	Eradication or Presumed Eradication	n (%)	145 (74.4)	129 (69.7)	4.6
		Unstratified 95% CI [1]	(67.80, 79.98)	(62.76, 75.89)	(-4.37, 13.58)
	Persistence or Presumed Persistence	n (%)	50 (25.6)	56 (30.3)	
ESBL+ Enterobacteriaceae		N1	84	73	
	Eradication or Presumed Eradication	n (%)	56 (66.7)	52 (71.2)	-4.6
		Unstratified 95% CI [1]	(56.05, 75.82)	(59.99, 80.35)	(-18.56, 9.93)
	Persistence or Presumed Persistence	n (%)	28 (33.3)	21 (28.8)	
Enterobacter cloacae		N1	17	16	
	Eradication or Presumed Eradication	n (%)	11 (64.7)	8 (50.0)	14.7
		Unstratified 95% CI [1]	(41.30, 82.69)	(28.00, 72.00)	(-17.42, 43.12)
	Persistence or Presumed Persistence	n (%)	6 (35.3)	8 (50.0)	
ESBL+ Enterobacter cloacae		N1	1	1	

	Eradication or Presumed Eradication	n (%)	0	0	N/A
		Unstratified 95% CI [1]	(0.00, 79.35)	(0.00, 79.35)	N/A
	Persistence or Presumed Persistence	n (%)	1 (100.0)	1 (100.0)	
Escherichia coli		N1	51	42	
	Eradication or Presumed Eradication	n (%)	43 (84.3)	33 (78.6)	5.7
		Unstratified 95% CI [1]	(71.99, 91.83)	(64.06, 88.29)	(-9.96, 22.08)
	Persistence or Presumed Persistence	n (%)	8 (15.7)	9 (21.4)	
ESBL+ Escherichia coli		N1	20	10	
	Eradication or Presumed Eradication	n (%)	18 (90.0)	8 (80.0)	10.0
		Unstratified 95% CI [1]	(69.90, 97.21)	(49.02, 94.33)	(-14.69, 41.81)
	Persistence or Presumed Persistence	n (%)	2 (10.0)	2 (20.0)	
Klebsiella oxytoca		N1	14	12	
	Eradication or Presumed Eradication	n (%)	13 (92.9)	8 (66.7)	26.2
		Unstratified 95% CI [1]	(68.53, 98.73)	(39.06, 86.19)	(-5.00, 54.41)
	Persistence or Presumed Persistence	n (%)	1 (7.1)	4 (33.3)	
ESBL+ Klebsiella oxytoca		N1	0	3	
	Eradication or Presumed Eradication	n (%)	0	2 (66.7)	N/A
		Unstratified 95% CI [1]	N/A	(20.77, 93.85)	N/A
	Persistence or Presumed Persistence	n (%)	0	1 (33.3)	
Klebsiella pneumoniae		N1	86	91	
	Eradication or Presumed Eradication	n (%)	63 (73.3)	65 (71.4)	1.8
		Unstratified 95% CI [1]	(63.05, 81.47)	(61.43, 79.69)	(-11.30, 14.77)
	Persistence or Presumed Persistence	n (%)	23 (26.7)	26 (28.6)	
ESBL+ Klebsiella pneumoniae		N1	53	52	
	Eradication or Presumed Eradication	n (%)	33 (62.3)	38 (73.1)	-10.8
		Unstratified 95% CI [1]	(48.81, 74.06)	(59.75, 83.23)	(-27.67, 6.99)
	Persistence or Presumed Persistence	n (%)	20 (37.7)	14 (26.9)	
Proteus mirabilis		N1	24	20	
	Eradication or Presumed Eradication	n (%)	18 (75.0)	14 (70.0)	5.0
		Unstratified 95% CI [1]	(55.10, 88.00)	(48.10, 85.45)	(-20.19, 30.47)
	Persistence or Presumed Persistence	n (%)	6 (25.0)	6 (30.0)	
ESBL+ Proteus mirabilis		N1	10	11	
	Eradication or Presumed Eradication	n (%)	7 (70.0)	7 (63.6)	6.4
		Unstratified 95% CI [1]	(39.68, 89.22)	(35.38, 84.83)	(-30.63, 40.54)
	Persistence or Presumed Persistence	n (%)	3 (30.0)	4 (36.4)	
Serratia marcescens		N1	18	12	
	Eradication or Presumed Eradication	n (%)	11 (61.1)	9 (75.0)	-13.9
		Unstratified 95% CI [1]	(38.62, 79.69)	(46.77, 91.11)	(-41.55, 19.91)
	Persistence or Presumed Persistence	n (%)	7 (38.9)	3 (25.0)	
ESBL+ Serratia marcescens		N1	6	2	
	Eradication or Presumed Eradication	n (%)	3 (50.0)	2 (100.0)	-50.0
		Unstratified 95% CI [1]	(18.76, 81.24)	(34.24, 100.00)	(-81.24, 22.80)
	Persistence or Presumed Persistence	n (%)	3 (50.0)	0	
Acinetobacter baumannii		N1	24	14	
	Eradication or Presumed Eradication	n (%)	11 (45.8)	10 (71.4)	-25.6
		Unstratified 95% CI [1]	(27.89, 64.93)	(45.35, 88.28)	(-50.21, 6.72)
	Persistence or Presumed Persistence	n (%)	13 (54.2)	4 (28.6)	
Haemophilus influenzae		N1	22	16	
	Eradication or Presumed Eradication	n (%)	20 (90.9)	11 (68.8)	22.2
		Unstratified 95% CI [1]	(72.19, 97.47)	(44.40, 85.84)	(-3.19, 47.37)
	Persistence or Presumed Persistence	n (%)	2 (9.1)	5 (31.3)	

Notes: n=Number of subjects in specific category. N=Number of subjects in specific population. N1=Number of subjects in specific population of pathogen or pathogen category.
Percents are calculated as 100 x (n/N1). ESBL+ includes any ESBL enzyme.
[1] The 95% CIs of % difference are unstratified Newcombe CIs. The 95% CIs of each treatment are unstratified Wilson CIs.

Source: [P008MK7625A: analysis-adsl; admb]

Superinfection and new infection rates in the mITT population

Superinfections in the mITT population were generally comparable between treatment groups with the number of subjects having a superinfection being 54/264 (20.5%) in the ceftolozane/tazobactam group vs. 51/247 (20.6%) in the meropenem group. The most common superinfecting pathogen, isolated in >5% of the subjects, was *A. baumannii* found in 24/264, 9.1% and 28/247, 11.3% of subjects in the ceftolozane/tazobactam and meropenem groups, respectively. Overall, the total number of new pathogens classified as superinfections was higher for the ceftolozane/tazobactam group compared to the meropenem group (74 vs. 58, respectively).

The most common new infecting pathogen was *P. aeruginosa* found in 8/264, 3.0% and 5/247, 2.0% of subjects in the ceftolozane/tazobactam and meropenem groups, respectively, closely followed by *K.*

pneumoniae with 7/264, 2.7% in the ceftolozane/tazobactam group vs. 3/247, 1.2% in the meropenem group.

Emergence of non-susceptibility to study drug in the mITT population

Table 45. Emergence of non-susceptibility for baseline infecting pathogens (mITT population)

Category	Statistic	Ceftolozane/ Tazobactam (N=264)	Meropenem (N=247)	% Difference (Meropenem minus Ceftolozane/Tazobactam)
Subjects with a Susceptible Pathogen at Baseline	N1	229	234	
Subjects with Emergence of Non-Susceptible Pathogen(s) by EOT Visit	n (%) Unstratified 95% CI [1]	26 (11.4) (7.87, 16.12)	25 (10.7) (7.34, 15.30)	-0.7 (-6.49, 5.11)
Subjects with Emergence of Non-Susceptible Pathogen(s) by TOC Visit	n (%) Unstratified 95% CI [1]	29 (12.7) (8.96, 17.60)	28 (12.0) (8.41, 16.75)	-0.7 (-6.78, 5.35)

Notes: n=Number of subjects in specific category. N=Number of subjects in mITT population. N1=Number of subjects with a susceptible pathogen at baseline.
Percents are calculated as 100 x (n/N1).
Emergence of non-susceptibility is defined as a subject with a pathogen that is susceptible at baseline, but is non-susceptible after baseline.
Analysis is based on susceptibility data from the central microbiology lab when available. For subjects without central lab susceptibility data at baseline local lab data is used.
[1] The 95% CIs of % difference are unstratified Newcombe CIs. The 95% CIs of each treatment are unstratified Wilson CIs.

Source: [P008MK7625A: analysis-adsl; adms]

Agreement between Clinical Response and Per-Subject Microbiological Response

Clinical responses at the TOC and EOT visits were consistent with microbiological responses in the mITT population and the ME population in both treatment groups.

Table 46. Agreement between clinical response and per-subject microbiological response by visit (mITT population)

Visit Clinical Response	Per-Subject Microbiological Response	Ceftolozane/Tazobactam (N=264) n/N1 (%)	Meropenem (N=247) n/N1 (%)
Test of Cure (TOC) Visit			
Cure	Cure or Presumed Cure	148/160 (92.5)	124/140 (88.6)
	Failure or Presumed Failure	12/160 (7.5)	16/140 (11.4)
Failure	Cure or Presumed Cure	45/104 (43.3)	44/107 (41.1)
	Failure or Presumed Failure	59/104 (56.7)	63/107 (58.9)
End of Therapy (EOT) Visit			
Cure	Cure or Presumed Cure	173/195 (88.7)	160/180 (88.9)
	Failure or Presumed Failure	22/195 (11.3)	20/180 (11.1)
Failure	Cure or Presumed Cure	30/69 (43.5)	28/67 (41.8)
	Failure or Presumed Failure	39/69 (56.5)	39/67 (58.2)

Notes: n=Number of subjects within a specific category. N1= Number of subjects for each clinical response.
N=Number of subjects in mITT population. Percents are calculated as 100 x (n/N1).
For subjects with clinical failure response at EOT but missing clinical response at TOC, they are counted in failure category at TOC.

Source: [P008MK7625A: analysis-adsl; adef1; adef2]

Table 47. Clinical Cure Rates at Test of Cure (TOC) Visit by Key Baseline LRT Pathogen (mITT population)

Gram-Negative Group or Pathogens	Ceftolozane/Tazobactam n/N (%)	Meropenem n/N (%)
Enterobacteriaceae		
Klebsiella pneumoniae	53/86 (61.6)	58/91 (63.7)
Escherichia coli	32/51 (62.7)	26/42 (61.9)
Proteus mirabilis	13/24 (54.2)	11/20 (55.0)
Serratia marcescens	9/18 (50.0)	7/12 (58.3)
Enterobacter cloacae	10/17 (58.8)	4/16 (25.0)
Klebsiella oxytoca	9/14 (64.3)	7/12 (58.3)
Klebsiella (Enterobacter) aerogenes	4/8 (50.0)	3/8 (37.5)
ESBL+ Enterobacteriaceae	48/84 (57.1)	45/73 (61.6)
Pseudomonas aeruginosa	36/63 (57.1)	39/65 (60.0)
MDR Pseudomonas aeruginosa	13/24 (54.2)	6/11 (54.5)
Haemophilus influenzae	19/22 (86.4)	8/16 (50.0)

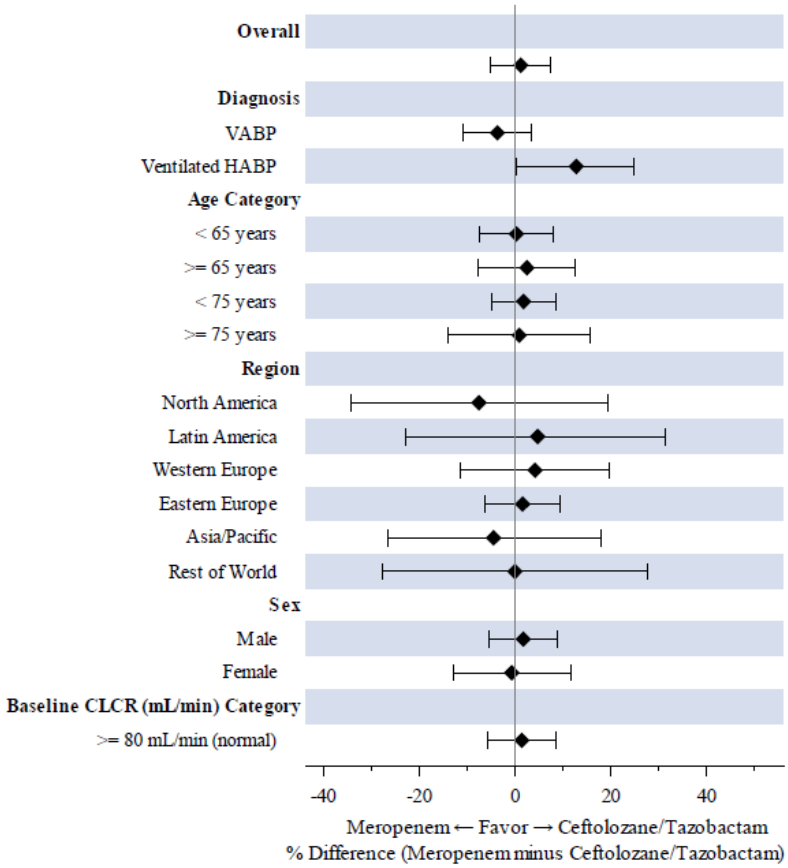
Notes: N=Number of subjects in specific category at baseline. n=Number of subjects with clinical cure at TOC visit in specific category.
Percents are calculated as 100 x (n/N). ESBL+ includes any ESBL enzyme.
Multidrug resistant (MDR) is defined as being non-susceptible to at least one antibiotic from at least 3 of the following antibiotic classes: aminoglycosides, carbapenems, cephalosporins, fluoroquinolones, polymixins, monobactams and penicillins/beta-lactamase, inhibitor combination.

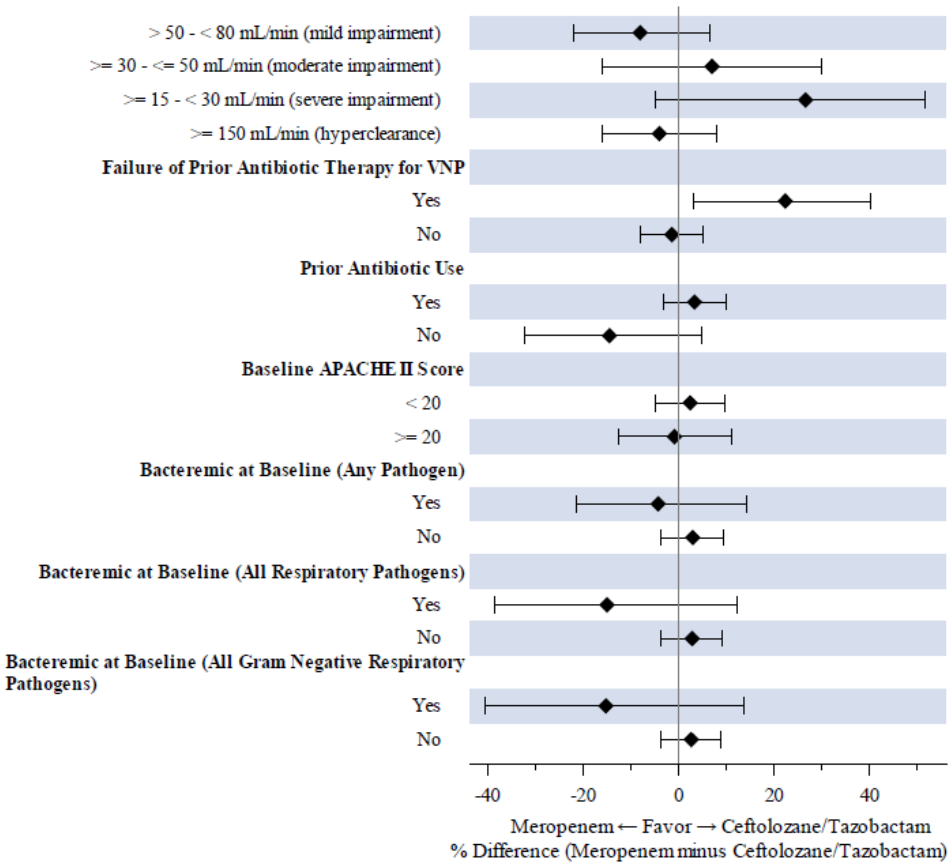
Source: [P008MK7625A: analysis-admb]

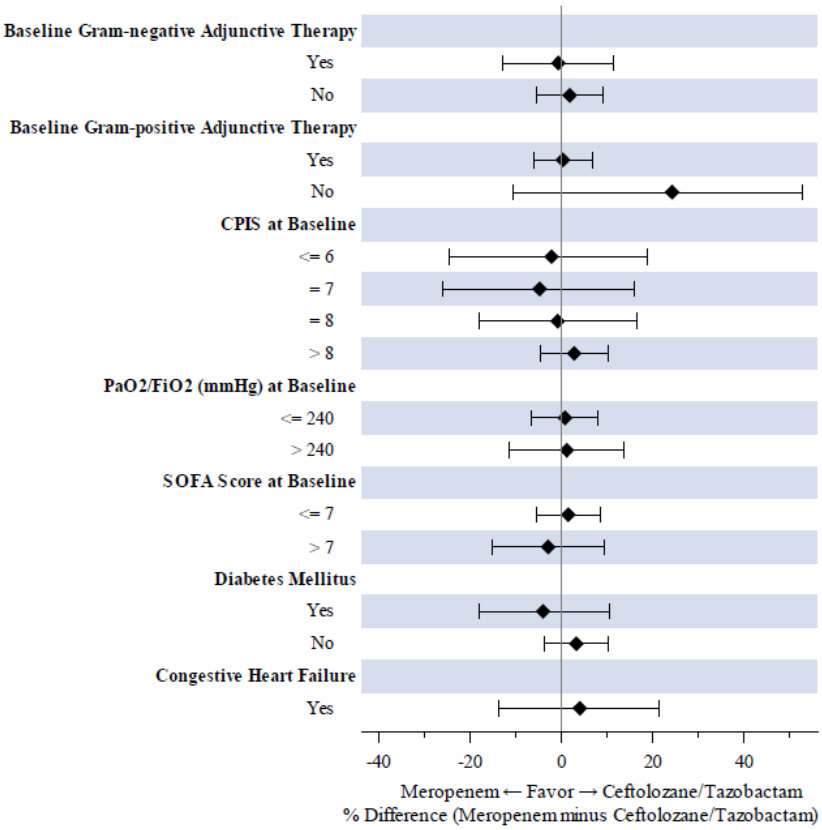
Ancillary analyses

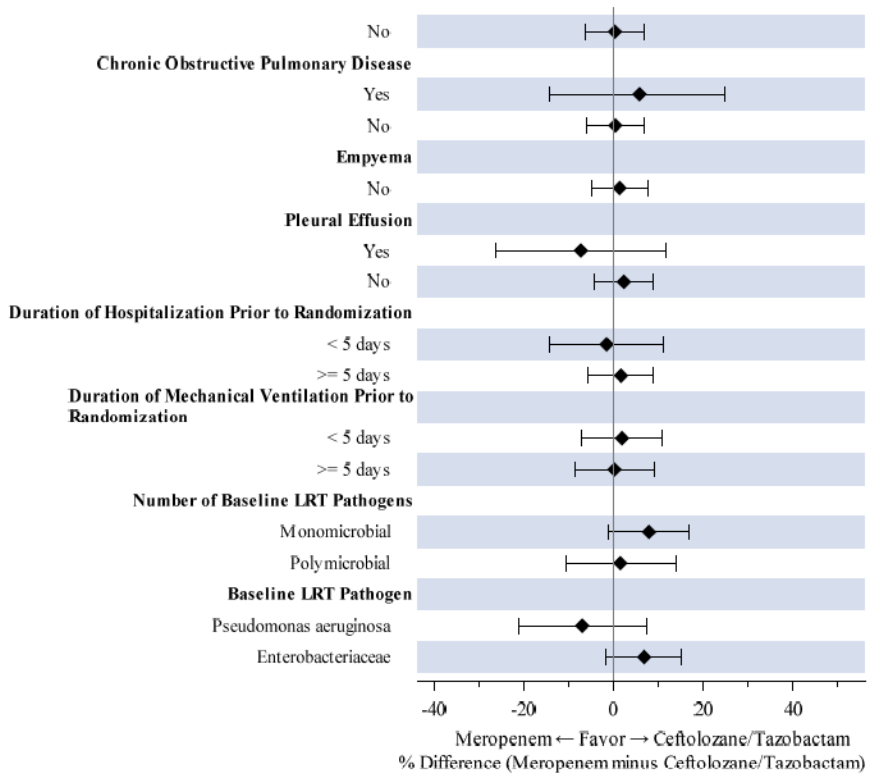
Subgroup analyses

The Forest plots below present a summary of difference in Day 28 All-cause mortality rate by subgroup (ITT population).


Overall
Diagnosis
VABP
Ventilated HABP
Age Category
< 65 years
>= 65 years
< 75 years
>= 75 years
Region
North America
Latin America
Western Europe
Eastern Europe
Asia/Pacific
Rest of World
Sex
Male
Female
Baseline CLCR (mL/min) Category
>= 80 mL/min (normal)
-40
-20
0
20
40
Meropenem ← Favor → Ceftolozane/Tazobactam
% Difference (Meropenem minus Ceftolozane/Tazobactam)


> 50 - < 80 mL/min (mild impairment)
>= 30 - <= 50 mL/min (moderate impairment)
>= 15 - < 30 mL/min (severe impairment)
>= 150 mL/min (hyperclearance)
Failure of Prior Antibiotic Therapy for VNP
Yes
No
Prior Antibiotic Use
Yes
No
Baseline APACHE II Score
< 20
>= 20
Bacteremic at Baseline (Any Pathogen)
Yes
No
Bacteremic at Baseline (All Respiratory Pathogens)
Yes
No
Bacteremic at Baseline (All Gram Negative Respiratory Pathogens)
Yes
No
-40
-20
0
20
40
Meropenem ← Favor → Ceftolozane/Tazobactam
% Difference (Meropenem minus Ceftolozane/Tazobactam)

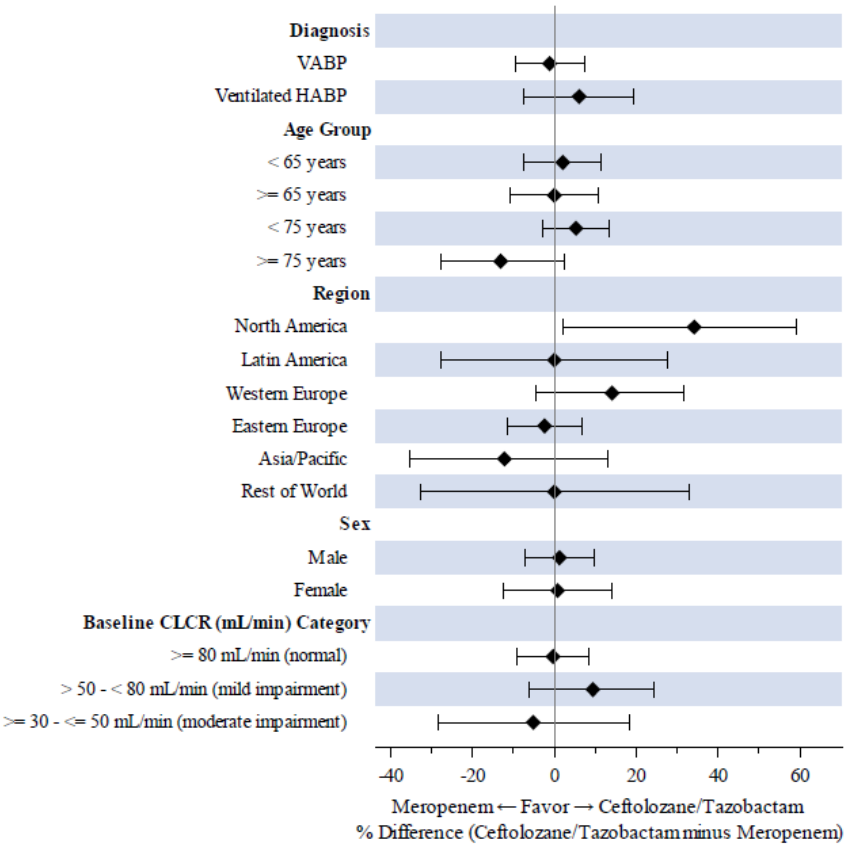


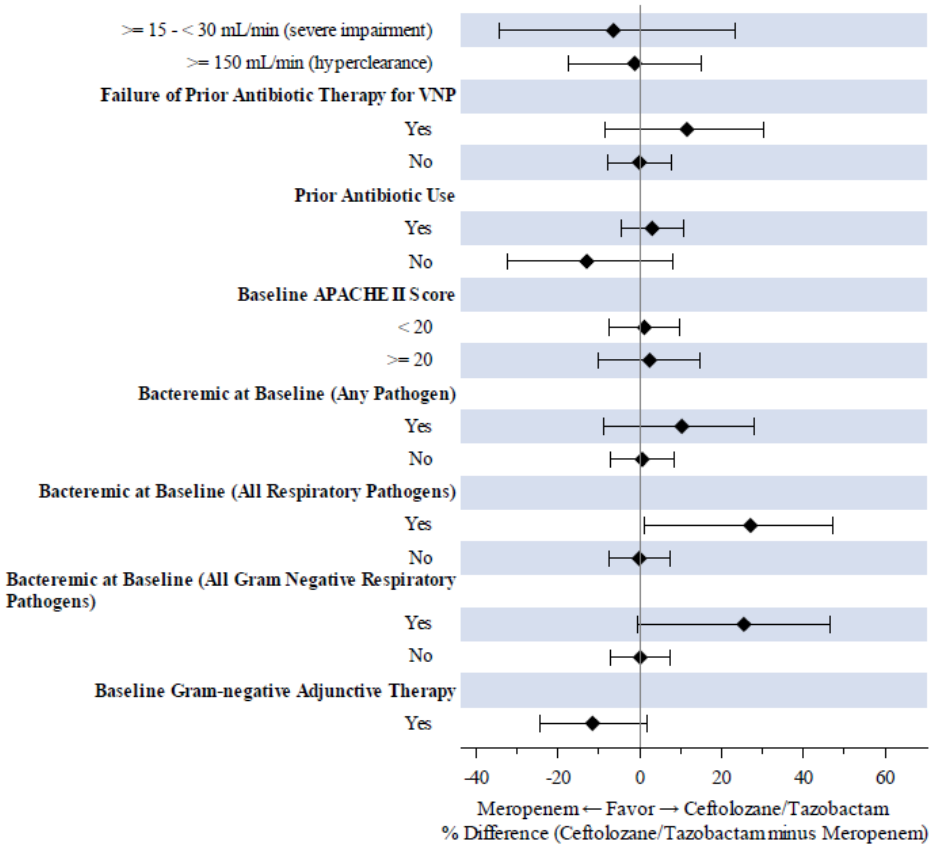


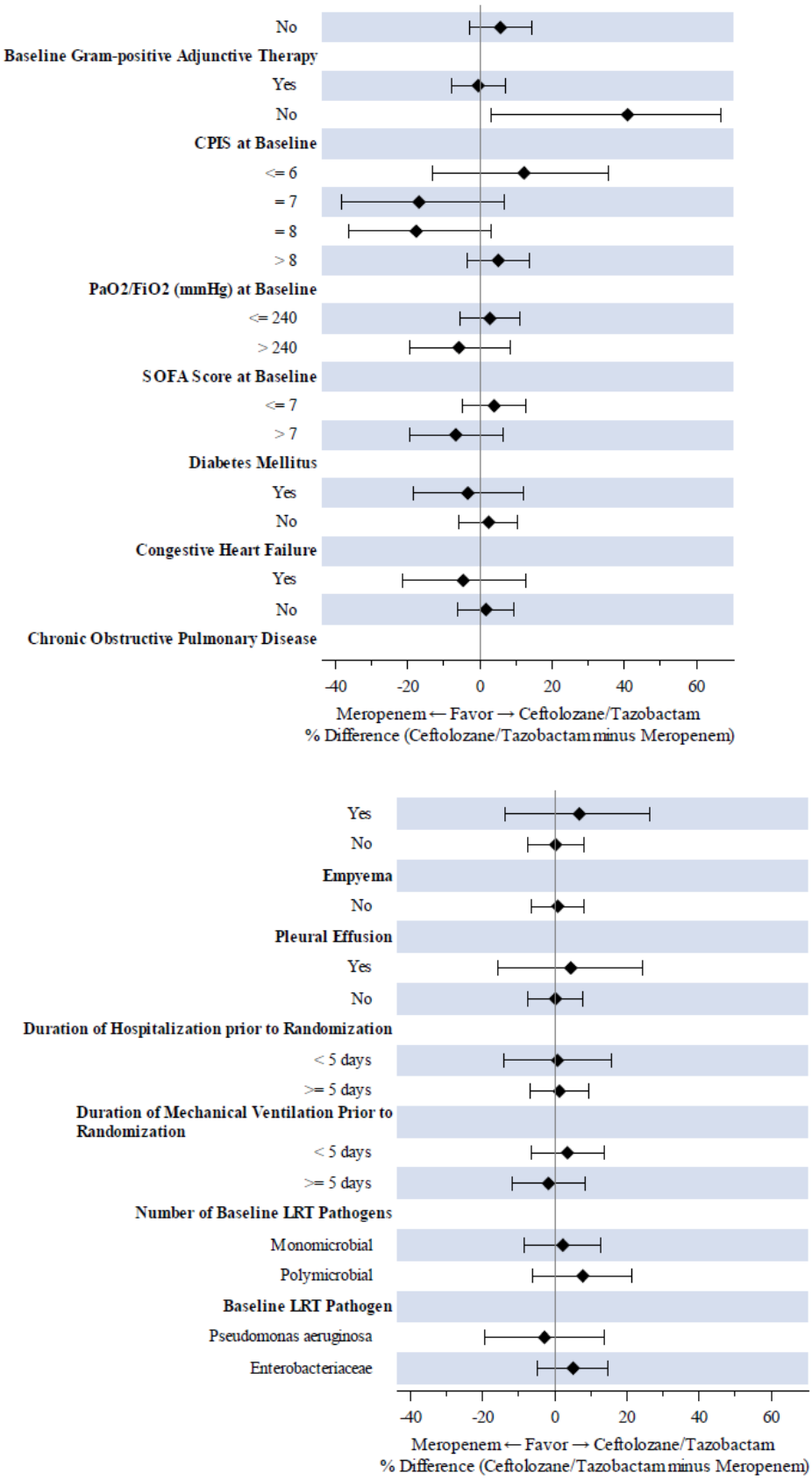
Notes: Subjects whose Day 28 mortality outcomes are missing or unknown are analyzed as deceased. The 95% CIs are unstratified Newcombe CIs. Source: [P008MK7625A: analysis-adsl; adef1]

Figure 16. Difference in Day 28 All-cause mortality rate by subgroup (ITT population)

The Forest plots below present a summary of difference in clinical response at the TOC visit by subgroups.







Notes: The 95% CIs are unstratified Newcombe CIs. Source: [P008MK7625A: analysis-adsl; adef1]

Figure 17. Difference in Clinical Response at Test of Cure (TOC) Visit by Subgroup (ITT Population)

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial PN008

Title: A prospective, randomized, double-blind, multicenter, Phase 3 study to assess the safety and efficacy of intravenous ceftolozane/tazobactam compared with meropenem in adult patients with ventilated nosocomial pneumonia		
Study identifier	EudraCT: 2012-002862-11 NCT: NCT02070757 IND: 104,490	
Design	A phase 3, multicenter, double-blind, randomised, parallel-group, comparative study to determine the efficacy and safety of ceftolozane/tazobactam versus meropenem in the treatment of nosocomial pneumonia including ventilator-associated pneumonia	
	Duration of main phase:	First patient first visit: 16 January 2015 Last patient last visit: 06 June 2018
Hypothesis	For the primary endpoint: Non-inferiority was declared if the lower bound of the stratified 2-sided 97.5% CI for the overall treatment difference in clinical response rate at the TOC visit was greater than -12.5%. For the key secondary endpoint non-inferiority was declared if the lower bound of the stratified 2-sided 97.5% CI for the overall treatment difference in the Day 28 all-cause mortality rate was greater than -12.5%.	
Treatment groups	Ceftolozane/tazobactam	3000 mg (2000 mg ceftolozane and 1000 mg tazobactam) q8h. Infusion time 60 min, 8-14 days duration, 362 patients randomised
	Meropenem	1000 mg q8h, infusion time 60 min, 8-14 days duration, 364 patients randomised

<table>
<tr><td rowspan="2">Endpoints and definitions</td><td>Primary endpoint
Clinical response at the TOC visit in the ITT population</td><td>Clinical response at the TOC visit (7 to 14 days after the EOT visit) is defined as cure, failure or indeterminate.
Cure:
• Complete resolution of all or most of the clinical signs and symptoms of VNP which were present at baseline, AND
• No new signs, symptoms or complications attributable to VNP, AND
• No additional antibiotic therapy administered for VNP*, except for the approved adjunctive therapy, AND
• Patient is alive
*Subjects receiving potentially effective concomitant antibiotic therapy for an indication other than VNP may still be considered a clinical cure provided they meet all other Cure criteria.

Failure:
• Progression, relapse, or recurrence of new symptoms or complications attributable to VNP, OR
• Lack of resolution (persistence), insufficient improvement in signs and symptoms of VNP which were present at baseline, study drug discontinuation due to resistant LRT pathogens, or need for alternative or prolonged antibiotic therapy for treatment of VNP, OR
• Patient died of VNP

Indeterminate:
• Subject prematurely discontinued study drug due to No Growth or only S. aureus isolated from the baseline LRT culture, OR
• Study data are not available for the evaluation of efficacy for any reason including:
o Lost to follow-up
o Withdrawal of consent
o Subject died from cause other than VNP
o Randomized not treated</td></tr>
<tr><td>Key secondary endpoint
Day 28 all-cause mortality in the ITT population</td><td></td></tr>
<tr><td>Database lock</td><td colspan="2">27 July 2018</td></tr>
<tr><td colspan="3">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="2">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="2">Intent to treat population at Test-of Cure (TOC)
ITT population defined as all randomised patients, regardless of whether they received study drug</td></tr>
<tr><td rowspan="3">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>Ceftolozane/tazobactam</td><td>Meropenem</td></tr>
<tr><td>Number of subject</td><td>362</td><td>364</td></tr>
<tr><td>Clinical response</td><td>197 (54.4%)</td><td>194 (53.3%)</td></tr>
</table>

	rate		
	Clinical failure	165 (45.6%)	170 (46.7%)
Effect estimate per comparison	**Primary endpoint**	Comparison groups	Ceftolozane/tazobactam vs. meropenem
		% difference in clinical response rates in ITT analysis set at TOC	1.1%
		Stratified 97.5% Confidence interval	-7.20%, 9.31%
Notes	The 97.5% CIs of % difference are stratified Newcombe CIs. The 97.5% CIs of each treatment are stratified Wilson CIs.		
Analysis description	**Key secondary analysis**		
Analysis population and time point description	All-cause mortality in the Intent to treat population at Day 28		
Descriptive statistics and estimate variability	Treatment group	Ceftolozane/tazobactam	Meropenem
	Number of subject	362	364
	Day 28 All-cause Mortality	87 (24.0%)	92 (25.3%)
Effect estimate per comparison	**Key secondary endpoint**	Comparison groups	Ceftolozane/tazobactam vs. meropenem
		Difference in Day 28 All-cause mortality in ITT analysis set at TOC	1.1%
		Stratified 97.5% Confidence interval	-6.03%, 8.28%
Notes	The 97.5% CIs of % difference are stratified Newcombe CIs.		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Supportive studies

Please refer to Section on Pharmacokinetics.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

One pivotal phase 3 trial (PN008) and three phase 1 trials (**PN018**, **PN028**, **PN007**) have been submitted in order to support the variation application for Zerbaxa (ceftolozane/tazobactam). The applied extension of indication for ceftolozane/tazobactam is as follows: “Nosocomial pneumonia, including ventilator-associated pneumonia.”

Study design. The pivotal trial **PN008** is a multicentre, randomised, double-blind, active-controlled phase 3 study, comparing the efficacy and safety of ceftolozane/tazobactam to meropenem in adult patients with nosocomial pneumonia (NP) (including ventilator-associated pneumonia [VAP] and ventilated hospital-acquired pneumonia [HAP]). Patients were randomised 1:1 to receive either

ceftolozane/tazobactam or meropenem. The treatment duration was 8-14 days. Of note, according to IDSA treatment guideline 2016, the usual treatment duration for nosocomial pneumonia is 7 days. However, there exist situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters. Originally, in the first approved protocol, a fixed treatment duration of 8 days was set, with an exception for when *Pseudomonas* was isolated from baseline culture; in such cases, it was allowed to extend the treatment to 14 days. However, when 433 subjects were enrolled, the protocol was amended to a treatment duration range of 8 to 14 days for all patients. The length of treatment for the patients was at each investigator's discretion. It is acknowledged that patients with these very serious and potentially life-threatening infections have to receive treatment as long as it is considered necessary, however, a set of clinical criteria, common for all participating study centres, guiding the investigators for when the patients should be given treatment beyond 8 days would have led to a more standardized approach across the study centres instead of completely leaving this decision to the individual investigator.

Study population. Patients diagnosed with either ventilated HAP or VAP were eligible to participate in the study provided that: for ventilated HAP: the patient had been either hospitalised for ≥ 48 hours or been discharged from a hospital within the prior 7 days, for VAP: mechanical ventilation had to be received ≥ 48 hours. For both conditions specified clinical signs or/and symptoms had to be fulfilled, in addition to chest radiograph/CT scan and a lower respiratory tract specimen at baseline. Several scoring systems were employed at baseline in order to assist the selection of a severely ill patient population (CPIS, SOFA and APACHE II score). Originally, the APACHE II score were part of the inclusion criteria (required a score of between 12-35 [inclusive]), but, this criterion was later removed after over 400 patients had been included into the study. Nevertheless, the score was still registered from all patients at baseline, but seemingly the change in score was not recorded post-baseline. Changes in the inclusion/exclusion criteria after a significant number of patients have been enrolled can introduce bias. Although the subgroup analysis of patients with APACHE score > 20 or < 20 was inconclusive, a sensitivity analysis conducted on the subset of the 433 patients recruited prior to the change has been provided. This analysis reported the following: the observed treatment differences (TOL/TAZ – meropenem) and their 95% CIs were 4.4 (-9.55, 18.31) for Day 28 All-cause Mortality Rate by stratum and 1.9 (-13.46, 17.08) in the clinical response at Test of Cure (TOC) visit by stratum – EMA analysis. Hence, subjects enrolled under different protocol versions (ITT population) were both similar to overall results, although with more variability and wider confidence intervals, likely due to smaller sample sizes.

Overall, the inclusion and exclusion criteria, including diagnoses, were in line with the CHMP guidance and considered to ensure an enrolment of patients who are representative for the sought indication. It is, however, noted that patients with various comorbidities, such as e.g., NYHA Stage IV congestive heart failure, were excluded from the study, thereby excluding the most severely ill patients.

Concomitant/adjunctive treatments. As ceftolozane/tazobactam only covers infections caused by gram-negative pathogens, the patients were required to receive empiric gram-positive adjunctive treatment (i.e., linezolid or an alternative if viewed necessary) at baseline. Only patients whose culture grew *S. aureus* (MRSA or MSSA) were to continue with linezolid (or alternative). This is acceptable. Subjects were also allowed to receive empiric adjunctive gram-negative (i.e., aminoglycoside-amikacin) therapy for ≤ 72 hours started at baseline at sites with > 15% carbapenem resistant *P. aeruginosa* pending baseline results. This cut-off of 15% was questioned by the SAWP/CHMP. It would require that all study sites had very high quality centre-specific data on recent rates of carbapenem resistance. The applicant refers to the 2016 IDSA/ATS and 2017 International ERS/ESICM/ESCMID/ALAT guidelines which consider a range varying between >10-25% local prevalence of resistant pathogens as representing high-risk. This is acknowledged. Even if it is still unclear why the applicant chose a specific cut-off instead of a range, the study has been finalised and it is not considered that this choice has affected the study results. This issue will therefore not be further pursued.

The handling of patients with resistant pathogens was guided by clinical outcome in order to decide whether to continue or discontinue study therapy. However, there was a potential concern that this may compromise the blinding of the study as ceftolozane/tazobactam has shown good *in vitro* activity against *P. aeruginosa* strains, including meropenem-resistant strains. If laboratory culture data indicated resistance to one of the study drugs, while clinical improvement was observed in a patient, this may have led the investigator to conclude which study drug the patient was receiving. SAWP/CHMP therefore requested that the applicant should provide a justifiable strategy to manage this risk. It was originally proposed that if the patient was responding to therapy (i.e., improving clinical signs compared to baseline) the investigator may either continue study therapy alone (with close monitoring), or continue study drug and add a new non-study antibiotic (e.g. amikacin for *P. aeruginosa*). However, in the protocol version 7, it seems that the latter option no longer was allowed. Based on the patient's response on therapy, the study drug was to be either continued alone or discontinued. However, as the resistance pattern is partly different between ceftolozane/tazobactam and meropenem it could still be possible to reveal which treatment group the patient belonged to. However, as it seems that there were rather few isolates of e.g. resistant *P. aeruginosa* strains in the study, this probably have concerned only a very small number of patients and therefore neither influenced the clinical outcome nor compromised the blinding.

Dose. The chosen dose of ceftolozane/tazobactam was 3000 mg (i.e., 2000 mg ceftolozane and 1000 mg tazobactam) administered every 8 hours as an IV infusion over 1 hour. This dose is higher than the currently approved dose of 1500 mg (i.e., 1000 mg ceftolozane and 500 mg tazobactam) for the indications cIAI and cUTI. The adequacy of TAZ exposure in patients with ARC (hyper clearance) is of concern considering critical importance of the adequate initial antibiotic treatment in patients with NP/VAP and as most patients may likely experience ARC/be ventilated during the treatment period. The applicant is asked to justify acceptability of a PTA <90% for TAZ in patients with ARC considering the severity of infection, difficult-to-treat/less susceptible pathogens and potentially heavy bacterial load, and discuss whether there is a need for dose adjustment to optimize TAZ exposures in patients with different ARC-categories. The applicant is asked to provide additional simulations of alternative dosing regimens for TOL/TAZ with dose increment and/or prolonged infusion that may increase the chance of achieving pre-defined PD targets. For patients with severe renal impairment, the applicant has already proposed a dose adjustment for TOL/TAZ, which however resulted in slightly insufficient/borderline exposures of TAZ (i.e. with a PTA 84%). During the procedure the applicant has justified the acceptability of a PTA <90% for TAZ in patients with severe renal impairment. It is reassuring that very high PTA for TAZ was achieved in plasma (i.e.>98%) in addition to very high TOL PTAs both in ELF and plasma.

Comparator. Meropenem is considered to be a relevant comparator for patients with NP and is approved for use in patients with HAP and/or VAP. The choice of comparator was also discussed with the SAWP and found to be, overall, acceptable.

Meropenem was given in a dose of 1000 mg every 8 hours. In order to facilitate the blinding in the study, an IV infusion over 1 hour was chosen. The dose of meropenem is acceptable and already approved for these severe pneumonias, however, the infusion time is usually recommended to be 15-30 minutes. Taking into consideration that the activity of meropenem is dependent on the proportion of the dosing interval that the drug concentration is greater than the MIC, and that meropenem prepared for infusion is stable for up to 4 hours at room temperature, the 1-hour infusion time is not considered to adversely affect its efficacy. In line with the approved SmPC for meropenem, the dose was adjusted for renally impaired patients.

Conduct of the study

Protocol amendments

The protocol has been amended 10 times (6 global amendments and 4 country-specific amendments, resulting in 7 versions of the protocol), also after the study was initiated and patients enrolled. The protocol changed gradually during the study period including, among other things, removal of inclusion criterion (APACHE II score), change of the analysis population for the primary EMA endpoint, non-inferiority margin (changed in SAP version 5.0) and key secondary endpoint. The MAH has confirmed that all protocol amendments were performed before database lock. Furthermore, the MAH stated that the integrity of the study was not compromised by any changes made to the primary and key secondary endpoints, as these were only changes in the structure of the final statistical analysis and not changes in study conduct or design.

Protocol deviations

In total, there were over 30% of the subjects in the ITT population who had at least one important protocol deviation documented during the study. These deviations included mainly issues such as not meeting inclusion/exclusion criteria (in total 8.8%), lack in safety reporting (in total 2.5%) and not following trial procedures/study interventions (in total 26.2%). The number of patients with protocol deviations was, in general, similar between the two arms. The single protocol deviation that concerned most patients in both study arms was “Patients who were mis-stratified in Bracket (IXRS system)” (26/362, 7.2% in the ceftolozane/tazobactam arm vs. 32/364, 8.8% in the meropenem arm). The applicant conducted a sensitivity analysis (seemingly post-hoc) in order to evaluate the impact of this miss-stratification. This analysis concluded that the miss-stratification only had a minor impact on the result within each stratum of primary diagnosis factor. The high percentage of protocol deviations in the ITT population, led to a rather high percentage of subject data being excluded from the CE population (in total approximately 40%) which might have compromised the robustness of the estimates. In this study, clinical response in the CE population was a secondary endpoint. The results showed that the clinical cure rates were similar between the ceftolozane/tazobactam arm and the meropenem arm for this endpoint and as such supported the results achieved for the primary and key secondary endpoint.

Endpoints. The primary objective for the analysis to be presented to the EMA was to demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in adult subjects with ventilator-associated nosocomial pneumonia based on the difference in clinical response rates in the Intent-to-treat (ITT) population at the TOC visit (7 to 14 days after the EOT visit), using a non-inferiority margin of - 12.5%. Aiming to demonstrate non-inferiority towards an appropriate reference regimen is an acceptable strategy for the sought indication and in line with the recommendation of the CHMP guideline. Key secondary objective was comparison of the Day 28 all-cause mortality rates of subjects in the ceftolozane/tazobactam vs. meropenem arms in the ITT population.

There were a lot of secondary endpoints in this study, and all of these were in line with what is commonly evaluated in studies for antimicrobial medicinal products (i.e., per-subject and per pathogen microbiological responses in the microbiological populations ME in addition to clinical responses in the same populations as well as in the CE population at the EOT, TOC and LFU visits). The per-subject and per pathogen microbiological responses in the mITT population was chosen as exploratory endpoints, however, the results were still provided together with the corresponding results in the ME population.

However, the CHMP guideline and the SAWP/CHMP scientific advice, recommended to view the ITT and the CE population as co-primary. The advice was not followed by the applicant. This is considered unfortunate, as it would have been preferable that the evaluation of the clinical cure rates had been performed in both the ITT and CE populations using the same level of statistical power. It is acknowledged, though, that in the new draft CHMP guideline on the evaluation of medicinal products

indicated for treatment of bacterial infections from 14 January 2019, it is suggested that the primary analysis should be clinical outcome in only the ITT population at the TOC visit. However, this draft is out for consultation until 31 July 2019 and is therefore not yet put into force.

Sample size. The population comprised totally 726 patients; 362 patients in the ceftolozane/tazobactam group vs. 364 patients in the meropenem group. The study was designed to have at least 85.3% power to meet the non-inferiority for the primary endpoint, assuming a cure rate of 58.4% in both arms. It was initially powered at 88%, but power decreased due to the planned futility look by DSMB when approximately 30% of patients had been enrolled. Overall, the sample size used is considered adequate and the power of the study is deemed acceptable.

Statistical methods. The proposed primary analyses as well as the planned supportive analyses are endorsed. A Treatment Failure Approach was applied to handle missing data for mITT and ITT population. This seems conservative and hence is acceptable. Data-as-observed approach was applied to handle missing data for clinical responses in ME and CE populations. This approach is generally not recommended in confirmatory studies due to risk of population selection bias and reduction of power and underestimation of variability (EMA/CPMP/EWP/1776/99 Rev. 1). A sensitivity analysis whereby another imputation approach is applied was provided by the applicant during the procedure. This analysis demonstrated that the observed treatment differences (TOL/TAZ – meropenem) and their 95% CIs were 3.4 (-3.60, 10.32) in the CE at TOC population and 4.0 (-2.61, 10.58) in the ME at TOC population, both meeting the non-inferiority criterion of TOL/TAZ compared to meropenem.

Efficacy data and additional analyses

Baseline characteristics. Since patients with NP, in particular those receiving mechanically assisted ventilation, are usually very ill and have multiple co-morbidity factors, it is crucial for a clinical study on this condition to ensure that the included population is as representative as possible. In the current study, an adequate number of patients with different risk factors were included; APACHE II scores over 15 in > 70% (and mean value of 17), the majority of patients had CPIS score > 8, relatively high percentage of high age (44% ≥ 65 years old whereof > 20% ≥ 75 years of age) and > 70% were diagnosed with VAP. This is reassuring and contributes to the external validity of the study. Subjects were hospitalized for a mean duration of 10.4 days prior to randomization, and 49.3% were ventilated for ≥5 days prior to randomization. The fact that patients had been hospitalised as long as 10 days (on average) before randomisation would ensure that most patients have acquired infection from pathogens located in the hospital environment. Only 14.5% of patients had bacteraemia at baseline (in the pooled ceftolozane/tazobactam and meropenem group). There was a relatively low total number of subjects with moderate (8.4%) or severe renal failure (5.2%) and co-morbidities like COPD (12%), diabetes (22%) and congestive heart failure (16%), however, this is a consequence of the exclusion criteria which prevent the most severely ill patients from being included into the study.

Baseline microbiology. Endotracheal aspirate (ETA) was the dominant method for the specimen collection (ca. 50% in both arms). This is considered acceptable as ETA is now suggested as superior to invasive or non-invasive sampling with quantitative cultures (BMJ 2016). The pathogens isolated at baseline reflect the pattern of pathogens most commonly detected for NP. The most common gram-negative pathogens isolated at baseline in both treatment groups were *K. pneumoniae* (approx. 35%), *P. aeruginosa* (25%) and *E. coli* (18%). In total, approximately 63% of the randomised patients in the two study groups had a mono-microbial infection and at least one valid pathogen at baseline. Nearly all of the patients (98%) in the mITT population had a gram-negative LRT pathogen isolated at baseline.

Both ceftolozane/tazobactam and meropenem showed significant activity against most LRT pathogens. Overall, the ceftolozane/tazobactam and meropenem MIC distributions for the most common LRT pathogens at baseline were similar across the mITT and ME populations. The favourable

ceftolozane/tazobactam susceptibility data for *P. aeruginosa* is encouraging, and may pose an advantage for the study drug compared to alternative regimens. However, the number of isolates with MIC ≥8 µg/mL encountered in the study PN008 were in general limited, especially with *P. aeruginosa* isolates (n=5).

The susceptibility interpretation at baseline was performed using provisional breakpoints for ceftolozane/tazobactam. In general, the susceptibility data were comparable between ceftolozane/tazobactam and meropenem. It is noted, though, that 54/175 (30.9%) *K. pneumoniae* LRT isolates were resistant to ceftolozane/tazobactam compared to 1/176 (0.6%) isolates resistant to meropenem.

Primary and key secondary endpoint. Non-inferiority of ceftolozane/tazobactam compared to meropenem was demonstrated for both the primary endpoint "clinical response at TOC in the ITT population" (197/362, 54.4% in the ceftolozane/tazobactam arm vs. 194/364, 53.3% in the meropenem arm) and for the key secondary endpoint, "Day 28 all-cause mortality in the ITT population" (87/362, 24.0% in the ceftolozane/tazobactam arm vs. 92/364, 25.3% in the meropenem arm). The lower limits of the stratified 97.5% CIs were within -12.5% for the primary endpoint (**1.1** [-7.20, 9.31]) and for the key secondary endpoint (**1.1** [-6.03, 8.28]).

The results from the sensitivity analysis were consistent with the results achieved in the primary analysis and key secondary analysis for the ITT population, indicating that the stratification factors diagnosis (HAP or VAP) and age (≥ 65 or < 65 years) did not impact on the primary results, thereby demonstrating the robustness of the primary analyses.

Concerning the diagnosis VAP, the clinical response rate was similar for patients in the ceftolozane/tazobactam group and patients in the meropenem group (i.e., 147/263, 55.9% vs. 146/256, 57.0%, respectively). A tendency towards a numerically higher Day 28 all-cause mortality rate was observed for the diagnosis VAP in the ceftolozane/tazobactam group (63/263, 24.0%) vs. the meropenem group (52/256, 20.3%). For the diagnosis ventilated HAP, a tendency towards numerically higher cure rate in the ceftolozane/tazobactam group vs. the meropenem group (50/99, 50.5% vs. 48/108, 44.4%) and lower mortality rate (24/99, 24.2% vs. 40/108, 37.0%) was seen.

Other secondary endpoints.

Clinical response rates. The clinical cure rates in the CE population were similar between the ceftolozane/tazobactam and meropenem arms (139/218, 63.8% vs. 143/221, 64.7%, respectively). For both groups, the rate was higher compared to the cure rate reported for the ITT population (primary analysis). However, as already previously mentioned, due to the high percentage of exclusion of patients from this population (ca. 40%), the robustness of the estimates might have been compromised.

In the mITT and ME populations the clinical cure rates were similar to the results seen in the CE population. They were also comparable between the two treatment arms. It is noted that the clinical cure rate at TOC showed a numerical trend in favour of ceftolozane/tazobactam in the ME population (87/115, 75.7% vs. 78/118, 66.1% in the meropenem arm).

Microbiological response rates.

Per-subject microbiological response: The majority of subjects in the mITT population in both the ceftolozane/tazobactam group (193/264 [73.1%] subjects) and the meropenem group (168/247 [68.0%] subjects) had a favourable microbiological response. The results were consistent between the mITT and ME populations in both study groups for the TOC visit.

Per-pathogen microbiological response: In general, the microbiological response rates by pathogen showed similar response rates for ceftolozane/tazobactam compared to meropenem. It is unclear how many of the isolates that were eradicated and how many were only presumed eradicated. In the

applicant's response, it was clarified that for nearly half of the baseline pathogens, the highest percentage was presumed eradicated and this was the case for both arms. Overall, the differences between the eradicated rate and the presumed eradicated rate for the two arms were rather small and consistent with the observations made for the eradication and presumed eradication rate taken together as previously presented by the applicant.

The microbiological eradication rates were higher in the ceftolozane/tazobactam group compared with the meropenem group for *P. aeruginosa* (47/63, 74.6% vs. 41/65, 63.1%), Enterobacteriaceae (145/195, 74.4% vs. 129/185, 69.7%) and *H. influenzae* (20/22, 90.9% vs. 11/16, 68.8%). The response rates were lower for ceftolozane/tazobactam vs. meropenem for ESBL+ *K. pneumoniae* (33/53, 62.3% vs. 38/52, 73.1%). Although there was approximately 11% difference in the microbiological response rates in the mITT population, it is difficult to draw any firm conclusions regarding the efficacy toward these isolates considering the overall outcomes. As already noted, 49.5% (52/105) of ESBL + *K. pneumoniae* isolates treated in the study were resistant to ceftolozane/tazobactam while none were resistant to meropenem (0/105). The distribution of these isolates between the study arms is, however, unknown. The applicant was asked to specify the distribution of resistant isolates to the study arms, and discuss whether this might explain the lower microbiological response rates for ESBL + *K. pneumoniae* in the ceftolozane/tazobactam arm compared to the meropenem arm (i.e. 62.3% [33/53] vs. 73.1% [38/52], respectively). The applicant presented the microbiological outcome in the ceftolozane/tazobactam arm for subjects with ESBL positive *K. pneumoniae* that were resistant to ceftolozane/tazobactam. stating that 28 ESBL + *K. pneumoniae* resistant isolates were present in the ceftolozane/tazobactam arm. Comparisons were made between the patients with ESBL + *K. pneumoniae* resistant isolates as baseline LRT pathogen and the overall patient population receiving ceftolozane/tazobactam with regards to clinical response rate and the Day 28 all-cause mortality rate. Furthermore, the results for the per-pathogen microbiological response rate for the total ESBL + *K. pneumonia*e (susceptible + intermediate + resistant) in the ceftolozane/tazobactam arm were compared to the per-pathogen microbiological response rate for the ceftolozane/tazobactam arm with only ESBL + *K. pneumoniae* resistant isolates. The results showed that all the rates were comparable between the two groups, and therefore it seems like the observed difference noted between the treatment arms for the species was not entirely driven by resistance against ceftolozane/tazobactam. However, as the number of ESBL + *K. pneumoniae* resistant isolates was very limited, the results could also be random. It is therefore not possible to draw any firm conclusions and the issue will not be further pursued.

The applicant was asked to discuss the risks associated with using ceftolozane/tazobactam empirically in clinical settings in case of infections caused by ESBL+ *K. pneumoniae* and propose risk mitigation measures to avoid that risk. In their response, the MAH referred to that in the setting of empiric use, local epidemiology and susceptibility patterns will inform whether ceftolozane/tazobactam is likely to provide benefit to the patient. The answer from the MAH is noted. In addition, the information in Section 5.1 in the SmPC now adequately reflects the pathogens that are susceptible and resistant respectively towards ceftolozane/tazobactam in order to guide prescribers in choosing the most potentially effective antibacterial agent in an empirical setting. The MAH states in the RMP that they will continue to monitor the emergence of bacterial resistance to ceftolozane/tazobactam through routine PV.

Concerning *P. aeruginosa* overexpressing AmpC (9 isolates in the ceftolozane/tazobactam group vs. 6 in the meropenem group), the number of samples was unfortunately too low to make any valid assumptions.

Overall, the results in the ME analysis population were consistent with those in the mITT population for both study groups. It is noted that in this population the response rates for ESBL+ *K. pneumoniae* were similar for the ceftolozane/tazobactam and meropenem group, respectively (20/30, 66.7% vs. 18/27, 66.7%).

No trend for outcome by MIC could be discerned.

Non-study concomitant antibiotic medication. Twenty-one percent (77/362) of patients in the ceftolozane/tazobactam arm received carbapenems as non-study concomitant antibiotic medication. Of these patients, 17.4% (63/362) received meropenem. The concomitant antibiotics could be administered at any time during the treatment period. It is therefore uncertain at which time point patients might have received carbapenems and for which duration. This concomitant administration of carbapenems (including meropenem) as "any non-study concomitant antibiotic medication" to the patients in the ceftolozane/tazobactam arm might have impacted the clinical and microbiological response rates. This hampers the interpretation of the efficacy outcomes due to the assumed bias, and raises a question whether the efficacy of ceftolozane/tazobactam might have been overestimated. During the procedure the MAH clarified that 58/362 (16%) in the ceftolozane/tazobactam group and 39/364 (10.7%) in the meropenem group received carbapenems as non-study concomitant medication before TOC. According to the MAH, given that, only 2 subjects received ≥1 dose of a non-study carbapenem concomitantly with study drug treatment (i.e., until EOT), there is no expected impact on the results of the primary endpoints or microbiological response rates. While this is agreed, considering that clinical cure at TOC is the primary endpoint, it is the number of patients receiving a non-study carbapenem from study start to TOC visit that is of interest and could have an impact on the primary endpoint results. As requested, the MAH has performed a sensitivity analysis where the 10/58 patients in the ceftolozane/tazobactam arm receiving non-study carbapenems up until TOC vs. the corresponding 7/39 patients in the meropenem arm, were calculated as clinical failures. This analysis demonstrated that this re-calculation did not impact the final study results (clinical response at TOC: 187/362, 51.7% [failures: 175/362, 48.3%] for the ceftolozane/tazobactam arm vs. 187/364, 51.4% [failures: 177/364, 48.6%] for the meropenem group). Most of the patients receiving concomitant carbapenems were clinical failures at EOT and needed further treatment for the pneumonia. Since the results from the sensitivity analysis in which patients receiving concomitant carbapenems were regarded as clinical failures were comparable to the results in the overall study population, it is agreed that the use of concomitant carbapenems before TOC probably have not affected the clinical outcome of the study.

Subgroups. In general, for the majority of the subgroups the cure rates or mortality rates showed no or only minor difference between the two study groups or were numerically in favour of the ceftolozane/tazobactam group. However, imbalances were observed between the following subgroups: The Day 28 All-cause mortality rate in the subgroup of patients with *P. aeruginosa* as baseline LRT pathogen, tended to be higher in the ceftolozane/tazobactam group vs. the meropenem group (16/63, 25.4% vs. 12/65, 18.5%, respectively). The same tendencies were also seen for the subgroups bacteremic at baseline (all respiratory pathogens, 14/29, 48.3% vs. 7/21, 33.3%) and bacteremic at baseline (all gram-negative respiratory pathogens, 13/25, 52.0% vs. 7/19, 36.8%). The MAH clarified that there are differences in the demographics of TOL/TAZ versus meropenem: a higher percentage of subjects ≥75 years old in the TOL/TAZ group (23.8%) compared to the meropenem group (16.9%), a higher rate of subjects that had failed prior antibiotic therapy (17.5% vs. 6.2%) and of subjects that were bacteremic at baseline (27.0% vs. 10.8%). In addition, there was a higher proportion of subjects with different co-morbidities (i.e. diabetes, congestive heart failure) in the TOL/TAZ group than in the meropenem group. It is agreed that these differences in demographic factors between the treatment groups might have affected the study results.

Clinical cure rates for ceftolozane/tazobactam compared to meropenem tended to be lower in those ≥75 years of age (35/83, 42.2% vs. 42/76, 55.3%), having had no prior antibiotic therapy (19/44, 43.2% vs. 23/41, 56.1%) and having had baseline gram-negative adjunctive therapy (47/103, 45.6% vs. 64/112, 57.1%). During the procedure the MAH clarified that increased failure rate in patients >75 years of age as well as patients who did not receive any antibiotic therapy prior to study entry may be attributed to the differences in demographics of ceftolozane/tazobactam versus meropenem-treated subjects in this

subgroup as ceftolozane/tazobactam subjects displayed more high-risk characteristics at baseline. This is considered reasonable. It is also agreed that rates of susceptibility to study therapy which were lower in the subjects with Enterobacteriaceae in the ceftolozane/tazobactam group compared to the meropenem group (84.4% vs. 100%) could contribute to a lower clinical response rate in the ceftolozane/tazobactam group.

Furthermore, the applicant was asked to state how many of the patients with impaired renal function did receive the per-protocol (CE) defined reduced dose regimen and specify the outcome. The MAH clarified that all subjects with moderate/severe renal impairment at baseline received the per-protocol reduced dose within the treatment period. Fifty-two (14.4%) patients with moderate/severe renal impairment were treated with TOL/TAZ, while 47 (12.9%) were treated with meropenem. In 32 (61.5%) and 26 (55.3%) patients treated with TOL/TAZ and meropenem, respectively, the treatment failed.

2.4.4. Conclusions on the clinical efficacy

In general, the included patient population is considered to be representative for the applied indication. Non-inferiority of ceftolozane/tazobactam to meropenem has been clearly demonstrated in these patients for the primary and key secondary endpoint. The issues related to efficacy has been adequately addressed. No outstanding concerns remains. Conclusion on the efficacy of ceftolozane/tazobactam in the indication of NP including VAP is considered demonstrated. Hence, Zerbaxa may be granted an extension of the current indication from the efficacy point of view.

2.5. Clinical safety

Introduction

The safety assessment is based on a single phase III study **PN008** (P008MK7625A) where ceftolozane/tazobactam 3 g dose is compared to meropenem 1 g dose. A total of 361 patient were exposed to ceftolozane/tazobactam.

Current tabulated adverse reactions (SPC).

Table 48. Adverse reactions identified during clinical trials with ceftolozane/tazobactam (N=1,015)

System organ class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Infections and infestations		Candidiasis including oropharyngeal and vulvovaginal, *Clostridium difficile* colitis, fungal urinary tract infection
Blood and the lymphatic system disorders	Thrombocytosis	Anaemia
Metabolism and nutrition disorders	Hypokalemia	Hyperglycaemia, hypomagnesaemia, hypophosphataemia
Psychiatric disorders	Insomnia, anxiety	
Nervous system disorders	Headache, dizziness	Ischemic stroke
Cardiac disorders		Atrial fibrillation, tachycardia, angina pectoris
Vascular disorders	Hypotension	Phlebitis, venous thrombosis
Respiratory, thoracic, and mediastinal disorders		Dyspnoea
Gastrointestinal disorders	Nausea, diarrhoea, constipation, vomiting, abdominal pain	Gastritis, abdominal distension, dyspepsia, flatulence, ileus paralytic
Skin and subcutaneous tissue disorders	Rash	Urticaria
Renal and urinary disorders		Renal impairment, renal failure
General disorders and administration site conditions	Pyrexia, infusion site reactions	
Investigations	Alanine aminotransferase increased, Aspartate aminotransferase increased	Coombs test positive, increased serum gamma-glutamyl transpeptidase (GGT), increased serum alkaline phosphatase

Table 49. Summary of Safety Concerns (from current RMP)

Important identified risks	• Hypersensitivity reactions • Clostridium difficile-associated diarrhoea • Renal impairment • Medication errors
Important potential risks	• Emergence of bacterial resistance to ceftolozane/tazobactam • Severe skin reactions • Haemolytic anaemia
Missing information	• Safety and efficacy in paediatric patients < 18 years old • Safety and efficacy in immunocompromised patients • Off-label use

Patient exposure

In study P008MK7625A in nosocomial pneumonia, a total of 726 subjects were randomized: 362 subjects to ceftolozane/tazobactam and 364 subjects to meropenem. All subjects randomized were included in the ITT population. The safety population consisted of all subjects in the ITT that received any amount of study drug: 361 in the ceftolozane/tazobactam arm and 359 in the meropenem arm.

Table 50. Disposition of subjects (P008MK7625A Pneumonia)

	Ceftolozane/Tazobactam (N=362)	Meropenem (N=364)	Total (N=726)
Number of Subjects Randomized but Did Not Receive Study Drug [1]	1 (0.3)	5 (1.4)	6 (0.8)
Number of Subjects Completing Study Drug [1]	263 (72.7)	271 (74.5)	534 (73.6)
Number of Subjects Prematurely Discontinuing Study Drug, N1 [1]	98 (27.1)	88 (24.2)	186 (25.6)
Reasons for Premature Discontinuation of Study Drug [2]			
All baseline LRT pathogens resistant to both study drugs	13 (13.3)	11 (12.5)	24 (12.9)
Gram-negative adjunctive therapy continued/started beyond 72 hours or study treatment regimen changed	4 (4.1)	2 (2.3)	6 (3.2)
Investigator decision based on no growth or only S. aureus isolated on baseline LRT culture	4 (4.1)	4 (4.5)	8 (4.3)
Development of ESRD [CrCL <15 mL/min], oliguria [<20 mL/h urine output over 24 hours], or requirement for dialysis or hemofiltration	3 (3.1)	0	3 (1.6)
Adverse event	36 (36.7)	42 (47.7)	78 (41.9)
Suspected or confirmed pregnancy or nursing	0	0	0
Insufficient therapeutic effect	23 (23.5)	15 (17.0)	38 (20.4)
Lost to follow-up	1 (1.0)	0	1 (0.5)
Withdrawal by subject	2 (2.0)	1 (1.1)	3 (1.6)
Investigator decision	8 (8.2)	7 (8.0)	15 (8.1)
Protocol deviation	2 (2.0)	1 (1.1)	3 (1.6)
Other	2 (2.0)	5 (5.7)	7 (3.8)
Number of Subjects Completing Study [1]	245 (67.7)	250 (68.7)	495 (68.2)
Number of Subjects Prematurely Withdrawing from Study, N2 [1]	117 (32.3)	114 (31.3)	231 (31.8)
Reasons for Premature Withdrawal from Study [3]			
Lost to Follow Up	7 (6.0)	4 (3.5)	11 (4.8)
Adverse Event	107 (91.5)	99 (86.8)	206 (89.2)
Protocol Deviation	0	4 (3.5)	4 (1.7)
Withdrawal by Subject, Decline Follow up	1 (0.9)	3 (2.6)	4 (1.7)
Investigator Decision	0	2 (1.8)	2 (0.9)
Other	2 (1.7)	2 (1.8)	4 (1.7)

Notes: n=Number of subjects in specific category. N=Number of subjects in ITT population. N1=Number of subjects prematurely discontinuing study drug in ITT population. N2=Number of subjects prematurely withdrawing from study in ITT population.
ESRD: end stage renal disease. Premature discontinuation or withdrawal due to adverse event includes death.

The majority (63%) of subjects received between 8 and 14 days of study therapy as specified in the protocol, with comparable mean duration of exposure in both treatment groups; 20.7% of subjects received less than the specified minimum treatment course of 8 days.

Adverse events

A high proportion of subjects in both treatment groups experienced TEAEs (84.6%), including a substantial proportion of subjects who experienced serious TEAEs (39%) and fatal TEAEs (28.6%). In general, the incidence of TEAEs and deaths were reported in a similar proportion of subjects in each treatment group. None of the deaths were considered to be related to the study drug therapy. The incidence of drug-related TEAEs, drug-related serious TEAEs, and TEAEs leading to discontinuation of study drug were low and similar between the treatment groups. Overall, 45.8% of subjects had TEAEs that were mild to moderate in severity whereas 38.8% had severe TEAEs. The proportion of subjects in

each category of severity was similar between the treatment groups. The incidence of serious TEAEs was higher in the ceftolozane/tazobactam group (42.1%) compared with the meropenem group (35.9%).

Table 51. Overall Summary of Treatment Emergent Adverse Events (Safety Population)

Adverse Event Category	Ceftolozane/Tazobactam (N=361) n (%)	Meropenem (N=359) n (%)	Total (N=720) n (%)
Number of Subjects with Any TEAEs	310 (85.9)	299 (83.3)	609 (84.6)
Number of Subjects with Any TEAE by Maximum Severity [1]			
Mild	69 (19.1)	58 (16.2)	127 (17.6)
Moderate	98 (27.1)	105 (29.2)	203 (28.2)
Severe	143 (39.6)	136 (37.9)	279 (38.8)
Number of Subjects with Any Treatment-Related TEAE [2]	38 (10.5)	27 (7.5)	65 (9.0)
Number of Subjects with Any Serious TEAE	152 (42.1)	129 (35.9)	281 (39.0)
Number of Subjects with Any Treatment-Related Serious TEAE [2]	8 (2.2)	2 (0.6)	10 (1.4)
Number of Subjects with Any TEAE Leading to Discontinuation of Study Drug	37 (10.2)	42 (11.7)	79 (11.0)
Number of Subjects with Any Treatment-Related TEAE Leading to Discontinuation of Study Drug [2]	4 (1.1)	5 (1.4)	9 (1.3)
Number of Subjects with Any TEAE which Resulted in Death	105 (29.1)	101 (28.1)	206 (28.6)
Number of Subjects with Any Treatment-Related TEAE which Resulted in Death [2]	0	0	0

Notes: n=Number of subjects in specific category. N=Number of subjects in Safety population. Percents are calculated as 100 x (n/N).
Adverse events are coded using MedDRA version 17.0. TEAE=Treatment Emergent Adverse Event. A TEAE is defined as an AE that starts on/after the first study drug administration.
For each category, subjects are counted only once, even if they experienced multiple events in the category.

1. If subjects have multiple events, they are counted only once with the maximum (highest) severity rating. The orders of severity from worst case to best case are severe, moderate, and mild.
2. If subjects have multiple events and at least one is related, then the AE is counted as related to study drug.

Most Frequently Reported Adverse Events

In general, the incidence of subjects with TEAEs and the types of TEAEs seen were generally similar between the 2 treatment groups, distributed across multiple body systems, and typical of ventilated subjects with NP receiving antibiotic therapy, many of whom had significant underlying comorbidities and multiple concomitant therapies which contributed to the reported events.

Anemia, urinary tract infection, diarrhea, and decubitus ulcer were the most frequently reported TEAEs (>5% of subjects overall) during the study and occurred in a similar proportion of subjects in each treatment group. TEAEs that occurred in ≥5% of subjects in the ceftolozane/tazobactam group included anemia, decubitus ulcer, urinary tract infection, diarrhea, and increased ALT and AST. The majority of the TEAEs of increased ALT and AST in the ceftolozane/tazobactam group were mild or moderate in severity and not related to study drug therapy. In the meropenem group, anemia, urinary tract infection, diarrhea, hydrothorax, and hypotension occurred in ≥5% of subjects. Note that for each preferred term, subjects were counted only once even if they experienced multiple events of the preferred term. No TEAE was reported in more than 10% of subjects overall; the only TEAE preferred term reported in >10% of subjects in either treatment group was anemia reported in the meropenem group.

The SOCs with the highest percentage of subjects with TEAEs were infections and infestation (35.3% of subjects overall) and gastrointestinal disorders (24.6% of subjects overall) and occurred in a similar proportion of subjects in each treatment group.

Severity

Overall, 45.8% of subjects had TEAEs that were mild to moderate in severity, whereas 38.8% had severe TEAEs. The proportion of subjects with mild, moderate, or severe TEAEs was similar between the treatment groups. The high percentage of severe TEAEs was not unexpected in this critically ill population with underlying comorbid conditions.

Related to Study Treatment

The incidence of investigator-assessed, drug-related TEAEs was low and comparable in the 2 treatment groups (38 [10.5%] subjects in the ceftolozane/tazobactam group and 27 [7.5%] subjects in the meropenem group. Diarrhea, increased ALT and AST, and increased hepatic enzyme were the most common drug-related TEAEs (≥0.8% of subjects overall) and occurred in a similar proportion of subjects in each treatment group.

A total of 8 (1.1%) subjects (5 [1.4%] subjects in the ceftolozane/tazobactam group and 3 [0.8%] subjects in the meropenem group) had drug-related TEAEs that were considered severe. In the ceftolozane/tazobactam group, the events were bradycardia, diarrhea, hepatic failure, systemic candida, increased ALT, increased AST, and increased gamma glutamyl transferase. The events of increased ALT, AST, and gamma glutamyl transferase, which were considered serious TEAEs and resulted in discontinuation of study therapy, all occurred in a single subject. These increases did not meet laboratory criteria for potential drug-induced liver injury. The TEAE of hepatic failure, which resulted in discontinuation of study therapy, represented a worsening of a baseline medical history of hepatic failure in this subject admitted following cardiac arrest. The event was not considered serious and did not meet laboratory criteria for potential drug-induced liver injury. In the meropenem group, the drug-related TEAEs that were considered severe were diarrhea, cholestatic hepatitis, and *C. difficile* infection.

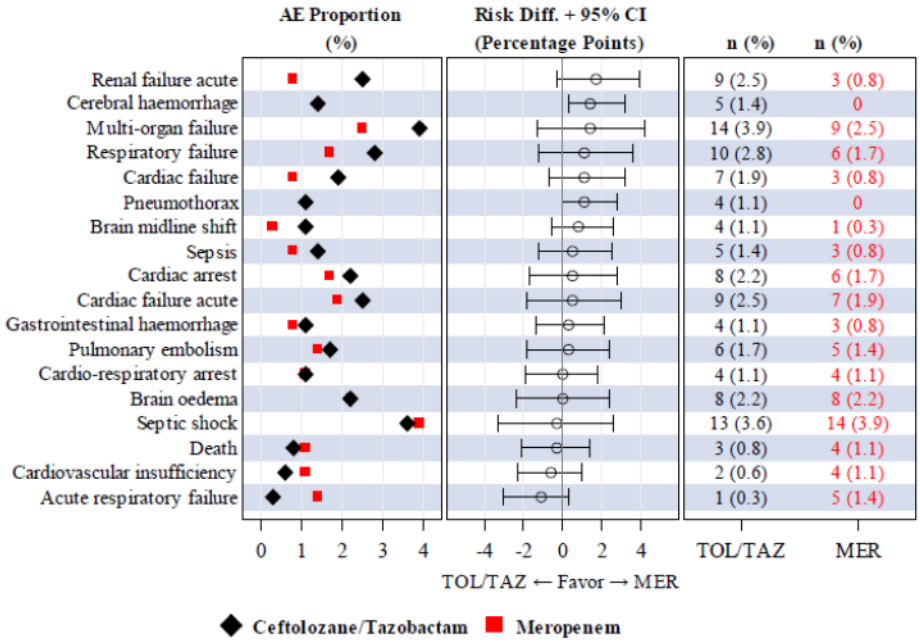
Serious adverse event / deaths / other significant events

Serious Adverse Events

A substantial proportion of subjects experienced serious TEAEs (281 [39%]) in both treatment groups, consistent with the critically ill population under study. The proportion of subjects with serious TEAEs was higher in the ceftolozane/tazobactam group (42.1%) compared to the meropenem group (35.9%). No single SOC or preferred term was responsible for this imbalance.

A post-hoc safety analysis was conducted to evaluate the magnitude of treatment differences in serious TEAE rates and associated 95% CIs for various serious TEAEs. Results of these analyses confirm that the 95% CI for the overall treatment difference in the serious TEAE rate included 0. The serious TEAEs that occurred more frequently in the ceftolozane/tazobactam group were widely distributed among a variety of SOCs and preferred terms.

Figure 18. Analysis of Subjects with Serious Adverse Events (Incidence >=1% Subjects in One or More Treatment Groups) (Safety Population) Ceftolozane/Tazobactam (N=361) vs. Meropenem (N=359)



Notes: TOL/TAZ = Ceftolozane/Tazobactam; MER = Meropenem
Source: [P008MK7625A: analysis-adsl; adae]

The 12 serious TEAE preferred terms that occurred in >1% of subjects and were more frequent in the ceftolozane/tazobactam group were distributed across 7 different SOCs. Among these, cerebral hemorrhage, which occurred in 5 subjects in the ceftolozane/tazobactam group and no subjects in the meropenem group, was the only serious TEAE preferred term with a 95% CI for risk difference that did not include 0. In 4 of these 5 subjects, the cerebral hemorrhage represented a worsening of underlying intracranial hemorrhage that was present as an admission diagnosis on medical history. The remaining subject was admitted with an ischemic stroke and the cerebral hemorrhage occurred 1 day after the subject received thrombolytic therapy for a pulmonary embolism. In 3 of the 5 subjects, the cerebral hemorrhage occurred after completion of study drug therapy. None of the 5 events were considered by the investigator to be related to study drug therapy. There was no change in mean prothrombin time or decrease in mean platelet count from baseline through the EOT visit in the ceftolozane/tazobactam group to suggest an induced hypocoagulable state. There was no imbalance in serious TEAEs related to hemorrhage at other anatomical sites.

No serious TEAE was reported in >4% of subjects in either treatment group. The SOCs with the highest percentage of subjects with serious TEAEs were cardiac disorders (10.0% of subjects overall) and infections and infestations (9.0% of subjects overall), each occurring in a similar proportion of subjects in the 2 treatment groups. Septic shock and multi-organ failure were the most commonly reported serious TEAE preferred terms (>3% of subjects overall) and occurred in a similar proportion of subjects in each treatment group.

Serious TEAEs related to the study drug

Among subjects that had serious TEAEs, only 10 subjects (8 in the ceftolozane/tazobactam group versus 2 in the meropenem group) experienced serious TEAEs that were considered related to study drug by the investigator. Only *C. difficile* colitis was reported by more than 1 subject as a treatment-related serious TEAE (*C. difficile* colitis was reported by 2 subjects in the ceftolozane/tazobactam group). All treatment-related serious TEAEs had resolved or were resolving at the end of the study.

Table 52. Treatment-Related Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Ceftolozane/Tazobactam (N=361) n (%)	Meropenem (N=359) n (%)	Total (N=720) n (%)
Number of Subjects with Any Treatment-related Serious Treatment Emergent Adverse Event	8 (2.2)	2 (0.6)	10 (1.4)
Cardiac disorders	1 (0.3)	0	1 (0.1)
Bradycardia	1 (0.3)	0	1 (0.1)
Gastrointestinal disorders	1 (0.3)	0	1 (0.1)
Ileus	1 (0.3)	0	1 (0.1)
Hepatobiliary disorders	1 (0.3)	1 (0.3)	2 (0.3)
Hepatitis cholestatic	1 (0.3)	1 (0.3)	2 (0.3)
Infections and infestations	4 (1.1)	1 (0.3)	5 (0.7)
Clostridium difficile colitis	2 (0.6)	0	2 (0.3)
Clostridium difficile infection	0	1 (0.3)	1 (0.1)
Enterobacter bacteraemia	1 (0.3)	0	1 (0.1)
Septic encephalopathy	1 (0.3)	0	1 (0.1)
Investigations	1 (0.3)	0	1 (0.1)
Alanine aminotransferase increased	1 (0.3)	0	1 (0.1)
Aspartate aminotransferase increased	1 (0.3)	0	1 (0.1)
Gamma-glutamyltransferase increased	1 (0.3)	0	1 (0.1)

Notes: n=Number of subjects in specific category. N=Number of subjects in Safety population. Percents are calculated as 100 x (n/N).
Adverse events are coded using MedDRA version 17.0. For each system organ class and preferred term, subjects are counted only once, even if they experienced multiple events in the system organ class or preferred term.

Deaths

A total of 206 (28.6%) deaths were reported during the study and occurred in a similar proportion of subjects in the 2 treatment groups. Fatal serious TEAEs were distributed across multiple SOCs. The SOCs with the highest percentage of subjects with fatal TEAEs were cardiac disorders (6.7% of subjects overall) and nervous system disorders (6.0% of subjects overall), each occurring in a similar proportion of subjects in the 2 treatment groups. Multi-organ failure, septic shock, brain edema, and cardiac failure acute were the most commonly reported TEAE preferred terms leading to death (>2% of subjects overall) and occurred in a similar proportion of subjects in each treatment group.

All TEAEs leading to death were considered unrelated to study drug therapy by the investigator and in general were related to underlying comorbidities or complications that developed while the subject was enrolled in the study.

Laboratory findings

A comparable number of subjects in each treatment group experienced a shift from baseline in laboratory values. The incidence and magnitude of the shifts were consistent between the 2 treatment groups.

Hematology

The baseline hematology parameters were similar between the 2 treatment groups. For all scheduled visits (Day 3, Day 8, EOT, TOC, and LFU), no apparent differences were seen in mean values and mean changes from baseline between the 2 treatment groups in any particular parameter.

The overall incidence of Grade 3 and Grade 4 toxicity was low and similar between the 2 treatment groups. For hemoglobin, the majority of subjects that had Grade 3 or 4 toxicity at EOT had abnormal values of Grade 2 to 4 at baseline. Considering the severity of illness in this study population, the incidence of worsening grade shifts during treatment was low and comparable for both treatment groups.

Seroconversion of direct Coombs test from negative to positive is a known side effect of β-lactam exposure. A higher proportion of subjects in the ceftolozane/tazobactam group compared to the meropenem group seroconverted from a negative result at baseline to a positive direct Coombs test result at EOT, 36% versus 3.6%. The seroconversion rates observed were similar to those seen in other cephalosporin clinical trials. There were no TEAEs or laboratory abnormalities suggestive of hemolytic anemia in these subjects, and rates of TEAEs of anemia were similar between the ceftolozane/tazobactam and meropenem groups.

Clinical Chemistry

The baseline chemistry parameters were similar between the 2 treatment groups. For all scheduled visits (Day 3, Day 8, EOT, TOC, and LFU), no apparent differences were seen in mean values and mean changes from baseline between the 2 treatment groups in any particular parameter.

The overall incidence of Grade 3 and Grade 4 toxicity was low. Considering the severity of illness in this study population, the incidence of worsening grade shifts during treatment was low and comparable for both treatment groups.

Mild, transient transaminase elevations are a known side effect of β-lactam therapy. The number of subjects who demonstrated shifts from baseline in ALT or AST values and the magnitude of the shifts were similar in both treatment groups at each time point assessed. Mean serum transaminases increased slightly during therapy in both treatment groups, peaking mostly at the EOT visit.

Six subjects met predefined laboratory criteria for potential drug-induced liver injury (Hy's law) (an AST or ALT value ≥3 times the ULN and a total bilirubin level ≥2 times the ULN with concurrent alkaline phosphatase value <2 times the upper limit of normal): 2 subjects in the ceftolozane/tazobactam group and 4 in the meropenem group. Both subjects in the ceftolozane/tazobactam group had medical histories of liver disease prior to study enrollment. One of these subjects in the ceftolozane/tazobactam group had a medical history of cirrhosis and met the laboratory criteria for potential drug-induced liver injury at baseline prior to initiation of study drug therapy, precluding drug-induced hepatotoxicity related to ceftolozane/tazobactam as a cause for the LFT abnormalities. The other subject had a nonserious TEAE of "elevated LFT" considered unrelated to study drug therapy that was reported on study Day 4 after hospital admission for cardiac arrest. This subject completed a 10-day course of ceftolozane/tazobactam. There were no clinical, hepatic-related TEAEs reported in this subject.

Safety in special populations

Safety in elderly subjects

In PN008, the incidence of TEAEs, SAEs and fatal TEAEs were higher in subjects ≥65 years of age compared to those <65 years of age. The higher incidence of TEAEs among elderly subjects was observed in both treatment groups, and was not associated with higher rates of drug-related TEAEs or

discontinuations due to TEAEs, suggesting that this difference was related to the subjects' underlying condition and not the study medication.

Safety in subjects with renal impairment or hyperclearance

In PN008, increased incidence of TEAEs and serious TEAEs was observed in subjects with moderate and severe renal impairment at baseline in both treatment groups compared with subjects with mild renal impairment, normal renal function, or hyperclearance (defined as CrCL >150 mL/min). There were no drug-related serious TEAEs in subjects with moderate or severe renal impairment in either treatment group. TEAEs with higher incidence in subjects with moderate and severe baseline renal impairment compared to subjects with normal renal function were distributed across multiple body systems. TEAE rates in subjects with hyperclearance were comparable to rates in subjects with normal renal function. TOL and TAZ plasma. The number of drug-related TEAEs in subjects with hyperclearance was low in both treatment groups.

Safety related to drug-drug interactions and other interactions

The potential for DDIs has been extensively evaluated in non-clinical *in vitro* studies, showing that TOL/TAZ has minimal potential for cytochrome P450- and transporter mediated DDIs in humans at clinically relevant concentrations. A clinical study to evaluate the potential of TOL/TAZ to influence the PK of substrates metabolized by CYP1A2 and CYP3A4 or transported by OAT1/OAT3 showed minimal impact on the PK profiles of these substrates. Inhibition of OAT has been shown to increase the half-life of TAZ by 71%. Overall, based on these evaluations, the potential for clinically-relevant DDIs with TOL/TAZ and any consequent impact on safety is low.

Discontinuation due to adverse events

A total of 79 (11.0%) subjects discontinued study drug due to a TEAE. The proportion of discontinuations was similar between the 2 treatment groups. The majority of TEAEs that led to discontinuation of study drug were AEs that resulted in death.

The SOCs with the highest percentage of TEAEs that lead to discontinuation from study drug therapy were infections and infestations (2.2% of subjects overall) and nervous system disorders (2.2% of subjects overall), each with a similar proportion of subjects in the 2 treatment groups. TEAEs that lead to discontinuation from study drug therapy reported in >1% of subject in either treatment group were septic shock and brain edema, which occurred in a similar proportion of subjects in each treatment group, and renal failure acute, which occurred in the ceftolozane/tazobactam group.

Among the TEAEs leading to discontinuation, drug-related treatment discontinuations were low in incidence and similar between the 2 treatment groups.

Post marketing experience

Current post-marketing experience with TOL/TAZ (ceftolozane/ tazobactam) relates to the approved dose of 1.5 g administered every 8 hours in populations with cIAI and cUTI. While there are differences in the dose and patient population between these currently approved indications and the proposed NP indication, available post-marketing data are summarized below to provide overall context for the current known safety profile of TOL/TAZ.

TOL/TAZ was first approved for use for cIAI and cUTI in the U.S. on 19-DEC-2014 and is registered in 66 countries as of 01-AUG-2018. There have been no records of any registration being revoked or withdrawn for safety reasons.

A cumulative review of post-marketing adverse events was conducted through 30-JUN-2018 and did not identify new safety issues.

Post marketing Exposure

The number of vials of TOL/TAZ (1 vial=1 g TOL and 0.5 g TAZ) distributed worldwide cumulatively since market introduction (19-DEC-2014 to 30-JUN-2018) was approximately 1,535,761. The usual dose of TOL/TAZ is 1 vial administered every 8 hours. The number of patient treatment-days for the cumulative period is 511,920 [1,535,761 vials ÷ 3 vials/day]. The usual duration of therapy is from 4 to 14 days, depending on the type of infection. This would imply that the estimated number of treatment courses would theoretically range between 36,566 (511,920 patient treatment days ÷ 14 days) and 127,980 (511,920 patient treatment days ÷ 4 days). These treatment courses represent an estimate of the number of patients receiving TOL/TAZ in the post-marketing environment.

Post marketing Adverse Events

A total of 951 reports (159, 17% serious) containing 1,517 events (263, 17% serious) were identified. The SOCs in which AEs were most commonly reported were Injury, poisoning and procedural complications (925 events), General disorders and administration site conditions SOC (277 events), and Infections and infestations SOC (80 events).

The most commonly reported preferred terms in the Injury, poisoning and procedural complications SOC were off label use (n=407) and product use in unapproved indication (n=279). Off label/unapproved use involved treatment of pneumonia or respiratory tract infections in the majority of the reports.

Because of extensive “off-label” use the MAH has been instructed to provide a cumulative review of all cases including unapproved indication, prescribing error and incorrect drug administration duration. The worry is that “off-label” use may increase the risk of resistance development. Approval of the new indication of nosocomial pneumonia has a potential to lower the widespread “off-label” use.

The most commonly reported preferred term in the Infections and infestations SOC was pathogen resistance (n=25). The other preferred terms reported in this SOC reflect the critically-ill nature of patients receiving TOL/TAZ or infections TOL/TAZ was being utilized to treat. For the resistance events, limited clinical and microbiologic data precluded thorough assessment of reports. Risk factors for development of resistance were often present including use of multiple antimicrobial agents to treat infections caused by multidrug resistant organisms and failure to properly remove infected foci. In addition, the dosing regimen for off label use of TOL/TAZ for NP was often not provided. In some of the reports where dose was included, 1.5 g was administered instead of the 3 g dose used in the clinical trial for NP (PN008). Insufficient antimicrobial levels are also a risk factor for development of antimicrobial resistance.

In addition to the most commonly reported events described above, events known to be associated with TOL/TAZ, including hypersensitivity reactions and CDAD, were reviewed. One report coded to the preferred term anaphylaxis was retrieved. Available data in the case was limited and the event described redness and skin eruption with no other signs or symptoms. For CDAD, 6 reports, all serious, were retrieved. These reports described patients who had been administered other broad spectrum antibiotics and had significant comorbid conditions. Of the 5 CDAD reports containing outcome information, outcome was recovered in 2, recovering in 1, and not recovered in 2.

Other events which have been reported following exposure to the cephalosporin class, including severe cutaneous reactions and renal impairment, were also reviewed. No reports of severe cutaneous adverse reactions were identified. Cumulatively, a total of 21 events, including 18 SAEs, have been reported in the Renal and urinary disorders SOC. These reports either contained limited information or the events occurred in patients with underlying high morbidity due to medical history and/or concurrent conditions

which precluded a meaningful drug-event causality assessment. No new safety signals were identified based upon review of these data.

The applicant has an established process for continuous monitoring of medication errors for its products. Evaluation of the data on medication errors received for TOL/TAZ identified a potential for dosing errors following approval of TOL/TAZ in the U.S. The presentation of the strength statement on the vial label was cited as a cause of confusion which could lead to administration of more drug than was prescribed. The vial label was subsequently updated and a Dear Health Care Provider letter was distributed in the U.S. in JUN-2015. No further reports of this type of potential for medication error have been received. Review of AEs reported cumulatively through 30-JUN-2018 for preferred terms related to medication use issues do not indicate a new safety concern, and associated AEs were generally consistent with the known safety profile of TOL/TAZ.

2.5.1. Discussion on clinical safety

The dose of 3 g (every 8 hours) was used in three phase 1 studies and a single phase 3 study. Only 71 subjects were exposed in the three phase 1 studies, 35 healthy subjects and 36 critically ill. Because of low numbers and variable disease status of subjects in the phase 1 studies, safety is only reported for the phase 3 study in this report and no pooling of data was performed, which is considered adequate.

Number of subjects randomized/treated/ongoing/discontinued in study PN008:

- In the ceftolozane/tazobactam group, 362 subjects were randomized, 361 (99.7%) were treated, 263 (72.7%) completed and 98 (27.1%) discontinued trial treatment, and 245 (67.7%) completed and 117 (32.3%) withdrew from the study.
- In the meropenem group, 364 subjects were randomized, 359 (98.6%) were treated, 271 (74.5%) completed and 88 (24.2%) discontinued trial treatment, and 250 (68.7%) completed and 114 (31.3%) withdrew from the study.

The population consisted of seriously ill subjects. Subjects were hospitalized for a mean duration of 10 days prior to randomization and 49% were ventilated for ≥5 days prior to randomization. A total of 35.6% had renal impairment at baseline, 21.9% were ≥75 years of age, and 12.8% had failed prior therapy for the current episode of ventilated nosocomial pneumonia. Ventilator-associated bacterial pneumonia accounted for 71.5% of ventilated nosocomial pneumonia diagnoses, and 14.5% of subjects were bacteremic at baseline. Mortality was as high as 28-29% and 88% of subjects received non-study antibiotic treatment within 14 days prior to study drug treatment.

Only adults 18 years or older were included in the study for this indication. No data on paediatric patients have been submitted for the 3 g dose used for this indication. The median age was 62 years, minimum and maximum 18 years and 98 years, with 160 (44%) being 65 years or older in the ceftolozane/tazobactam group. The number of patients exposed to ceftolozane/tazobactam at the 3 g dose recommended for nosocomial pneumonia is considered acceptable for safety evaluation.

A complicating factor in evaluating the relation between study drug and adverse reactions is the high use of concomitant non-study antibiotics (58% of ITT population). The majority of those on non-study antibiotics received concomitant antibiotics after discontinuing study drug, while 21.3% received non-study antibiotics while on study drug therapy. In addition, 94% received gram-positive adjunctive therapy (according to protocol). Gram-negative adjunctive therapy was allowed at baseline for a maximum of 72 hours according to protocol at sites with meropenem-resistant *P. aeruginosa.* A total of 29% of patients received gram-negative adjunctive therapy.

A total number of 84% of patients reported any TEAE, of which 17% were mild, 28% moderate and 38% severe. TEAEs that occurred in ≥5% of subjects in the ceftolozane/tazobactam group included anemia,

decubitus ulcer, urinary tract infection, diarrhea, and increased ALT and AST. Drug-related TEAEs were reported in 10% of the ceftolozane/tazobactam group and 7% of the meropenem group. Drug-related TEAEs that were considered severe in the ceftolozane/tazobactam group included bradycardia, diarrhoea, hepatic failure, systemic candida, increased ALT, AST, and γ-glutamyl transferase.

The SOCs with the highest percentage of subjects with serious TEAEs were cardiac disorders (10.0% of subjects overall) and infections and infestations (9.0% of subjects overall). Septic shock and multi-organ failure were the most commonly reported serious TEAE preferred terms (>3% of subjects overall), and all occurred in a similar proportion in each treatment group. Cerebral hemorrhage, which occurred in 5 subjects in the ceftolozane/tazobactam group and no subjects in the meropenem group, was the only serious TEAE preferred term with a 95% CI for risk difference that did not include 0. In 4 of these 5 subjects, the cerebral hemorrhage represented a worsening of underlying intracranial hemorrhage that was present as a diagnosis on medical history

More subjects experienced serious TEAEs in the ceftolozane/tazobactam group (8) compared to the meropenem group (2). Only *C. difficile* colitis was reported by more than 1 subject as a treatment-related serious TEAE (*C. difficile* colitis was reported by 2 subjects in the ceftolozane/tazobactam group). All treatment-related serious TEAEs had resolved or were resolving at the end of the study. Two patients in the ceftolozane/tazobactam group reported serious drug-related TEAE of *C. difficile* colitis, while none of these were reported as severe drug-related TEAEs. Also hepatic cholestatic is reported as serious drug-related TEAE in one patient, while hepatic failure but not hepatic cholestatic is reported as severe TEAE from the same group. During the procedure the applicant has described the use of classification of severity and seriousness for some of the TEAEs related to *C. difficile* colitis and hepatic events. A large proportion of patients discontinued the study, 32% in the ceftolozane/tazobactam group and 31% in the meropenem group. The majority discontinued study because of adverse event (86-91%). Also, the proportion of patients that discontinued study drug was high, 27% for the ceftolozane/tazobactam group and 24% for the meropenem group. The most common reason for discontinuation of study drug was adverse event (36% ceftolozane/tazobactam and 47% meropenem) and insufficient therapeutic effect (23% ceftolozane/tazobactam group and 17% meropenem). The majority of TEAEs that led to discontinuation of study drug were AEs that resulted in death. The high proportion of discontinuation from the drug and study mirrors the severity of disease in this population with high mortality.

Among the TEAEs leading to discontinuation, drug-related treatment discontinuations were low in incidence and similar between the 2 treatment groups (1.1 and 1.4%).

2.5.2. Conclusions on clinical safety

No new safety signals have been detected from the study supporting the nosocomial pneumonia indication.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of

Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.1.
No new safety concerns according to GVP module 5 were identified, thus neither risk minimisation nor Pharmacovigilance activities are necessary.

2.7. Update of the Product Information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The applicant also took the opportunity to implement editorial changes in sections 5.2 of the SmPC and to bring Section 4.4 of the SmPC and section 2 of the PL in line with the latest Annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applied extension of indication for ceftolozane/tazobactam is:

"*Treatment of adults with nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP)*".

3.1.2. Available therapies and unmet medical need

Nosocomial pneumonia, including ventilator-associated pneumonia is a severe disease, and can be a life-threatening condition. The mortality risk increases when the NP infection is caused by MDR bacteria and in patients with concurrent bacteraemia. The mortality rate attributable to NP ranges from 33% to 50%.

Due to the increasing prevalence of antibiotic-resistant bacteria, few antibiotic agents are broadly active against the gram-negative organisms frequently isolated from NP infections. The WHO (2017) identified carbapenem-resistant *P. aeruginosa* as a critical threat with an urgent need of new antibiotics. Recent data show an increase in the prevalence of NP caused by MDR pathogens, most commonly *P. aeruginosa*, with documented resistance to β-lactams, carbapenems, aminoglycosides, and fluoroquinolones. Although increasing drug resistance has diminished the utility of established antipseudomonal β-lactam antibiotics, there are still some antibacterial agents that are effective in treatment of NP/VAP patients. However, considering the high prevalence and severity of these infections, as well as increasing prevalence of antibiotic-resistant bacteria, effective treatment options are still needed. Particularly, there is an unmet medical need for treatment of patients infected with certain pathogens such as MDR-resistant *P. aeruginosa*.

3.1.3. Main clinical studies

The clinical program for ceftolozane/tazobactam comprises one pivotal phase 3 clinical study (**PN008**).

The pivotal study **PN008** is a multicentre, randomised, double-blind, active-controlled phase 3 study, comparing the efficacy and safety of ceftolozane/tazobactam to meropenem in adult patients with NP (including VAP and ventilated hospital-acquired pneumonia [HAP]). Patients were randomised 1:1 to receive either ceftolozane/tazobactam or meropenem.

3.2. Favourable effects

Non-inferiority of ceftolozane/tazobactam compared to meropenem was demonstrated for the primary endpoint clinical response in the ITT population at the Test-of Cure (TOC) visit (54.4%, 197/362 in the ceftolozane/tazobactam arm vs. 194/364, 53.3% in the meropenem arm). Non-inferiority of ceftolozane/tazobactam compared to meropenem was also demonstrated for the key secondary endpoint Day 28 all-cause mortality in the ITT population (87/362, 24.0% in the ceftolozane/tazobactam arm vs. 92/364, 25.3% in the meropenem group). For both the primary endpoint and the key secondary endpoint, the lower limits of the stratified 97.5% CIs were within the non-inferiority margin of -12.5% (*i.e.* 1.1% [-7.20, 9.31] and 1.1% [-6.03, 8.28], respectively).

The above-mentioned results were supported by the sensitivity analyses of the primary efficacy outcomes and of the findings in the secondary endpoint of clinical response at TOC for the clinically evaluable (CE) population.

In the microbiologically Intent-to-Treat (mITT) population, at the TOC visit, 193/264 (73.1%) patients in the ceftolozane/tazobactam arm and 168/247 (68.0%) subjects in the meropenem arm had a favourable microbiological response. The corresponding results achieved for the Microbiologically Evaluable (ME) population were in support of the findings in the mITT population.

For the most commonly isolated pathogens (*i.e.* Enterobacteriaceae, *K. pneumoniae*, *E. coli*, *P. aeruginosa*) the per-pathogen clinical and microbiological response rates in the mITT population were, in general, comparable between the ceftolozane/tazobactam arm and the meropenem arm. However, for *P. aeruginosa* the microbiological response rates were higher in the ceftolozane/tazobactam arm compared to the meropenem arm (47/63, 74.6% vs. 41/65, 63.1%, respectively).

3.3. Uncertainties and limitations about favourable effects

Approximately 30% of the patients in the ITT population had at least one important protocol deviation during the study. These deviations included mainly issues such as not meeting inclusion/exclusion criteria (in total 64/229, 8.8%), lack of safety reporting (in total 18/229, 2.5%) and not following trial procedure/study interventions (in total, 190/229, 26.2%). Approximately 40% of the important protocol deviations led to exclusion of patient data from the CE population.

The Day 28 All-cause mortality rate in the subgroup of patients with *P. aeruginosa* as baseline LRT pathogen, was higher in the ceftolozane/tazobactam arm vs. the meropenem arm (16/63, 25.4% vs. 12/65, 18.5%, respectively). The same tendency of higher mortality rates was also observed for the subgroups of patients that were bacteremic at baseline “all respiratory pathogens” (14/29, 48.3% vs. 7/21, 33.3%) and bacteremic at baseline “all gram-negative respiratory pathogens” (13/25, 52.0% vs. 7/19, 36.8%) in the ceftolozane/tazobactam arm vs. the meropenem arm, respectively.

Clinical cure rates for ceftolozane/tazobactam compared to meropenem were lower in patients $\geq$ 75 years of age (35/83, 42.2% vs. 42/76, 55.3%), patients who had no prior antibiotic therapy (19/44, 43.2% vs.

23/41, 56.1%) and patients who had baseline gram-negative adjunctive therapy (47/103, 45.6% vs. 64/112, 57.1%) in the ceftolozane/tazobactam arm vs. the meropenem arm, respectively.

The microbiological response rates for ESBL+ *K. pneumoniae* were 33/53, 62.3% in the ceftolozane/tazobactam arm compared to 38/52, 73.1% in the meropenem arm. Although the results in the ME population was overall consistent with the results in the mITT population, the microbiological response rates for ESBL+ *K. pneumoniae* were similar between ceftolozane/tazobactam and meropenem in this population (20/30, 66.7% vs. 18/27, 66.7%, respectively).

Although higher microbiological response rates were observed in the mITT population for Amp C – producing *P. aeruginosa* in the ceftolozane/tazobactam group vs. the meropenem group, the number of isolates was limited to 15 in total.

3.4. Unfavourable effects

The dose of 3 g (every 8 hours) was used in three phase 1 studies and a single phase 3 study. Because of low numbers and variable disease status of subjects in the phase 1 studies, safety is reported only for the phase 3 study in this report.

The population consisted of seriously ill subjects. Subjects were hospitalised for a mean duration of 10 days prior to randomization and 49% were ventilated for ≥5 days prior to randomization. A total of 35.6% had renal impairment at baseline, 21.9% were ≥75 years of age, and 12.8% had failed prior therapy for the current episode of ventilated nosocomial pneumonia. Ventilator-associated bacterial pneumonia accounted for 71.5% of ventilated nosocomial pneumonia diagnoses, and 14.5% of subjects were bacteremic at baseline. Mortality was as high as 28-29% and 88% of subjects received non-study antibiotic treatment within 14 days prior to study drug treatment. A large number of patients discontinued study treatment or did not complete the study:

- In the ceftolozane/tazobactam group, 362 subjects were randomized, 361 (99.7%) were treated, 263 (72.7%) completed and 98 (27.1%) discontinued trial treatment, and 245 (67.7%) completed the study.
- In the meropenem group, 364 subjects were randomized, 359 (98.6%) were treated, 271 (74.5%) completed and 88 (24.2%) discontinued trial treatment, and 250 (68.7%) completed the study.

A total number of 84% of patients reported any TEAE, of which 17% were mild, 28% moderate and 38% severe. TEAEs that occurred in ≥5% of subjects in the ceftolozane/tazobactam group included anemia, decubitus ulcer, urinary tract infection, diarrhea, and increased ALT and AST. Drug-related TEAEs were reported in 10% of the ceftolozane/tazobactam group and 7% of the meropenem group. Drug-related TEAEs that were considered severe in the ceftolozane/tazobactam group included bradycardia, diarrhoea, hepatic failure, systemic candida, increased ALT, AST, and γ-glutamyl transferase.

The SOCs with the highest percentage of subjects with serious TEAEs were cardiac disorders (10.0% of subjects overall) and infections and infestations (9.0% of subjects overall). Septic shock and multi-organ failure were the most commonly reported serious TEAE preferred terms (>3% of subjects overall), and all occurred in a similar proportion in each treatment group.

More subjects experienced serious TEAEs in the ceftolozane/tazobactam group (8) compared to the meropenem group (2). Only *C. difficile* colitis was reported by more than 1 subject as a treatment-related serious TEAE (*C. difficile* colitis was reported by 2 subjects in the ceftolozane/tazobactam group). All treatment-related serious TEAEs had resolved or were resolving at the end of the study.

A large proportion of patients discontinued the study, 32% in the ceftolozane/tazobactam group and 31% in the meropenem group, the majority because of adverse event (86-91%). Also, the proportion of patients that discontinued study drug was high, 27% for the ceftolozane/tazobactam group and 24% for the meropenem group and the most common reason was adverse event (36% ceftolozane/tazobactam and 47% meropenem) and insufficient therapeutic effect (23% ceftolozane/tazobactam group and 17% meropenem). The majority of TEAEs that led to discontinuation of study drug were AEs that resulted in death. Drug-related treatment discontinuations were low in incidence and similar between the 2 treatment groups (1.1 and 1.4%).

No new safety signals have been detected from the study supporting the nosocomial pneumonia indication.

3.5. Uncertainties and limitations about unfavourable effects

A complicating factor in evaluating the relation between study drug and adverse reactions is the high use of concomitant non-study antibiotics (58% of ITT population), defined as non-study antibiotics received from the first dose of study therapy to the Late follow-up. The majority of these subjects received non-study antibiotics after discontinuing study drug, while 21.3% received non-study antibiotics while on study drug therapy. In addition, 94% received gram-positive adjunctive therapy (required per protocol). Gram-negative adjunctive therapy was allowed at baseline for a maximum of 72 hours according to the protocol at sites with meropenem-resistant *P. aeruginosa*.

Based on the current guidelines, the removal of the important identified and potential risks as well as missing information is supported.

Tazobactam crosses the placenta, while this is not known for ceftolozane. As described in the SmPC reproductive toxicity has been shown in an animal study (rat) with tazobactam. Also, with ceftolozane there was a finding of decreased auditory startle response in rat pups. The clinical significance of these animal data is not known as there are no data in pregnant or lactating woman. Pregnant women might be exposed if the prescriber considers “benefit outweighs the possible risks to the pregnant woman and foetus” and the new indication for Zerbaxa combined with a doubling of the dose will increase exposure in pregnant and lactating woman. It is considered important to focus on obtaining experience from pregnant and lactating women, which could be through routine PV and reporting in PSURs. There is a critical gap in knowledge for use in pregnant and lactating women; such use should be reported in the PSUR.

3.6. Effects Table

Effects Table for ceftolozane / tazobactam for nosocomial pneumonia including VAP

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
	NP including VAP Phase 3 study Clinical response (ITT)	n/N (%)	Ceftolozane/ tazobactam 197/362 54.4%	Meropenem 194/364 53.3%	Non-inferiority margin was met 97.5% CI 1.1 (-7.20, 9.31)	Study PN008
	Day 28 All-cause mortality (ITT)		87/362 24.0%	92/364 25.3%	97.5% CI 1.1 (-6.03, 8.28)	
					All sensitivity analyses supported the primary analysis	
Unfavourable Effects						
	Anemia		8.9	10.6	Treatment emergent AEs with highest frequency	
	Urinary tract infection		6.6	7.0		
	Decubitus ulcer		6.9	4.7		
	Diarrhoea		6.4	7.0		
	Increased ALT/AST		5.8	3.9		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Non–inferiority of ceftolozane/tazobactam to meropenem has been clearly demonstrated for both the primary and the key secondary endpoints in the patients with NP/VAP that is considered to be representative of the target population. The similar rates of clinical cure achieved for the primary endpoint at TOC for ceftolozane/tazobactam and meropenem indicate that ceftolozane/tazobactam has the potential to be an alternative to meropenem in the treatment of NP/ VAP.

The Day 28 All-cause mortality rate in the subgroup of patients with *P. aeruginosa* as baseline LRT pathogen, was higher in the ceftolozane/tazobactam arm vs. the meropenem arm (16/63, 25.4% vs. 12/65, 18.5%, respectively). The same tendency of higher mortality rates was also observed for the subgroups of patients that were bacteremic at baseline “all respiratory pathogens” (14/29, 48.3% vs. 7/21, 33.3%) and bacteremic at baseline “all gram-negative respiratory pathogens” (13/25, 52.0% vs. 7/19, 36.8%) in the ceftolozane/tazobactam arm vs. the meropenem arm, respectively.

There were differences in the demographics of ceftolozane/tazobactam versus meropenem: a higher percentage of subjects ≥75 years old in the ceftolozane/tazobactam group (23.8%) compared to the meropenem group (16.9%), a higher rate of subjects that had failed prior antibiotic therapy (17.5% vs. 6.2%) and of subjects that were bacteremic at baseline (27.0% vs. 10.8%). In addition, there was a higher proportion of subjects with different co-morbidities (i.e. diabetes, congestive heart failure) in the

ceftolozane/tazobactam group than in the meropenem group. It is agreed that these differences in demographic factors between the treatment groups might have affected the study results.

Clinical cure rates for ceftolozane/tazobactam compared to meropenem were lower in patients ≥ 75 years of age (35/83, 42.2% vs. 42/76, 55.3%), patients who had no prior antibiotic therapy (19/44, 43.2% vs. 23/41, 56.1%) and patients who had baseline gram-negative adjunctive therapy (47/103, 45.6% vs. 64/112, 57.1%) in the ceftolozane/tazobactam arm vs. the meropenem arm, respectively.

Increased failure rate in patients >75 years of age as well as patients who did not receive any antibiotic therapy prior to study entry may be attributed to the differences in demographics of ceftolozane/tazobactam versus meropenem-treated subjects in this subgroup as ceftolozane/tazobactam subjects displayed more high-risk characteristics at baseline. The rates of susceptibility to study therapy were lower in the subjects with Enterobacteriaceae in the ceftolozane/tazobactam group compared to the meropenem group (84.4% vs. 100%) and this might also have contributed to a lower clinical response rate in the ceftolozane/tazobactam group.

It is acknowledged that given the small number of patients studied overall and in the individual subgroups, definite conclusions are difficult to draw both in terms of efficacy and safety.

Despite not being allowed according to the study protocol, concomitant administration of carbapenems (including meropenem) as “any non-study concomitant antibiotic medication” was given to the patients in the ceftolozane/tazobactam arm. This might have impacted the clinical and microbiological success rates. However, the results from a sensitivity analysis in which patients receiving concomitant carbapenems were regarded as clinical failures were comparable to the results in the overall study population. It is therefore agreed that the use of concomitant carbapenems before TOC probably have not affected the clinical outcome of the study.

No new safety signals have been detected from the study supporting the NP indication.

It should be emphasized that ceftolozane/tazobactam does not address an unmet medical need for treatment of all resistant pathogens against meropenem such as ESBL-producing Enterobacteriaceae and MDR *P. aeruginosa*. Nevertheless, it might likely be efficacious in some patients infected with *P. aeruginosa* that is resistant to several other antibacterial drugs, including carbapenems. Ceftolozane/tazobactam with comparable efficacy and safety to meropenem, including efficacy in patients with infections caused by beta-lactam-resistant Enterobacteriaceae and *P. aeruginosa*, would be a clinically relevant and useful addition to the available treatment options.

3.7.2. Balance of benefits and risks

The benefit/risk balance for Zerbaxa (ceftolozane/tazobactam) is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Zerbaxa is positive for the extension of the applied indication to hospital-acquired pneumonia, including ventilator-associated pneumonia.

4. Recommendations

Outcome

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) for Zerbaxa, based on results from the randomised, double-blind, multicentre clinical trial CXA-NP-11-04 (PN008).

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet (sections 1, 2, 3, 4 and 6) is updated in accordance with the SmPC.

The applicant also took the opportunity to implement editorial changes in sections 5.2 of the SmPC and to bring Section 4.4 of the SmPC and section 2 of the PL in line with the latest Annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'.

Version 2.1 of the RMP was also submitted.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

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

Risk management plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Zerbaxa is not similar to Cayston (aztreonam) and Tobi Podhaler (tobramycin) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix.