Combined population PK modelling of cefepime and enmetazobactam to characterize their individual and combined PK from the phase 1 to 3 studies

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Background:

Antimicrobial resistance (AMR) is a global health threat. The most frequent mechanism of resistance in Enterobacterales is the expression of Class A extended-spectrum β-lactamases. Cefepime/enmetazobactam (FEP-META) is a new β-lactam–β-lactamase inhibitor combination with activity against multidrug-resistant Enterobacterales. FEP-META is approved in Europe for the treatment of complicated urinary tract infections (cUTI), hospital-acquired pneumonia, including ventilator-associated pneumonia and bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Goal:

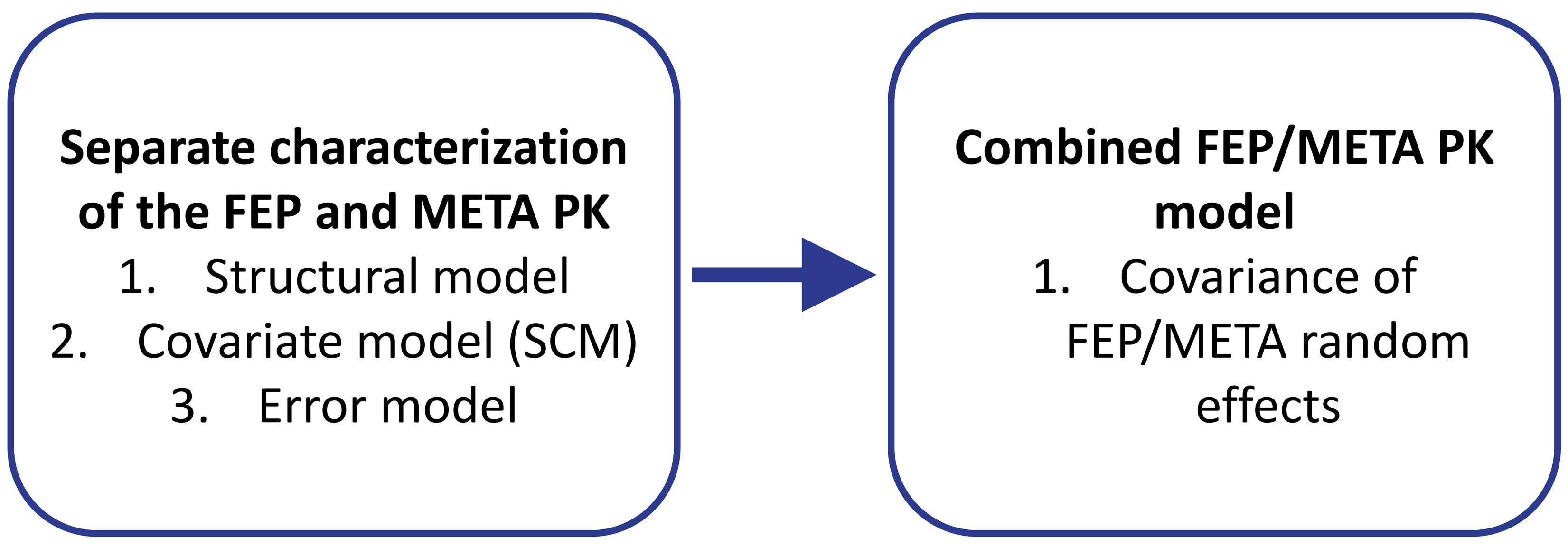
The objective of this study was to characterize the FEP and META population pharmacokinetics (PK) from the combined phase 1, 2 and 3 trials, including the intra-patient correlation of the FEP and META PK parameters.

Methods:

Plasma PK samples were available from a total of 663 subjects in three phase 1 (n=132), one phase 2 (n=43) and one phase 3 (n=488) clinical trial. The population included healthy volunteers (n=113), subjects with renal impairment (n=19) and patients with cUTI (n=531).

A compartmental population PK modelling approach was used. Monolix Suite 2019R2 was used for parameter estimation. For model development, a stepwise model building was employed (**Figure 1**). In the combined population PK model, the covariance of FEP and META random effects of central volumes of distribution and clearances were assessed. To best characterize the between subject variability in the cUTI patient population independent inter-individual variabilities for healthy and cUTI patients were estimated.

Figure 1: *Step-wise modelling approach with the model optimizations conducted in each of the steps.*



Results:

The PK of both compounds was best described using two-compartmental models with linear clearance from the central compartment.

Figure 2: *Structural PK model for both compounds.*

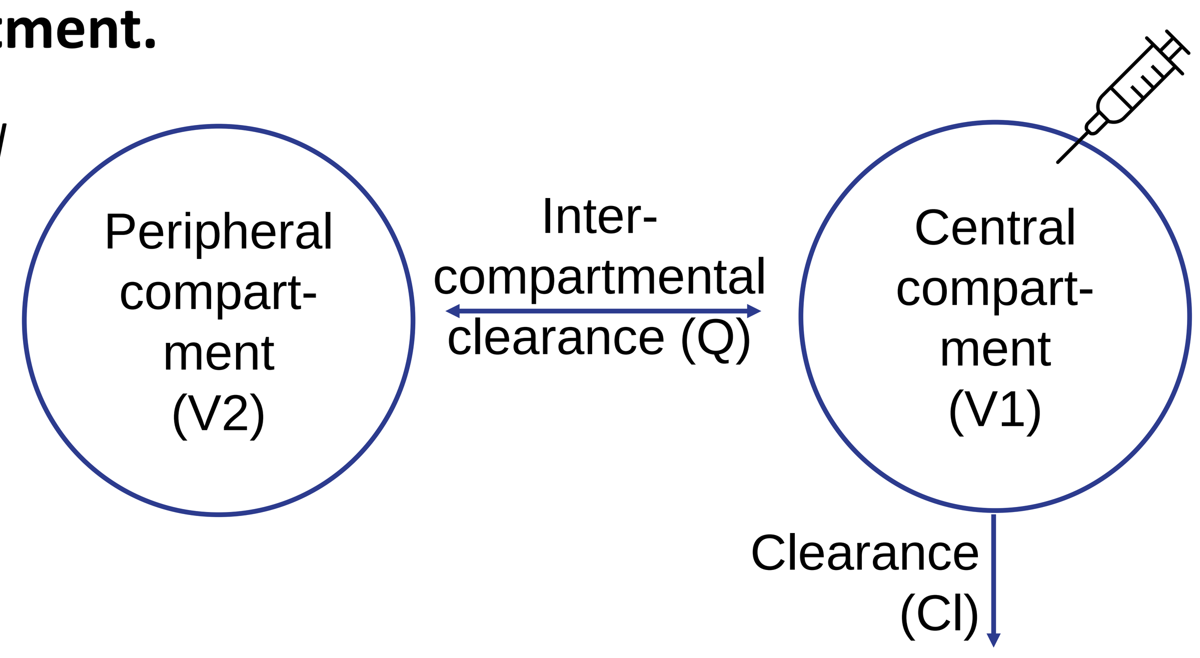


Table 1. Final combined population PK model parameter estimates for a reference individual excluding cross-compound correlations of the random effects.

Description	Enmetazobactam (META)			Cefepime (FEP)		
	Estimate (%CV)	RSE (%)	p-value***	Estimate (%CV)	RSE (%)	p-value***
Fixed effects						
Clearance, Cl (L/h)	7.67 (16, 37)*	1.1		5.92 (17, 30)	1	
Central volume of distribution, V1 (L)	13.4 (6, 52)*	2		11.4 (-, 45)*	2.1	
Intercompartmental clearance, Q (L/h)	7.16 (-)	fixed		7.22 (-)	fixed	
Peripheral volume of distribution, V2 (L)	5.28 (7)	3.4		5.57 (15)	2.7	
Intra-compound correlations						
V1 and Cl	-, 0.288**	-,17**		0.996, 0.455**	30, 8.8**	
Covariate coefficients						
De-indexed eGFR on Cl	0.896	2.1	<2.2e-16	0.817	2.1	<2.2e-16
De-indexed eGFR on V2	0.302	19	1.8e-07	-	-	-
cUTI infection on V1	0.13	19	1.4e-07	-	-	-
Age on V1	0.151	19	1.6e-07	0.161	20	8.4e-07
Body weight on V1 & V2	0.407	9.9	<2.2e-16	0.553	7.9	<2.2e-16
Gender on V2	0.18	21	2.5e-06	-	-	-
Observational error						
Constant error (ng/mL)	40.1	12		-	-	
Proportional error (-)	0.236	1.1		0.253	1.2	

Reference individual with a body weight = 70 kg, Age = 50 y, De-indexed eGFR = 100 mL/min, Sex = Female, and Infection status = 'healthy' (i.e. not infected).
Abbreviations: CV= coefficient of variability; eGFR=estimated glomerular filtration rate; META=enmetazobactam; FEP=cefepime; RSE=relative standard error.
* First value in brackets is %CV for healthy and second for patients
** First value is for healthy and second for patients
*** Wald test if covariate coefficient is different from zero.

Intra-patient, cross-compound correlations of the random effects identified strong similarities in the PK between the compounds.

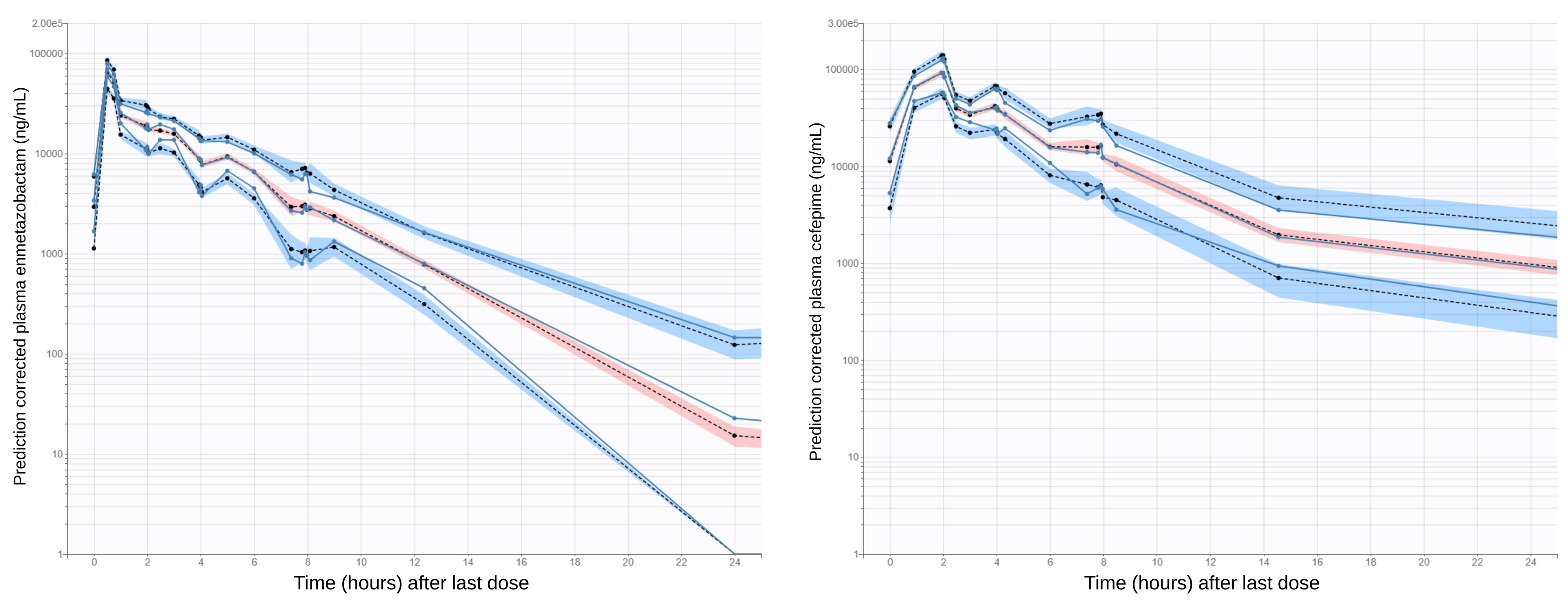
Table 2. Cross-compound correlations of the random effects included in the final population PK model.

	FEP Cl	FEP V1
META Cl	0.934 (1.1)*	0.359 (13)*
META V1	0.295 (16)*	0.963 (2.2)*

*Estimates (RSE); META = enmetazobactam; FEP = cefepime, Cl = Clearance, V1 = Central volume of distribution

Observed cefepime and enmetazobactam plasma concentrations were well described by the model.

Figure 3: *Observed (solid lines) and predicted (dashed) prediction-corrected enmetazobactam (left) and cefepime (right) median, 10th and 90th percentile with 90% confidence intervals (areas) across all studies with time after last dose on the x-axis.*



Conclusions:

- A combined population PK model was developed for FEP and META.
- Highly similar PK properties with strong intra-patient, cross-compound correlations of the random effects were identified.
- This justified the same dosing frequency for both compounds (q8h).
- Both clearances were found to depend on de-indexed eGFR with covariate coefficients (β) close to 1.
- This suggested that renal filtration is the predominant clearance mechanism.
- The final model was judged to be adequate for Monte-Carlo simulations which were used to select the doses required to achieve the desired probability of target attainment (PTA) and test if any dose adjustments are required in subpopulations.

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