Population pharmacokinetics of Murepavadin (POL7080) and Monte Carlo simulations to develop clinical dosing regimen, including the renally impaired.

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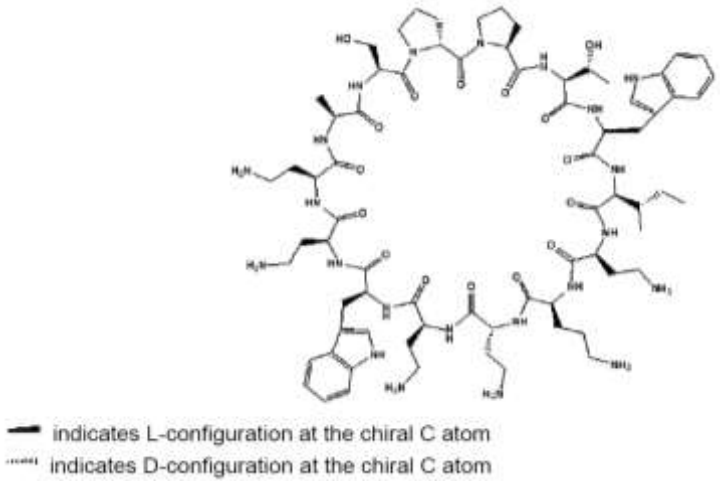


Disclosures

Indirect disclosures

- Wockhardt
- Basilea
- Eumedica
- Polyphor
- Nordic pharma

Introduction

Background Murepavadin

- New peptidomimetic antibiotic
- Specifically aimed at *Pseudomonas aeruginosa,* including multidrug resistant strains
- Mechanism of action: interaction with LptD, a target critical in the outer membrane biogenesis.
- Indication pneumonia

- Aim study: describe the pharmacokinetics and perform MCS to design dosing regimen.

Materials

Data for population PK analysis

- 211 subjects
- 2656 concentration-time observations
- Doses ranged from 0.05 mg/kg up to 10 mg/kg

Covariate	Median	range
Male gender (% of the group)	79%	
Age (years)	44	18 – 81
Body weight (kg)	79	39 – 110
Height (cm)	173	149 – 196
Body Mass Index (kg/m^2)	26	16 – 49
Body surface area (m^2)	1.9	1.3 – 2.35
Creatinine concentration (umol/L)	82	34 - 368
Cleatinine clearance (mL/min)	112	15 – 244
VAP (number)	23	

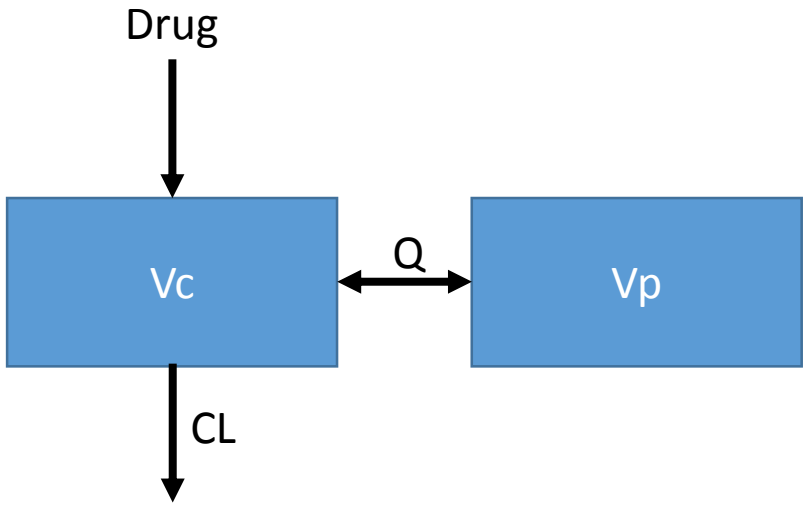
Methods

Methods

- Population pharmacokinetic model
  - NONMEM
  - Rstudio, Xpose, Pirana
  - 1-, 2-, 3 compartment models
  - Covariate model
  - Validation of the final model: NPDE (normalised prediction distribution errors)
- Monte Carlo simulations
  - NONMEM
  - Used the popPK model without covariates (general) and with covariates for adjustments renal impairment
  - 1000 simulations per regimen
  - Total concentrations
  - PK/PD target: AUC/MIC >208

Results

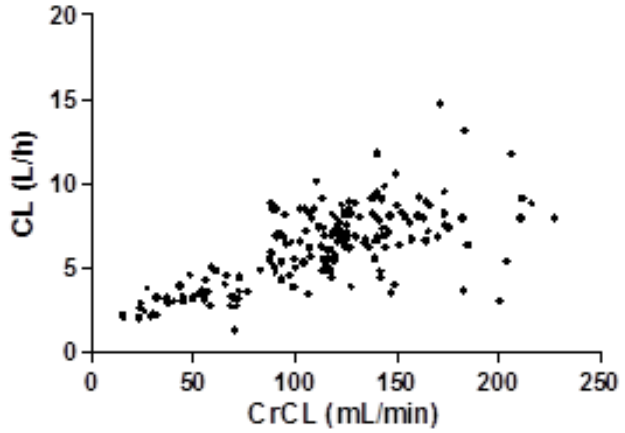
Results population PK

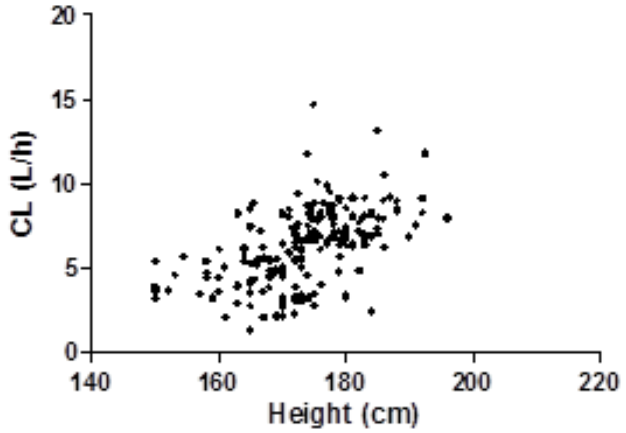


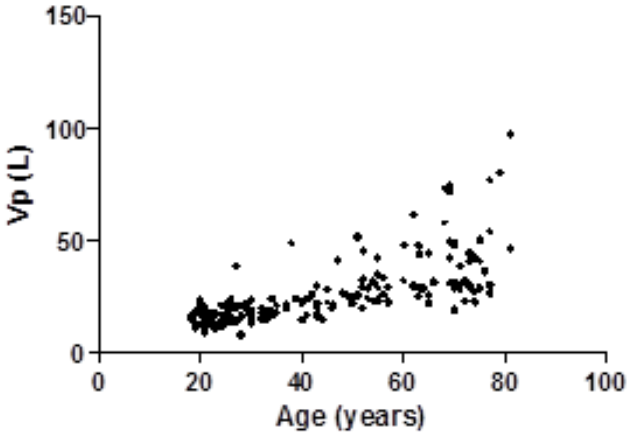
Parameter	Structural model Mean	Covariate model Mean (RSE)
Clearance (L/h)		
TVCL (L/h)	5.89	7.03 (2%)
A (influence of CRCL)		0.714 (5%)
B (influence of height)		1.71 (17%)
IPV (%)	40.2	21.4 (7%)
Central volume of distribution (L)	13.6	13.6 (2%)
IPV (%)	21.1	21.5 (14%)
Intercompartmental clearance (L/h)		
TVQ	5.15	4.66 (3%)
C (influence of VAP)		2.64 (12%)
IPV (%)	48.3	27.1 (14%)
Peripheral volume of distribution (L)		
TVVp	22.4	24 (3%)
D (influence of age)		0.663 (11%)
IPV (%)	48.0	26.8 (9%)
Residual error	0.181	0.182 (6%)

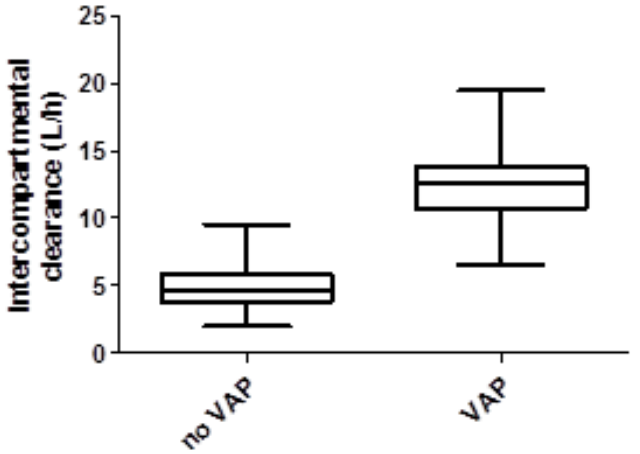
Results

Covariate model









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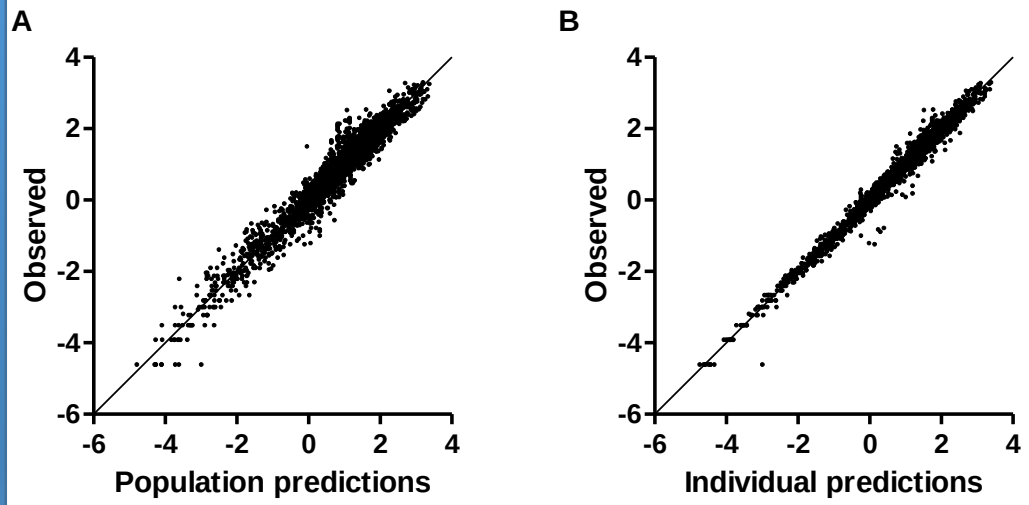
IPV (%)	
Residual error	0.182 (6%)

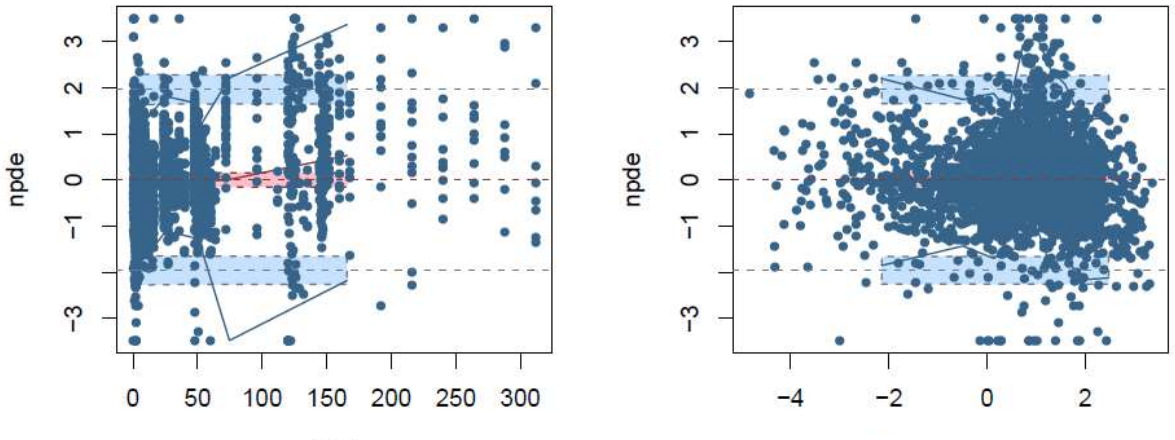
Results

Validation of the PK model



Goodness-of-fit plots

normalised prediction distribution errors (npde)



Time (h)

log transformed concentrations

No systematic errors indicating a good model fit

Methods 2

Methods

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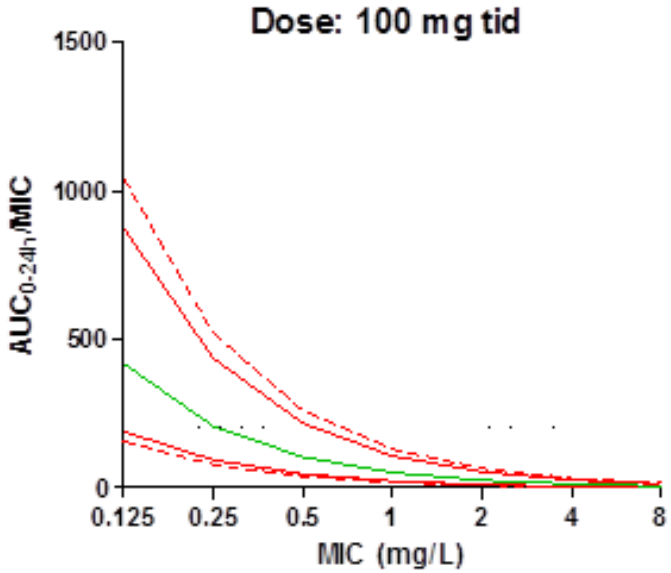
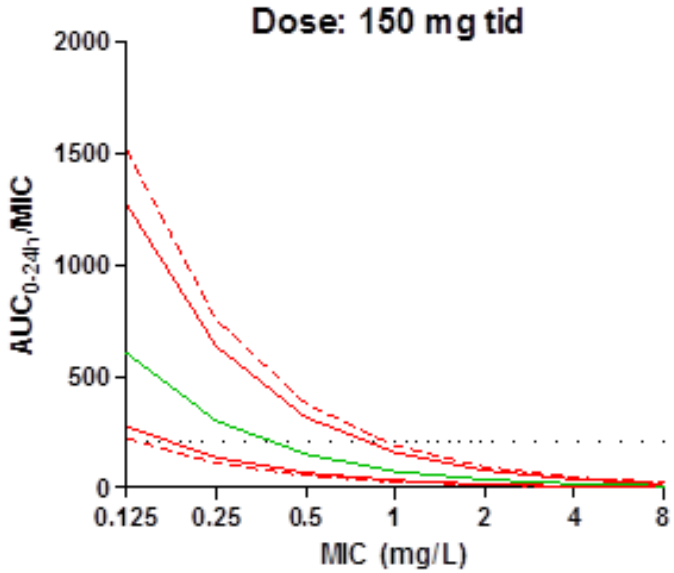
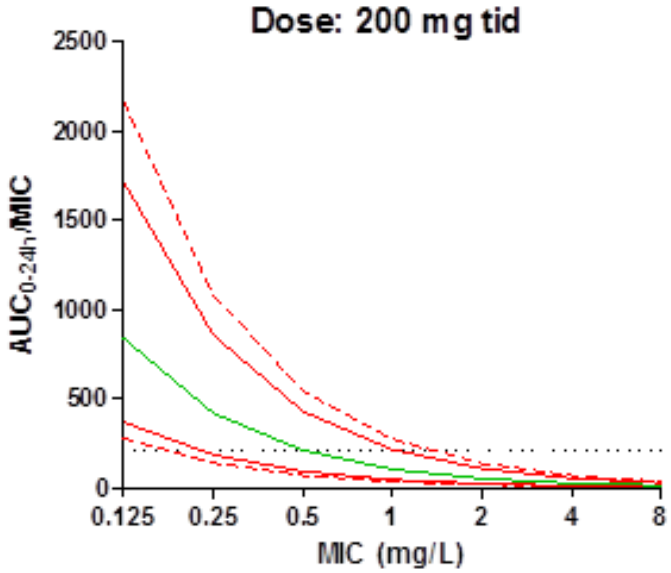
  - Covariate model
  - Validation of the final model: NPDE (normalised prediction distribution errors)
- Monte Carlo simulations
  - NONMEM
  - Used the popPK model without covariates (general) and with covariates for adjustments renal impairment
  - 1000 simulations per regimen
  - Total concentrations
  - PK/PD target: AUC/MIC >208
  - Target MIC 0.25 mg/L
  - Duration of infusion 2hours

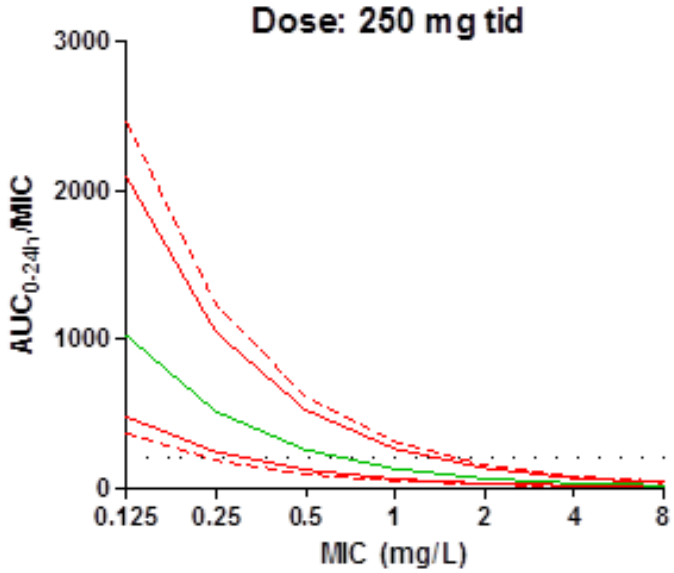
Results

MCS


Dose: 100 mg tid
AUC0-24h/MIC
1500
1000
500
0
0.125
0.25
0.5
1
2
4
8
MIC (mg/L)

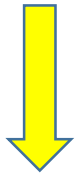

Dose: 150 mg tid
AUC0-24h/MIC
2000
1500
1000
500
0
0.125
0.25
0.5
1
2
4
8
MIC (mg/L)


Dose: 200 mg tid
AUC0-24h/MIC
2500
2000
1500
1000
500
0
0.125
0.25
0.5
1
2
4
8
MIC (mg/L)


Dose: 250 mg tid
AUC0-24h/MIC
3000
2000
1000
0
0.125
0.25
0.5
1
2
4
8
MIC (mg/L)

Results

Target attainment with normal renal function



MIC	0.125 mg/mL	0.25 mg/mL	0.5 mg/mL
AUC	26	52	104
Target attainment for dose regimen:			
100mg tid	95.5%	50.6%	3.1%
150mg tid	99.6%	81.0%	21.7%
200mg tid	100%	94.2%	50.6%
250mg tid	100%	**98.8%**	69.9%

Results

Target attainment in renally impaired individuals

Creatinine clearance	120 mL/min	70 mL/min	30 mL/min
MIC=0.25 mg/mL (AUC≥52)			
100mg tid	18.9%	81.7%	**100%**
150mg tid	82.7%	**99.6%**	100%
200mg tid	**99.3%**	100%	100%
250mg tid	100%	100%	100%
MIC=0.5 mg/mL (AUC≥104)			
100mg tid	0%	0.9%	67.4%
150mg tid	1.4%	32.5%	**98.7%**
200mg tid	17.5%	79.8%	100%
250mg tid	53.9%	**97.2%**	100%

Conclusions

Conclusions

- Population pharmacokinetics can be described adequately
- Standard dosing regimen: 250 mg tid Murepavadin if ECOFF is 0.25 mg/L
- MCS indicates dosing regimen:
  - For an MIC of 0.25 mg/L and Target Attainment Rate of 99%
    - For a creatinine clearance of 120 ml/min: 200 mg tid
    - For a creatinine clearance of 70 ml/min: 150 mg tid
    - For a creatinine clearance of 30 ml/min: 100 mg tid

Acknowledgment

Acknowledgment

ErasmusMC, Rotterdam, the Netherlands:

- Brenda de Winter
- Johan Mouton

Polyphor Ltd, Allschwil, Switserland

- Glenn Dale
- Achim Wach