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Population pharmacokinetics and optimal design of paediatric studies for Famciclovir

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Introduction

- Famciclovir
  - orally administered pro-drug of the antiviral agent penciclovir
  - little or no parent compound is recovered in blood or urine
  - licensed in adults for treatment of herpes zoster and herpes simplex infections (125 – 750 mg)
- PK extensively studied in adults – clinical success
- No population PK analysis has been published
- Limited information about the PK in paediatrics
  - Two attempts (post filing) were terminated early – recruitment issues, probably related to relatively intensive sampling

Aims

- To develop a population PK model
  - Adults and paediatrics (appropriate covariates)
- Design single dose studies in four paediatrics age groups (1month – 1 yr, 1 - 2 yr, 2 – 5 yr and 5 - 12 yr)
  - Appropriate dose
  - Limited sampling designs
  - Adequate number of patients

Data

- Plasma data from 6 clinical trials was provided by Novartis (including 2 paediatric studies, a bioavailability and a renal impairment study)

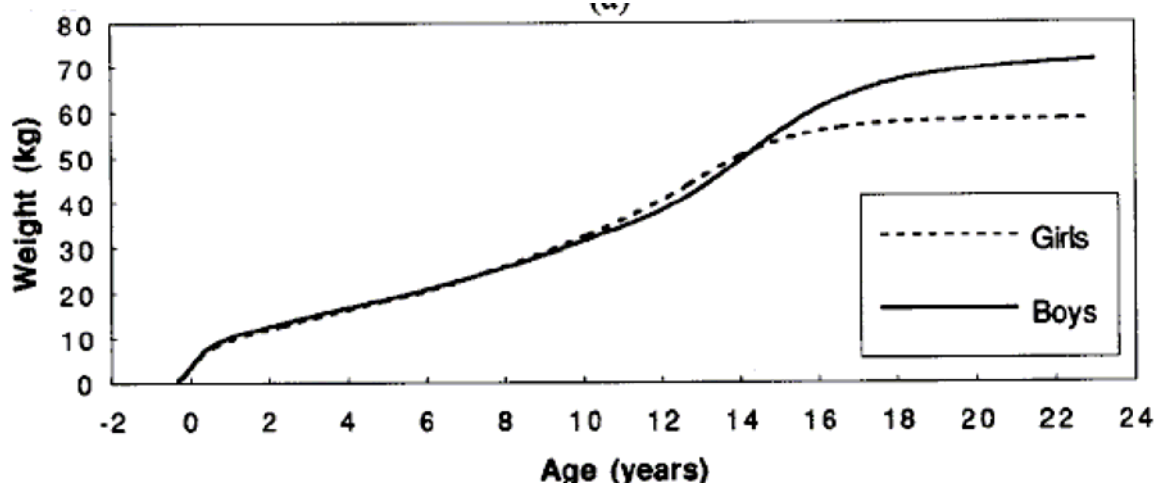
Covariate	Combined			Paediatrics			Adults		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	
Number of subjects	69	-	-	23	-	-	46	-	-
Number of occasions	160	-	-	39	-	-	121	-	-
Total plasma conc. data	1676	-	-	322	-	-	1354	-	-
Age (years)	26.5	15.8	2-63	8.1	3.4	2-17	35.8	10.6	20-63
Weight (kg)	59.3	23.7	13.9-94.6	29.5	12.2	13.9-59.8	74.1	9.7	56.4-94.6
Serum creatinine ($mg.dL^{-1}$)	0.94	0.33	0.28-1.94	0.60	0.13	0.28-0.78	1.10	0.27	0.69-1.94
Sex (M/F)	62/7	-	-	17/6	-	-	45/1	-	-
Creatinine clearance ($mL.min^{-1}$)	87.9	34.5	27.6-175.6	58.2	19.9	27.6-122.5	102.8	30.4	45.5-175.6

Method - modelling

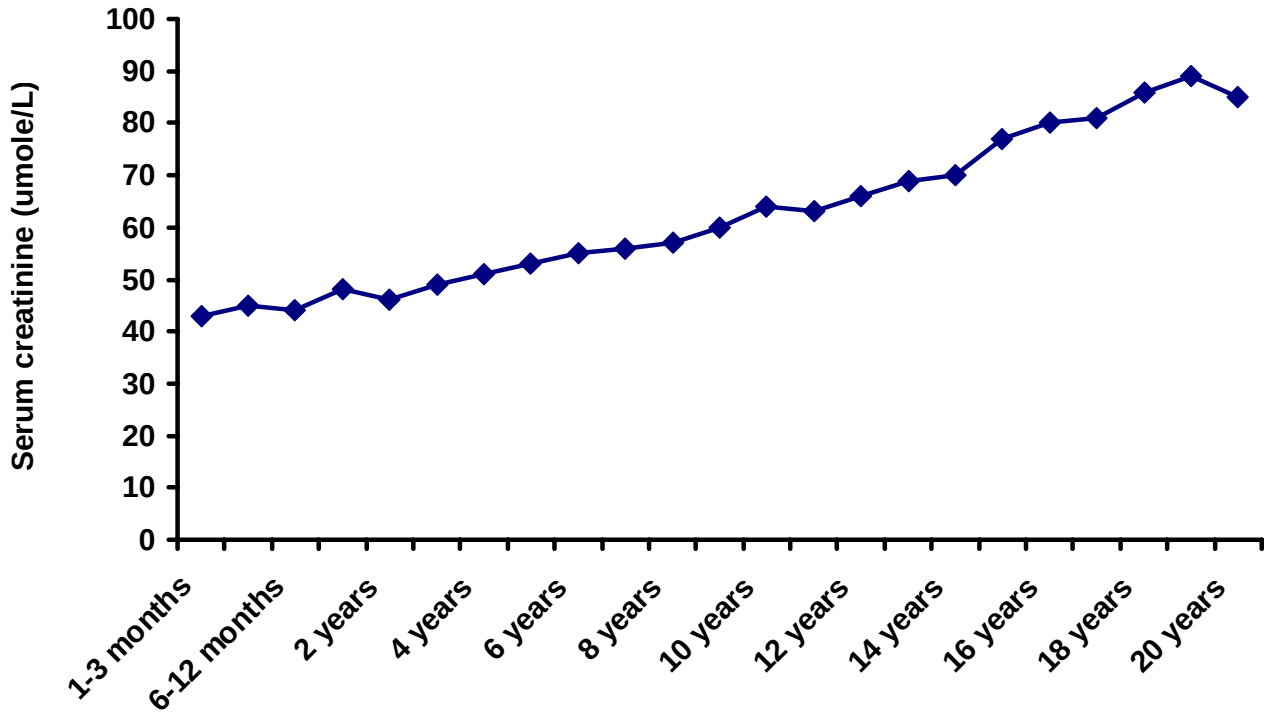
- NONMEM V1 (FOCE/INTERACTION)
- 1,2,3 compt first order absorption PK models were tested
- Add, Exp IIV models and add, prop or combined residual error models were tested
- Covariates – difference in obj function and graphics
- An allometric weight model was applied to volume and clearance parameters
- Several age and CRCL models were tested
- Bootstrap analysis of the final model

Method - dose adjustment

- Simulations
  - Reference values obtained for weight and serum creatinine (adults and paediatric age groups) to allow extrapolation of PK model
  - Dose adjusted to achieve the same AUC and Cmax as obtained for a 500mg adult dose



Savory, AnnClinBiochem 1990; 27: 99-101



Method - optimisation of sampling times and windows

- Model based approach – population Fisher information matrix (PFIM) in MATLAB
- Optimisation of sampling times
  - Modified Fedorov exchange algorithm (grid size 0.25)
  - PFIM evaluated by simultaneous Monte Carlo integration over covariate distributions (Latin hypercube sampling)
  - Design region between 0 and 8 hr, single elementary design and 5 times per patient
- Optimisation of sampling windows
  - Sampling windows around D-optimal time points
  - Assuming 95% mean efficiency level and uniform sample distribution

Sample size calculations

- Determined using simulations in NONMEM based on confidence interval approach
- Power of the final sampling windows design to estimate 95% confidence interval on the mean of a parameter of choice (CL and V) within specified precision levels
- Precision limits – 30, 40 and 50%
- 200 simulations in NONMEM (FOCE/INTERACTION)

Results - modelling

- Final model – 2 compartment first order absorption model with lag time
- Proportional IIV and exponential residual error model
- Covariates
  - allometric weight on CL, V1, V2 and Q
  - empirical fractional age model on CL
  - empirical CRCL power model on CL

$$CL_{<40\,yrs} = \theta_{CL} * \left(\frac{WT}{WT_{STD}}\right)^{3/4} * \left(\frac{K_{AGE<40} - AGE}{K_{AGE<40} - AGE_{STD}}\right) * \left(\frac{CLCR}{CLCR_{STD}}\right)^{P_{CLCR}}$$

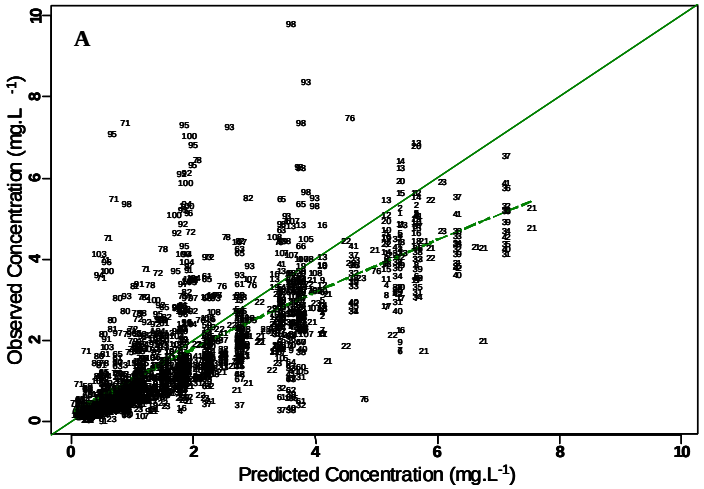
$$CL_{\geq 40\,yrs} = \theta_{CL} * \left(\frac{WT}{WT_{STD}}\right)^{3/4} * \left(\frac{K_{AGE\geq 40} - AGE}{K_{AGE\geq 40} - AGE_{STD}}\right) * \left(\frac{CLCR}{CLCR_{STD}}\right)^{P_{CLCR}}$$

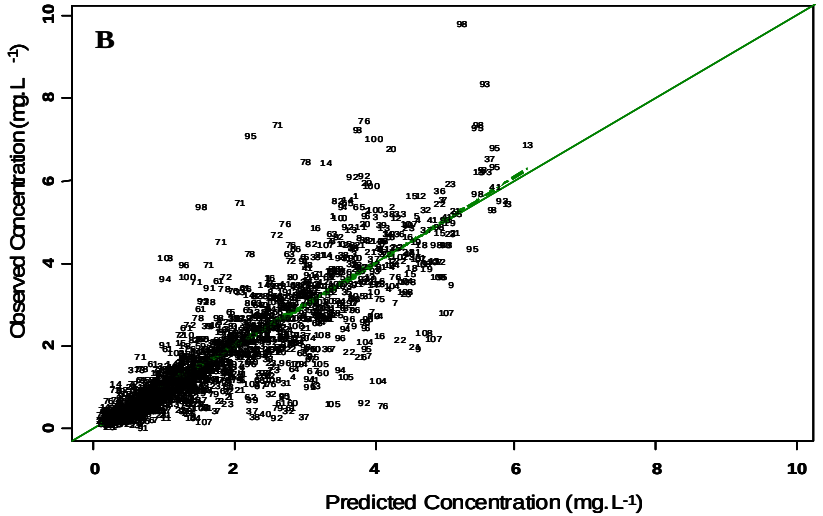
$$V_1 = \theta_{V_1} * \left(\frac{WT}{WT_{STD}}\right)^{1}, V_2 = \theta_{V_2} * \left(\frac{WT}{WT_{STD}}\right)^{1}, Q = \theta_{Q} * \left(\frac{WT}{WT_{STD}}\right)^{3/4}$$

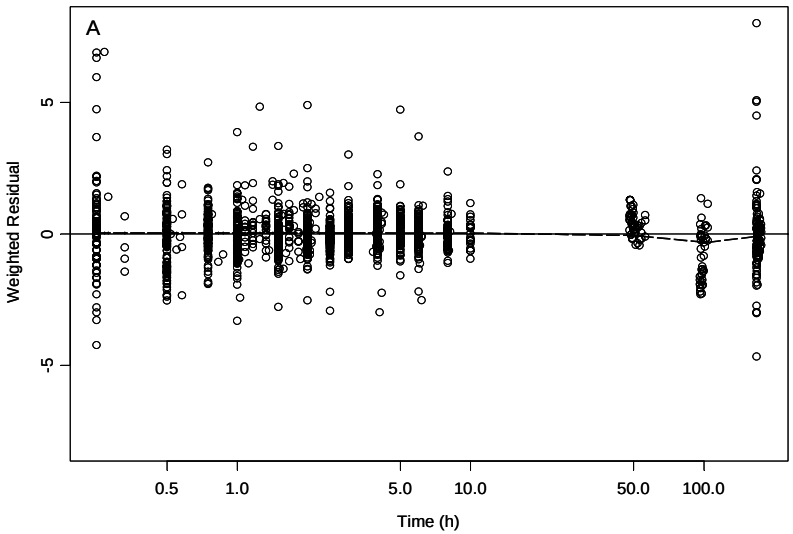
Results - modelling

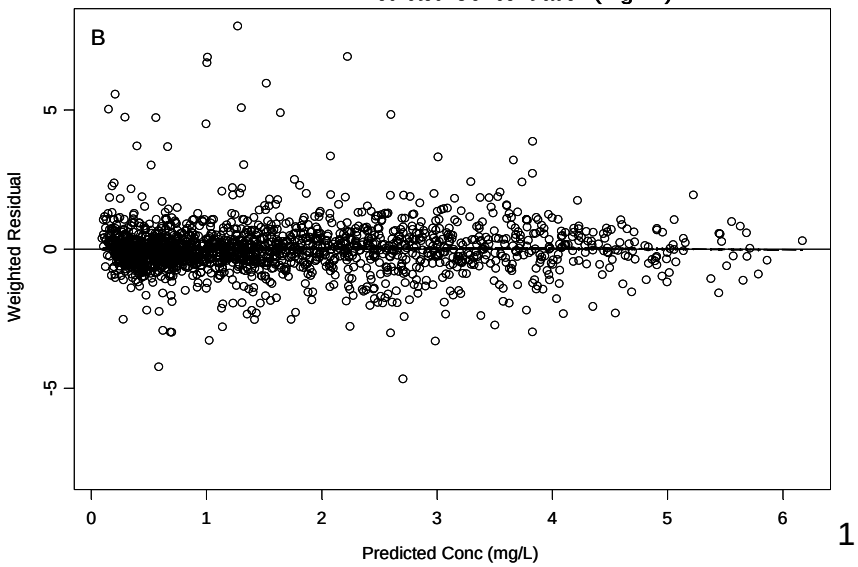
Parameter	Original data		Bootstrap procedure	
	Estimate	CV (%)	Estimate	CV (%)
ka (h^{-1})	1.86	10.3	1.87	10.7
CL ($L.h^{-1}.70kg^{-1}$)	31.2	6	31.3	6.27
V1 ($L.70kg^{-1}$)	28.6	6	28.5	6.19
V2 ($L.70kg^{-1}$)	54.5	4.9	54.7	5.03
Q ($L.h^{-1}.70kg^{-1}$)	60.2	7.1	60.3	7.03
F	0.598	2.9	0.598	2.97
T-lag (h)	0.206	2.2	0.206	2.39
$K_{AGE<40}$	159	37.4	-	-
$K_{AGE\geq 40}$	113	24.4	-	-
exponent of FCL_{CR}	0.28	45.7	0.270	47.9
BSV_{ka}	0.640	25.9	0.627	12.8
BSV_{CL}	0.23	22.3	0.220	11.4
BSV_{V1}	0.003 fix	-	0.003 fix	
BSV_{V2}	0.255	29.3	0.250	14.8
BSV_{Q}	0.342	59.4	0.331	27.7
Proportional error	0.221	9.6	0.221	4.74
Additive error ($mg.L^{-1}$)	0.01 fix	-	0.01 fix	

Results - modelling

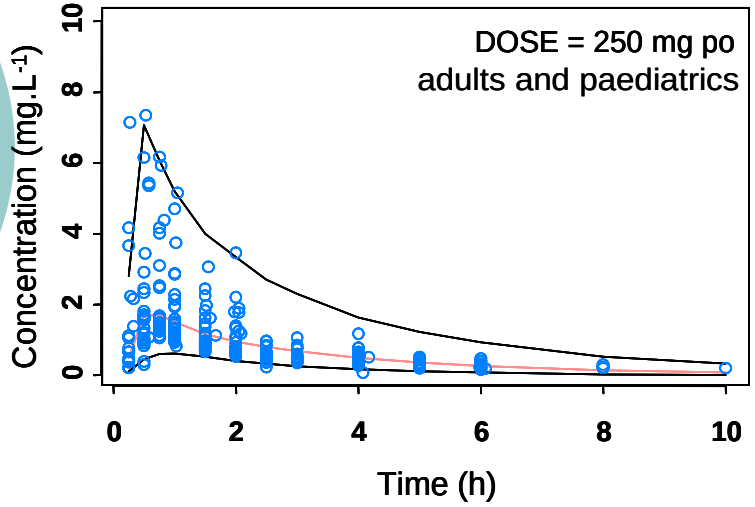


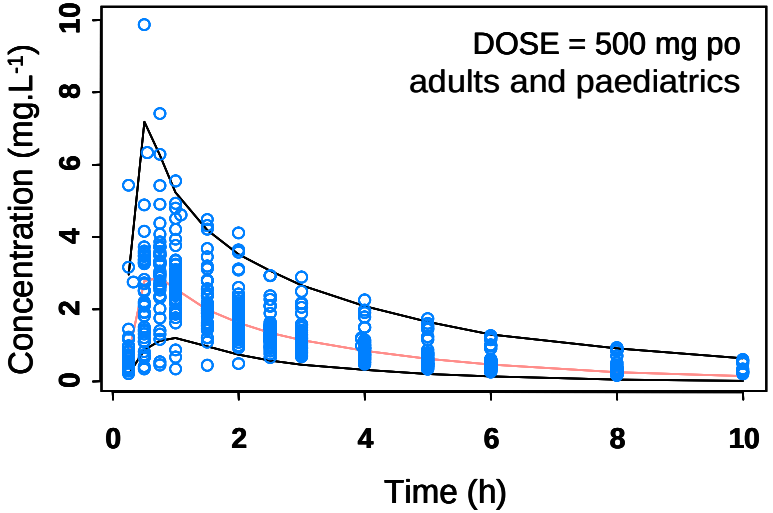


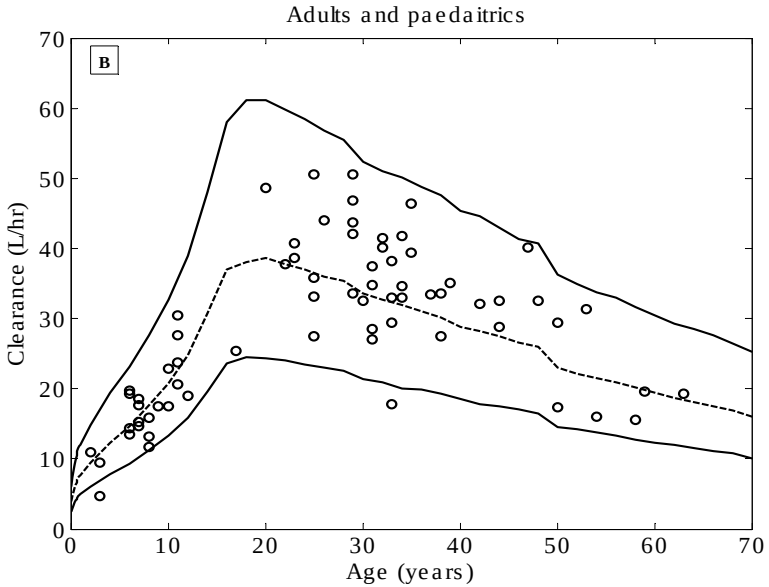


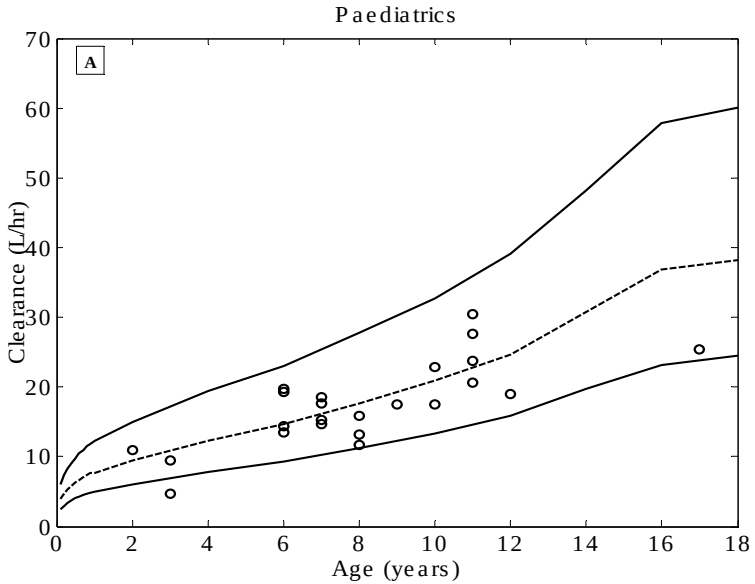


Results - modelling



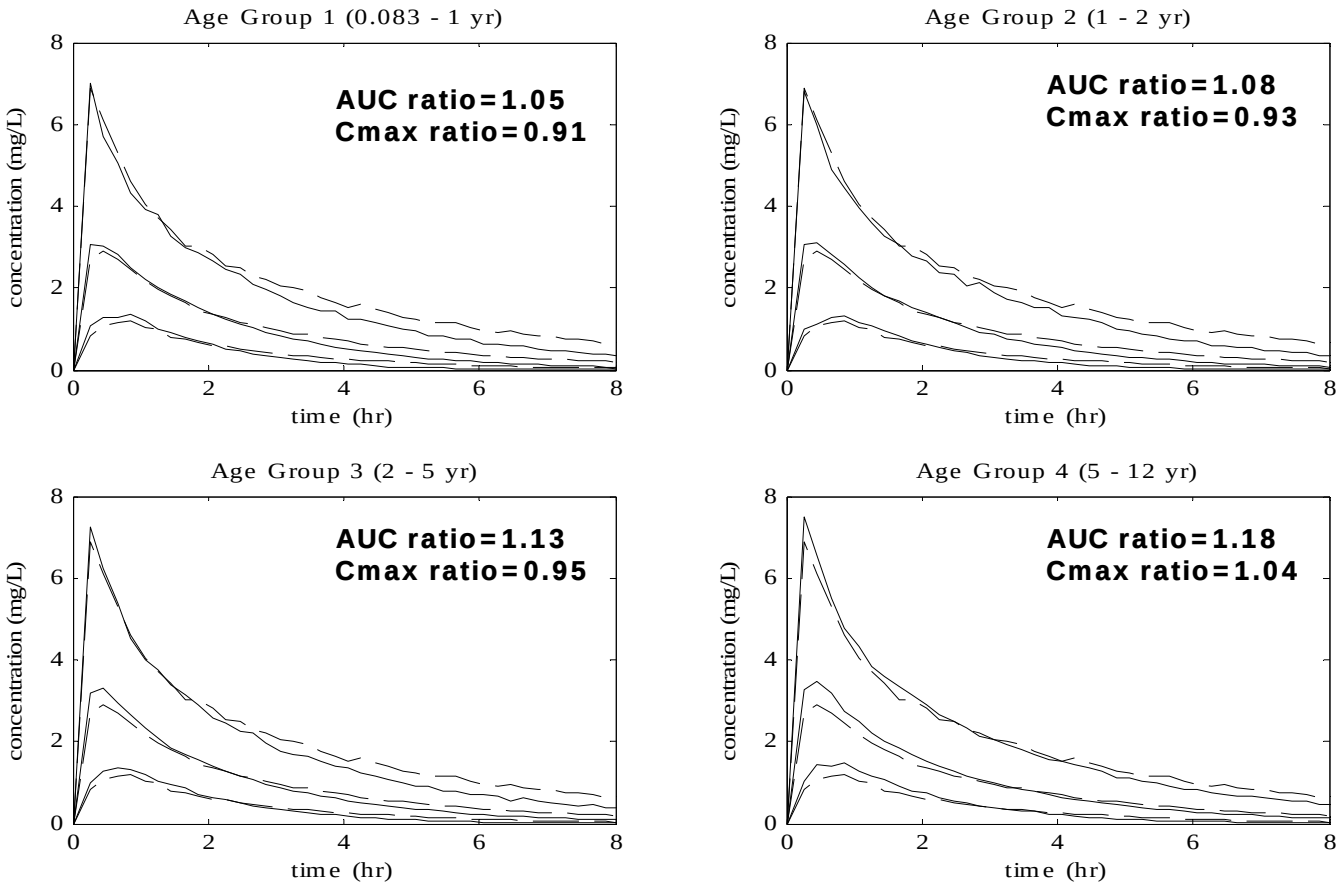






Results – dose adjustment

- 10mg/kg gave the best AUC ratio and Cmax ratio



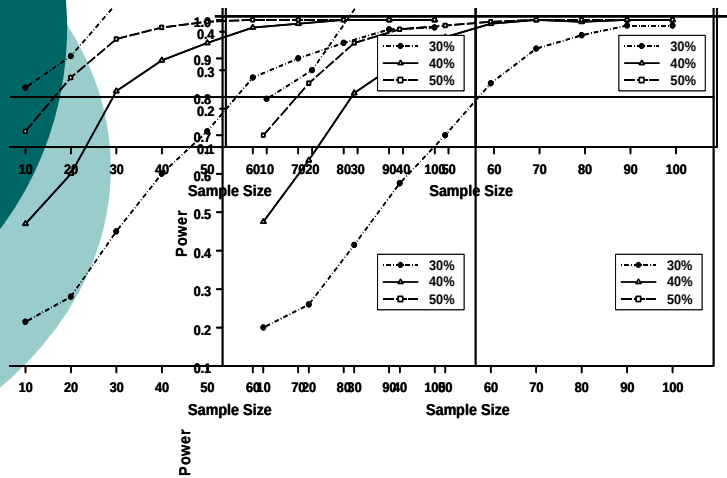
dashed=adults, continuous=paediatrics

Results – sampling times and windows optimisation

Sampling Properties	Sample Number	Age Groups 1	2	3	4
Optimal Sampling Times (hr)	1	0.25	0.25	0.25	0.25
	2	0.65	0.70	0.70	0.85
	3	1.35	1.35	1.30	1.00
	4	3.15	3.05	3.00	2.80
	5	8.00	8.00	8.00	8.00
Optimal Sampling Windows (hr)	1	0.25 - 0.28	0.25 - 0.28	0.25 - 0.28	0.25 - 0.27
	2	0.53 - 0.78	0.58 - 0.82	0.58 - 0.82	0.62 - 1.08
	3	0.93 - 1.77	0.70 - 2.00	0.66 - 1.94	0.26 - 1.73
	4	2.41 - 3.89	2.47 - 3.63	2.48 - 3.52	2.61 - 2.99
	5	7.37 - 8.00	7.45 - 8.00	7.48 - 8.00	7.78 - 8.00

- Windows very close in all age groups
- High sensitivity (narrow window) with window 1
- Overlap between windows 2 and 3
- New single sampling windows for all paediatrics: 0.25 – 0.4, 0.5 – 1, 1.25 – 1.75, 2.75 – 3.5 and 7.25 – 8 hr
- Final windows – 85% efficient for all paediatric age groups

Results – sample size calculations



- Based on V1
- Final criterion – 80% power and 40% precision limits
- 30 patients for each age groups (120 in total)
- Final sample size - SE(%) for ka, CL, V1, V2, Q is 25, 5, 25, 10 and 26

Conclusion

- A population PK model for adults and paediatrics has been described
- Adult clearance and total volume of distribution values are comparable to published values from non-compartmental analysis
- Age and CRCL in addition to weight are needed to explain the IIV on clearance
- There is a need for dose adjustment in paediatrics and 10mg/kg weight is adequate based on simulation
- An important area of application of optimal design is paediatric population (limited sampling - ethical and practical constraint) – help to define only the important sampling times
- Future famciclovir paediatric studies using appropriate dose, limited sampling designs and adequate number of subject have been determined