Population Pharmacokinetics of Mycophenolic Acid (MPA) and its Metabolites (MPAG and AcMPAG)

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Conferència de Recerca. Facultat de Farmàcia, 29 Novembre 2011

Outline

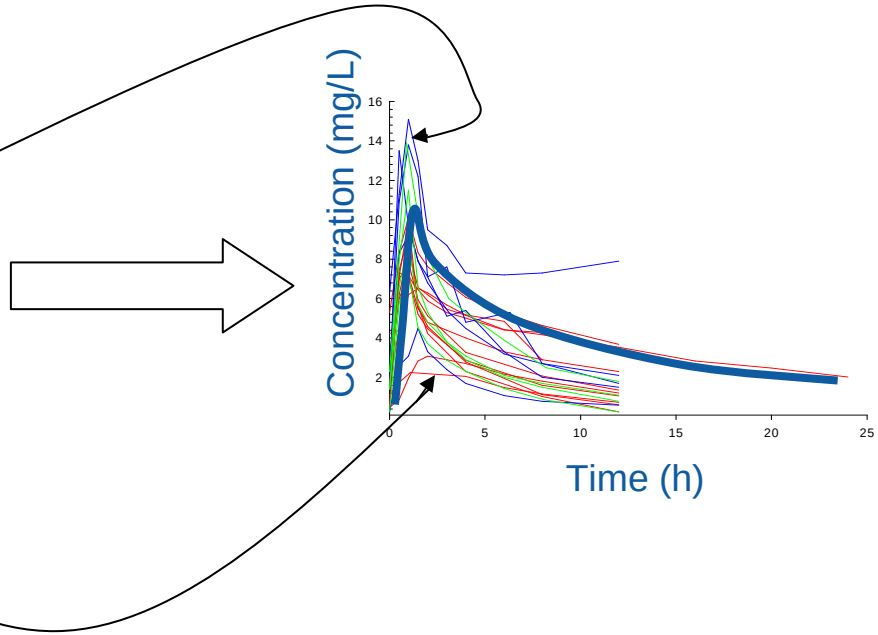
- Background
  - Population pharmacokinetics
    - Definition
    - Aim
    - Advantages and disadvantages
  - MPA, MPAG, AcMPAG Pharmacokinetics
- Population Pharmacokinetic study of MPA and its glucoconjugated metabolites (MPAG and AcMPAG). The influence of MRP2 polymorphism:The Symphony study
  - Background
  - Methods
  - Results
  - Conclusions

Background

Definition

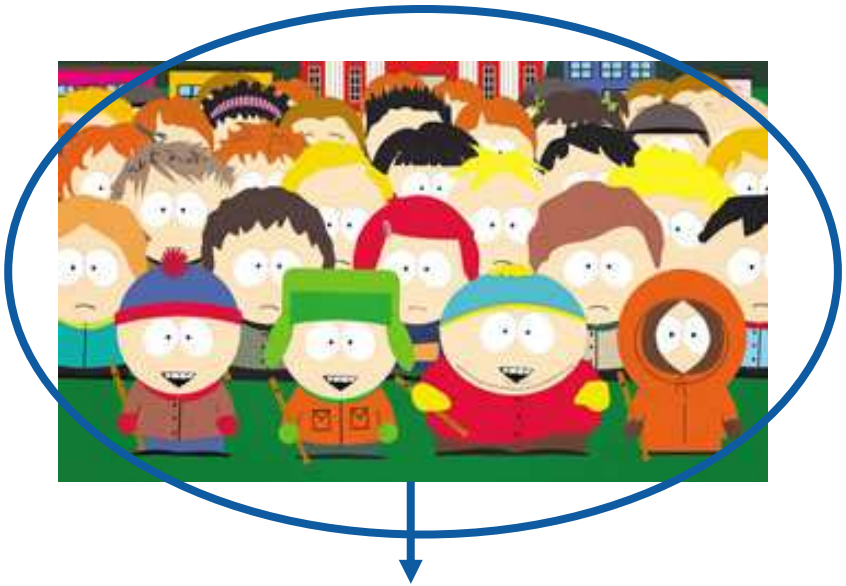
- Population PK is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest.

Guidance for Industry.Population Pharmacokinetics
U.S. Department of Health and Human Services
Food and Drug Administration.Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
February 1999 CP 1

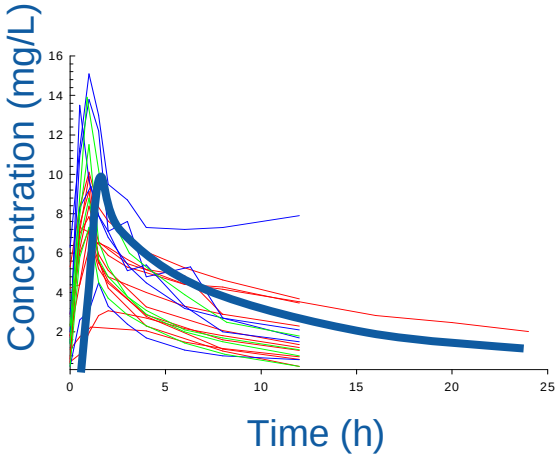


Background

- Aims
  - To describe the pharmacokinetics of a given drug in the target population
    - ¿What is the mean population PK behaviour?



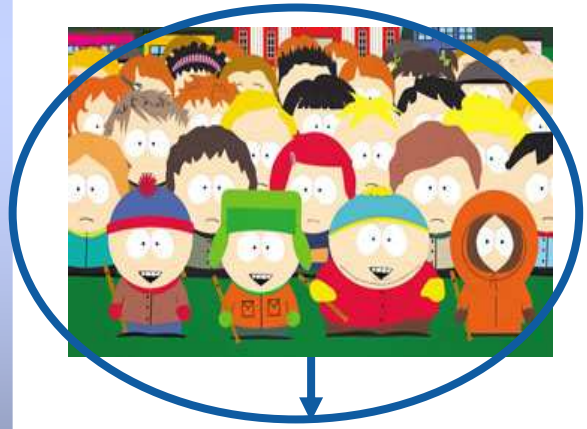
TVCL, TVV



Typical value

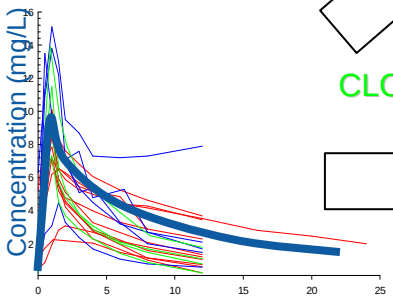
Background

- Aims
  - To describe the pharmacokinetics of a given drug in the target population
    - ¿Which factors influence the mean population PK behaviour?

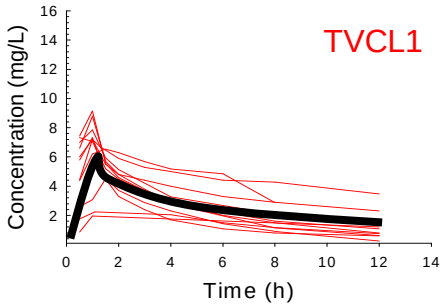


TVCL, TVV

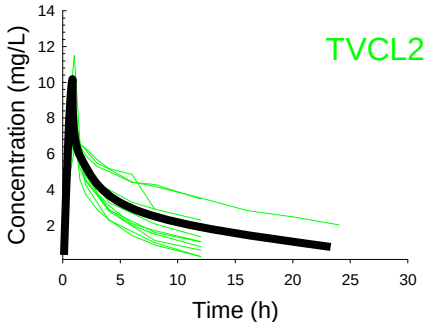
Typical value



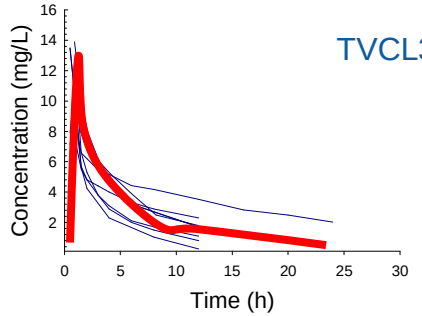
CLCR=90 mL/min



CLCR=60 mL/min

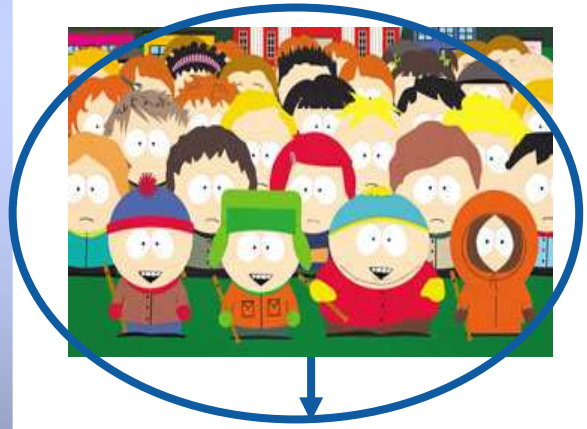


CLCR=30 mL/min



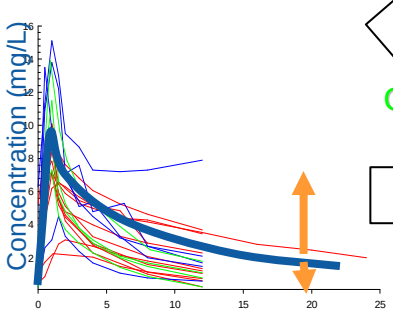
Background

- Aims
  - To describe the pharmacokinetics of a given drug in the target population
    - ¿What is the uncertainty degree associated to the mean population PK behaviour?

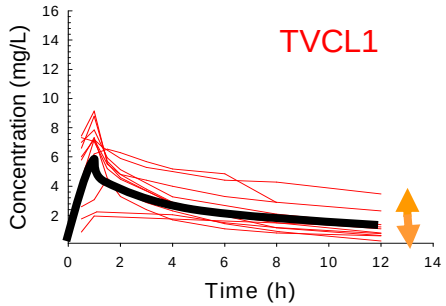


TVCL, TVV

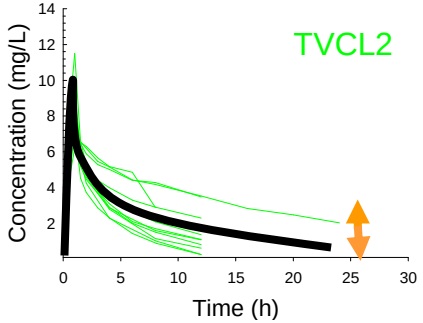
Typical value



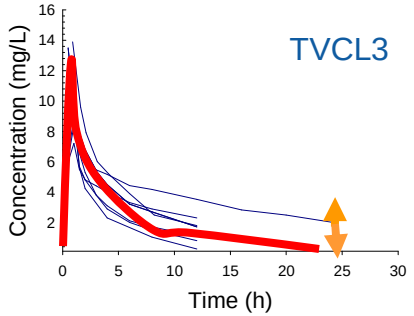
CLCR=90 mL/min



CLCR=60 mL/min



CLCR=30 mL/min



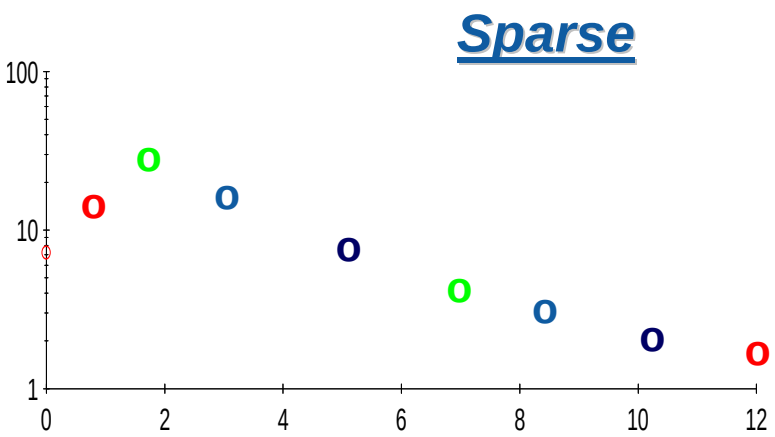
Advantages

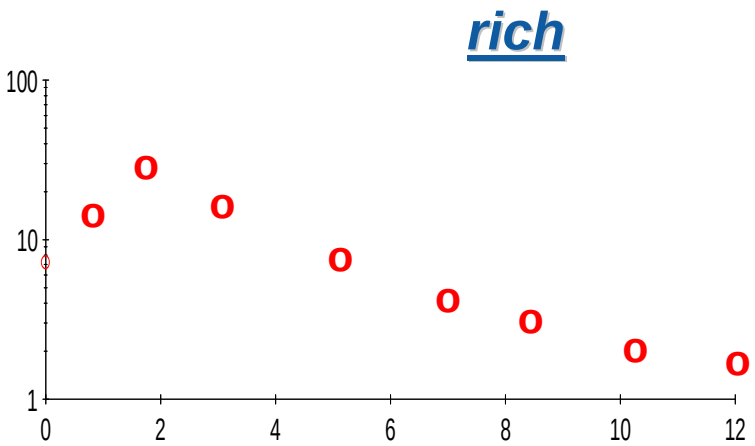
- It allows:
  - Simultaneous PK analysis of concentration-time data of parent compound and metabolites, plasmatic and urine concentrations, several doses, several administration routes
  - Sparse data (2/3 sampling time per subject / patient)
    - Observational data
    - Clinical studies phase II/III
    - Special populations (neonates, children, geriatrics….transplant, VIH)
    - Drugs to be monitored (ex. Antiepileptic drugs)
  - High number of patients with low restrictions concerning to inlcusion and exclusion criteria
  - Non balanced studies; different number of samples per subject
  - Intensive sampling studies (rich data) and studies where subjects are characterized extensively.

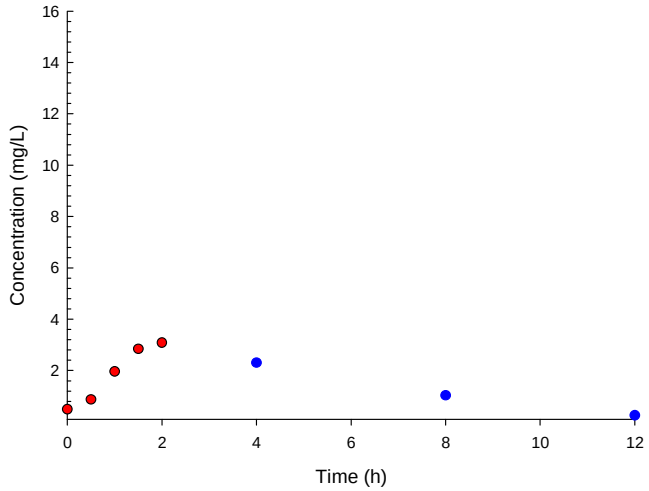
Disadvantages

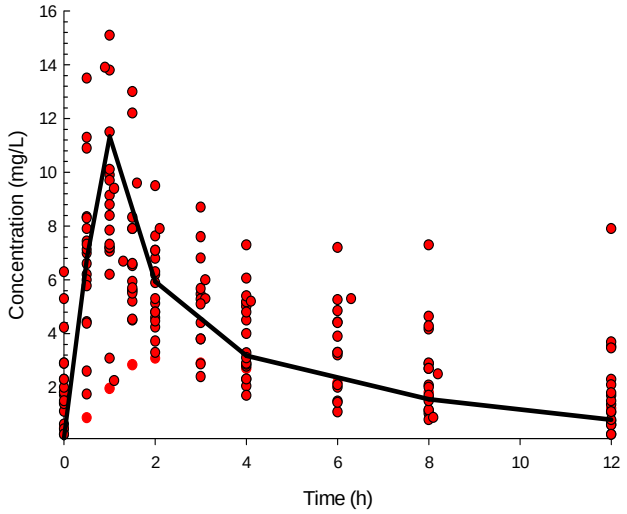
- Complexity and long runing times sometimes!!!!

Sparse vs rich data analysis









Applicability

- **Preclinical and clinical development:**
  - Better Knowledge during the different steps of drug development:
    - PK model (concentration-time profile)
    - PD model (Response-concentration)
    - PK/PD model (Response –time profile)
- **Clinical practice (drugs of narrow therapeutic index)** ↓
  - Prediction of the PK behaviour of the drug in subpopulations (renal and hepatic impairment,aged populations, neonates): ¿Dose tailoring?
  - Prediction of PK behaviour of the drug administered with other drugs (Interactions):¿Dose tailoring?
  - Simulation of new scenarios , dosage regimens, sampling designs, patient characteristics…., etc.

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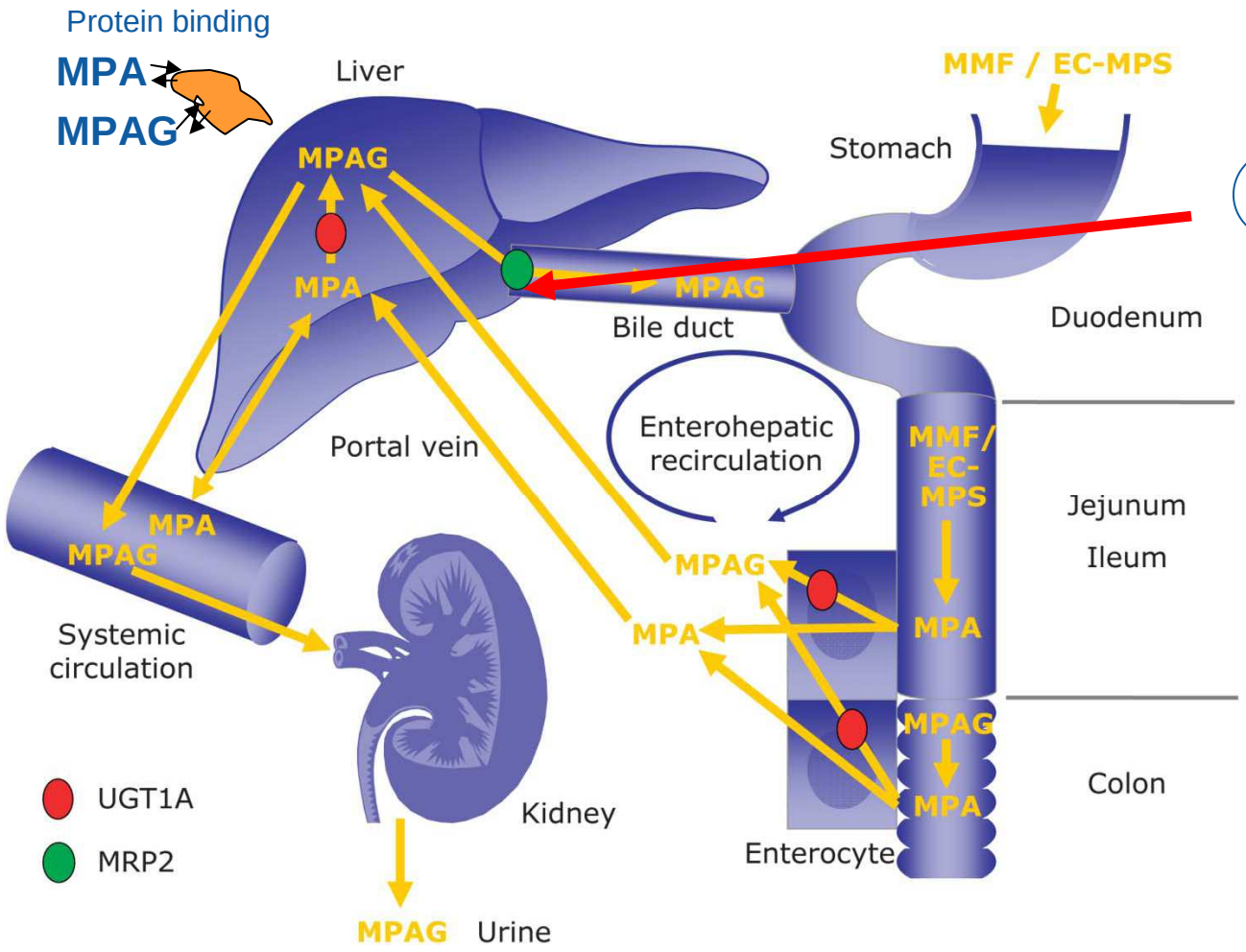
MPA, MPAG Pharmacokinetics

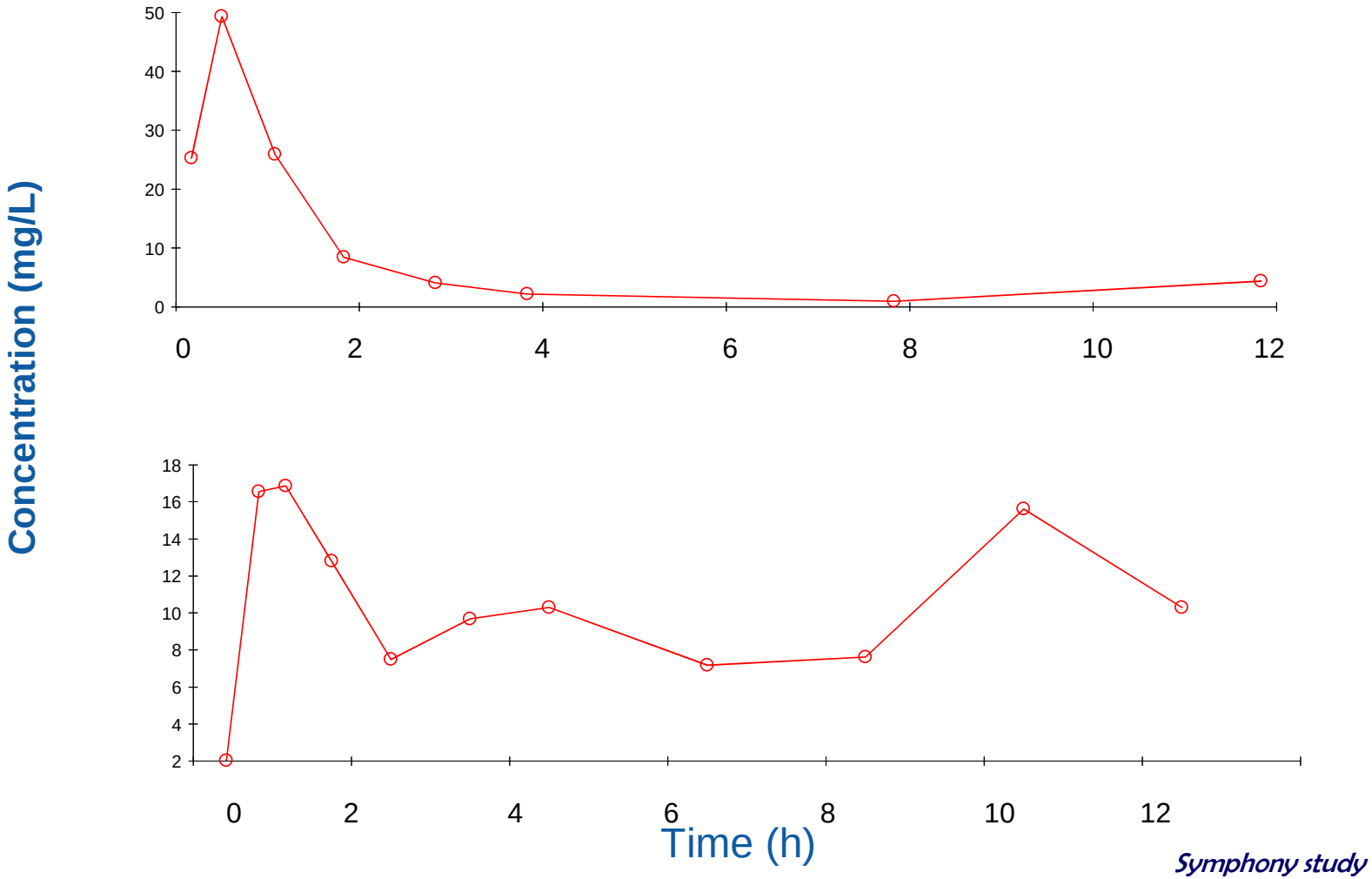


Cyclosporine : MRP2 inhibitor

MRP2 SNP

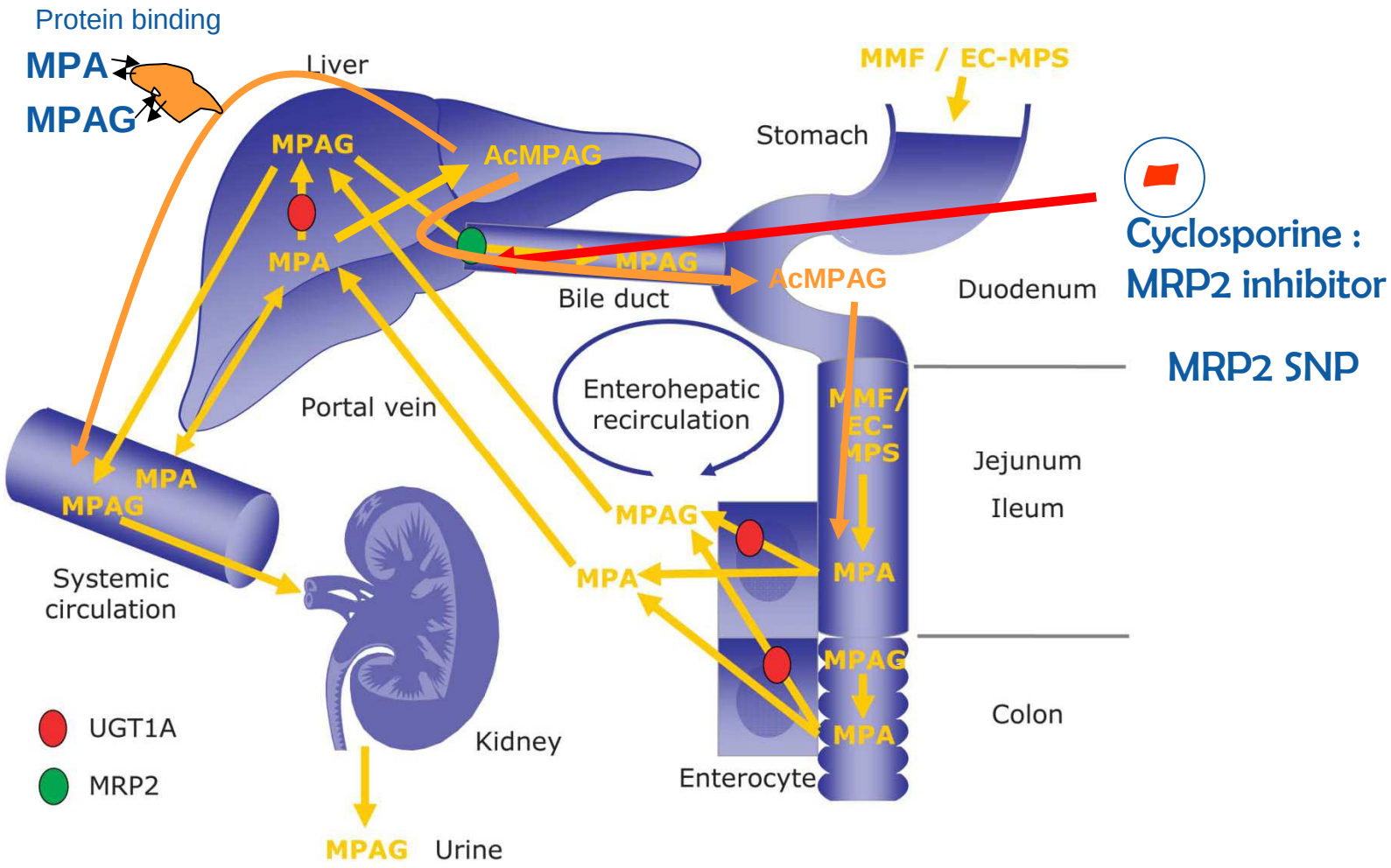
Naessens, TDM, 2009

tMPA, Pharmacokinetics



Symphony study

MPA, MPAG, AcMPAG Pharmacokinetics

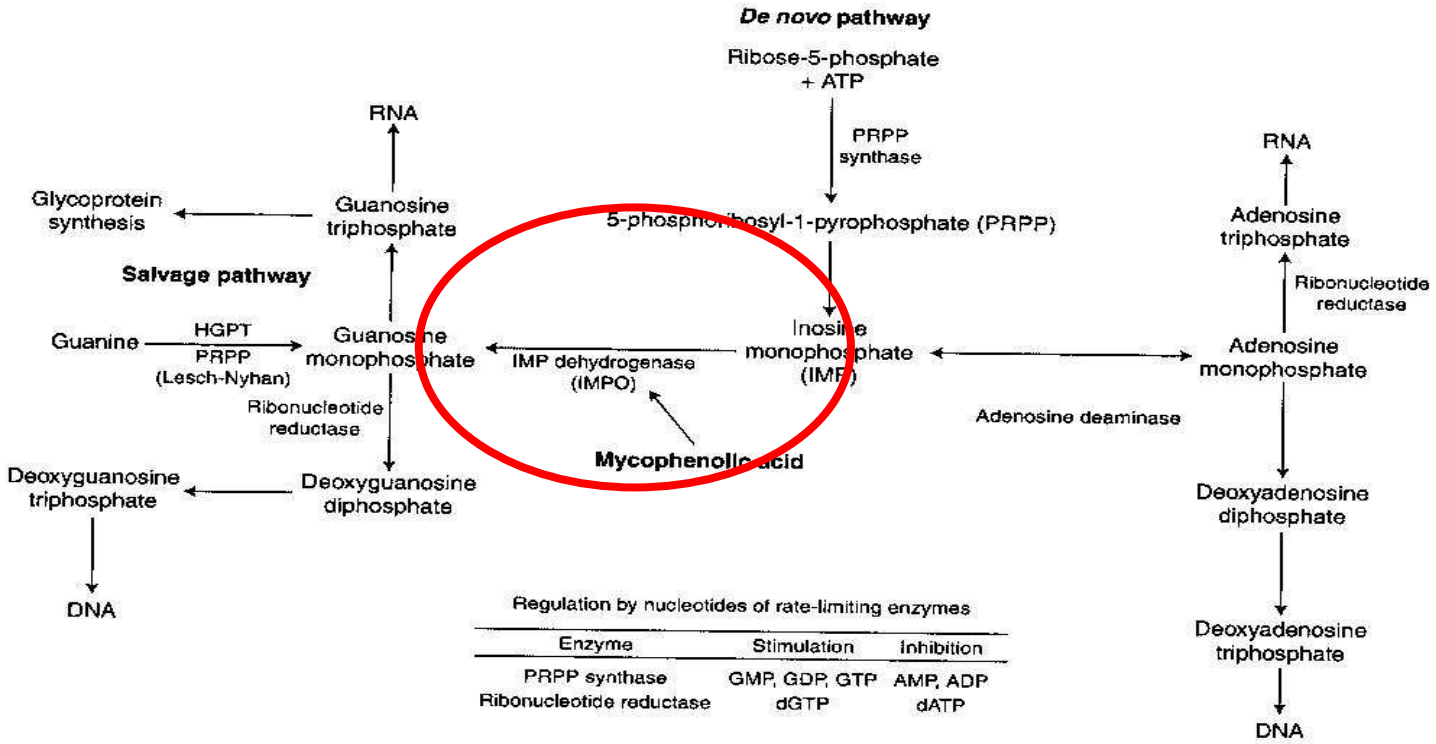


Naessens, TDM, 2009

MPA exposure variability?

- Changes in Albumin concentrations
- Changes in Renal function (CLCR)
- Immunosuprresive co-medication
- Genetic polymorphism, MRP2, UGT

MPA Pharmacodynamics



MPA is widely used for maintenance immunosuppressive therapy and prevention of renal allograft rejection in renal transplant recipients. MPA inhibits inosine monophosphate dehydrogenase (IMPDH), an enzyme involved in the two novo synthesis of purine nucleotides, thus suppressing both T-cell and B-cell proliferation.

The pharmacodynamics depends on the free MPA concentrations and also the adverse events

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SYMPHONY: Comparison of 3 low-toxicity regimens with standard immunosuppression

POPULATION PHARMACOKINETICS OF MYCOPHENOLIC ACID AND ITS METABOLITES IN COMBINATION WITH FREE OR REDUCED DOSES OF CALCINEURIN INHIBITORS DURING THE RENAL POST-TRANSPLANT PERIOD: THE SYMPHONY STUDY.

[8]COLOM H, [1,9]LLOBERAS N, [1]CALDÉS A, [1]ANDREU F, [2]OPPENHEIMER F, [4]SÁNCHEZ PLUMED J, [5]GENTIL M, [6]KUYPERS D, [2,3]BRUNET M, [7]EKBERG H, [1]GRINYÓ J.

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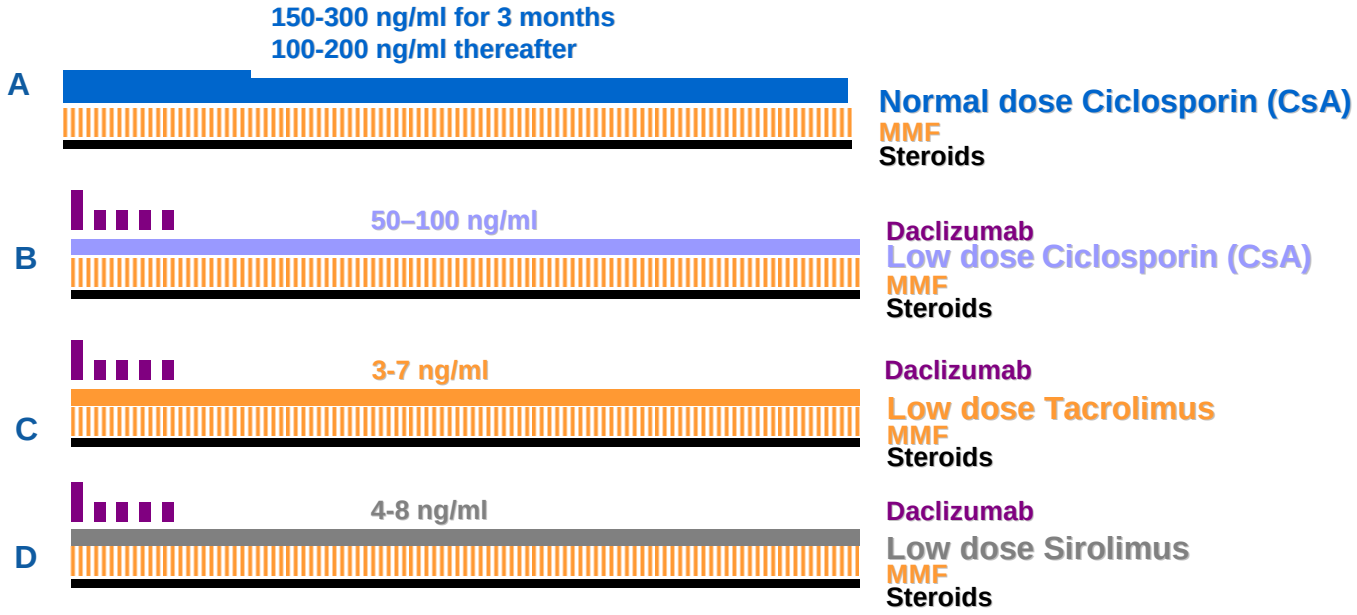
9Pharmacogenetic group of the symphony study in Spain

Supported by funding from F. Hoffmann-La Roche

Background

SYMPHONY Pharmacokinetic (PK) Sub-Study

♪ Patients from 9 sites in Spain and 1 in Belgium

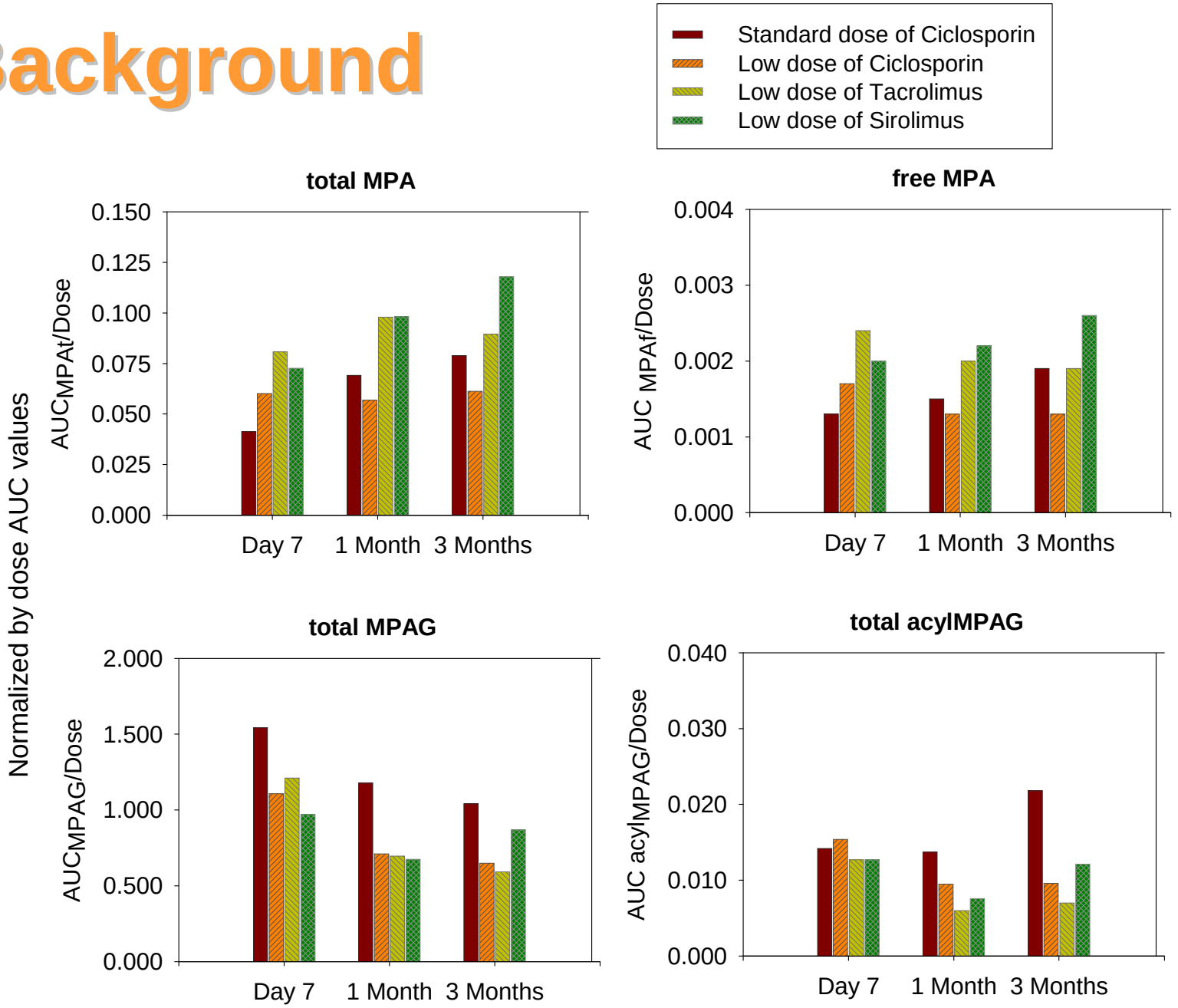


♪ PK sampling on Day 7 and 1, 3, 6 and 12 months post-transplant

♪ Sampling times: before dosing and at 20, 40, 75 min, 2, 3, 6, 8, 10 and 12 h post-dosing

♪ Patients were genotyped for C24T SNPs in MRP2 (CC, CT,TT)

Background

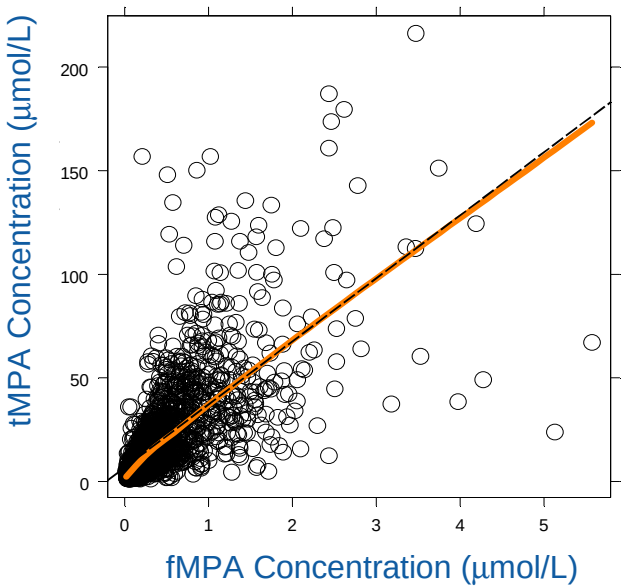


Grinyó et al, Nephrol Dial transplant, 2009

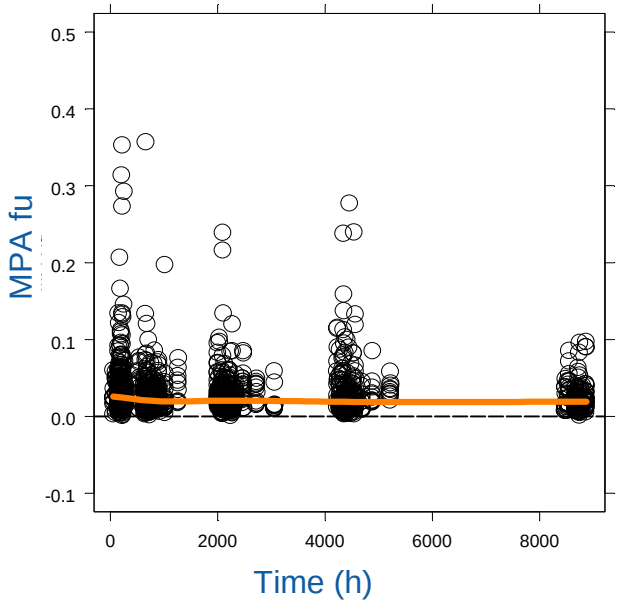
*N Lloberas et al. Nephrol Dial transplant, **2011***

Background

tMPA vs fMPA



Fu vs time



tMPA=bMPA+fMPA

Fu=unbound fraction of MPA

$$C_{BMPA} = \frac{B_{max} \cdot C_{fMPA}}{K_D + C_{fMPA}}$$

$$C_{bMPA} = K_{PB} \cdot C_{fMPA}$$

Aim

- To develop a population PK model in order to:
  - Describe relationship among MMF doses and total MPA, free MPA,total MPAG and total acylMPAG exposures
  - Identify potential predictive patients' demographic and clinical characteristics for dose tailoring during the post-transplant immunosuppresive treatment.

Methods

Patients' characteristics

	Units	Median (range)
Number of patients	-	56
Standard Cyclosporine (A)	n	11
Low Cyclosporine (B)	n	17
Low Tacrolimus (C)	n	10
Low Sirolimus (D)	n	18
Creatinine clearance*	mL/min	59.51 (8.43 - 134.9)
Albumin	g/L	42.0 (28.0 - 67.0)
Patients with low graft function (y/n)	n	4/56
Cyclosporine Daily Doses	mg	
Standard dose group (A)		150 (50 - 300)
Low dose group (B)		100 (40 - 225)
Cyclosporine trough concentrations	ng/mL	
Standard dose group (A)		175 (47 - 500)
Low dose group (B)		87 (26 - 480)
MRP2 Polymorphisms		
C24T (CC/TT/CT)	n	36/ 1/ 19

* CL_{CR} values estimated according to Cockroft-Gault

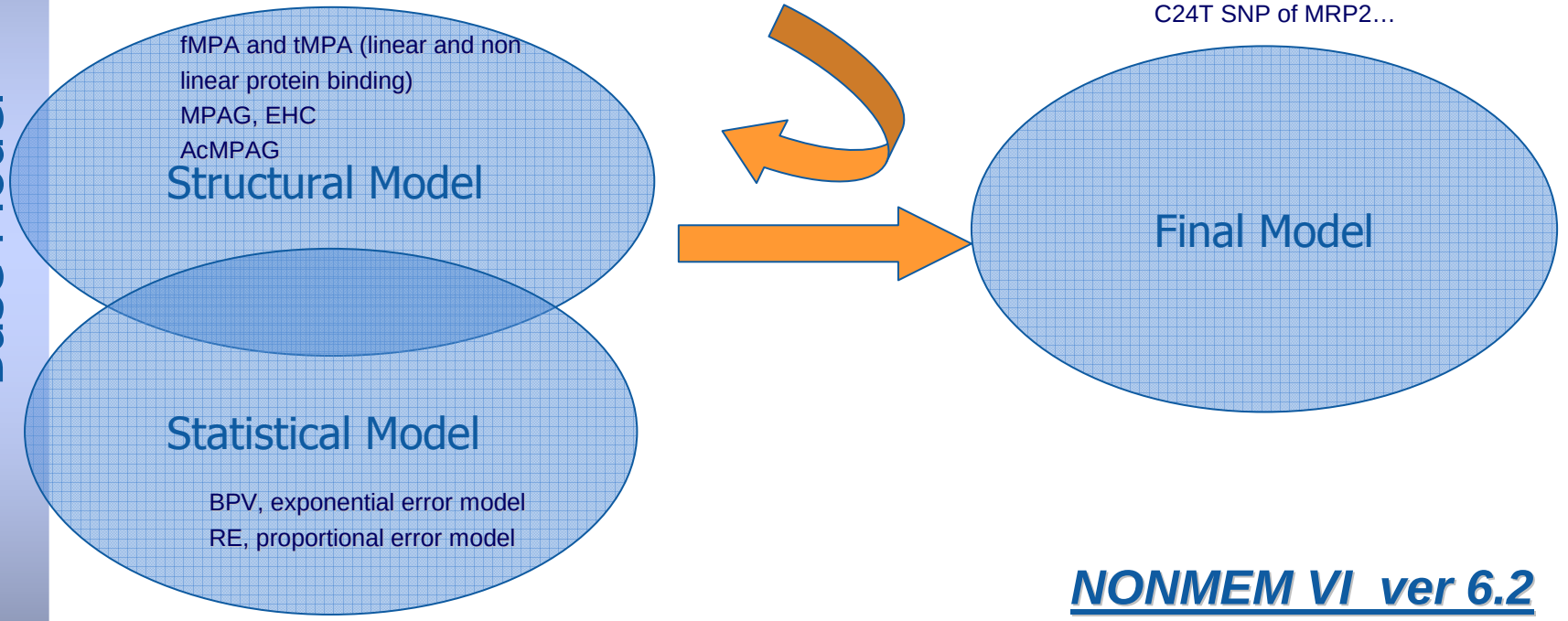
Patients with low graft function (y): CL_{CR} ? 25 mL/min

(n): CL_{CR} >25 mL/min

CC: non carrier, TT:homozygous T carrier, CT:heterozygous carrier

Methods:Population PK
Pharmaco-statistical model

Base Model



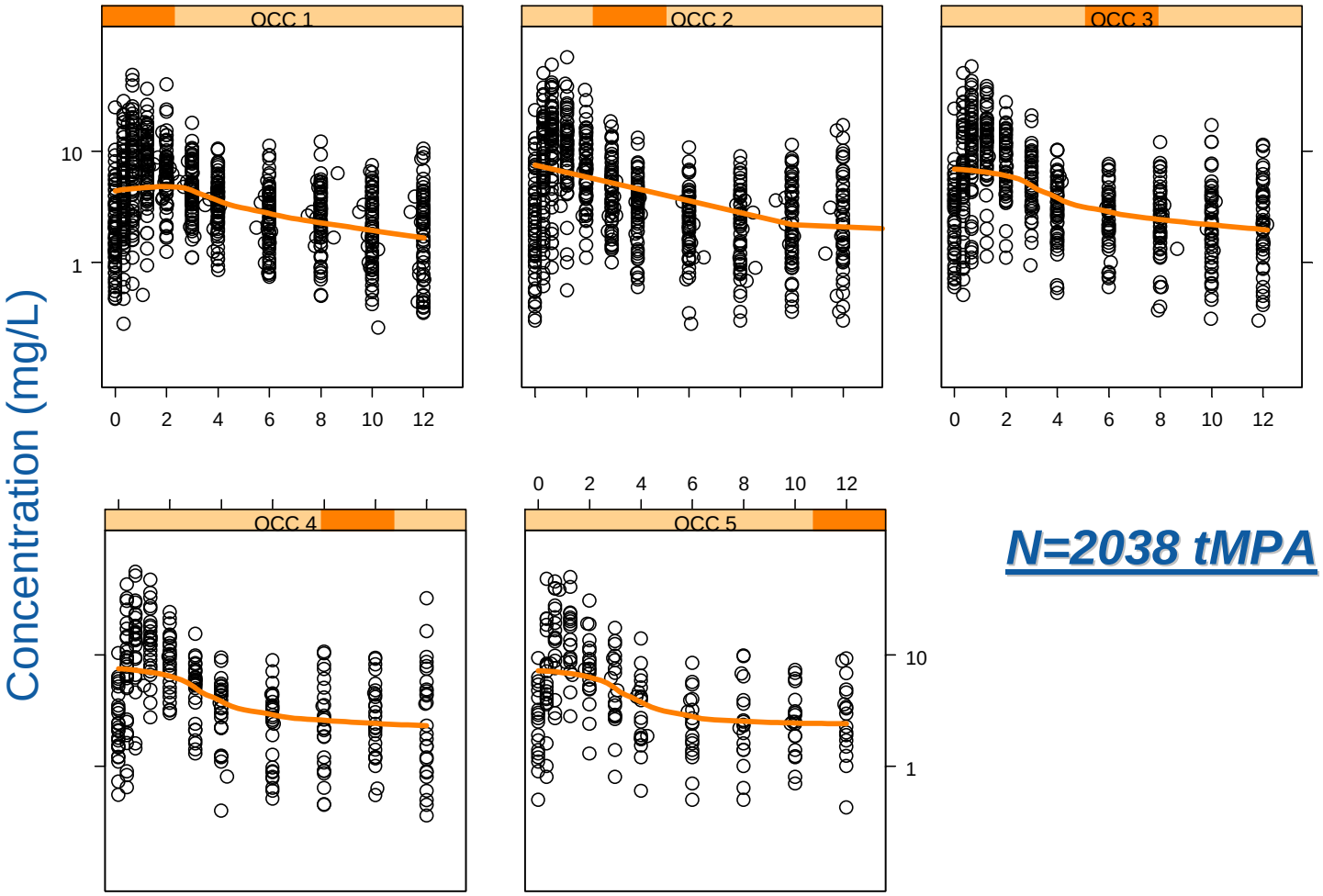
NONMEM VI ver 6.2

PK Model and error model (IIV and RE) Base model+covariates

Methods:Model evaluations

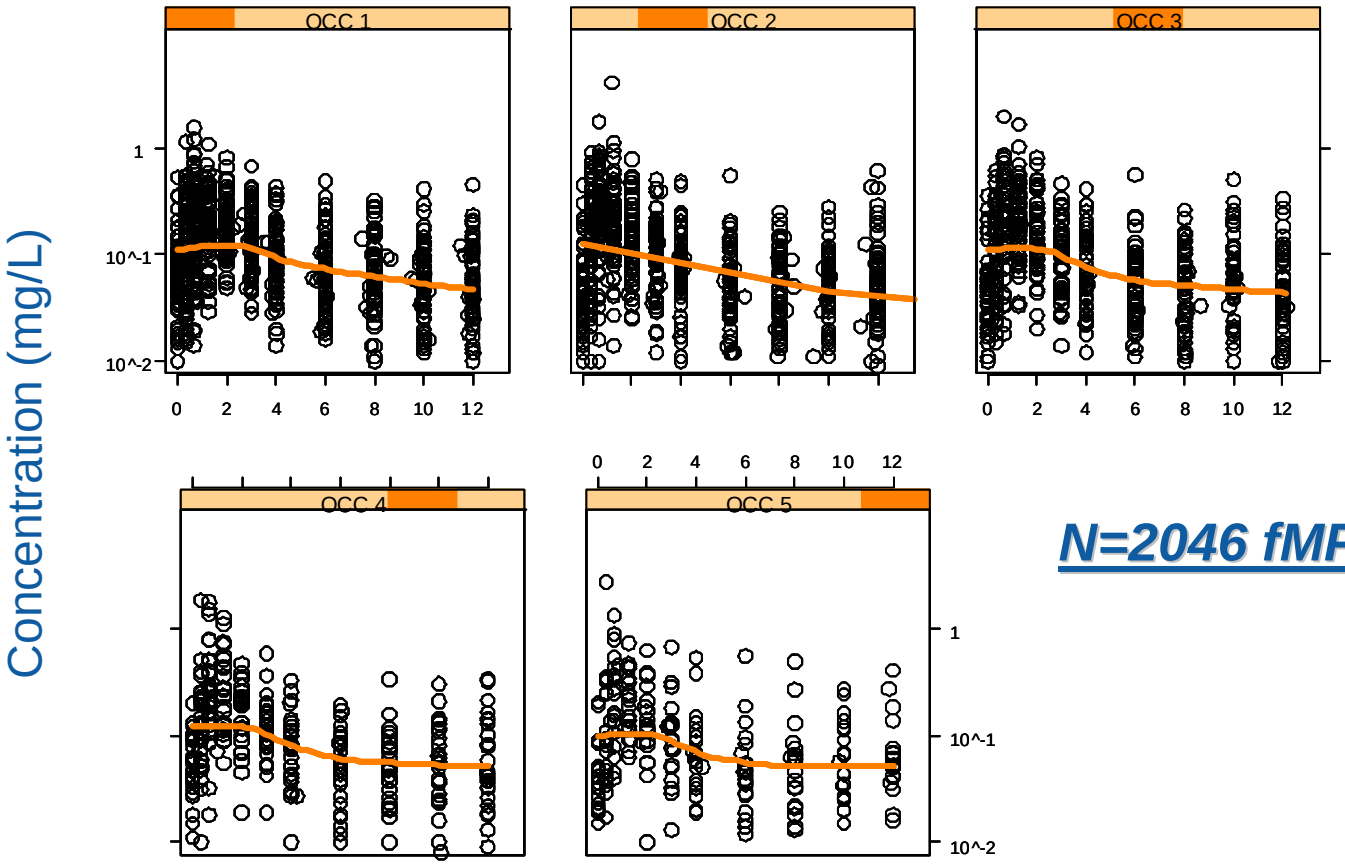
- Model evaluations
  - Non hierarchical models: AIC values
  - Hierarchical models ΔMOFV (7.879 units, $p<0.005$)
  - Parameter precision (RSE%)
  - Goodness-of-fit plots
  - Reduction of BPV
  - Covariate model backward elimination (10.8 units, $p<0.001$)
- Internal model validation
  - VPC, visual predictive check
  - PPC, posterior predictive check

Results: tMPA



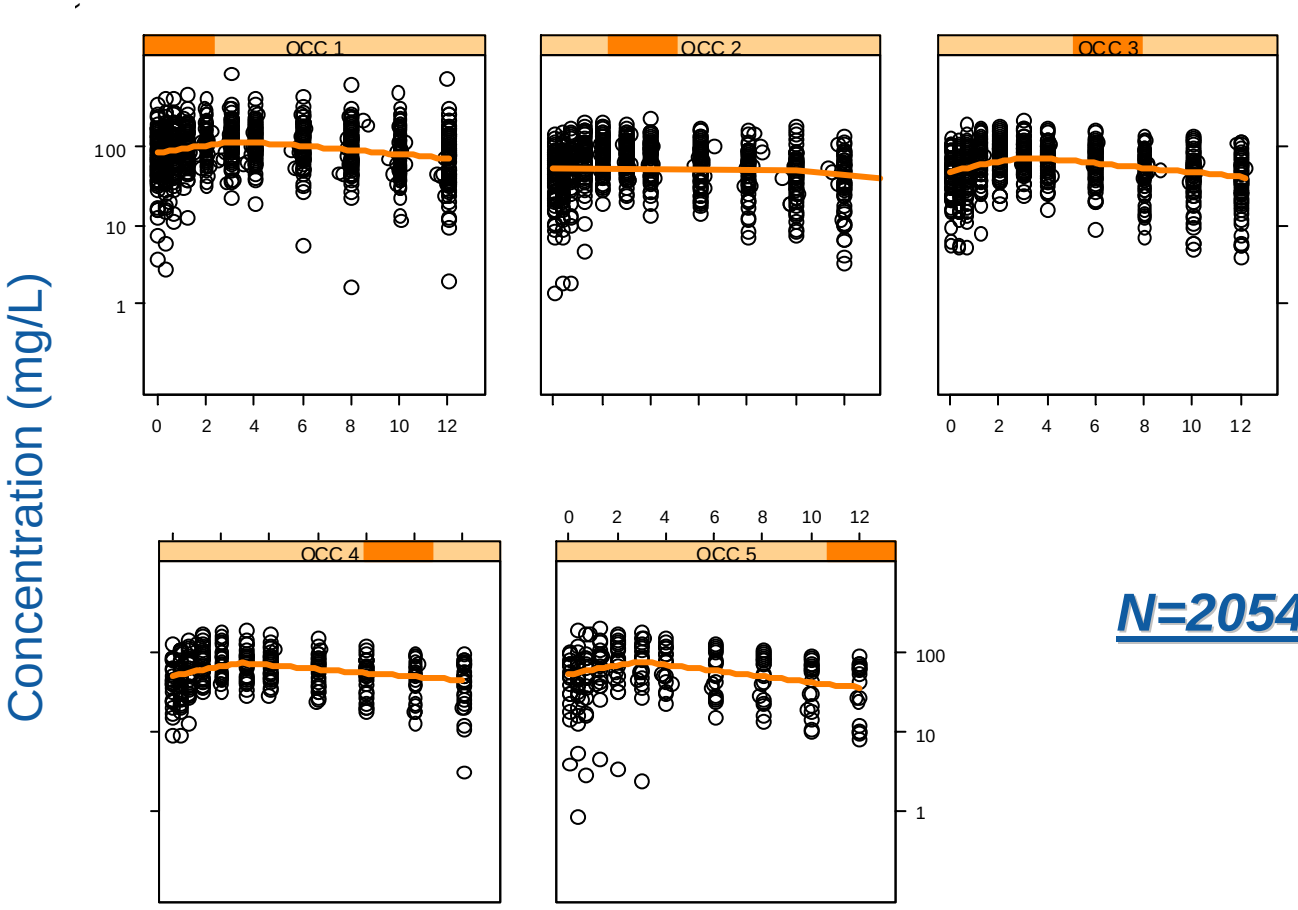
N=2038 tMPA

Results: fMPA



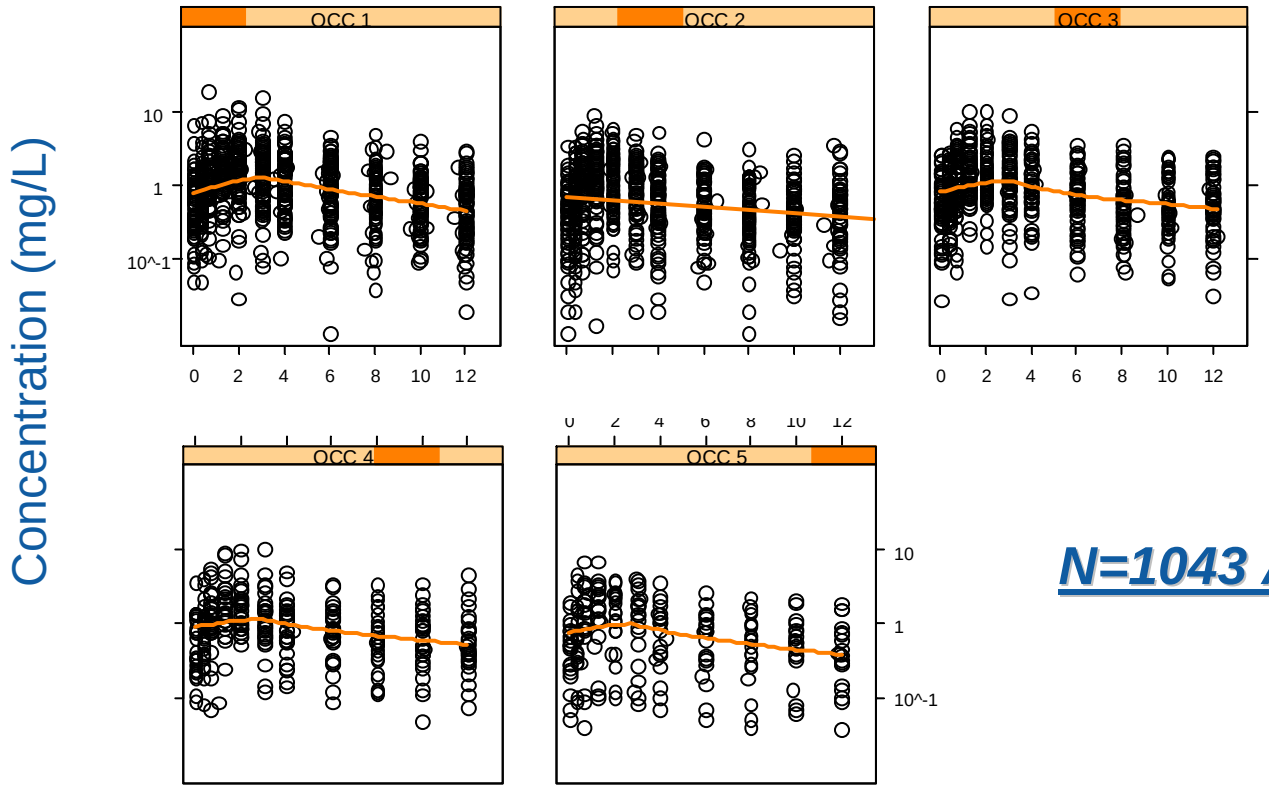
N=2046 fMPA

Results: tMPAG



N=2054 MPAG

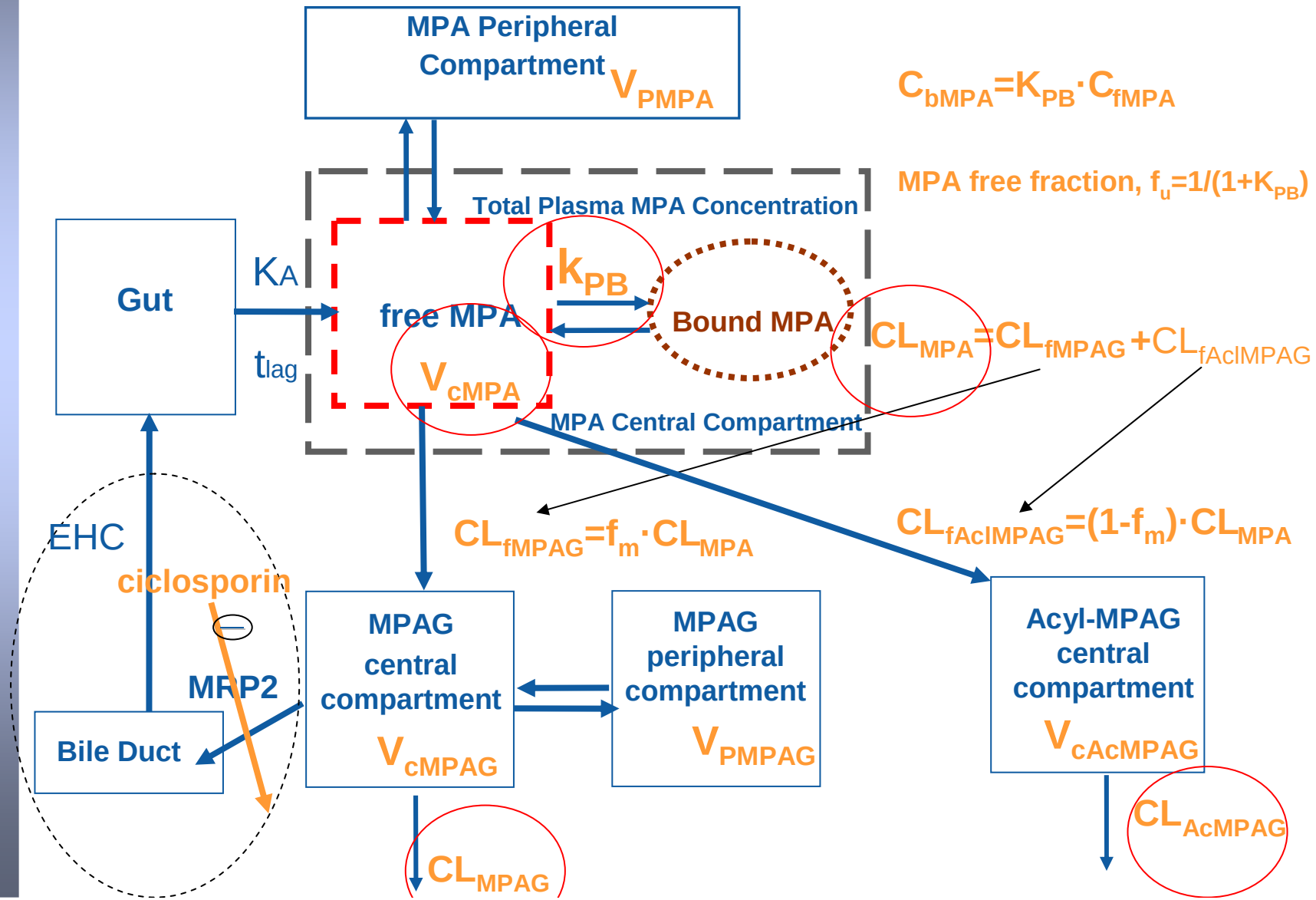
Results: tAcMPAG



N=1043 AcMPAG

Results

Base PK model



Results

Covariate PK model

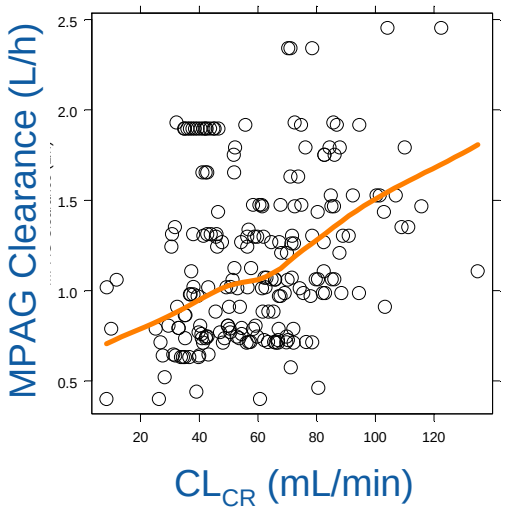
K_{PB} { Albumin concentration; MPAG concentration

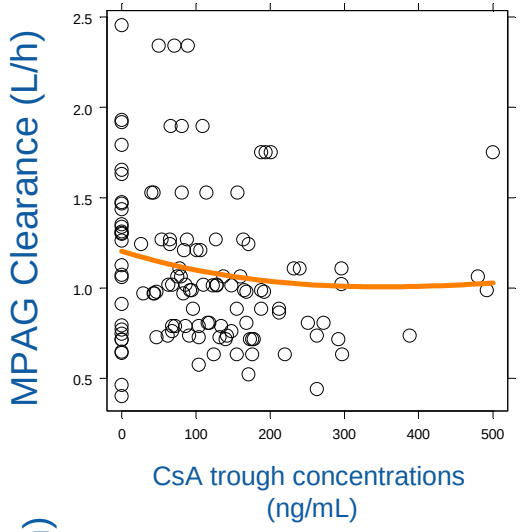
$C_{bMPA}=K_{PB} \cdot C_{fMPA}$

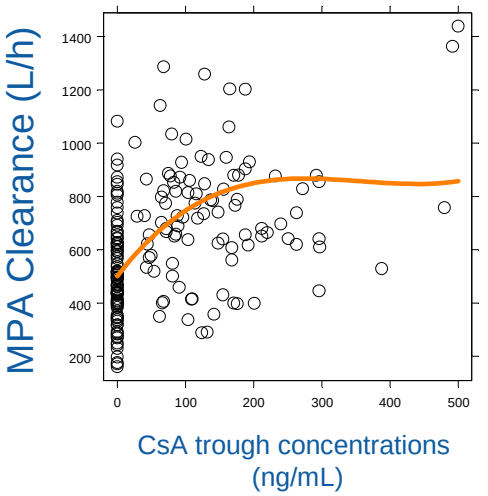
CL_{MPAG}, $CL_{AcylMPAG}$ { CL_{CR}, CsA trough concentrations; C24T SNPs MRP2

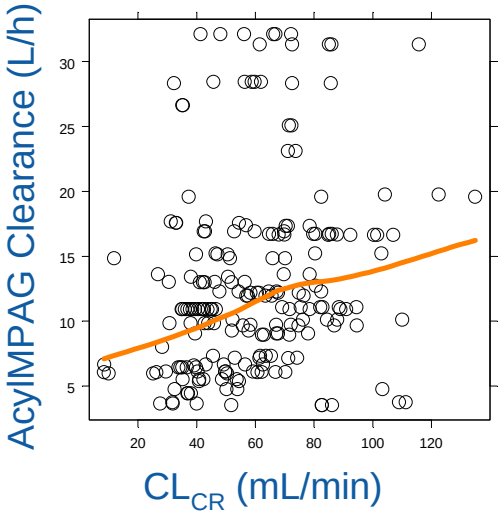
CL_{MPA} { CsA trough concentrations; C24T SNPs MRP2

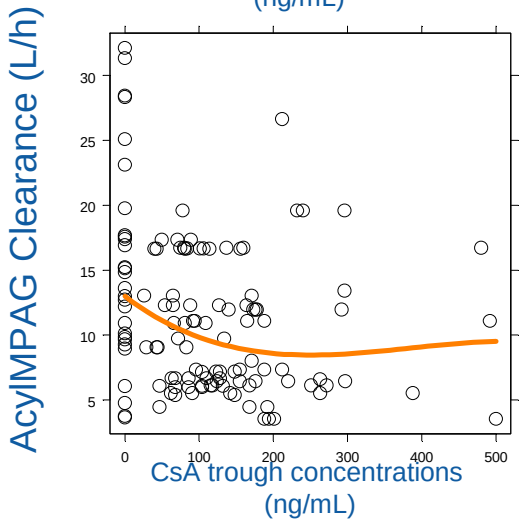
CL_{MPAG}, CL_{AcMPAG}, CL_{MPA}

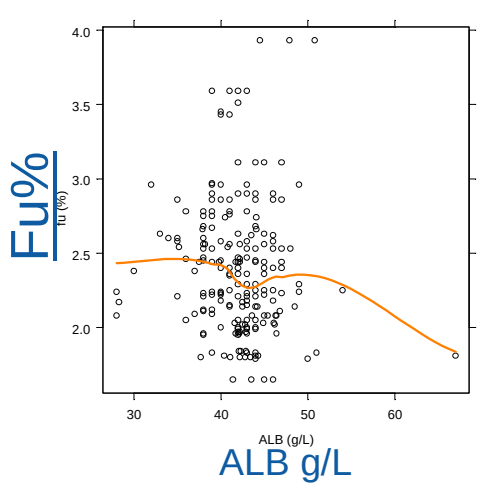












Results

Covariate PK model

Model	Ref. Model	Covariate relationships	┼MOFV
1		Base model	
2	1	$+TVCL_{MPAG}=┼_9\cdot(CL_{CR}/59.51)^{┼15}$	-1556.11
3	2	$+TVCL_{AcMPAG}=┼_{12}\cdot(CL_{CR}/59.51)^{┼16}$	-654.23
4	3	$+TVCL_{MPAG}=┼_9\cdot(CL_{CR}/59.51)^{┼15}\cdot(1-┼_{17}\cdot C_{CSA})$	-95.63
5	4	$+TVCL_{MPAG}=┼_9\cdot(CL_{CR}/59.51)^{┼15}\cdot(1-CSA\cdot┼_{17}\cdot C_{CSA})\cdot(1+(1-CSA)\cdot┼_{18}\cdot C24T)$	-28.11
6	5	$+TVCL_{AcMPAG}=┼_{12}\cdot(CL_{CR}/59.51)^{┼16}\cdot(1+(1-CSA)\cdot┼_{21}\cdot C24T)$	-299.48
7	6	$+TVCL_{MPA}=┼_1\cdot(1+┼_{22}\cdot CSA\cdot C_{CSA})$	-45.61
8	7	$+TVCL_{MPA}=┼_1\cdot(1+┼_{22}\cdot CSA\cdot C_{CSA})\cdot(1+┼_{23}\cdot(1-CSA)\cdot C24T)$	-24.78
9	8	$+TVCL_{MPA}=┼_1\cdot(1+┼_{22}\cdot CSA\cdot C_{CSA})\cdot(1+┼_{23}\cdot(1-CSA)\cdot C24T)\cdot(1+┼_{24}\cdot COURSE)$	-17.53

CsA=1, Std and low CsA

CsA=0, Macrolides

C24T=1, CT/TT carriers

C24T=0, CC non carriers

Course=1, Day7

Course=0, months 1, 3, 6, 12

Results

Final PK Model

Final model

$$+TVCL_{MPAG} = H_9 \cdot (CL_{CR}/59.51)^{H15} \cdot (1-CSA \cdot H_{17} \cdot C_{CSA}) \cdot (1+(1-CSA) \cdot H_{18} \cdot C24T)$$

$$+TVCL_{AcMPAG} = H_{12} \cdot (CL_{CR}/59.51)^{H16} \cdot (1+(1-CSA) \cdot H_{21} \cdot C24T)$$

$$+TVCL_{MPA} = H_1 \cdot (1+H_{22} \cdot CSA \cdot C_{CSA}) \cdot (1+H_{23} \cdot (1-CSA) \cdot C24T)$$

CsA=1, Std and low CsA
CsA=0, Macrolides

C24T=1, CT/TT carriers
C24T=0, CC non carriers

AUC~ D/CL

Results

Final model Parameters

Parameter	Units	Final model parameter estimate *(RSE%)*	BPV,% (RSE%)
fMPA			
CL_{MPA}	*L/h*	$414\ (9.3)\cdot (1+CSA\cdot 0.000966(69.1)\cdot C_{CsA})\cdot(1+(1-CSA)\cdot 0.158(88.0)\cdot C24T)$	28.9 *(32.6)*
V_{CMPA}	*L*	21.9 *(28.5)*	67.4 *(42.2)*
CL_{DMPA}	*L/h*	1030 *(7.3)*	-
V_{PMPA}	*L*	19800 *(48.2)*	-
fm	-	0.874 *(fix)*	-
K_{PB}	-	44.7 *(6.2)*	28.2 *(21.4)*
K_A	h^{-1}	1.26 *(28.6)*	-
LT	*h*	0.132 *(24.1)*	-
MPAG			-
CL_{MPAG}	*L/h*	$0.959\ (10.2)\cdot (CL_{CR}/59.51)^{0.904(15.7)}\cdot$	40.6 *(34.2)*
V_{CMPAG}	*L*	$(1-CSA\cdot 0.000687(34.6)\cdot C_{CsA})\cdot(1+(1-CSA)\cdot 0.242(69.8)\cdot C24T)$	-
CL_{DMPAG}	*L/h*	1.34 *(67.9)*	-
V_{PMPAG}	*L*	11.5 *(49.0)*	-
AcMPAG		3.44 *(25.4)*	-
CL_{AcMPAG}	*L/h*	$10.6\ (10.6)\cdot\ (CL_{CR}/59.51)^{0.788(19.7)}\ (1+(1-CSA)\cdot 1.31(31.9)\cdot C24T)$	62.4 *(30.3)*
$V_{CAcMPAG}$	*L*	5.36 *(26.3)*	-
Residual error			-
fMPA	*%*	71.9 *(14.0)*	-
tMPA	*%*	48.6 *(13.9)*	-
MPAG	*%*	31.0 *(20.3)*	-
AcMPAG	*%*	77.3 *(19.9)*	-

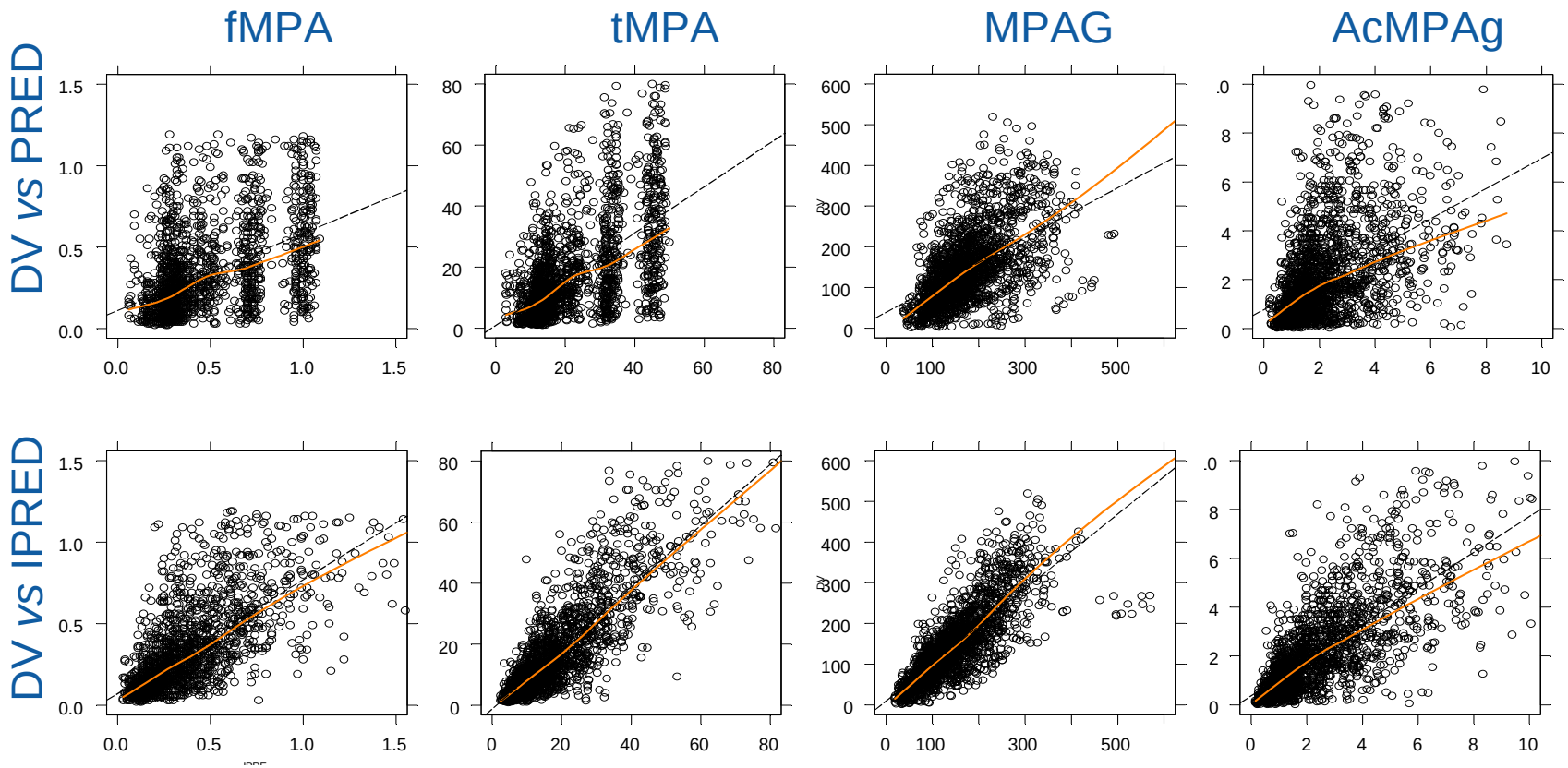
CsA: categorical covariate expressing cyclosporine administration or not. Patients treated with Cyclosporine CSA=1, Patients not treated with Cyclosporine CsA=0. C_{CSA} = cyclosporine trough concentrations

C24T=1 for CT/TT carriers; =0, for CC non carriers

CLCR=creatinine clearance in mL/min, estimated according to Crokroft-Gault

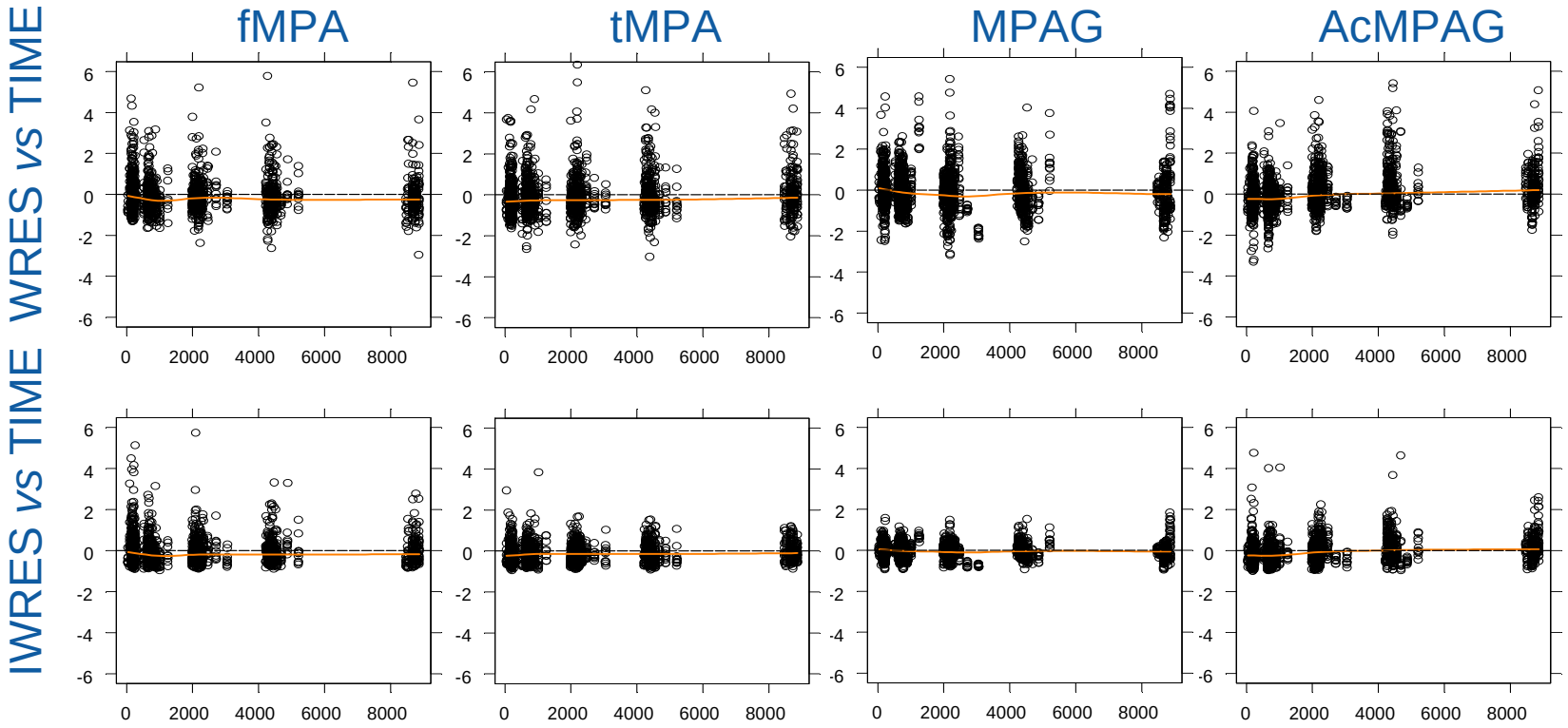
Goodness-of-fit plots

DV=Observed,
PRED=population Predictions
IPRED=individual predcitions

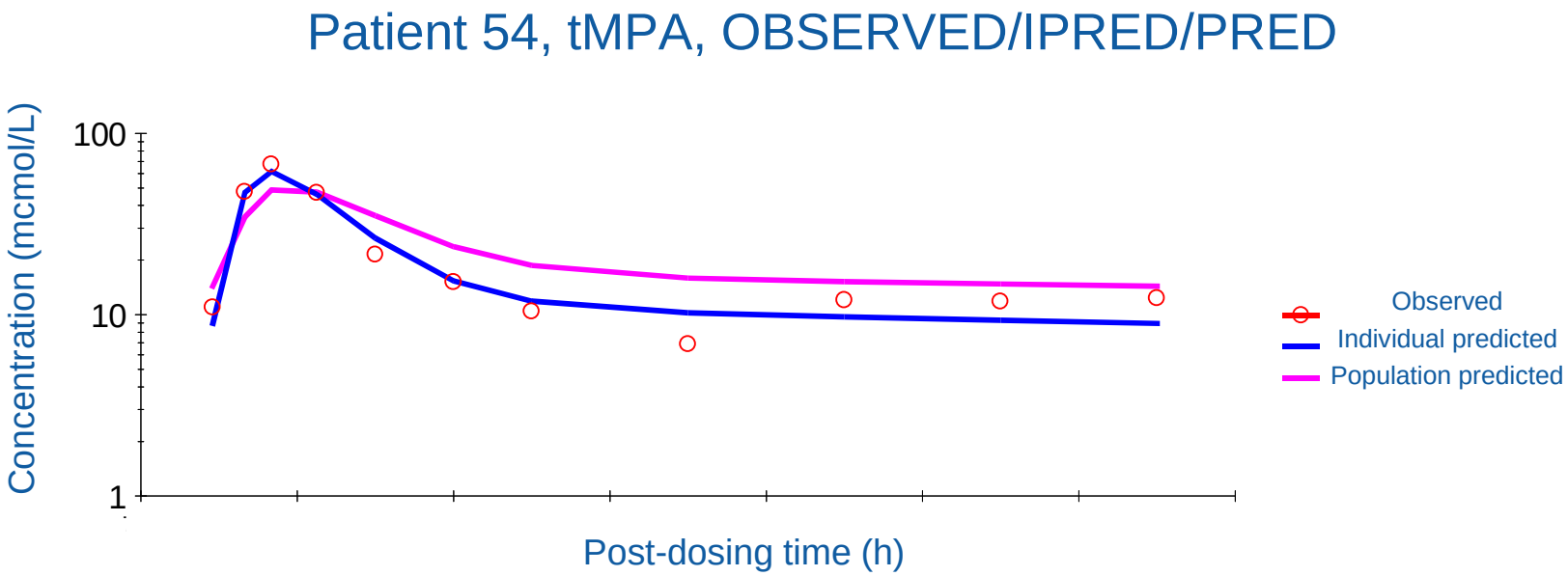


Goodness-of-fit plots

WRES=(Obs-PRED)/W
IWRES=(Obs-IPRED)/W

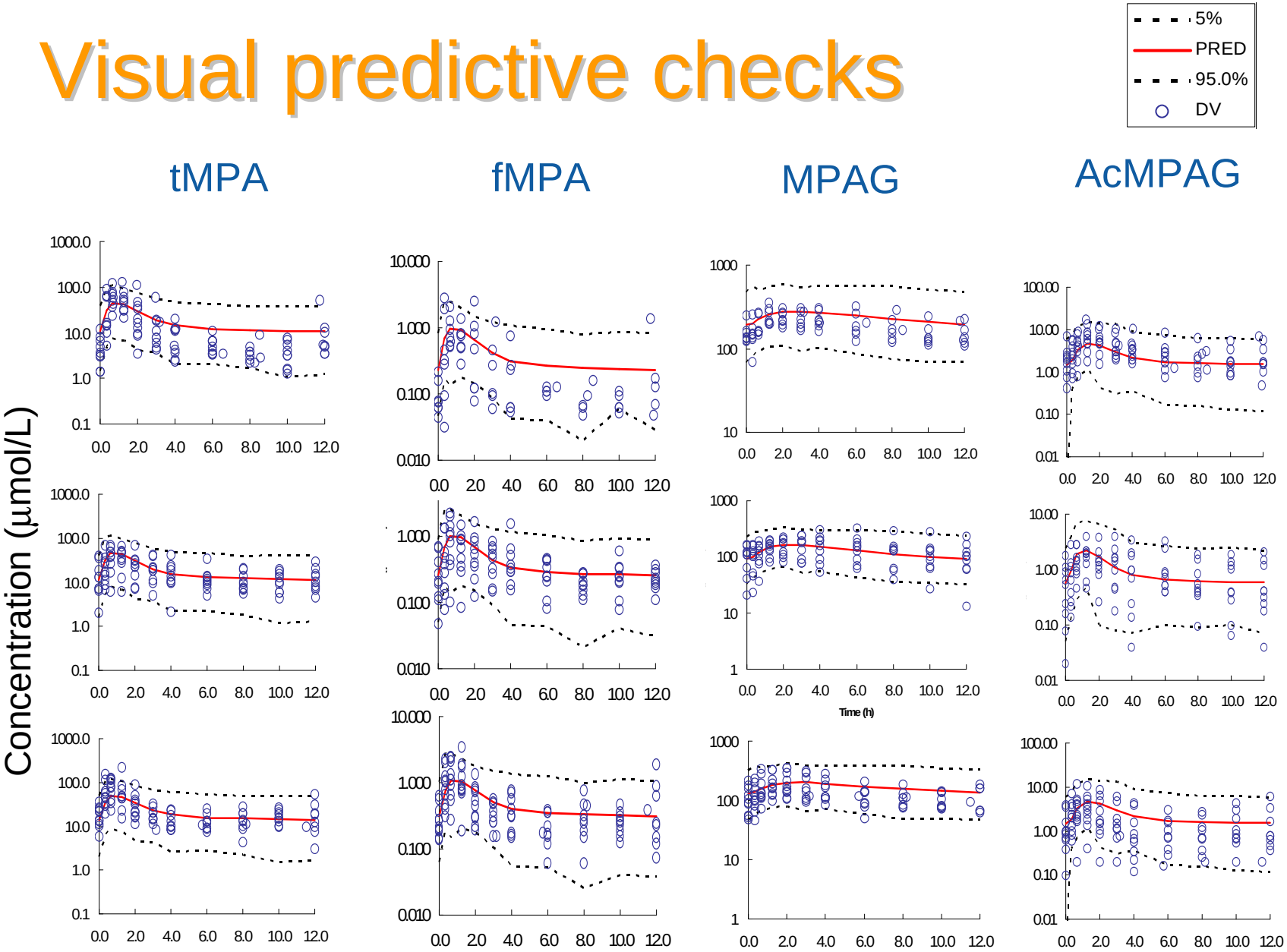


Goodness-of-fit plots

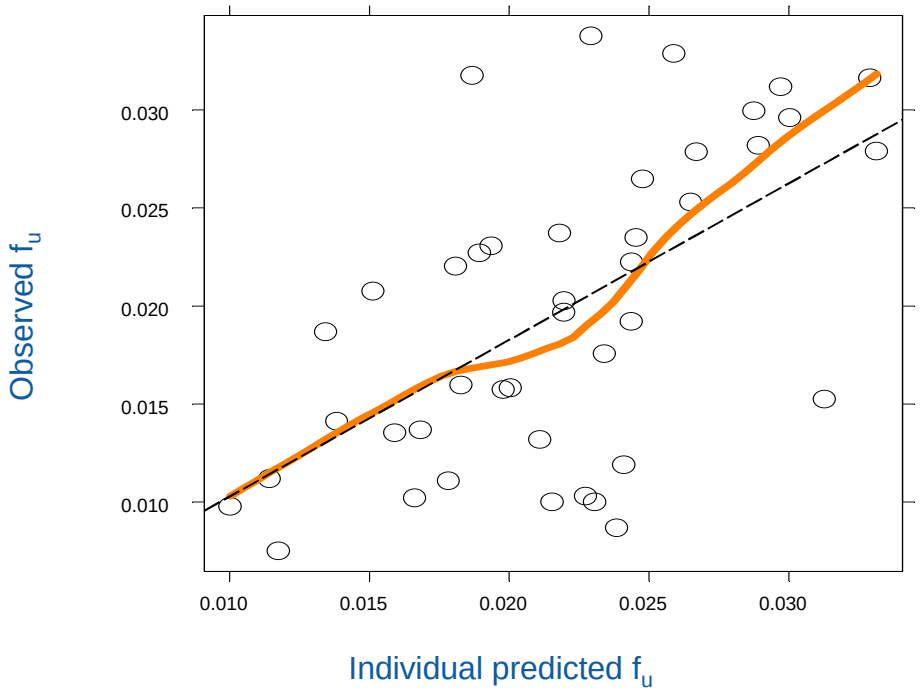


MMF+Tacrolimus

Visual predictive checks



Protein binding plots



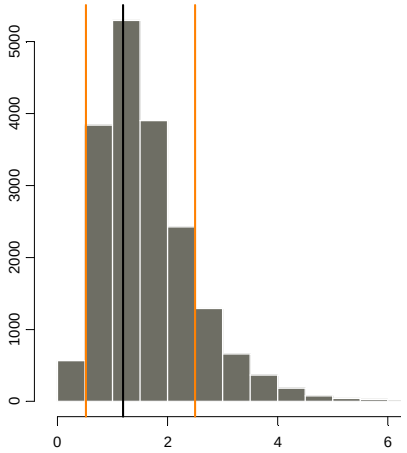
Posterior predictive check

Median ($P_{5\%}$-$P_{95\%}$)

fMPA

Obs: 1.19 (0.52-2.50)

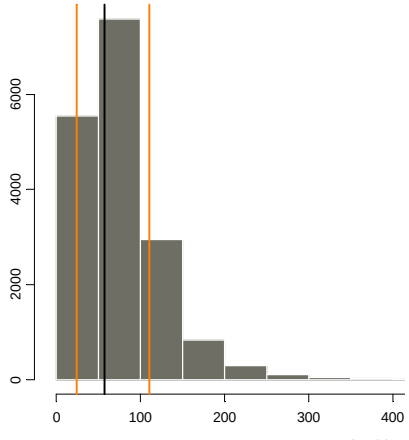
Sim:1.46 (0.58-3.32)



tMPA

Obs: 57.04 (24.24-110.80)

Sim: 66.74 (23.41-170.66)

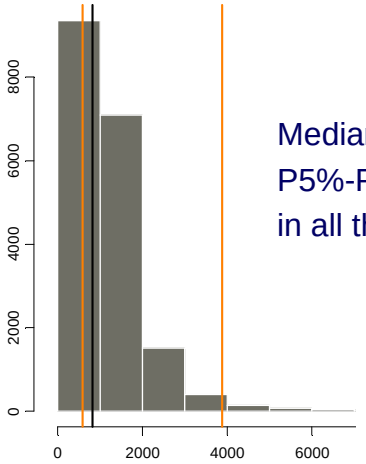


$AUC_{0\text{-}12}$

Obs: 825.25 (585.69-3887.88)

Sim: 999.81 (386.20-2773.01)

MPAG

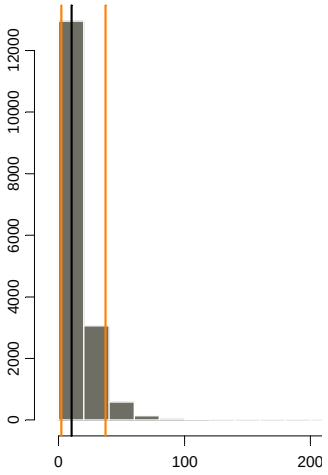


Median AUC simulated values are within the P5%-P95% interval of observed AUC values in all the cases

Obs: 10.46 (2.31-37.43)

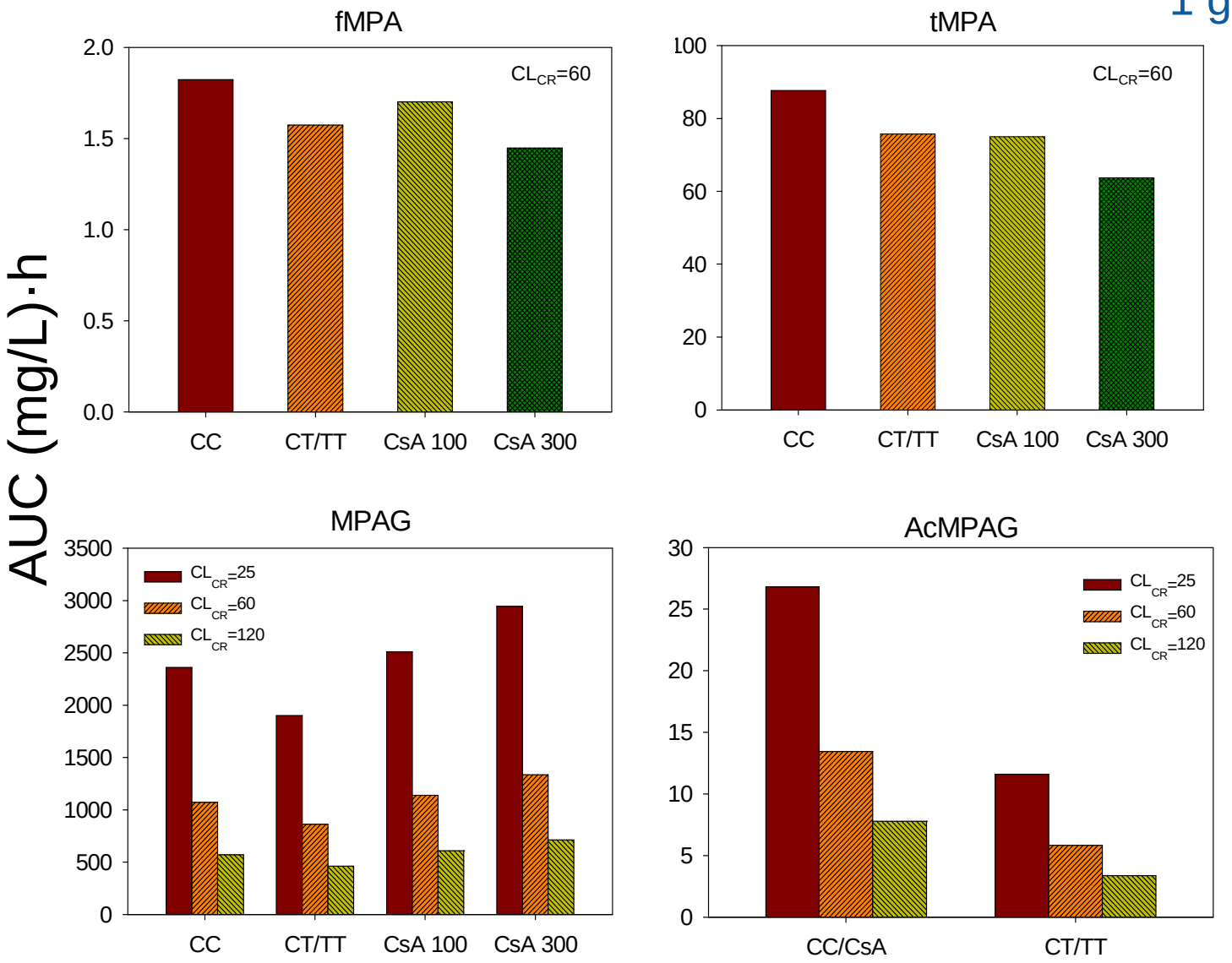
Sim: 11.35 (3.00-39.72)

AcMPAG



Aplicability:Model simulations

1 g MMF



Conclusions

- An integrated population PK model to describe the relationships among MMF and fMPA, tMPA, MPAG , AcMPAG concentrations has been developed.
- EHC has not been described by the current model
- The developped model did not allow to evaluate the impact of changes in albumin concentrations and renal function on tMPA and fMPA exposures.
- Renal function given by CL_{CR} is a predictor of both CL_{MPAG} and CL_{AcMPAG}.
- Cyclosporine trough concentrations are predictors of $CL_{MPA,and}$ CL_{MPAG} and C24T SNPs of MRP2 are predictors of $CL_{MPA,}$ and CL_{MPAG} and CL_{AcMPAG}
- The developed model allows to predicts fMPA exposures from tMPA concentrations.
- According to this model and for patients belonging to the studied population,patients under macrolides and non carriers of the C24T SNP would require lower doses than those under cyclosporine or those under macrolides and CT/TT carriers of the C24T SNP.
- PK Differences between day 7 and the remaining occasions have to be explained in future analyses

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Thank you