DDI PREDICTIONS WITH PBPK MODELLING AND OPTIMAL SAMPLING TIME DESIGN

Comparison of univariate/multivariate designs using POPDES

Analysis of real data with optimal sparse and empirical full designs

Application example : SX and MDZ

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Context

- A Drug-Drug Interaction (DDI) study was planned to evaluate the potential inhibitory effect of a phase I Servier compound (called SX) on a reference CYP3A4 substrate, Midazolam (MDZ).
- PBPK models allow to simulate SX & MDZ PK profiles when administered separately but also together (DDI) from *in vitro* parameters.
- Multiresponse design in PopDes allows to estimate joint optimal sampling times for 2 drugs.

Objectives

⇨ to design the clinical trial without any *in vivo* data using PBPK predictions, population PK modelling and multiresponse optimal design.

- To compare designs obtained by uniresponse & multiresponse designs.
- To compare *in vivo* results obtained by POP PK analyses using either the optimal sparse design (MD) or the empirical full design (FD).
- To evaluate the interaction of SX on MDZ in the *in vivo* study.

I- MATERIALS AND METHODS

I.1- Simulation of the DDI using PBPK models.

I.2- Development of population PK models using simulated data.

I.3- Optimisation of sampling times.

I.4- Comparison of univariate/multivariate designs by simulations.

I.5- Population PK analyses of *in vivo* results using MD and FD.

I.6- Statistical analysis of the interaction.

I.1 to I.4 → **M. Chenel, F. Bouzom, L. Aarons and K. Ogungbenro**. Drug-Drug Interaction Predictions with PBPK models and Optimal Multiresponse Sampling Time Designs: Application to Midazolam and a phase I compound. Part 1: Comparison of uniresponse and multiresponse designs using PopDes. **Submitted to JPP.**

I.5 & I.6→ **M. Chenel, F. Bouzom, F. Cazade, K. Ogungbenro, L. Aarons and F. Mentré**. Drug-Drug Interaction Predictions with PBPK models and Optimal Multiresponse Sampling Time Designs: Application to Midazolam and a phase I compound. Part 2: Analysis of real data. **Submitted to JPP.**

I- MATERIALS AND METHODS

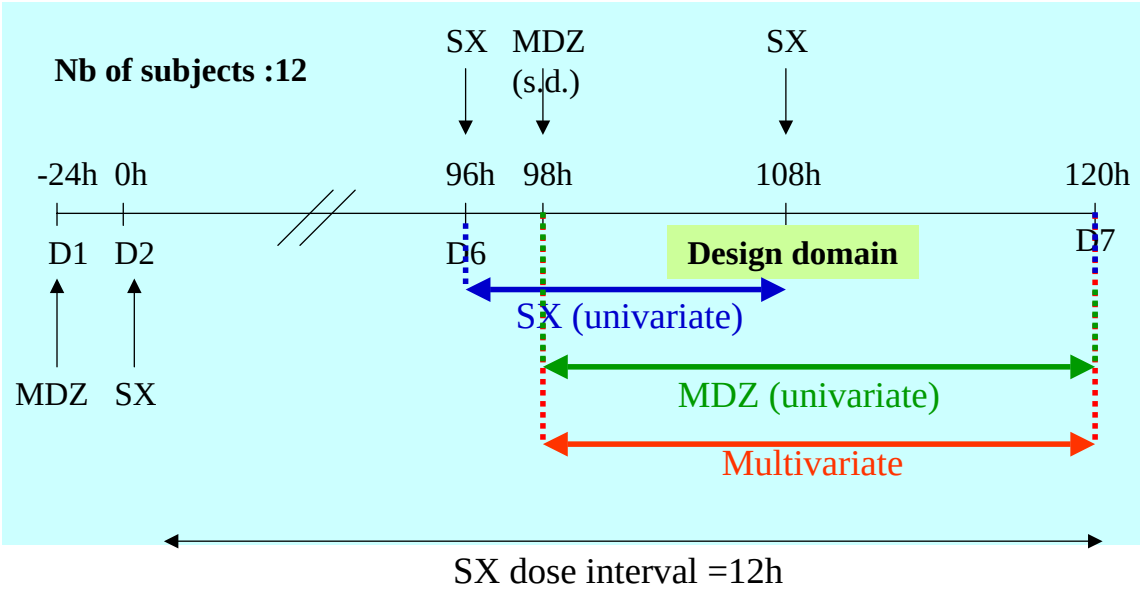
I.1- Simulation of the DDI using PBPK models

I.2- Development of population PK models using simulated data

- Datasets: made of PBPK simulations (DV=SX or MDZ concentrations)
- Software: NONMEM version V
- Optimisation method: FOCE INTER
- Criteria: LRT (+ goodness of fit, CVSE)
- Validation: Visual Predictive Check (1000 simulations + graphs)

[P5-P95 & median of simulations/observations]&[P5-P95 & median of medians of simulations/observations]

I.3- Optimisation of sampling times



I.3- Optimisation of sampling times

- Software: PopDes[1] version 2 under MATLAB
- Design options:
  - * local
  - * population
  - * univariate/multivariate
- Optimisation method: Modified Fedorov Exchange[2]
- Criteria: D-Optimality

1. 1. I. Gueorguieva, K. Ogungbenro, G. Graham, S. Glatt, and L. Aarons. A program for individual and population optimal design for univariate and multivariate response pharmacokinetic and pharmacodynamic models. *Comput. Methods Programs Biomed.* **86**(1): 51-61 (2007).

1. 2. K. Ogungbenro, I. Gueorguieva, G. Grahams, and L. Aarons. The use of a modified Fedorov Exchange Algorithm in Optimising Sampling Times for Population Pharmacokinetic Experiments. *Comp. Meth. Prog. Biomed.* **80(2)**: 115-125 (2005).

I.4- Comparison of univariate / multivariate designs

- Software:

  NONMEM

- Evaluation:

  1000 simulations & re-estimations

- Optimisation method:

  FOCEI

- Criteria:

  * RMSE

  * RSE given by PopDes / Empirical RSE / mean RSEs given by NONMEM

I.5- Population PK analyses of *in vivo* results using MD and FD

- Datasets (12 HV):

Dataset	Drug	Period	Design
1	SX	2	MD
2	SX	2	FD
3	MDZ	1	MD
4	MDZ	1	FD
5	MDZ	2	MD
6	MDZ	2	FD

- Use of the population PK models previously developed

- Software: NONMEM version V / MONOLIX version 2

- Optimisation method: FOCE INTER / SAEM

- Comparison of CL/F obtained with the Multiresponse Optimal Design (MD) and the Full Design (FD) using a Wald's test ($p<0.05$)

I- MATERIALS AND METHODS

I.6- Statistical analysis of the interaction: comparison tests

- For each treatment group (MDZ alone or co-administered with SX), determination of individual MDZ AUC and C_{max} by NCA (FD) and by POP PK (using either MD or FD).

- Student paired tests ($p<0.05$) applied to compare the log(AUC) and log(C_{max}) between the two treatment groups.

X. Panhard and F. Mentré. Evaluation by simulation of tests based on non-linear mixed-effects models in pharmacokinetic interaction and bioequivalence cross-over trials. *Statist. Med.* **24**: 1509-1524 (2005).

II- RESULTS

II.1- MDZ PBPK predictions

Table I. Pharmacokinetic parameters of MDZ calculated by NCA from simulated concentration-time profiles in 100 healthy volunteers after a single oral dose (7.5 mg) of MDZ administered alone or co-administered with SX (90 mg b.i.d. mg for 5 days). In the second case, MDZ was administered the last day of the SX drug administration, 2h after SX drug morning administration.

	Parameter	Minimum	5th percentile	Median	95th percentile	Maximum
MDZ (7.5 mg) alone	C_{max} (ng/mL)	21	29	43	89	143
	t_{max} (h)	0.33	0.33	0.39	0.50	0.53
	AUC (ng.h/mL)	47	66	114	239	455
	$t_{½,z}$ (h)	2.1	2.7	4.0	6.1	7.4
MDZ (7.5 mg) with SX	C_{max} (ng/mL)	25	32	52	96	151
	t_{max} (h)	0.33	0.35	0.40	0.53	0.58
	AUC (ng.h/mL)	59	80	140	301	621
	$t_{½,z}$ (h)	2.2	2.7	4.0	6.1	7.4
	$R_{I\ Cmax}$	1.1	1.1	1.1	1.3	1.5
	$R_{I\ AUC}$	1.1	1.1	1.2	1.7	2.1

In average, no interaction was predicted by the PBPK models.

II- RESULTS

II.2- Population PK modeling using simulated data

* SX

-2-compartment model + Ka fixed

-IIV on CL/F and V1/F

-Correlation between CL/F and V1/F

-Combined error model
(additive+proportional)

Parameters	Units	Estimate	CVSE	Parameters	SQRT%	CVSE
CL/F	*L/H*	13	4.2	IIV_CL/F	41	11
V1/F	*L*	17	1.6	IIV_V1/F	15	13
Q/F	*L/H*	1.5	1.3	IIV_Q/F	0	-
V2/F	*L*	71	24	IIV_V2/F	0	-
ka	H^{-1}	0.19	FIXED	IIV_ka	0	-
Add	*ng/mL*	0.2	FIXED		R	Value
Prop	*%*	2.2	0.8	CL/V1	0.82	0.05

* MDZ

-2-compartment model + k0 (D1)

-IIV on CL/F, V1/F, V2/F, Q/F and k0

-Correlation between CL/F and V1/F

-Combined error model
(additive+proportional)

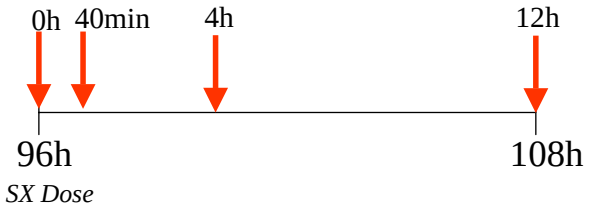
Parameters	Units	Estimate	CVSE	Parameters	SQRT%	CVSE
CL/F	*L/H*	87	4.8	IIV_CL/F	46	14
V1/F	*L*	206	3.6	IIV_V1/F	36	15
Q/F	*L/H*	25	4.4	IIV_Q/F	40	16
V2/F	*L*	183	6.0	IIV_V2/F	39	28
D1	H^{-1}	0.82	0.71	IIV_D1	6.8	35
Add	*ng/mL*	0.2	fixed		R	Value
Prop	*%*	0.056	1.0	CL/V1	0.97	0.16

II- RESULTS

II.3- Optimal sampling times

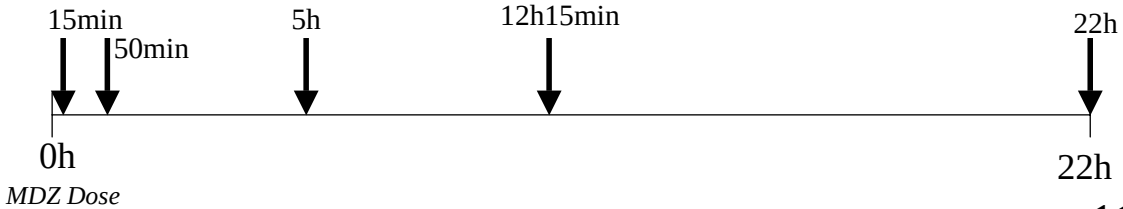
* Uniresponse – SX

Design 1-SX : [0-12h], 4 samples, det=46



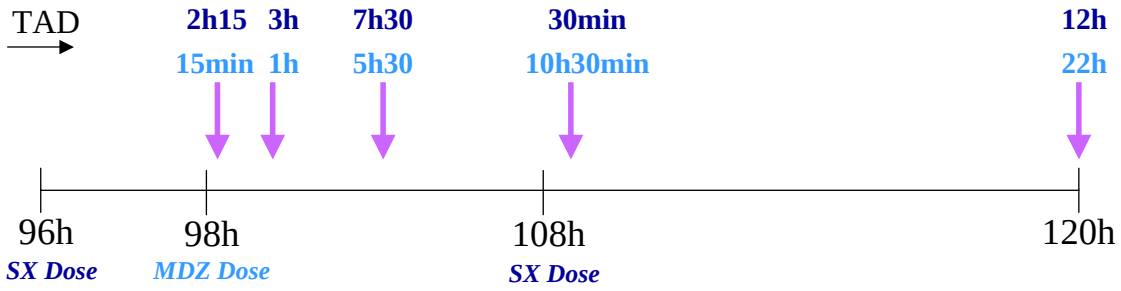
* Uniresponse – MDZ

Design 1-MDZ : [0-22h], 5 samples, det=7.14 10^{10}



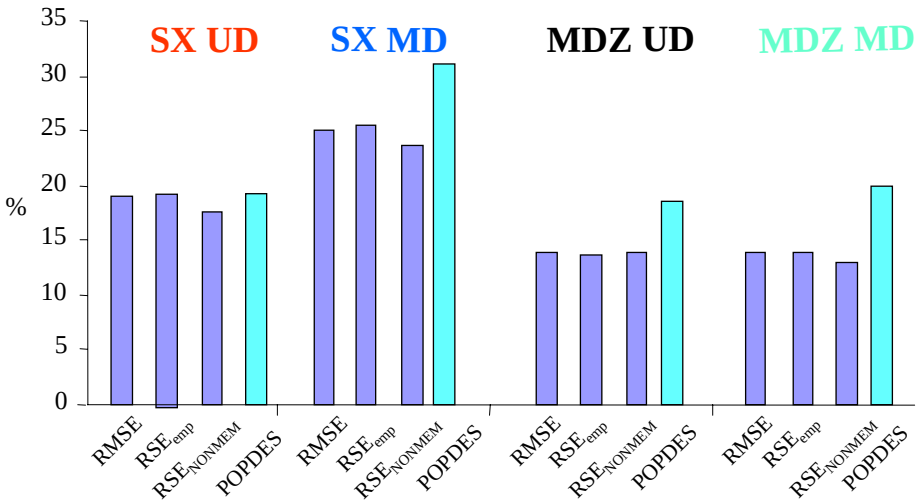
II.3- Optimal sampling times

* Multiresponse – SX+MDZ



Design 4-SX/MDZ : [98-120h], 5 samples, determinant= 9.6. 10^{11}

II.4- Comparison of uniresponse/multiresponse designs: **Accuracy of CL/F estimation and RMSE**



II- RESULTS

Under these clinical constraints and for these 2 population PK models, the multiresponse design gave a satisfactory level of results:

Thus, the sampling times proposed for the clinical trial were:

SX : Pre-dose and 40min; 1h; 2; 2h15; 2h30; 3h; 4h; 5h 6h; 7h30; 10h30; 12h; 12h30; 12h40; 14h30; 16h; 18h; 19h30; 24h; 48h

MDZ : Pre-dose and 15min; 30min; 1h; 2h; 3h; 4h; 5h30; 8h30; 10h30; 12h30; 22h

Empirical Full Design: 11 sampling times (11x12subjects=132)

Multiresponse Optimal Design: 5 sampling times (5x12subjects=60)

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II- RESULTS

Analysis of real data

PBPK predictions *vs* Observations

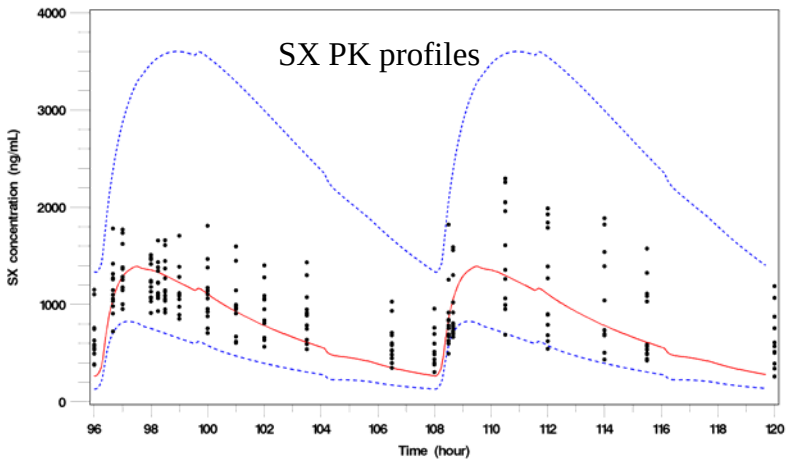

Fig. 3. Comparison of observed SX concentration-time data with simulated concentration-time profiles obtained using SX PBPK model. Dots correspond to observed SX concentration-time data, and plain line and both dotted lines correspond to the median and the 5th and 95th percentiles of simulated SX concentration-time data, respectively.

II- RESULTS

Analysis of real data

PBPK predictions *vs* Observations

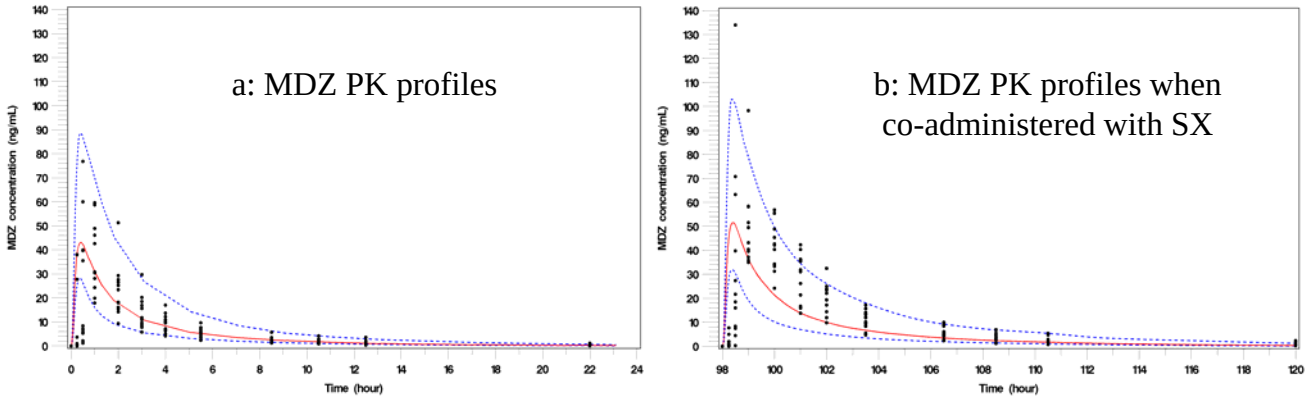

Fig. 4. Comparison of observed MDZ concentration-time data with simulated concentration-time profiles obtained using MDZ PBPK model. These results correspond to MDZ concentration-time data after a 7.5mg MDZ single oral dose **(a)** without SX co-administration, **(b)** with SX co-administration. Dots correspond to observed MDZ concentration-time data, plain line and both dotted lines correspond to the median and the 5th and 95th percentiles of simulated MDZ concentration-time data, respectively.

II- RESULTS

I.5- Population PK analyses of *in vivo* results using MD and FD

Comparison of results obtained with MD and FD

Drug	Treatment	Software	Wald's test (p<0.05)
SX		NONMEM	Vp/F (p<0.001), res_prop (p<0.048)
MDZ	alone	MONOLIX	ns
	co-administered with SX	MONOLIX	ns

-For MDZ data, NONMEM did not successfully minimized (error 134) with the sparse design, consequently MONOLIX was used.

-NONMEM and MONOLIX estimates were in the same range but the Wald's test could not be used with NONMEM (SE were not obtained).

II- RESULTS

I.6- Statistical analysis of the interaction: comparison tests

Table II. Comparison tests based on log (AUC) and log(C_{max}) individual parameters between groups (MDZ without SX and MDZ co-administered with SX).

		AUC median [min-max]		Log(AUC)	
stimation method	Design	MDZ alone	MDZ with SX	Estimate	Student paired test
				[90% CI] of ratio	
NCA	FD	103 [57-224]	201 [110-367]	1.9 [1.7-2.1]	p<0.0001
NONMEM	FD	98 [55-182]	182 [110-355]	1.9 [1.6-2.1]	p<0.0001
	MD	78 [51-123]	143 [99-226]	2.0 [1.8-2.2]	p<0.0001
MONOLIX	FD	102 [58-184]	180 [108-344]	1.8 [1.6-2.1]	p<0.0001
	MD	100 [67-166]	155 [110-250]	1.7 [1.6-1.9]	p<0.0001

		C_{max} median [min-max]		Log(C_{max})	
stimation method	Design	MDZ alone	MDZ with SX	Estimate	Student paired test
				[90% CI] of ratio	
NCA	FD	40 [18-77]	51 [35-134]	1.3 [1.1-1.7]	p=0.0224
NONMEM	FD	39 [17-70]	50 [34-125]	1.5 [1.1-1.9]	p=0.0195
	MD	26 [17-42]	33 [26-45]	1.3 [1.1-1.5]	p=0.0063
MONOLIX	FD	42 [18-75]	51 [32-102]	1.3 [1.1-1.7]	p=0.0487
	MD	35 [21-56]	34 [27-48]	1.1 [1.0-1.2]	p=0.1935

MDZ exposure increased by a factor 2 when co-administered with SX.

DISCUSSION - CONCLUSION

- This global approach including PBPK simulations, population PK modelling and multiresponse optimal design allowed without any *in vivo* data to design a clinical trial using sparse sampling able to detect a PK interaction between 2 co-administered drugs.

- For both compounds, no statistical differences were observed between CL/F estimates obtained with the two designs (full or sparse design).

- Real data analysis showed that the MD allowed to give the same conclusion (a factor 2 increase of the MDZ exposure (AUC) when co-administered with SX) than the empirical FD.

DRUG-DRUG INTERACTION STRATEGY

Early phase: Investigation of any potential inhibitory effect

PBPK simulations using Ki (*in vitro* data)

AUCi/AUC <2

Prediction of a non significant/weak inhibitory effect

Could we perform the DDI study in patient during phase II?

Optimal sampling time design

AUCi/AUC >2

Prediction of a significant inhibitory effect

DDI study asap in phase I with a rich sampling time design (NCA)

DRUG-DRUG INTERACTION STRATEGY

Phase II/III:

DDI study with a reference CYP3A4 substrate, the MDZ

AUCi/AUC <2

Observation of a non significant/weak inhibitory effect

5>AUCi/AUC >2

Observation of a significant inhibitory effect

Objective: To collect the maximum of information in patients for the dossier

Optimal sampling time design

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BACK UP

I.5- Population PK analyses of *in vivo* MDZ results using MD (MONOLIX)

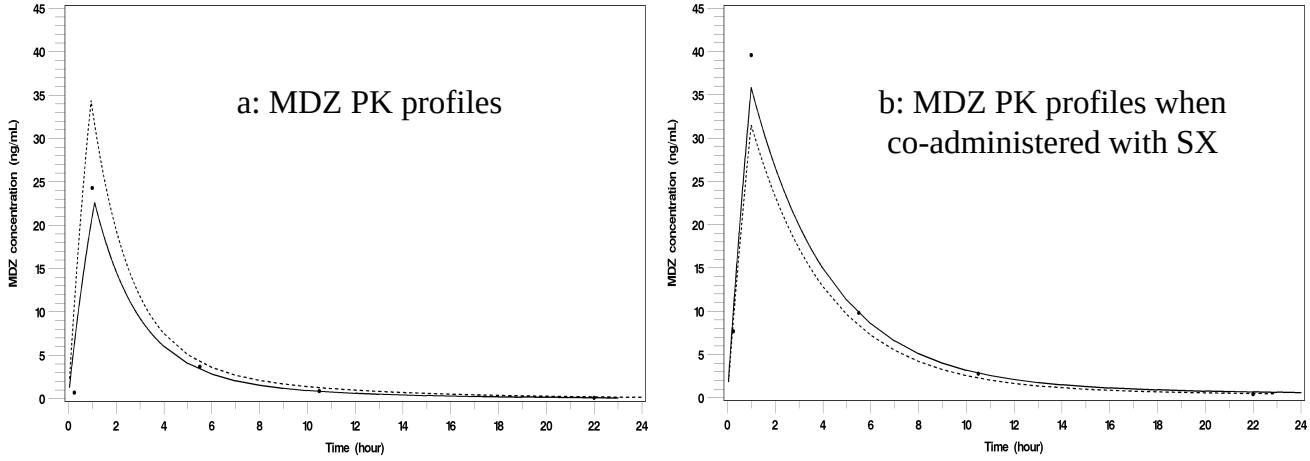

Fig. 2 MDZ concentration-time profile in a typical subject after a 7.5 mg MDZ single dose administration **(a)** and after a 7.5 mg MDZ single dose administration given to 2h after the first daily dose of SX **(b)**. Dots correspond to observed MDZ concentration-time data, lines correspond to individual predicted profiles and dotted lines correspond to population predicted profiles. Concentrations used were those measured at the optimal sampling times (sparse optimal sampling time design, MD) and modelling was performed with MONOLIX version 2.1.