

Introduction

A consistent description of the dose/exposure/effect relationship across conditions is a powerful tool in the context of model-based drug development. In this context, drug S and its active metabolite M were studied in a sequential PKPD approach in order to assess their effect on a surrogate biomarker SB, depending on two independent variables (time=IDV1 and IDV2).

Objective

To develop a single PKPD model of SB as a function of IDV1 (time) and IDV2 after the administration of drug S, describing the effect of drug S and its active metabolite M, consistently with in vitro activity assays and drug mechanism knowledge.

Methods

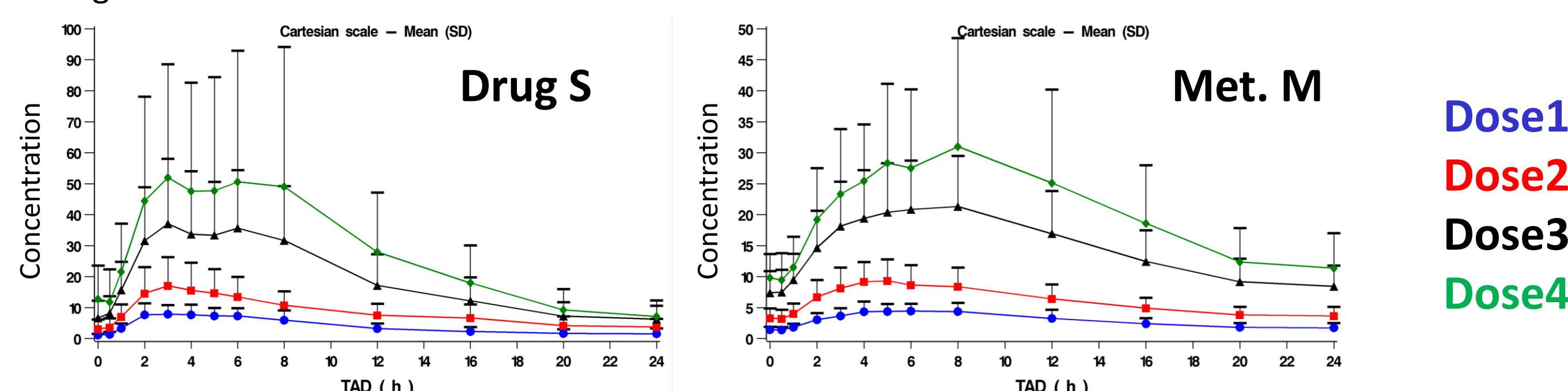
Study description:

2-groups, 3-periods, dose-escalation
Period duration : 1 week
Administration of drug S on D1-D5 each week (W1-W2-W3)

4 doses planned : Dose1 < Dose2 < Dose3 < Dose4
Group 1 (n=10): Dose1 during W1, Dose2 during W2, Dose3 during W3
Group 2 (n=15): Dose2 during W1, Dose3 during W2, Dose4 during W3

PK sampling in a period :

D3: predose; D4: predose; D5: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12 and 16 h after dosing; D6: 20 and 24 h after the morning dose of D5.



PD sampling in a period (IDV2 = 0):

D0: triplicate measurement at t=0, then 1, 2, 3, 4, 6, 8 and 12 h after theoretical D0 dose; D1: predose, 1, 2, 3, 4, 6, 8 and 12 h after dosing; D4: predose, 1, 2, 3, 4, 6, 8 and 12 h after dosing; D2, D3, D5: predose; D6: 24 h after the last dose.

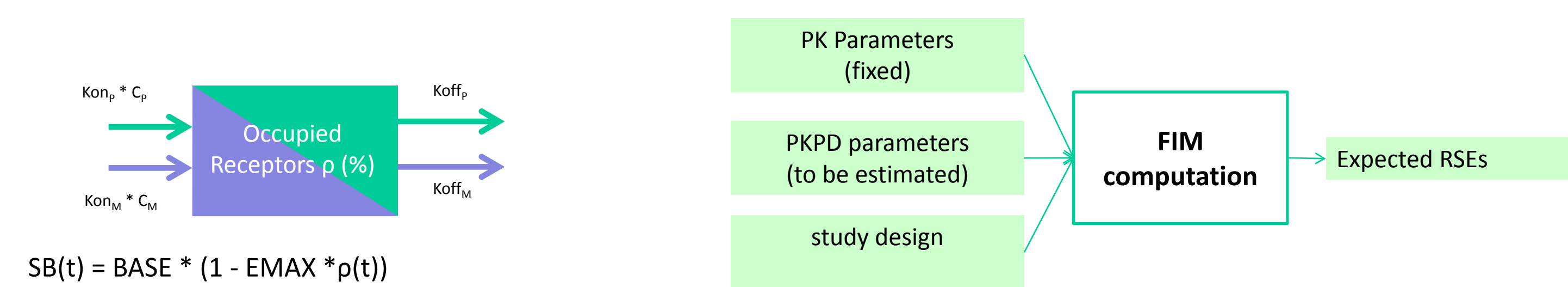
PD sampling in a period (IDV2 = {0, 1, ..., 6}):

D0: t=7h after theoretical D0 dose; D5: 3.5, 7, 11, 24h after D5 dose.

Model building strategy

- Sequential PK modelling was performed. First a PK model of drug S was built, then metabolite M was added and disposition parameters for M were estimated.
- PK parameters for S and M were input into a semi-physiological kon/koff PKPD model, and an identifiability analysis was performed in order to assess the data's and model's ability to estimate both S and M activities.
- Sequential approach (fit of SB(IDV1), then fit of SB(IDV1, IDV2)) and simultaneous approach (direct fit of SB(IDV1, IDV2)) [1] were used for final PKPD modelling of SB(IDV1, IDV2).

Identifiability analysis



Identifiability analysis was performed in order to evaluate the ability of the model to estimate a separate drug effect of S & M on SB(IDV1):

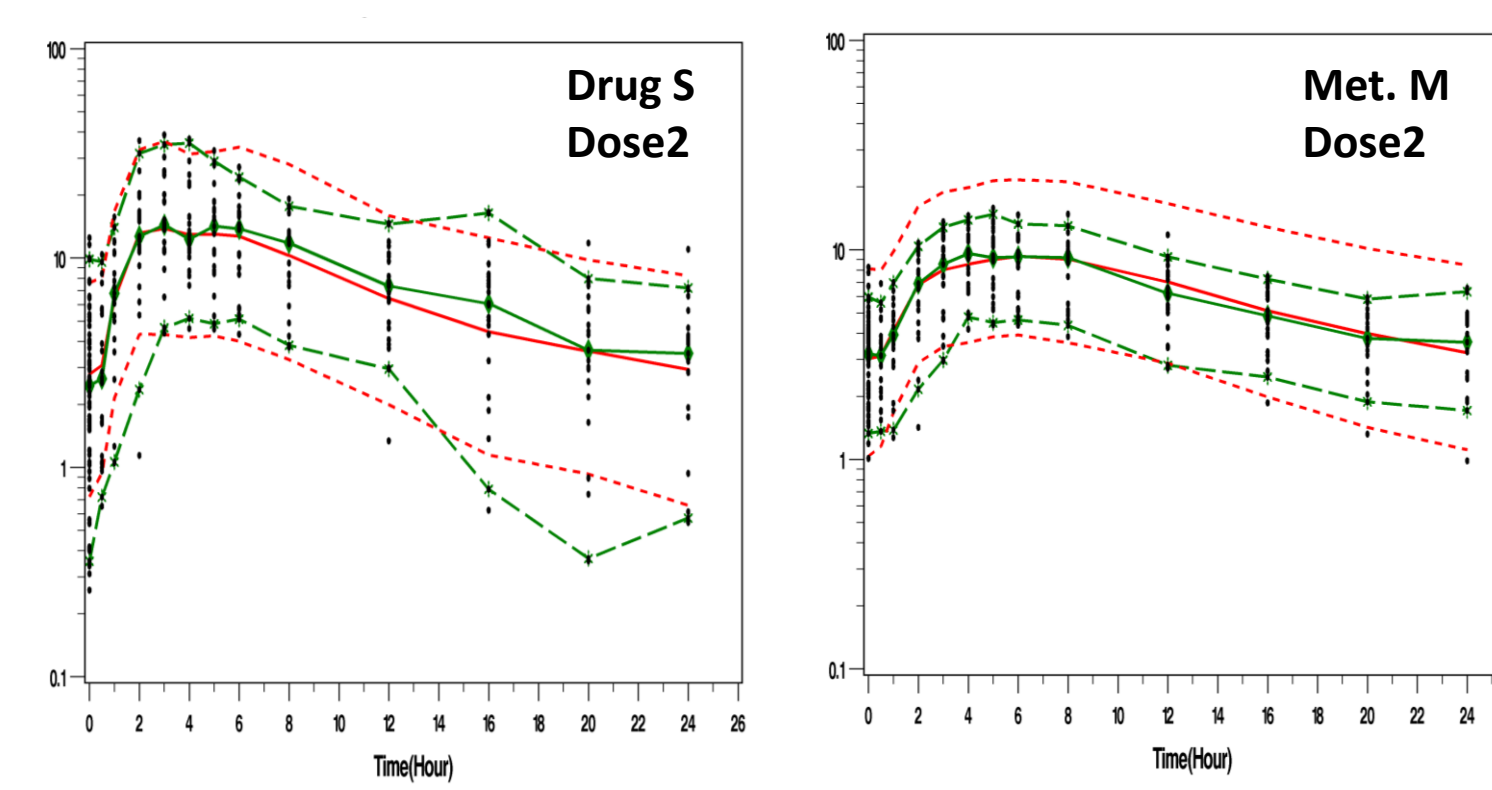
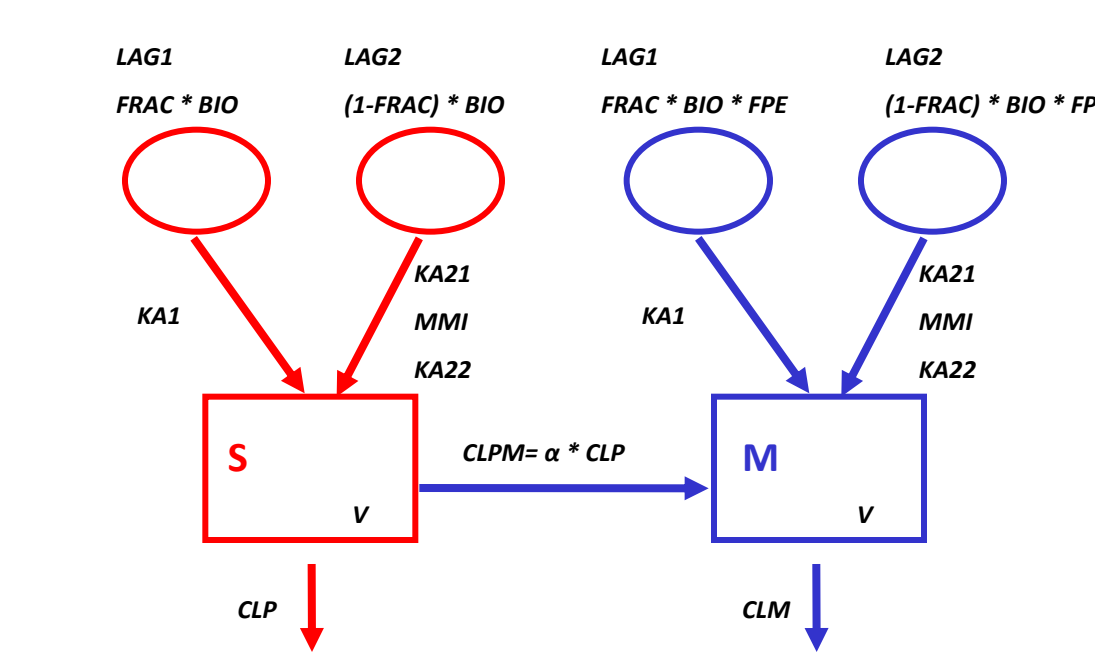
Final PK parameters and expected PKPD parameters were input into POPDES 4.0, together with study design. Kon and Koff values of the PKPD model first were assumed to be estimated for S and M. Other runs evaluated the ability to estimate a single value for KonD and KoffD, and assume a known relationship of the compound's activity (KonM = a * KonS and KoffM = b * KoffS).

Using the design evaluation feature of POPDES, the Fisher Information Matrix relative to the study design was computed, thus outputting expected RSEs. The expected precision of estimation of fixed effects parameters was considered too low when RSEs were greater than 40%.

Results

PK model

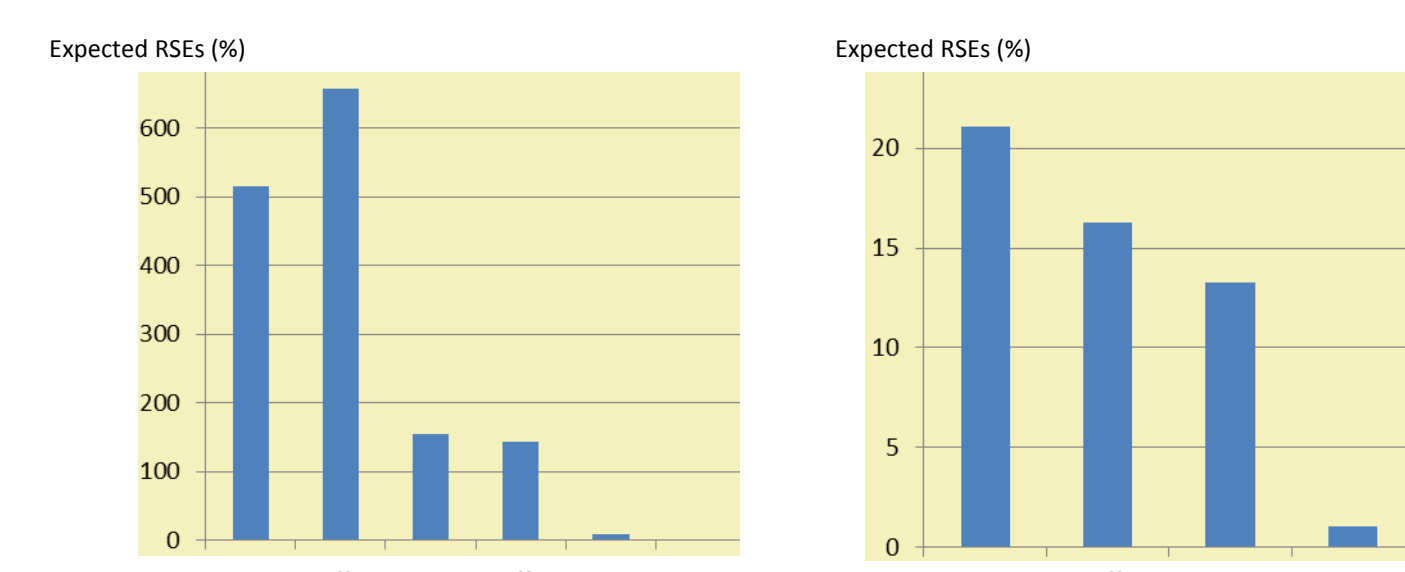
- Sequential first order absorption, with 2 depot compartments (KA1 and KA21 then KA22).
- 1-cpt disposition (M volume of distribution is set to S's) for both compounds
- First order elimination for both compounds
- Absorption is dissolution limited, thus assumed to be identical for S&M.
- M formation from S central compartment was set to a previously determined value (negligible compared to FPE).
- 2 occasion structure for IOV estimation: 1 occasion/week & 1 occasion/day



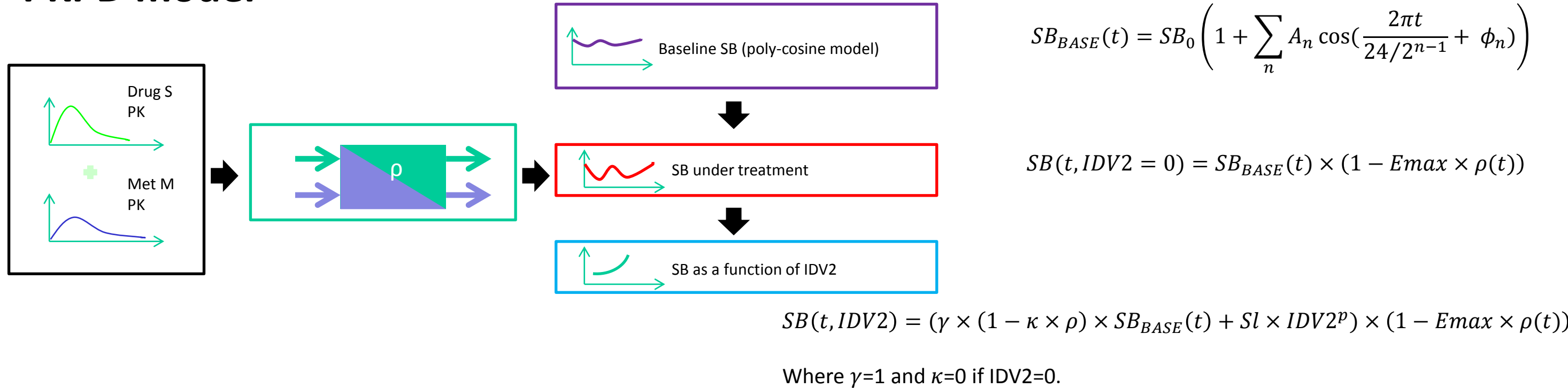
	THETA	RSE (%)	IOV (CV %)	RSE OMEGA (%)	Weekly IOV (CV %)	RSE GAMMA (%)	Daily IOV (CV %)	RSE GAMMA (%)
CLP (L/h)	160	7.19	-	-	-	-	-	-
V (L)	201	9.1	47.1	42.2	32.2	61.3	-	-
α (1)	0.031	FIX	-	-	-	-	-	-
CLM (L/h)	55.6	8.71	24.6	28.6	18.3	52.7	-	-
FPE	0.22	10.7	-	-	-	-	33.3	23
KA1 (1/h)	0.358	8.16	-	-	-	-	-	-
KA21 (1/h)	0.0073	17.7	63.8	53.1	66	31.5	-	-
KA22 (1/h)	0.00271	41.3	-	-	141	32.1	-	-
LAG1 (h)	0.754	5.8	-	-	-	-	-	-
LAG2 (h)	4.97	3.9	-	-	-	-	-	-
BIO	1	FIX	-	43.8	33	-	-	-
MMI (h)	5.59	7.58	-	-	-	-	-	-
FRAC	0.426	7.96	-	-	-	-	-	-
ADD_P (ng/ml)	0	FIX	-	-	-	-	-	-
PROPP_P (%)	0.30	15.4	-	-	-	-	-	-
ADD_M (ng/ml)	0.30	15.4	-	-	-	-	-	-
PROPP_M (%)	16.2	5.7	-	-	-	-	-	-

Identifiability analysis

- Estimating 2 different (kon/koff) parameters for S & M led to > 100% RSEs
- Estimating a single effect (i.e. fixing M's relative activity) led to < 25% RSEs.
- The relative activity of M compared to S was fixed to a value from an *in vitro* assay determining the binding kinetics of the 2 molecules.



PKPD model



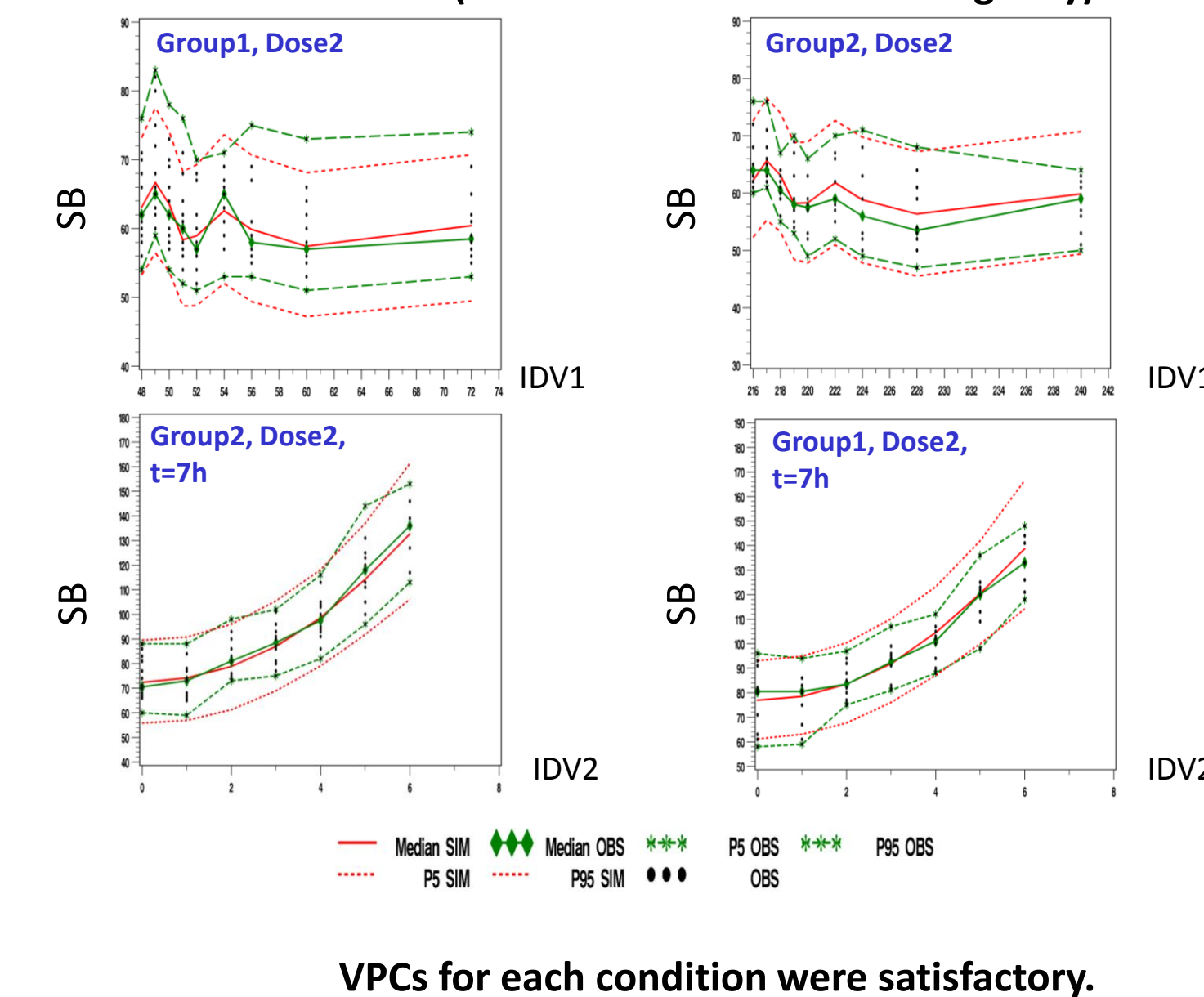
Final models parameters

After sequential & simultaneous model-building

	Sequential modelling (MVOF = 12601)				Simultaneous modelling (MVOF = 12571)			
	THETA	RSE (%)	IOV (CV %)	RSE OMEGA (%)	THETA	RSE (%)	IOV (CV %)	RSE OMEGA (%)
SB ₀	64.1	1.49	7.18	26	64.1	1.55	7.22	21.8
A ₁	-0.0332	10.5	-	-0.0426	10.1	-	-	-
φ ₁	0.987	12.2	-	1.14	9.82	-	-	-
A ₂	0.0204	29.9	-	0.0203	10.3	-	-	-
φ ₂	0.588	12.3	-	0.633	18.5	-	-	-
kon	0.0175	31.9	88.5	32.8	0.0221	16.8	58.1	31.2
koff	0.085	24.4	58.1	50.9	0.103	18.6	51.9	45.4
Emax	0.364	4.23	-	0.337	5.99	-	-	-
γ	1.26	1.64	6.07	27.7	1.26	1.91	6.27	31.3
sl	2.03	5.62	-	2.03	5.57	-	-	-
κ	1.72	21.7	5.11	44.1	1.72	21.6	5.06	44.5
κ ₀	0.149	24.8	-	0.173	26.5	-	-	-
φ _{obs} (IDV2=0)	3.97	3.45	-	4.1	3.07	-	-	-
φ _{obs} (IDV2=1)	5.26	4.07	-	5.19	4.12	-	-	-

Both final parameter estimates and precision of estimation were very similar after the 2 approaches.

Final model evaluation (simultaneous model-building only)



Conclusion

A PKPD model successfully described the effect of drug S and its metabolite M on SB with respect to two independent variables and will be used for further PKPD simulations. A sequential PD model-building and a simultaneous model-bulding led to very similar models in terms of both fixed effects and variances.

References

[1] Zhang, L., Beal, S. L., & Sheiner, L. B. (2003). Simultaneous vs. sequential analysis for population PK/PD data I: best-case performance. *Journal of pharmacokinetics and pharmacodynamics*, 30(6), 387-404.