

Pharmacokinetic-Receptor Occupancy Modeling to support Phase 2 Dose Selection

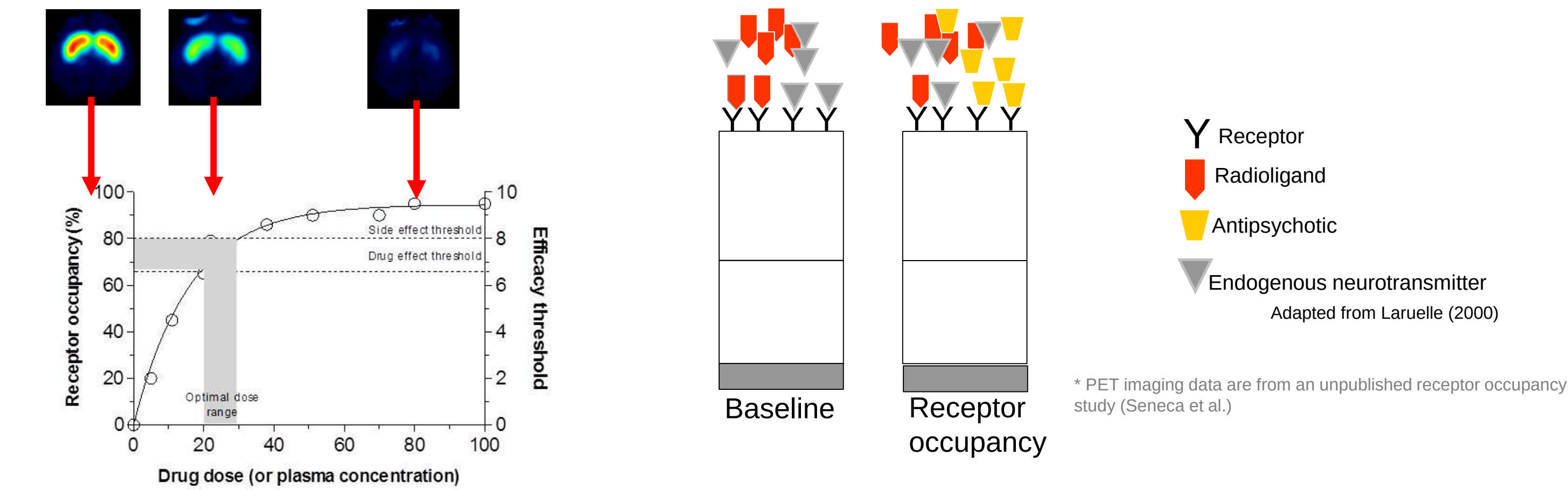


Candice Jamois¹, Vishak Subramoney², Eric Snoeck³ and Valérie Cosson¹

(1) Pharma Research and Early Development, Translational Research Sciences, F. Hoffmann-La Roche AG, Basel, Switzerland
(2) Pharma Research and Early Development, Translational Research Sciences, F. Hoffmann-La Roche Inc., Nutley, United States
(3) Exprimio NV, Mechelen, Belgium

Introduction

- Positron Emission Tomography (PET) technique is commonly used in Central Nervous System (CNS) drug development. PET scanning is a highly specialized imaging technique that uses short-lived radioactive substances to produce three-dimensional colored images (PET scans) of those substances to reveal specific and detailed information about how your tissues and organs are functioning.



- Drug X is currently in Phase 1 of development for CNS disorders. Receptor occupancy (RO) data from a region of interest in brain were generated in healthy subjects to guide the dose selection of the first study planned in the target population.

Objectives

- To develop a population pharmacokinetic-receptor occupancy (PKRO) model describing the relationship between receptor occupancy (RO) in a defined region of interest in brain and drug X plasma concentrations in healthy subjects and to simulate expected receptor occupancies at steady-state after various doses to be selected in the Phase 2 study.

Methods

Study design and dosing regimen

- Rich PK profiles from the SAD and MAD studies were used to characterize the PK of Drug X in 96 healthy subjects. Sparse PET measurements collected in 36 subjects in two PET studies were used to investigate the PKRO relationship.

Population PKPD modeling

- Non-linear mixed effect approach, using NONMEM 7, was used to characterize the pharmacokinetics (PK) and the exposure-RO relationship of Drug X. PK and PD data were modeled sequentially. First, a population PK model was developed to estimate the key PK properties of drug X and to describe inter- and intra-individual variation across the population (population PK parameters not shown). Thereafter RO response in a defined region of interest in brain was analyzed and related to plasma concentrations of drug X. FOCE interaction method was used for both population PK and PKRO analyses.

Simulation

- After qualification of the models by inspection of diagnostic plots, simulations were performed to illustrate in a large population the expected RO after given doses at steady-state, at C_{trough} . The percentage of subjects above defined thresholds of RO with the given doses were also predicted.
- Individual posthocs from all subjects who contributed to the PK analysis (SAD, MAD and PET studies) were used to simulate the response. Simulations were repeated 100 times.

Dose selection

- Three doses were proposed: one with maximum RO at PK steady-state in all simulated subjects, a second dose with maximum RO but in a lower percentage of subjects, and one with sub-optimal RO.

Results

PK results

- PK profile of drug X was accurately described by a one-compartment disposition PK model with first-order elimination and a saturable capacity limited binding [Figure 1]. The absorption was described by a sequential zero and first-order process.

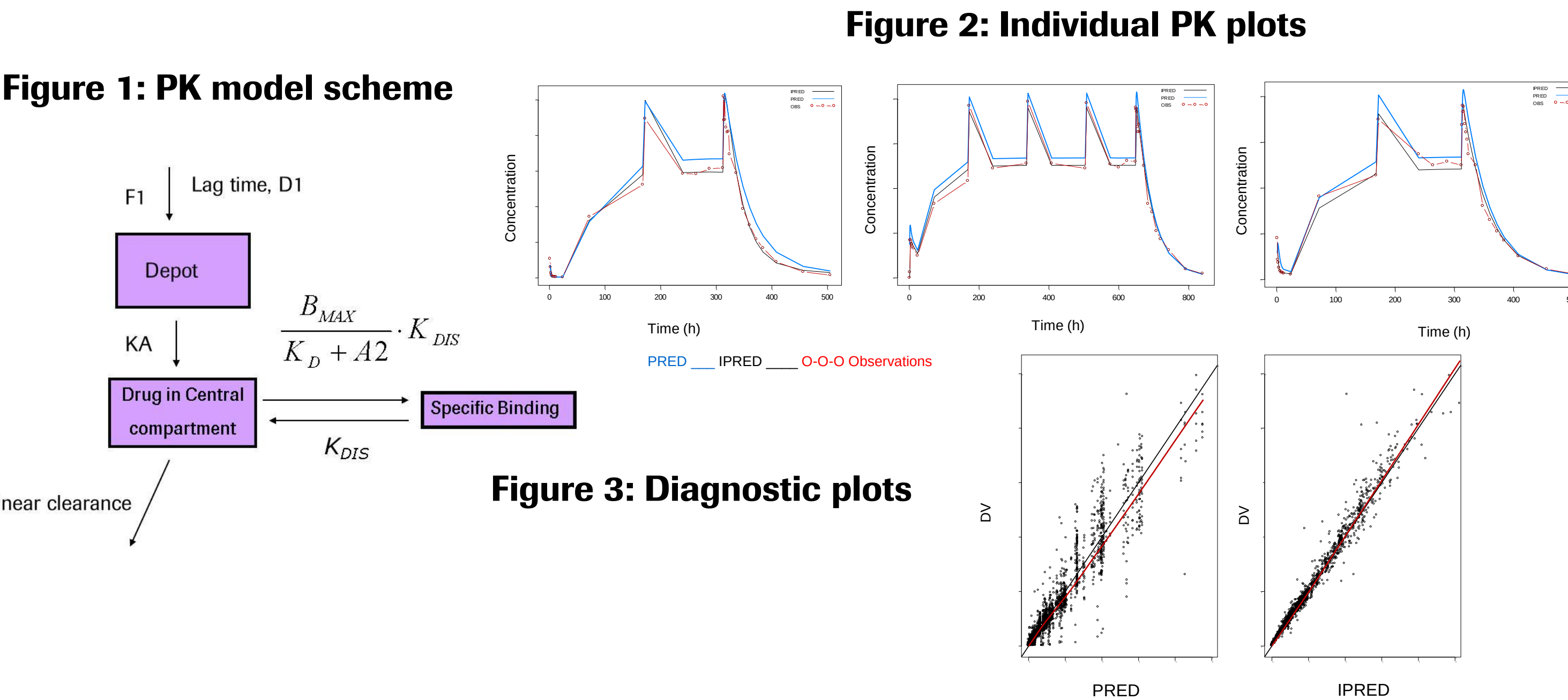


Figure 1: PK model scheme

Figure 2: Individual PK plots

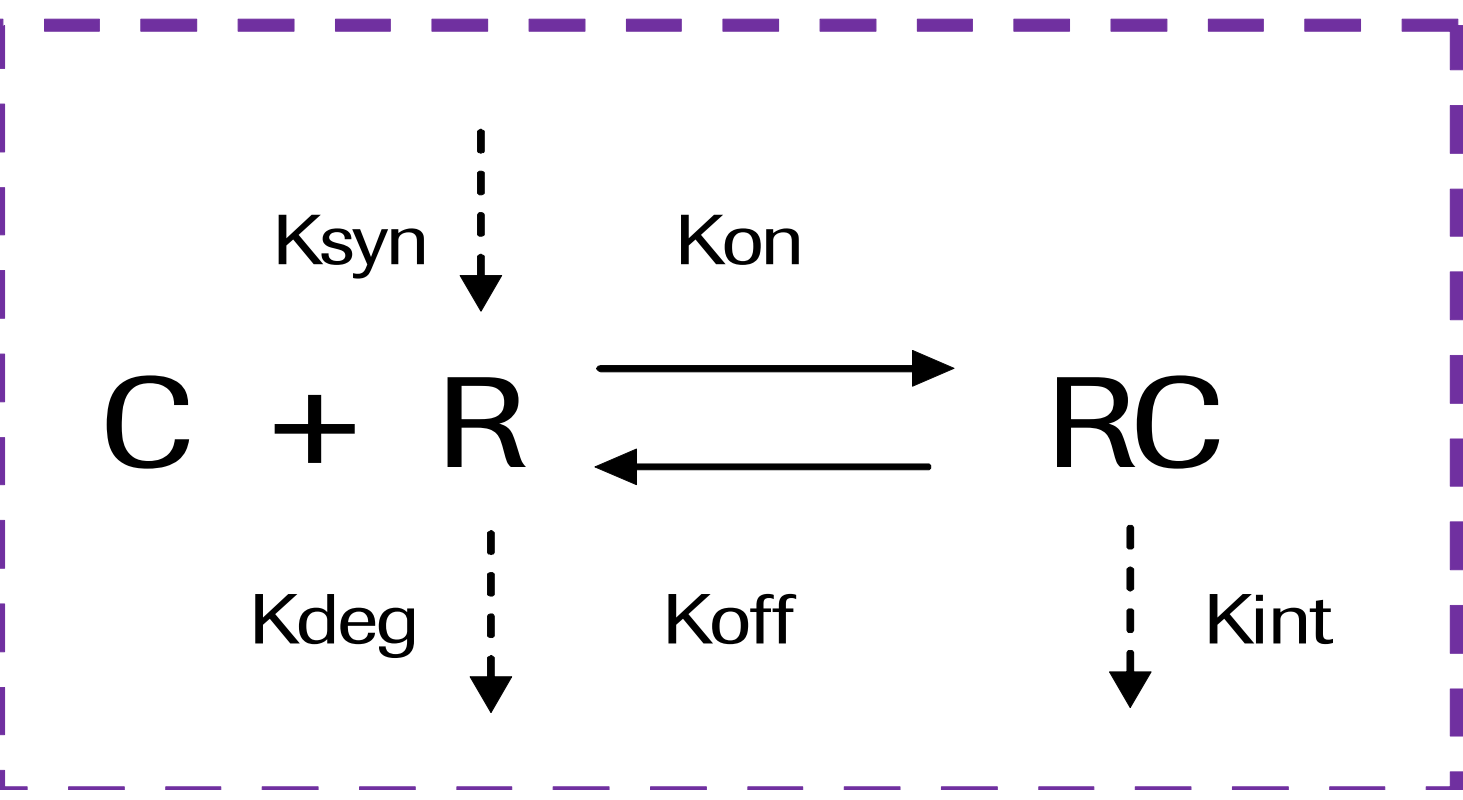
Figure 3: Diagnostic plots

Results (cont'd)

PKPD model development

- A delay exists between maximum PK and maximum RO. This has been described by a slowly reversible receptor binding model [Figure 4].

Figure 4. PKRO model*



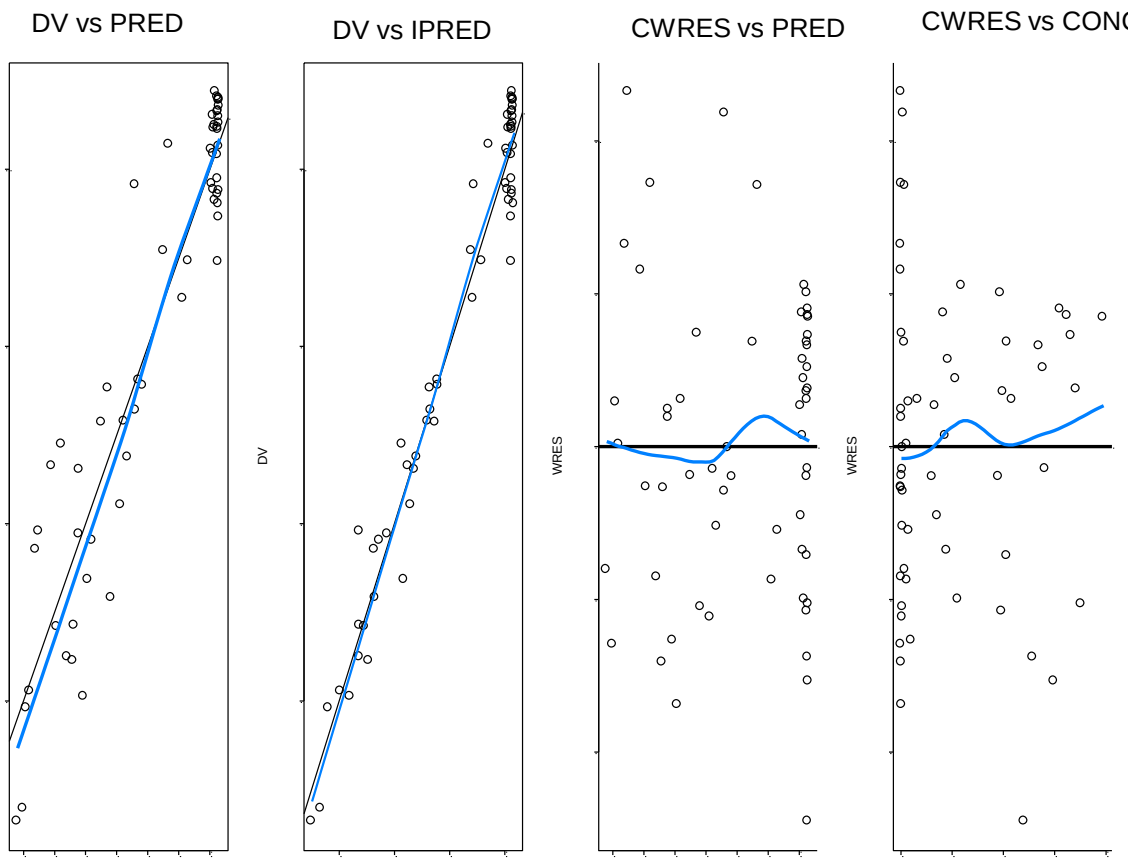
C: drug in central compartment (PK)
R: free receptor in the region of interest in brain
RC: complex drug-receptor
Kon: RC complex formation constant
Koff: RC complex degradation constant
Ksyn: free receptor synthesis constant
Kdeg: free receptor degradation constant
Kint: Internalisation constant of the complex
**The parameters associated to dotted lines are not estimated*

- In this specific case, RC was equated to RO with total receptor occupancy (RTOT) equals to R+RC
- The parameter estimates for the PKRO model are presented in Table 1. The η -Shrinkage was moderate for Kon with 33.7% and the ϵ -Shrinkage was 13.6%.

Table 1. Parameter estimates for the PKRO model

	Value (RSE%)	Inter subject variability (%) (RSE%)
Kon (h ⁻¹)	0.00731 (17.1)	50 (40.8)
Koff (h ⁻¹)	0.0107 (13.5)	
RTOT (%)	52.8 (1.2)	
Additive error (%)	5.38 (13)	

Figure 5: Diagnostic Plots



- The PKRO model described the data reasonably well as assessed by goodness of fits plots [Figure 5] and VPC (results not shown).

Illustration of the Drug response

- To support the phase 2 dose selection, RO following treatment with several doses of Drug X was simulated over 3 months, till PK steady-state (SS) was reached [Figure 6]. The relationship between RO and simulated doses at SS is displayed in Figure 7.

- Those simulations showed that doses above or equal to E will lead to full occupancy in at least half of the simulated population at C_{trough_ss} . Dose I will lead to full occupancy in all individuals while doses below E are associated with lower receptor occupancy [Table 2].

Figure 6: Time course of RO until PK SS

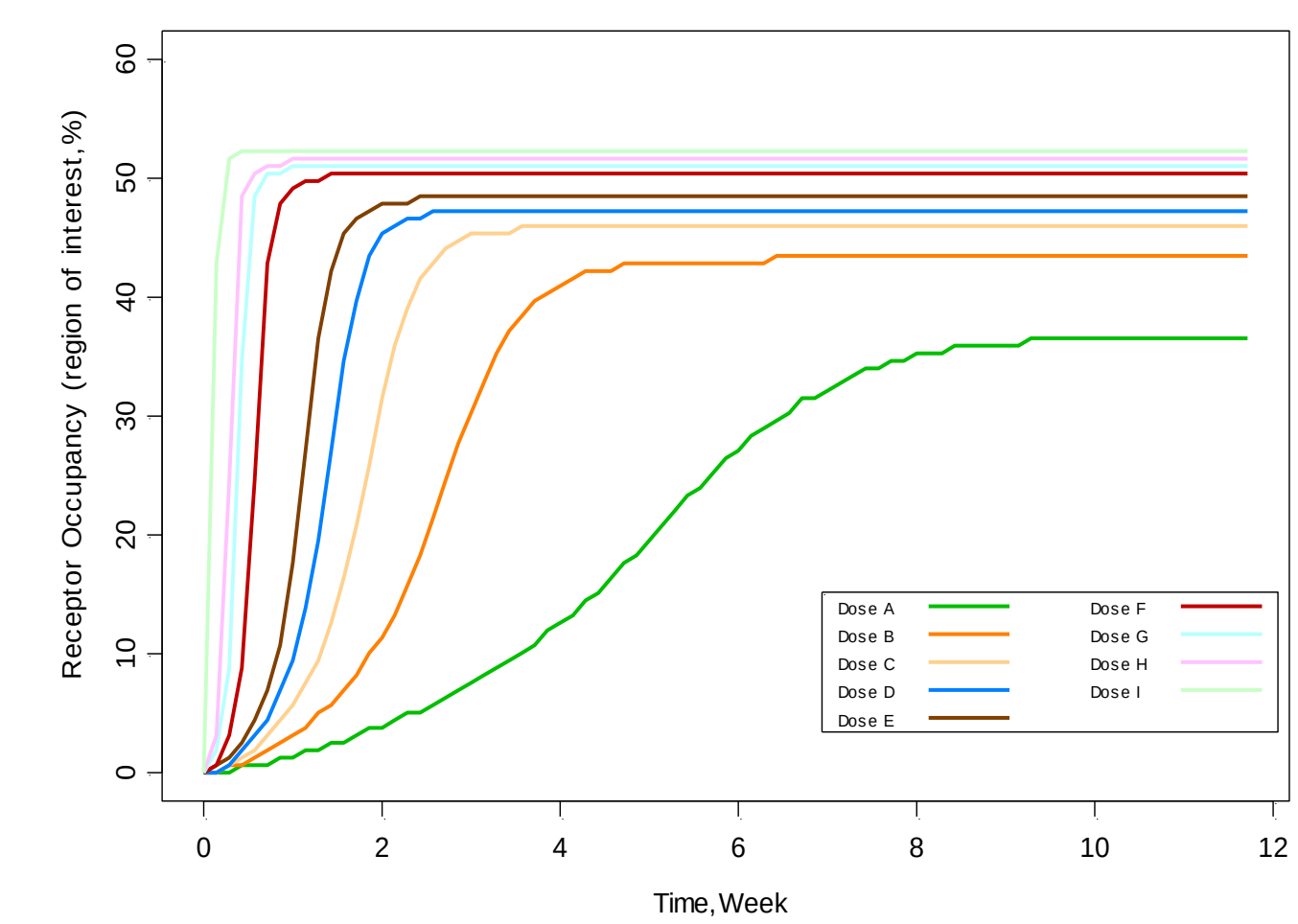


Figure 7: Relationship between RO and Doses

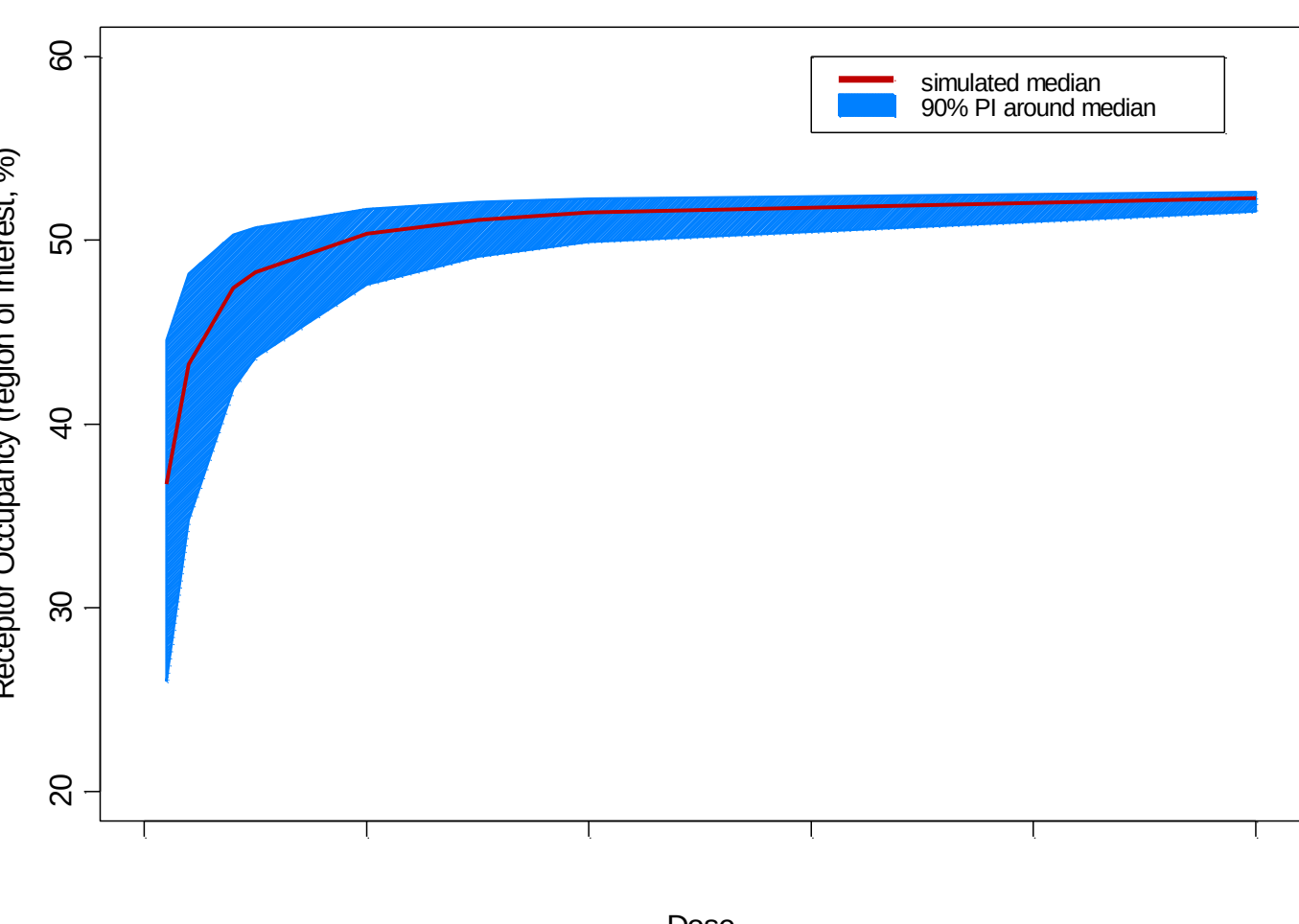


Table 2: Simulated Percentage of Subjects with RO above defined Thresholds at Steady-State

Receptor occupancy threshold (%)	Dose A	Dose B	Dose C	Dose D	Dose E	Dose F	Dose G	Dose I
20	100 (98-100)	100	100	100	100	100	100	100
25	96 (93-98)	100 (99-100)	100	100	100	100	100	100
30	80 (75-85)	98 (96-100)	100	100	100	100	100	100
40	42 (34-79)	87 (83-91)	100 (98-100)	100 (99-100)	100	100	100	100
45	6 (3-10)	41 (35-48)	86 (82-91)	93 (90-97)	100 (99-100)	100	100	100
50	0	0 (0-0.8)	5 (2-6)	9 (5-14)	48 (42-55)	76 (70-82)	90 (86-94)	100 (99-100)

- From the large simulated population, the maximal RO and the percentages of subjects with RO above thresholds ranging from 20 to 50% guided the choice of dose for Phase 2. One top dose with maximum RO in all subjects, one dose with maximal RO in approximately 50% of the subjects and one dose with lower RO were proposed.

Conclusion

- Three dose levels, (B, E, I) were selected to provide receptor occupancy above a given threshold in the brain area of interest in a sufficiently large number of patients treated chronically with drug X, assuming similar PKRO relationship between healthy subjects and target population. With doses B and E, it is predicted that 90 % of the population will have RO comprised between 35 and 48 % and between 48 and 52 % respectively; while dose I is expected to provide almost maximal receptor occupancy at C_{trough_ss} (53%) in all individuals of the simulated population.
- In the absence of information on RO differences between healthy subjects and patients, and on the relationship between RO and clinical endpoints, the modeling of RO in healthy subjects together with assumption on the level of occupancy required to obtain clinical efficacy is a valuable tool to support phase 2 dose selection.
- The population PKRO model will be re-evaluated with upcoming data in patients. Data from the phase 2 study will allow the characterization of the link between target RO and clinical efficacy.

References

- US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research Guidance for Industry: population pharmacokinetics. US Department of Health and Human Services Web site: 1-35.
- Beal S, Sheiner L. NONMEM User Guides. In: NONMEM Project Group. University of California at San Francisco: San Francisco; 1992
- Jusko. Pharmacokinetics of capacity limited system. J of Clin. Pharmacol., 1989; 29: 488-493
- Levy G. Pharmacologic target-mediated drug disposition. Clin Pharmacol Ther., 1994; 56 (3) 248-252.
- Mager D. Target mediated drug disposition and dynamics. Biochem Pharmacol., 2006; 72 (1):1-10.