Model-based sequential human PET study design for Optimal PK/RO assessment

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INTRODUCTION

Positron emission tomography (PET) is a non invasive imaging technique used to quantify ligand-receptor binding in the living brain. By acquiring scans in the absence and presence of cold drug it can be used to measure occupancy as a function of time in the human brain. These data can then be related to the plasma concentration using appropriate PK/RO models. Although information are available from preclinical species on the distribution of receptors and the affinity of a drug for these receptors (k*on*/k*off*), there is still a degree of uncertainty in translating these information from animals to humans to allow for good experimental designs.

OBJECTIVES

The purpose of this work is to demonstrate the added value of an adaptive-optimal PK/RO study, over and above the standard PET study design in which scans are typically scheduled at the time of maximum plasma concentration and at 24 hours post dose. Two different cases were studied:

1) Good predictability from preclinical data
2) Model mis-specification (koff parameter).

METHODS

A model which describes the relationship between plasma concentration of a drug and the resulting receptor occupancy is given by;

$$\frac{dRO}{dt} = k_{on} \cdot C_P \cdot (R_T - RO) - k_{off} \cdot RO$$

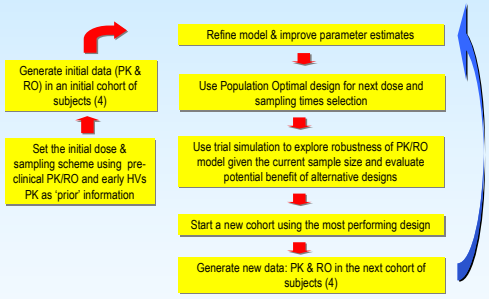
where C_P is the plasma concentration (assumed as input function), R_T the maximal occupancy (fixed at 100%), k_{on} and k_{off} the association and dissociation rate, respectively. [1]

A typical PET occupancy study design consists of ~12 volunteers dosed sequentially at 3 dose levels with PET scans recorded at approximately the time of C_{max} and 24 hours post dose. In our case, population PK information derived from FTIH studies, suggested C_{max} at around 6 hours.

The model-based sequential PET study design (optimal) consisted of 3 sequential cohorts of 4 subjects each. The PET scans of the first cohort were fixed at 6 and 24 hours, and in each subsequent simulated cohort an optimal design was applied based on information gathered from previous cohorts. PET scan times were adjusted at each step to allow the most informative assessment of the PK/RO relationship.

Three different dose levels were explored in both cases to 0.6, 1.5 and 4 mg.

Sequential Design Optimization: Modelling and Simulation Approach



Case 1		Case 2	
Kon (ml.ng^{-1}.h-1)	Koff (h^{-1})	Kon (ml.ng^{-1}.h^{-1})	Koff (h^{-1})
0.088	0.221	0.088	0.04

Standard Design		Optimal Design	
Scan time 1	Scan time 2	Scan time 1	Scan time 2
Coh1 6hr Coh2 6hr Coh3 6hr	Coh1 24hr Coh2 24hr Coh3 24hr	Coh1 6, 24hr	
Coh1 6hr Coh2 3hr Coh3 8hr	Coh1 24hr Coh2 12hr Coh3 36hr	Coh2 and 3 based on results from previous cohorts	

The adaptive-optimal PET study designs were obtained using WinPOPT® 1.1 software. Comparison between traditional and stepwise-optimal design were made using the D-optimality criterion. ([2], [3])

RESULTS

Simulations show that the sequential-optimal approach to designing PET occupancy studies provides added value compared to the typical PET study design. 40 trials (with 12 subjects/trial) were generated for both cases 1 & 2. In each case 20 optimally designed trials were compared to 20 standard design trials either where scan 1 and scan 2 were fixed to 6 and 24 hrs for all three cohorts, or varied for each cohort (2 time-points x cohort). Bias, precision and accuracy for the two case studies were reported in the tables and plots.

Case 1 – Good predictability from pre-clinical model

Performance	Measure	Standard (6 Fixed Time-points)		Standard (2 Fixed Time-points)		Optimal	
		Kon	Koff	Kon	Koff	Kon	Koff
Unscaled							
Bias	ME	0.427	1.293	0.126	0.331	0.0004	0.0067
Precision	Var	3.365	31.3	0.286	2.006	0.0003	0.0023
	SD	1.834	5.595	0.534	1.416	0.0160	0.0480
Accuracy	MSE	3.547	32.97	0.302	2.116	0.0002	0.0023
Scaled							
Bias	SME	4.85	5.85	1.44	1.50	0.0043	0.0303
Precision	CV	71.2	73.9	49.9	51.3	3.62	4.21

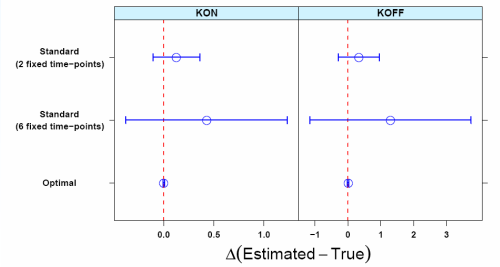
Case 2 – Model Mis-Specification on Parameters (Koff << from pre-clinical)

Performance	Measure	Standard (6 Fixed Time-points)		Standard (6 Fixed Time-points)		Optimal	
		Kon	Koff	Kon	Koff	Kon	Koff
Unscaled							
Bias	ME	1.98	1.518	6.804	4.162	0.0028	0.0069
Precision	Var	24.04	16.63	77.77	33.24	0.0002	0.0002
	SD	4.903	4.078	8.819	5.766	0.0158	0.0123
Accuracy	MSE	27.96	18.93	124.1	50.56	0.0002	0.0002
Scaled							
Bias	SME	22.5	37.9	77.3	104	0.0319	0.1730
Precision	CV	47.4	52.4	25.6	27.5	3.49	5.23

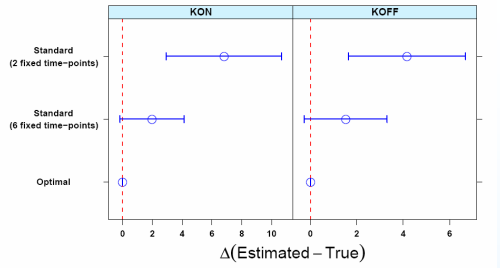
ME = mean error, Var = variance, SD = standard error, MSE = mean square error, SME = scaled mean error, CV = coefficient of variation (Walther and Moore, Ecography 28: 815-829, 2005)

The optimal study design approach provided more accurate and reliable model parameter estimates in both cases. In fact, in the optimal design, the population parameter estimates for each trial were within a two fold error with respect to the true value. In the standard approach, several population parameter estimates were far from the true values (>2 fold) ranging from 2 (~10% in case I) to 8 trials (40% in case 2).

CASE 1
(Confidence Intervals of the Mean between Estimated and True Values)



CASE 2
(Confidence Intervals of the Mean between Estimated and True Values)



The use of the proposed sequential model design increased the efficiency of the study for the PK/RO assessment, especially when a priori pre-clinical data is not reflective of the clinical situation (case 2).

CONCLUSIONS

Model-based sequential optimal study design allows a more rationale and data-driven decision making, especially in those studies were intensive sampling strategies are not allowed for operational or ethical reasons.

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