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ABSTRACT

Objectives: Define an optimal sparse sampling strategy to maximize knowledge gained on apixaban exposure in a diverse patient population, while limiting cost and maintaining compatibility with study logistics. Apixaban is an oral direct factor Xa inhibitor, intended to treat deep venous thrombosis (DVTx) and to prevent DVT in post-surgical and acutely ill medical patients (DVTp). In addition, apixaban is intended for the prevention of stroke in patients with atrial fibrillation (AFib), and for secondary prevention in patients with acute coronary syndrome (ACS).

Methods: A one-compartment exposure model was used for trial simulation. Optimal sparse sampling designs were selected using trial simulation: (step 1) narrow down sampling designs to a reasonable number of options (WinPOPT), (step 2) identify optimal sampling design with model-based trial simulation (NONMEM) based on accuracy (BIAS) and precision (mean absolute error (MAE)) criteria for the population exposure parameters, (step 3) identify optimal number of subjects with sparse sampling to be enrolled in each trial (WinPOPT). The quality of the apixaban exposure parameters for the selected optimal sparse sampling designs was compared to that for a design with one random sample only (reference).

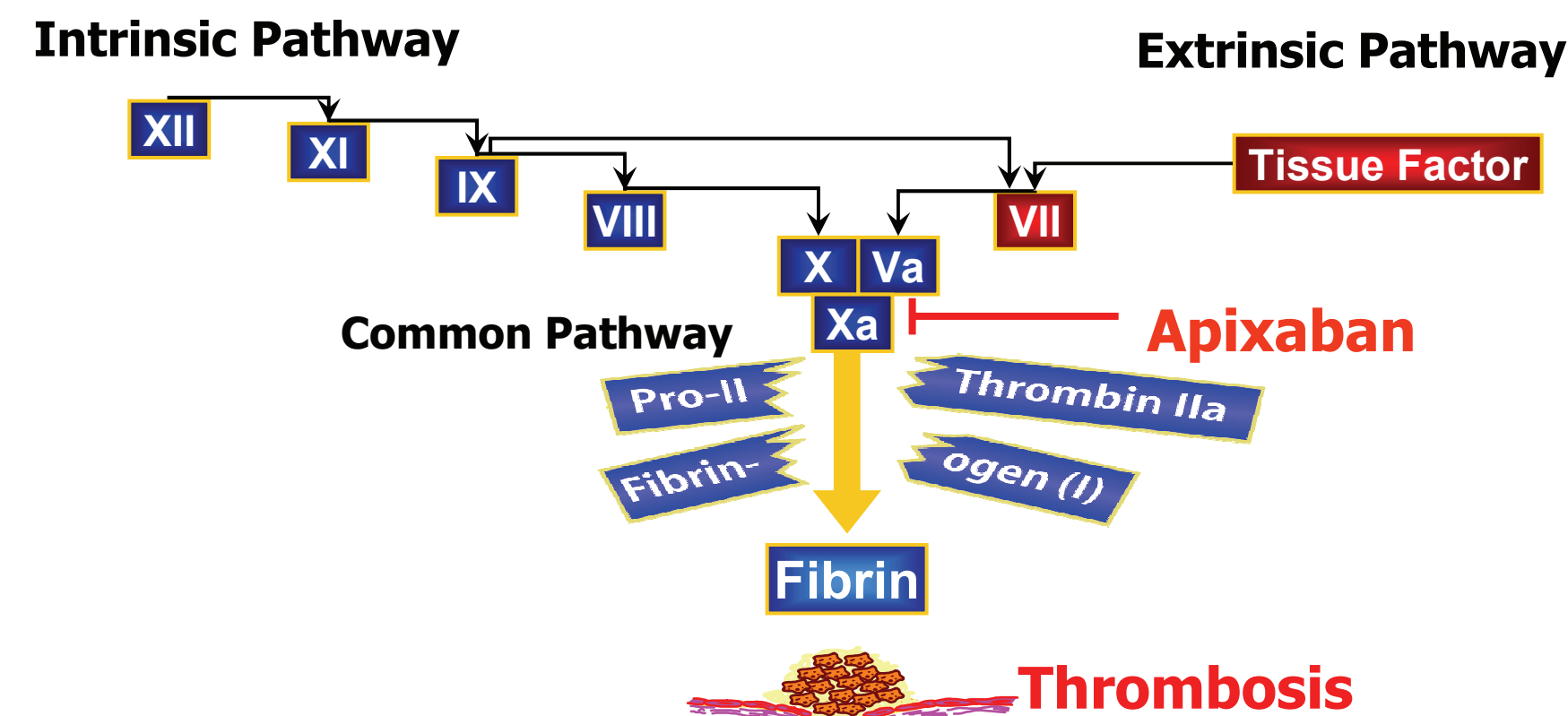
Results: The single random sample design (reference) showed a high bias (~80%) and MAE (~100%) in exposure parameters. Sampling designs with 4 sparse samples provided good estimation of exposure, with both BIAS and MAE remaining generally low, e.g. ~20% and ~30%, respectively. Enrollment of more patients (300-500) in the study trial allowed improvement of precision. The optimal sampling strategy for clinical trials recommended four samples to be drawn in at least 300 patients at specific time points and on two separate occasions.

Conclusion: Model-based trial simulation allowed optimal sampling to be proposed that could conveniently be implemented in apixaban Phase III studies, so that knowledge on exposure in the target patient population be maximized, while avoiding excessive costs and preserving study logistics.

INTRODUCTION

- Apixaban is an oral anti-thrombotic, direct factor Xa inhibitor
- Phase III studies will be conducted for diverse indications
 - Prevention of Deep Vein Thrombosis (DVTp)
 - Post-surgical (1)
 - Acutely ill medical patients (2)
 - Treatment of Deep Vein Thrombosis (DVTx) (3)
 - Prevention of stroke in patients with Atrial Fibrillation (AFib) (4)
 - Secondary prevention in Acute Coronary Syndrome (ACS) patients (5)
- Optimal PK sampling relates closely to the study type (in- or outpatients, duration, visits)
 - Study type I (Short Term) for indication (1)
 - Study type II (Long Term) for indications (2-5)

Figure 1. Factor Xa and Thrombosis



Adapted from "Management of Oral Anticoagulant Therapy, Principles & Practice", Jack Ansell, M.D., Jack Hirsh, M.D., Nanette K. Wenger, M.D.

METHODS

Step 1 – Sampling Designs (WinPOPT)

- Nine different sampling designs were selected for Study Type I (n=5) and Type II (n=4)

Step 2 – Trial Simulation (NONMEM)

- Each sampling design was simulated 500 times (500 trials with 300 patients)
- Individual BIAS and Absolute error (AE) were calculated for each population parameter estimate

$$BIAS \% = 100 \times \frac{P_{est} - P_{true}}{P_{true}} \quad AE \% = 100 \times \frac{|P_{est} - P_{true}|}{P_{true}}$$

- Mean BIAS and AE for the population parameters (PK), and their Inter-Individual Variability (IIV) were compared across the different sampling designs

Step 3 – Optimal Number of Patients (WinPOPT)

- The precision of the parameter estimates was compared across studies with different number of patients

$$Precision = 100 - RSE \%$$

STUDY DESIGN & MODEL PARAMETERS

Study Type I (Short Term)

- Dosing: 2.5 mg BID post-surgery for up to 35 days
- Patients are initially hospitalized for surgery and later ambulatory (1)
- Optimal sampling on Day 3-4 post-surgery

Study Type II (Long Term)

- Dosing: 2.5 or 5 mg BID for up to 40 months
- Patients are ambulatory and visit the clinic occasionally
- Optimal sampling any time at Steady-State
- Month 3 & 6 presented here as an example

Table 1. Apixaban Population Exposure Parameters

PK Parameters (PK)	Inter-Individual Variability (IIV)		Residual Error			
	Parameter (Units)	Value (CV%)	Parameter	Value (CV%)	Parameter (Units)	Value (CV%)
CL/F (L/hr)	2.84	(1.79)	ω^2 CL	0.170 (6.82)	Proportional (-)	0.311 (4.28)
V/F (L)	41.9	(6.25)	ω^2 V	0.191 (14.5)	Additive (ng/mL)	23.3 (12.1)
K _a (hr ⁻¹)	0.275	(11.6)	ω^2 K _a	0.415 (18.9)		

Table 2. Sampling Designs for Study Type I

Sampling Design #	Samples at Time (hrs) on Day 3							Day 4
	0	0.5	2	3	4	6	11	0
1	X		X			X		X
2	X		X		X			X
3	X	X		X				X
4	X		X	X		X	X	X
5	1 Random Sample							

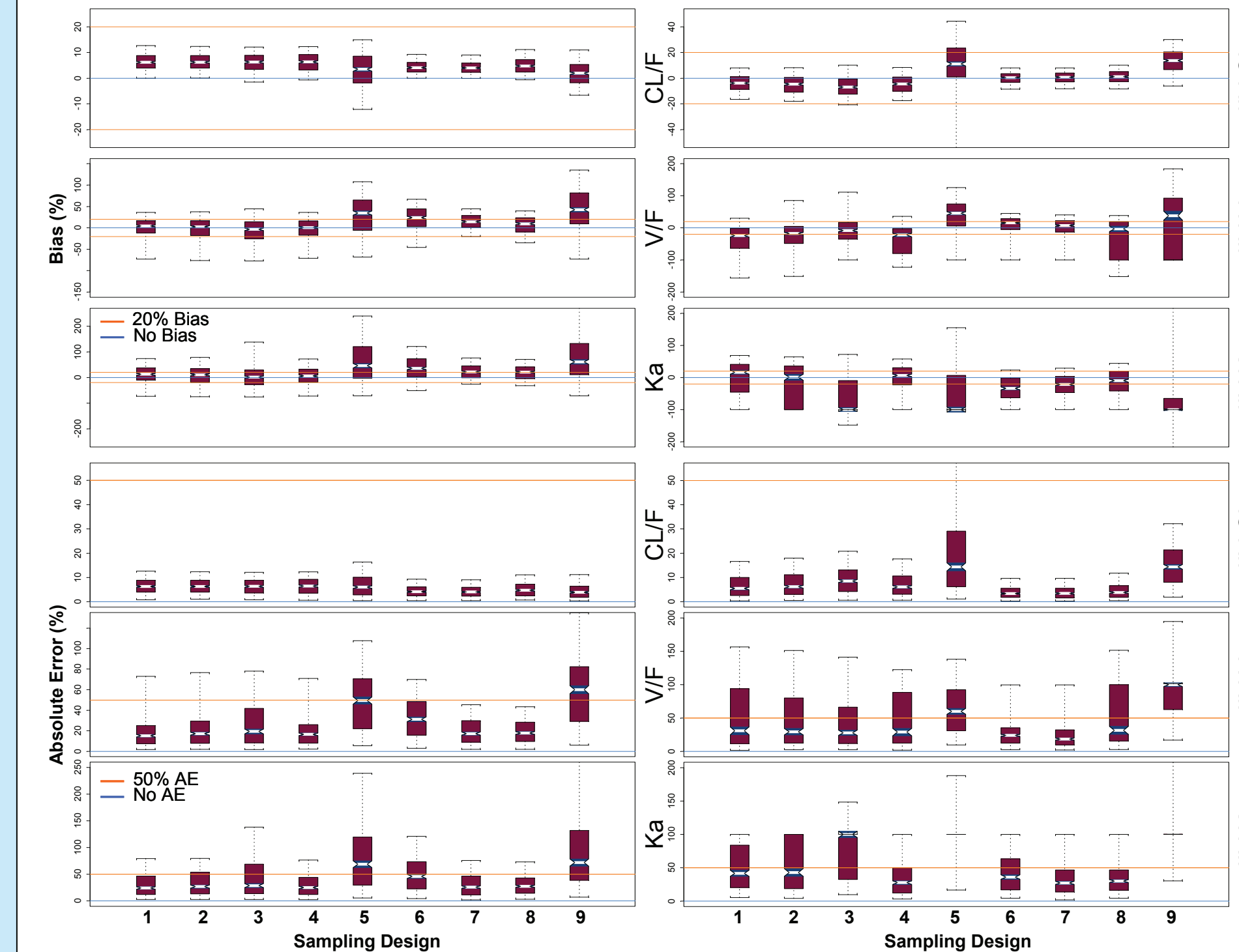
Table 3. Sampling Designs for Study Type II

Sampling Design #	Samples at Time (hrs) on Month 3						Month 6		
	-2	0	2	4	6	0	2	4	
6		X	X	X		X			
7		X	X		X	X			
8	X	X					X	X	
9	1 Random Sample						None		

RESULTS

Figure 2. Bias and AE in Parameter Estimates

- Sampling Designs # 1, # 2, and # 7, # 8 show the lowest BIAS and AE
- Sampling Designs # 5 and # 9 show the highest BIAS and AE



Center of bars represents median of 500 simulations ± Confidence interval. Bars extend to 25th and 75th percentiles. Staples represent 5th and 95th percentiles

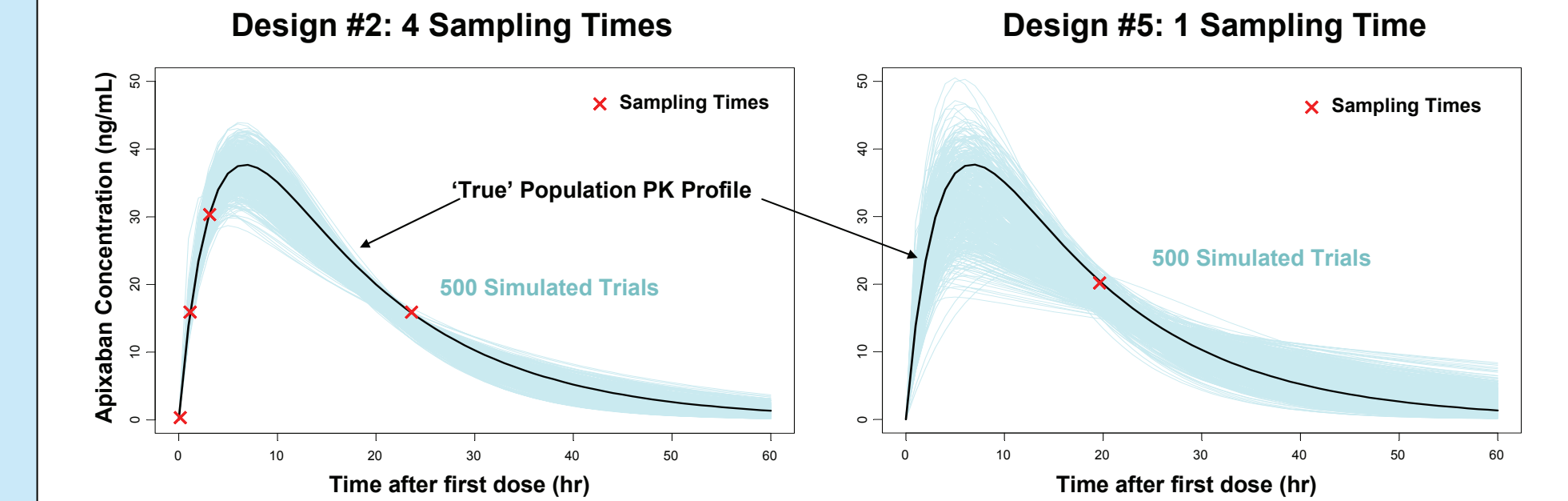
- Design #1 → Day 3: 0, 2, 6 hr; Day 4: 0 hr
- Design #2 → Day 3: 0, 2, 4 hr; Day 4: 0 hr
- Design #7 → Month 3: 0, 2, 6 hr; Month 6: 0 hr
- Design #8 → Month 3: -2, 0 hr; Month 6: 2, 4 hr
- Designs #1 and #2 provided comparable quality in parameter estimates; Design #2 is easier to implement
- Design #8 provided slightly better PK parameter estimates, but worse estimates of IIV as compared to Design #7; choice may depend on study logistics

Table 4. Mean Bias and MAE

	Mean Bias (%)						MAE (%)					
	PK			IIV			PK			IIV		
	CL/F	V/F	Ka	CL/F	V/F	Ka	CL/F	V/F	Ka	CL/F	V/F	Ka
Study Type I (Short Term)												
Design #1	6.26	-0.219	12.3	-3.94	-36.3	-5.5	6.44	20.1	31.7	6.8	49.4	50.4
Design #2	6.25	-4.49	8.57	-4.85	-27.9	-15	6.44	23.9	36	7.55	49.8	52
Study Type II (Long Term)												
Design #7	4.27	13.4	22.3	0.514	-1.28	-23.7	4.38	20.1	30.9	3.99	25.3	33.7
Design #8	4.92	6.72	19	1.13	-32.1	-14.8	5.12	20.3	31.4	4.64	52.1	36.9

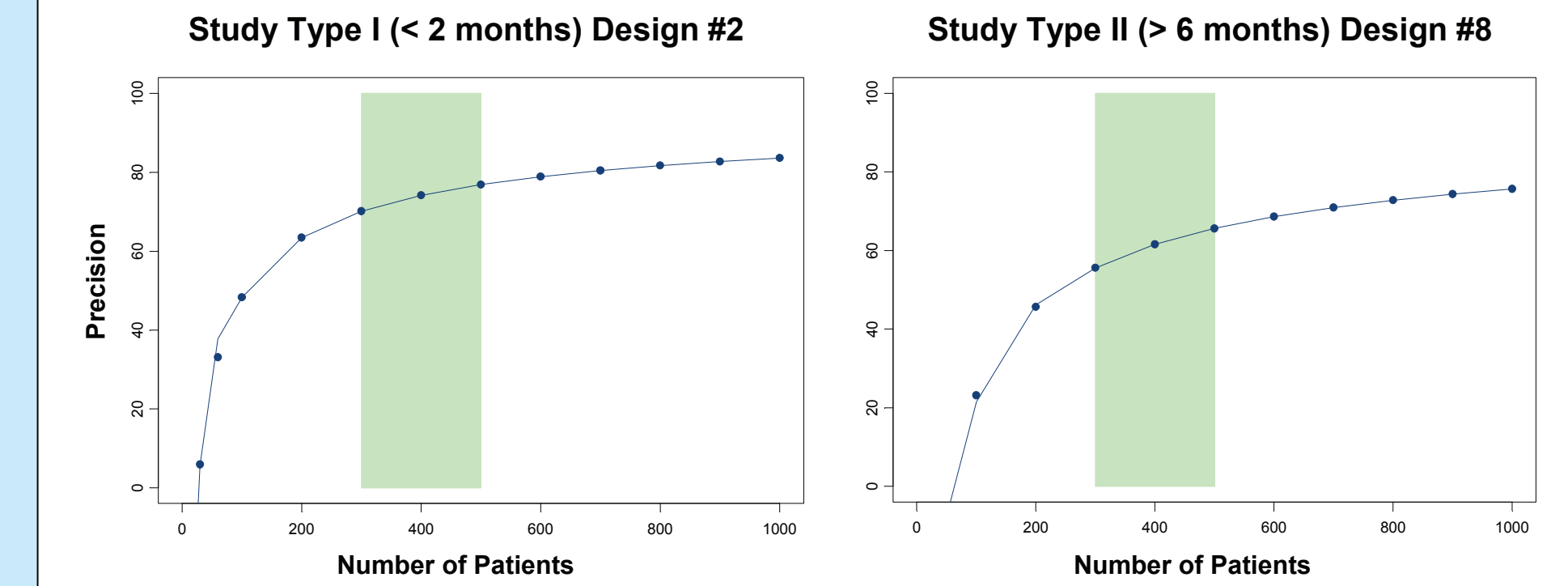
RESULTS (cont'd)

Figure 3. Population PK profiles from 500 simulated trials



4 sparse (Design #2) samples are much better than 1 random sample (Design #5) for estimation of population parameters

Figure 4. Number of Patients and Parameter Precision



- Precision on parameter estimates plateaus for >300-500 patients

CONCLUSIONS

- Model-based trial simulations provide
 - Insight on the precision of the PK parameter estimates and of their IIV
 - Knowledge on the number of patients to be enrolled in PK sampling
- An understanding of the quality of PK information that is retrieved from different sampling designs allowed sound decision making to maximize knowledge, reduce excessive costs and preserve study logistics

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