

Study design optimization of a morphine analgesia trial using PKPD modelling and simulation

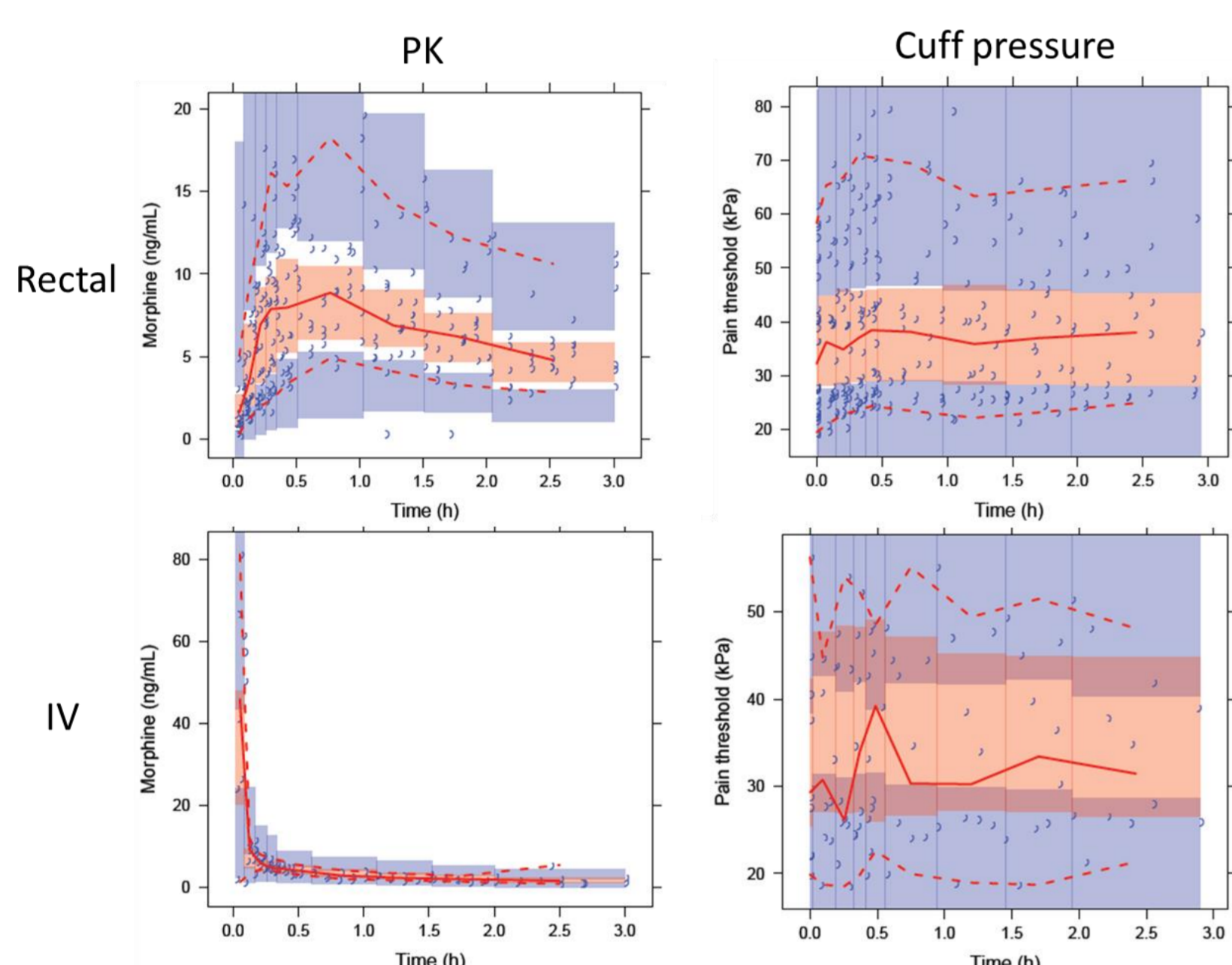
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Objective

Develop a population PKPD model based on a pilot study in healthy volunteers undergoing experimental pain stimulation in order to select an optimal morphine rectal dose for a forthcoming study using simulations, matching criteria's of ~ 15% peak response from baseline with maximum morphine plasma levels <50 ng/mL for safety

pcVPC for Morphine PKPD model

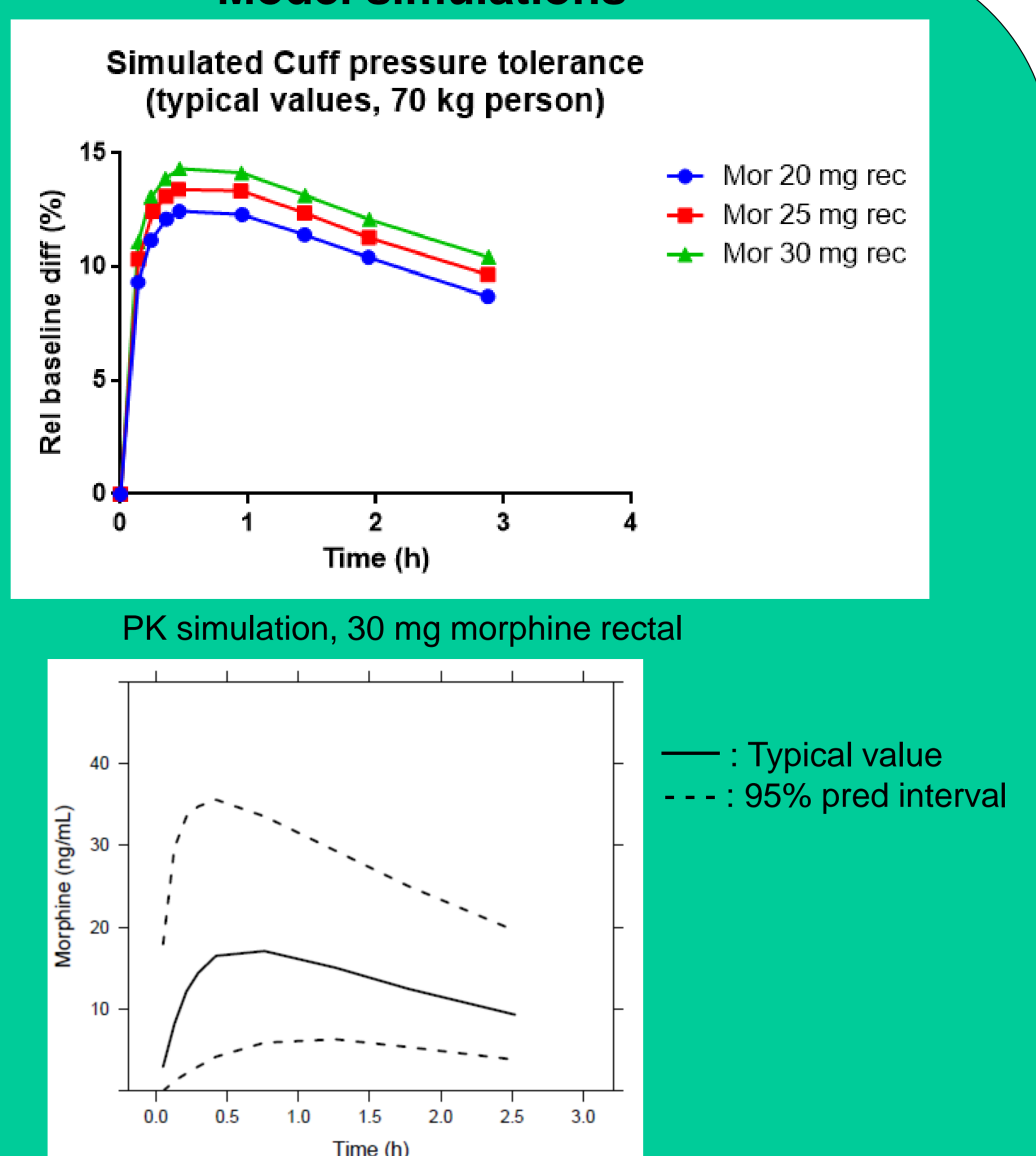


Morphine PKPD parameters

Parameter	Estimate (RSE%)	IIV (RSE%)	IOV (RSE%)	Description
CL * (WT/70) ^{0.75} (L/h)	79 (12)	22 (26)		Systemic clearance with allometric weight scaling
V2 * (WT/70) (L)	5.3 (36)		104 (18)	Central compartment with allometric weight scaling
V3 * (WT/70) (L)	113 (18)			Peripheral compartment with allometric weight scaling
Q3 * (WT/70) ^{0.75} (L/h)	173 (22)			Inter-compartmental clearance with allometric weight scaling
F (%)	22 (11)	30 (27)	31 (23)	Rectal bioavailability
k _a (h ⁻¹)	4.0 (60)	127 (34)		Transit compartment rate constant for rectal morphine absorption
k _a (h ⁻¹)	1.5 (32)		42 (24)	Absorption rate constant
σ _{1, prop error} (%)	24 (12)			Proportional residual error, PK
σ _{2, add error} (ng/mL)	0.29 (66)			Additive residual error, PK
σ _{3, PD add error} (kPa)	3.1 (14)			Additive residual error, PD
Baseline (kPa)	33 (11)	32 (10)	13 (12)	Cuff pressure tolerance baseline
Slope _{Drug}	0.050 (26)	3.2 (20)		Slope for drug effect vs ln[C _p]

RSE% relative standard error calculated as the ratio between the standard error and the estimate, and multiplied by 100. IIV: inter-individual variability in % of the parameter estimate; IOV: inter-occasion variability in % of the parameter estimate

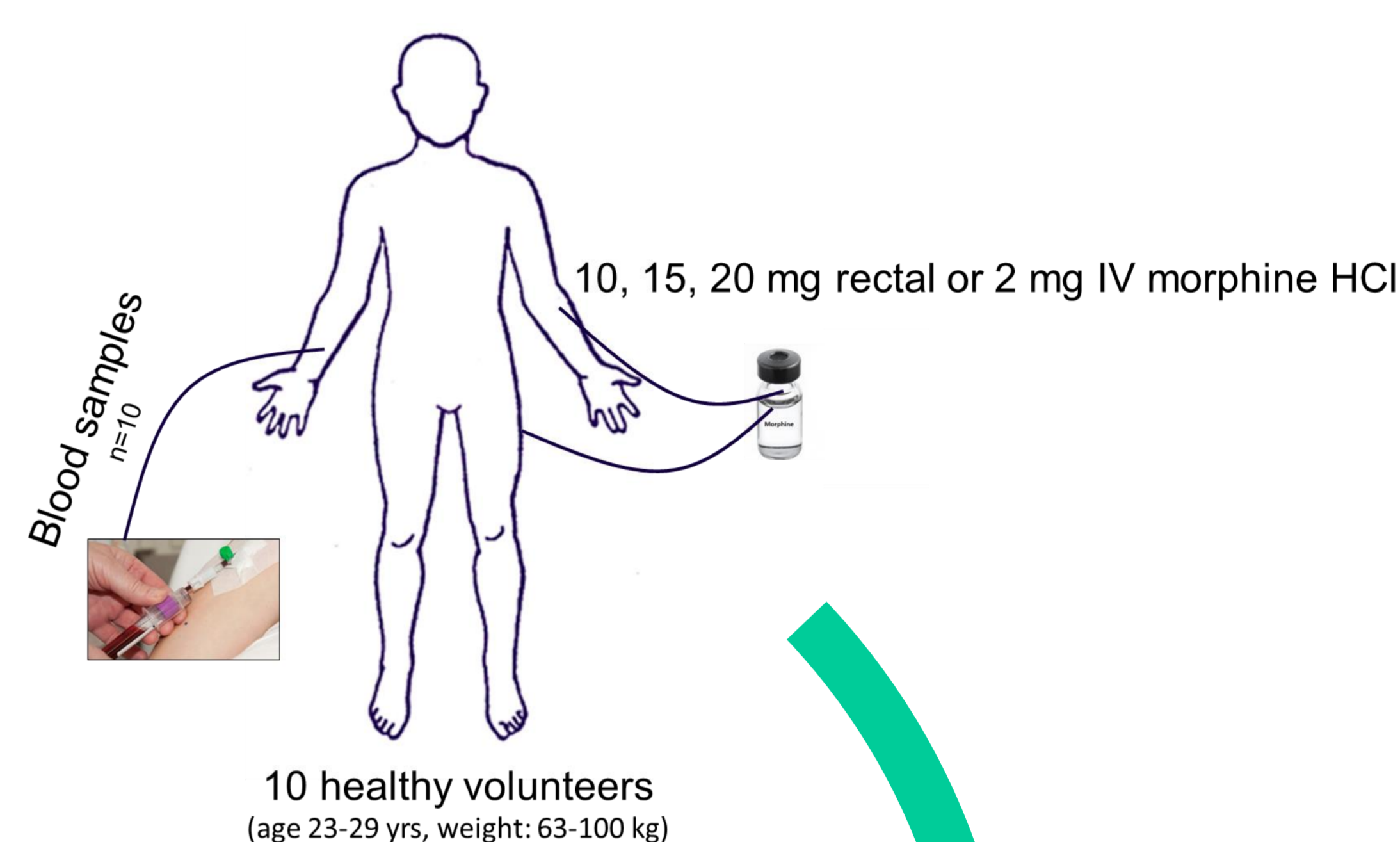
Model simulations



Conclusion

A non-linear mixed effect model was developed that adequately described morphine PK after IV and rectal administration, and the link to analgesia in healthy volunteers. A rectal morphine dose of 30 mg should provide target PK and PD response for a forthcoming study (assuming negligible placebo contribution).

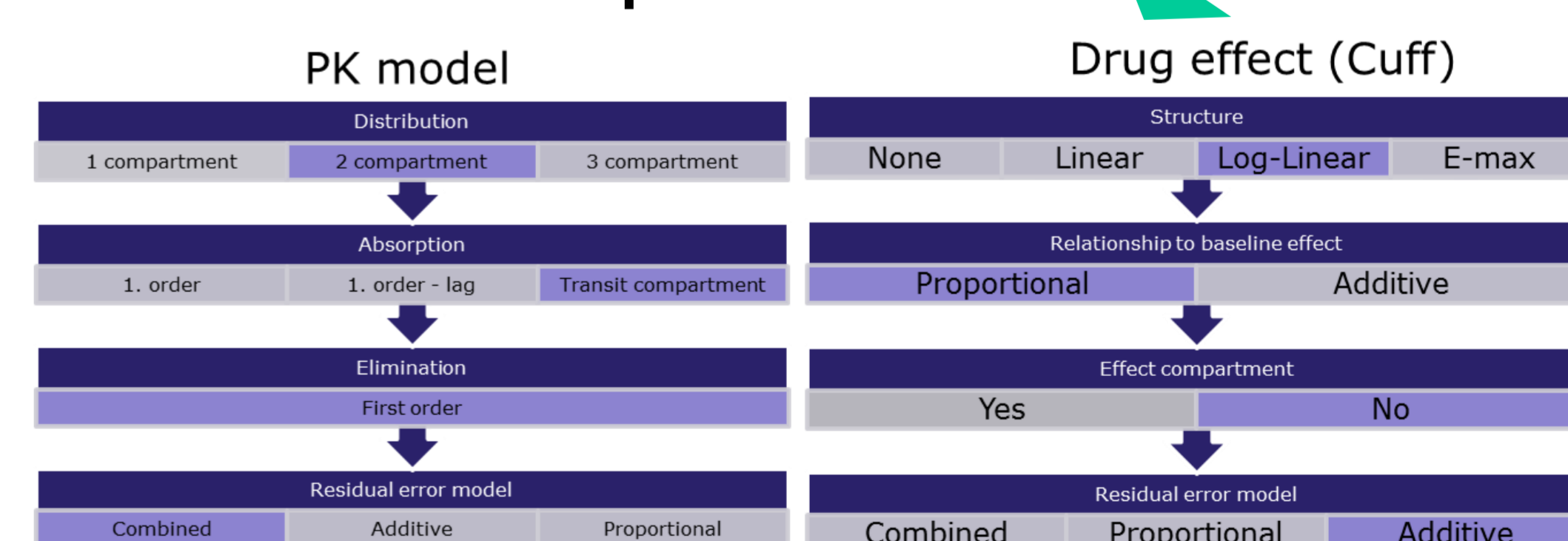
Study design



Experimental pain (Cuff pressure @ VAS= 7)



Base model development



Final model

