

I-104 Population PK/PD modeling of levobupivacaine and ropivacaine for motor block in spinal anesthesia

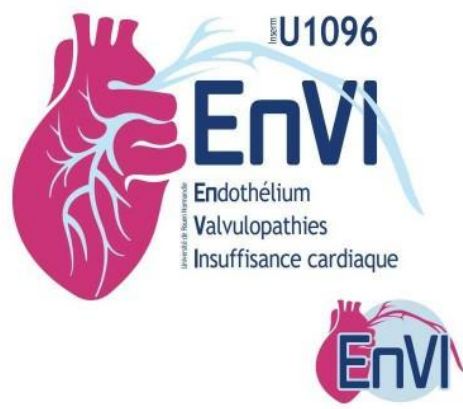
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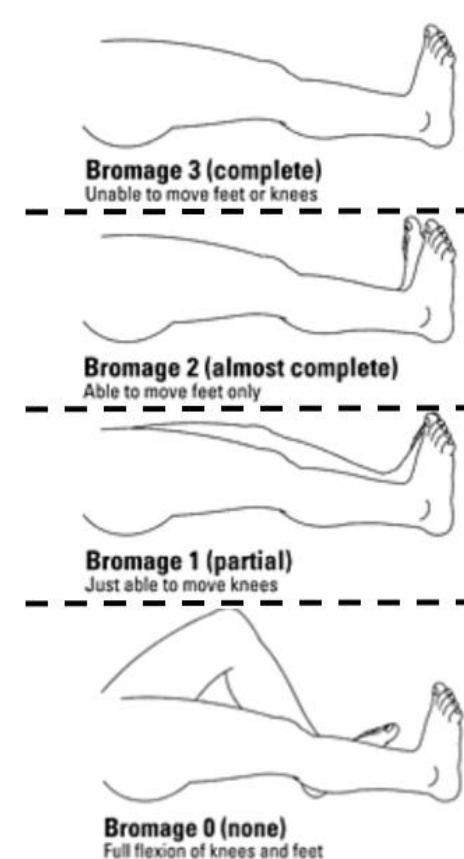
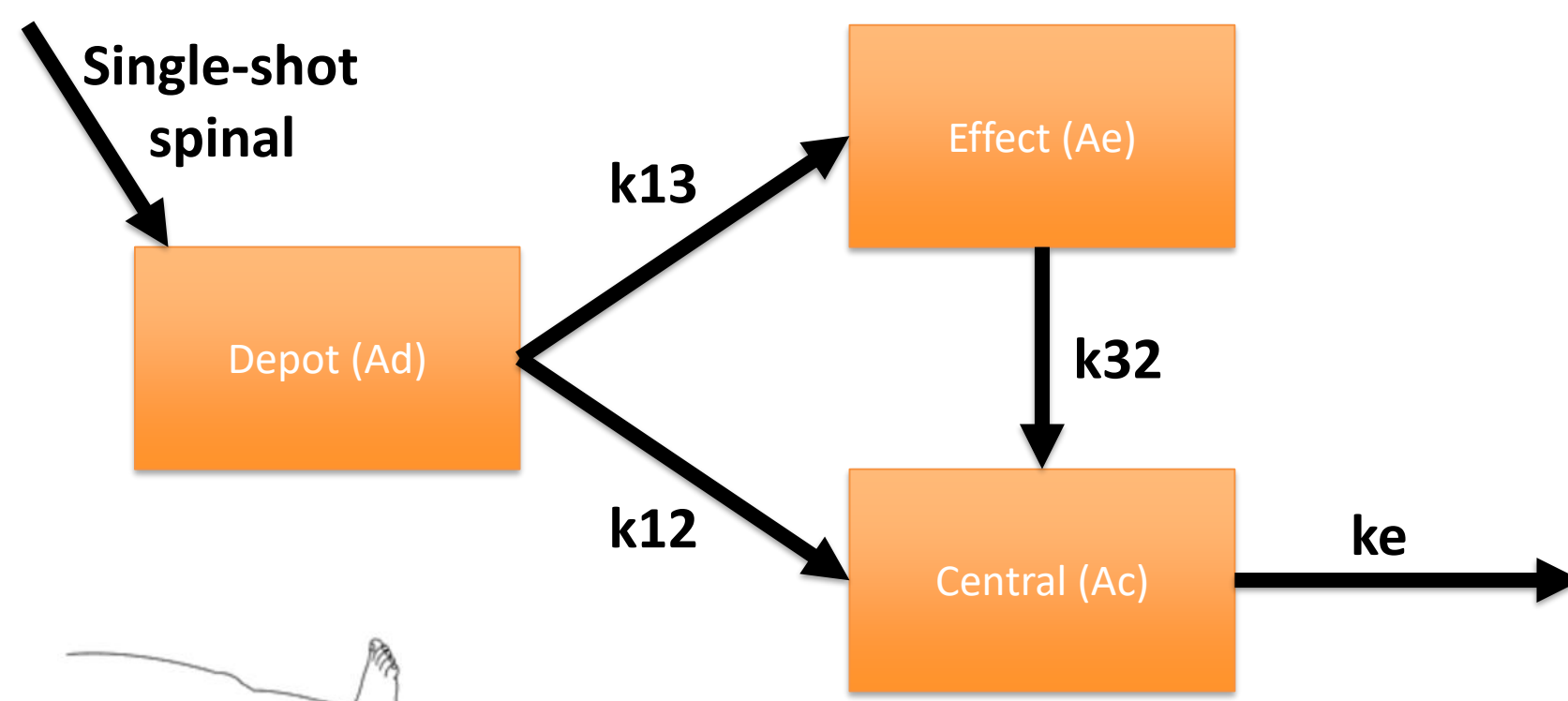


INTRODUCTION

- Clinical context:** Spinal anesthesia with long-acting local anesthetics remains the gold standard for lower abdominal and lower extremity surgery.
- Agents of interest:** To mitigate racemic bupivacaine's cardiotoxic risk, the S-enantiomer levobupivacaine and the structurally related ropivacaine are now preferred.
- Knowledge gap:** Although both drugs reliably produce motor block (graded by the Bromage scale 0–3), existing studies report only discrete PD milestones (e.g., time to Bromage 3), neglecting the full time-course and underlying PK contributions.
- Rationale for PK/PD modeling:** Integrating population pharmacokinetics with continuous pharmacodynamic profiling can elucidate how systemic exposure drives the onset, intensity, and recovery of motor block.
- Hypothesis:** When dosed for equipotent effect, levobupivacaine and ropivacaine will exhibit similar PD profiles for onset and duration.
- Study aim:** Fit a PK/PD model to observed data, verify dose equivalence between and benchmark against traditional motor block secondary endpoints

MATERIALS AND METHODS

- Study Design**
 - Open-label, prospective, monocenter, randomized trial
 - No pre-block vascular loading; standard cardio-respiratory monitoring
 - Intrathecal injection (N=60 patients)
 - Randomization to ropivacaine (15/20/25 mg) or levobupivacaine (10/12.5/15 mg)
- PK & PD Sampling**
 - PK: Blood draws at 0, 5, 15, 30, 60, 120, 240, 480, and 1 440 min post-dose
 - PD: Motor block scored via Bromage
 - Assessment frequency: q2.5 min (0–30 min), q5 min (30–60 min), q15 min (60–330 min)
- PK & PD Modeling**
 - MonolixSuite v2024R1[®]
 - Joint estimation of PK and PD parameters
 - PD: ordered categorical outcome via a cumulative logit link
 - Covariate assessment: age, BMI, sex, anesthetic type
 - Model Validation: RSE, GoF plots, residuals, BICc, bootstrap
 - Simulation: EBE at 1-minute resolution
- Secondary endpoints**
 - Area under the block curve (AUC)
 - Time to reach maximal block
 - Maximal block duration
 - Time to return to Bromage 0 or 1



$$\text{logit}(P(\text{block} \leq 2)) = \theta_1 + \theta_2 + \theta_3 - \beta\sqrt{Ae}$$

$$\text{logit}(P(\text{block} \leq 1)) = \theta_1 + \theta_2 - \beta\sqrt{Ae}$$

$$\text{logit}(P(\text{block} \leq 0)) = \theta_1 - \beta\sqrt{Ae}$$

RESULTS

- PK/PD Modeling**
 - Reliable results based on bootstrap.
 - Impact of BMI on ke, Age on k23 and treatment on β

Parameter	REFERENCE	MEAN	S.E.	R.S.E.(%)	P2.5	MEDIAN	P97.5	Bias(%)
Fixed Effects								
k12_pop	0.013	0.013	0.0016	12.47	0.0098	0.013	0.016	-3.03
v_pop	170.65	168.52	.11	6.53	149.01	168.36	190.74	-1.24
ke_pop	0.0025	0.0025	0.00015	6.06	0.0022	0.0025	0.0028	1.92
logTMC on ke	-1.26	-1.37	0.31	22.82	-2.01	-1.37	-0.77	9.12
k13_pop	0.022	0.02	0.0038	18.71	0.013	0.02	0.028	-6.5
k32_pop	0.015	0.016	0.0017	10.66	0.013	0.016	0.02	7.02
logAge on k32	-0.4	-0.42	0.16	37.23	-0.8	-0.4	-0.18	5.08
th1_pop	14.14	13.15	1.09	8.31	11.19	13.07	15.44	-6.98
th2_pop	3.95	3.85	0.45	11.71	3.03	3.82	4.79	-2.51
th3_pop	6.16	5.9	0.64	10.87	4.76	5.89	7.21	-4.18
β _pop	0.56	0.54	0.043	7.88	0.47	0.54	0.63	-3.34
Treatment (Ropivacaine) on β	-0.31	-0.29	0.067	23.16	-0.42	-0.29	-0.16	-7.02
Standard Deviation of the Random Effects								
omega_k12	0.74	0.72	0.12	17.24	0.47	0.72	0.97	-2.58
omega_v	0.41	0.4	0.052	12.97	0.31	0.4	0.51	-2.09
omega_k	0.35	0.34	0.047	13.76	0.24	0.34	0.42	-2.99
omega_k13	0.43	0.4	0.062	15.44	0.28	0.4	0.51	-7.47
omega_k32	0.33	0.31	0.088	28.15	0.18	0.29	0.52	-5.64
omega_th1	0.066	0.06	0.023	37.7	0.025	0.057	0.11	-9.37
omega_th2	0.68	0.65	0.084	12.97	0.49	0.64	0.82	-4.66
omega_th3	0.63	0.62	0.082	13.18	0.47	0.62	0.79	-1.92
omega_beta	0.084	0.066	0.029	43.78	0.023	0.062	0.13	-21.22
Error Model Parameters								
a1	1.14	1.2	0.24	20.31	0.79	1.17	1.73	5.84
b1	0.2	0.2	0.018	8.81	0.17	0.2	0.23	-0.38

Table 1: Model parameters

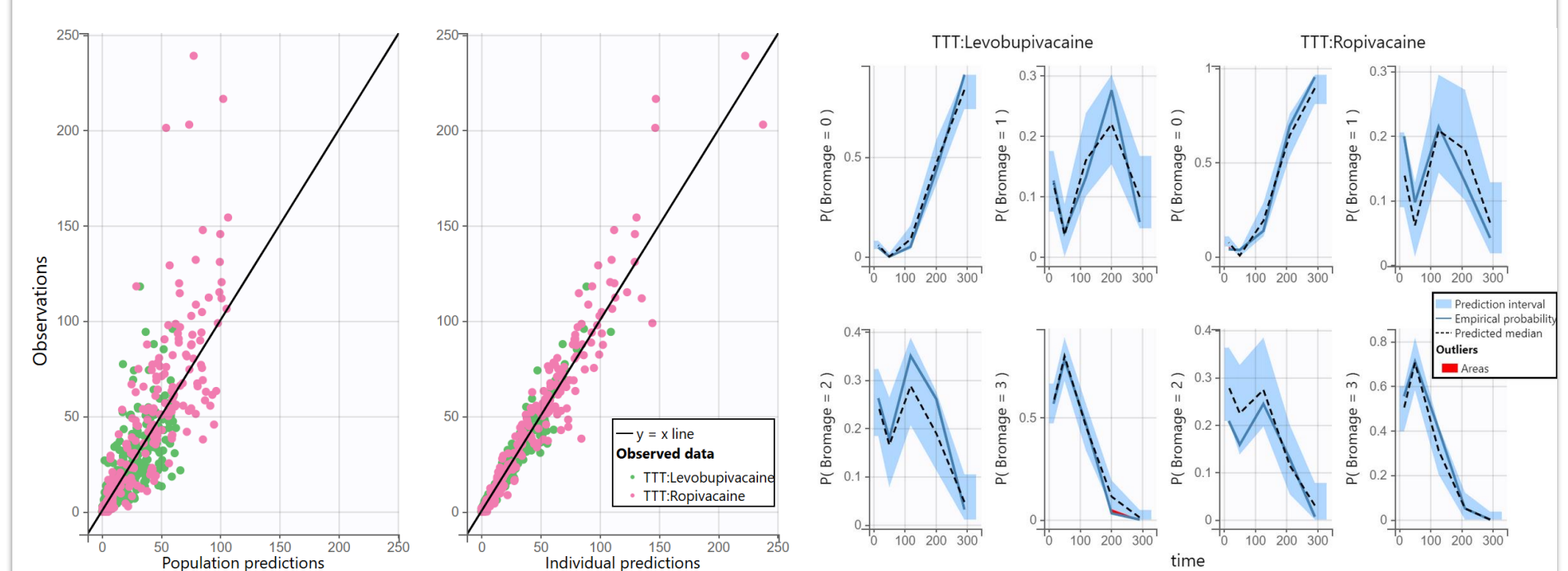


Figure 1: Observations vs. Predictions

Figure 2: PD Visual Predictive Check

- Dose equivalence for motor block is well supported**

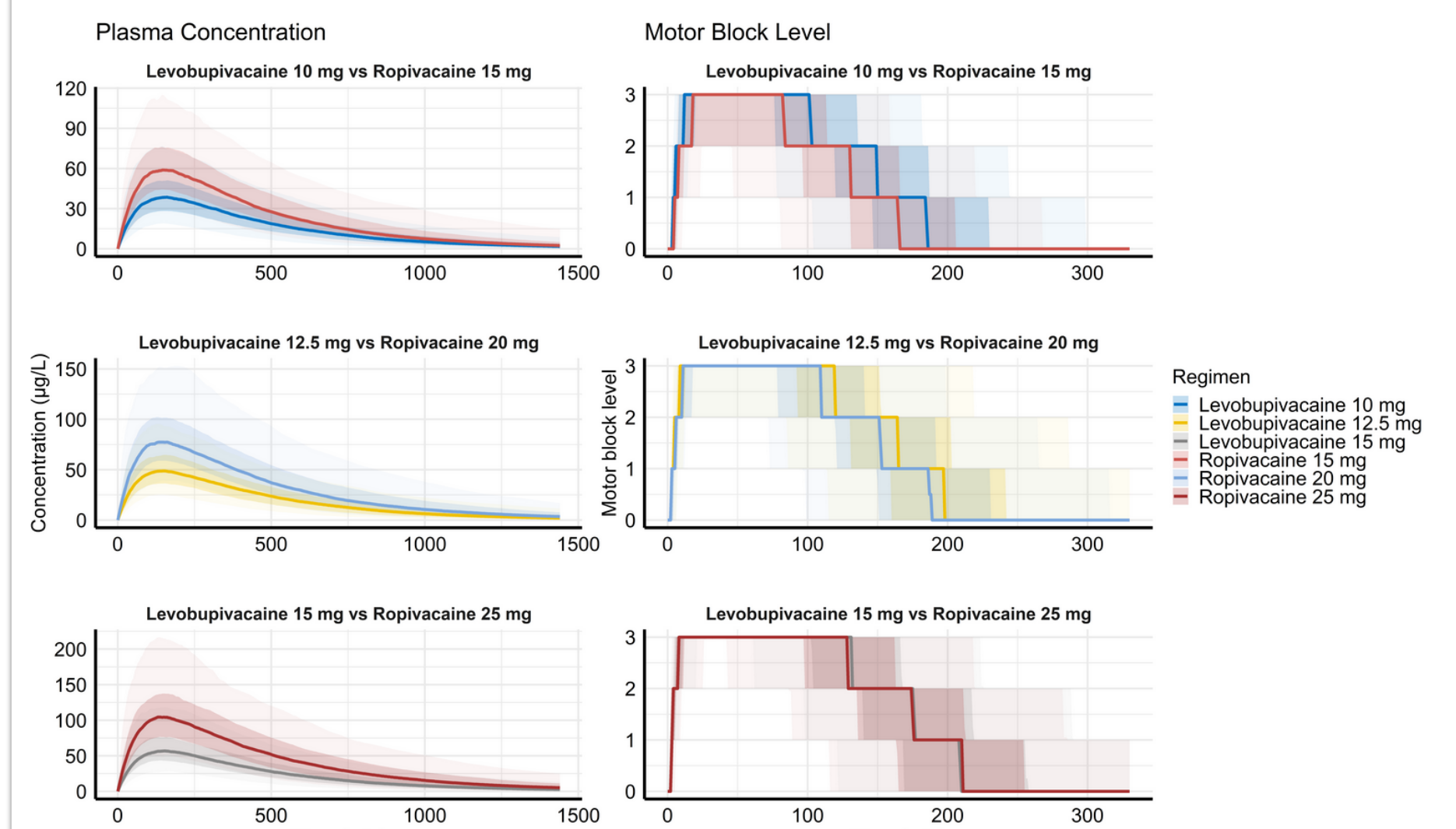


Figure 3: PK/PD of a typical individual with 25th-75th and 5th-95th percentiles

- Secondary endpoints**

- Effect of BMI, sex, age, treatment and dose**

Secondary Outcomes	Secondary Outcomes Mean \pm SD by Predictor Level											
	Standardized (Z-score) effect per group											
Block Exposure (block.min)	437 \pm 147	445 \pm 171	383 \pm 124	499 \pm 169***	299 \pm 156	396 \pm 149*	509 \pm 161***	351 \pm 139	506 \pm 105***	530 \pm 115***	459 \pm 169	432 \pm 154
Duration of Maximal block (min)	127 \pm 41	118 \pm 43	107 \pm 31	138 \pm 40***	110 \pm 68	125 \pm 33	135 \pm 46	105 \pm 39	119 \pm 23	136 \pm 38	132 \pm 53	118 \pm 35
Time to Return to Block = 0 (min)	207 \pm 46	197 \pm 57	180 \pm 40	225 \pm 53***	186 \pm 75	193 \pm 40*	211 \pm 50**	176 \pm 43	210 \pm 36**	242 \pm 36***	223 \pm 55	191 \pm 47**
Time to Return to Block = 1 (min)	157 \pm 69	156 \pm 60	133 \pm 49	179 \pm 70**	112 \pm 74	124 \pm 71*	177 \pm 55**	127 \pm 59	188 \pm 50**	189 \pm 42**	166 \pm 66	151 \pm 63
Time to Reach Block = 2 (min)	5.9 \pm 2.7	5.5 \pm 2.9	6.0 \pm 3.1	5.3 \pm 2.4*	6.9 \pm 1.6	6.1 \pm 2.0	4.7 \pm 2.0	7.7 \pm 4.4	4.3 \pm 1.6	6.0 \pm 2.9	6.6 \pm 3.7	5.2 \pm 2.0
Time to Reach Block = 3 (min)	9.6 \pm 3.6	8.5 \pm 2.7*	9.0 \pm 3.4	9.1 \pm 3.0	12.3 \pm 1.5	8.6 \pm 2.5*	7.2 \pm 1.0**	10.8 \pm 4.1	8.4 \pm 1.9*	9.8 \pm 4.6	9.5 \pm 3.3	8.8 \pm 3.2
Duration of Block > 0 (min)	207 \pm 51	194 \pm 58	176 \pm 40	225 \pm 56***	161 \pm 75	190 \pm 41*	209 \pm 50**	172 \pm 42	218 \pm 50**	238 \pm 36***	219 \pm 55	191 \pm 52**
Duration of Block > 1 (min)	151 \pm 70	150 \pm 61	127 \pm 50	174 \pm 72**	105 \pm 74	118 \pm 72	172 \pm 55**	119 \pm 60	184 \pm 51**	183 \pm 43**	161 \pm 68	145 \pm 64
Duration of Block > 2 (min)	79.6 \pm 67.0	101 \pm 62	79.6 \pm 52.4	101 \pm 66*	31.2 \pm 46.0	87.8 \pm 53.3**	127 \pm 61***	60.1 \pm 56.0	105 \pm 38**	109 \pm 62**	78.9 \pm 69.6	95.8 \pm 54.6
	Low BMI	High BMI	Younger	Older	Ropi Low Dose	Ropi Middle Dose	Ropi High Dose	Levo Low Dose	Levo Middle Dose	Levo High Dose	Female	Male

Figure 4: Heatmap of secondary outcomes by predictor

DISCUSSION / CONCLUSION

- Robust parameter estimates supporting the stability of the joint PK/PD model**
- Excellent predictive performance**
- Adequate PD model validation**
- BMI, sex and age exert moderate but consistent effects on secondary outcomes**
- Together, these results support tailoring spinal anesthetic dose to individual patient characteristics to balance block efficacy against recovery time.**