



Model-based dosage optimization of sirolimus for vascular anomalies on pediatrics.

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INTRODUCTION & PURPOSE

- Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, has emerged as a promising therapeutic agent for refractory vascular anomalies.[1] Sirolimus has currently been used off-label for pediatric patients with vascular anomalies.
- The Pharmaceuticals and Medical Devices Agency (PMDA) has approved a dosing regimen for these patients. According to the label, the starting dose of sirolimus is 2 mg once daily for patients with a body surface area (BSA) of 1.0 m² or more, and 1 mg once daily for those with a BSA of less than 1.0 m². Thereafter, the dosage is adjusted according to the blood trough concentration and the patient's condition but should not exceed 4 mg once a day. However, when the dosing regimen is based on BSA, pediatric patients up to 8 years of age are required to take 1 mg, which may result in high drug exposure in younger patients
- This study aims to provide safe usage information for sirolimus in pediatric patients with vascular malformations using population pharmacokinetic model.

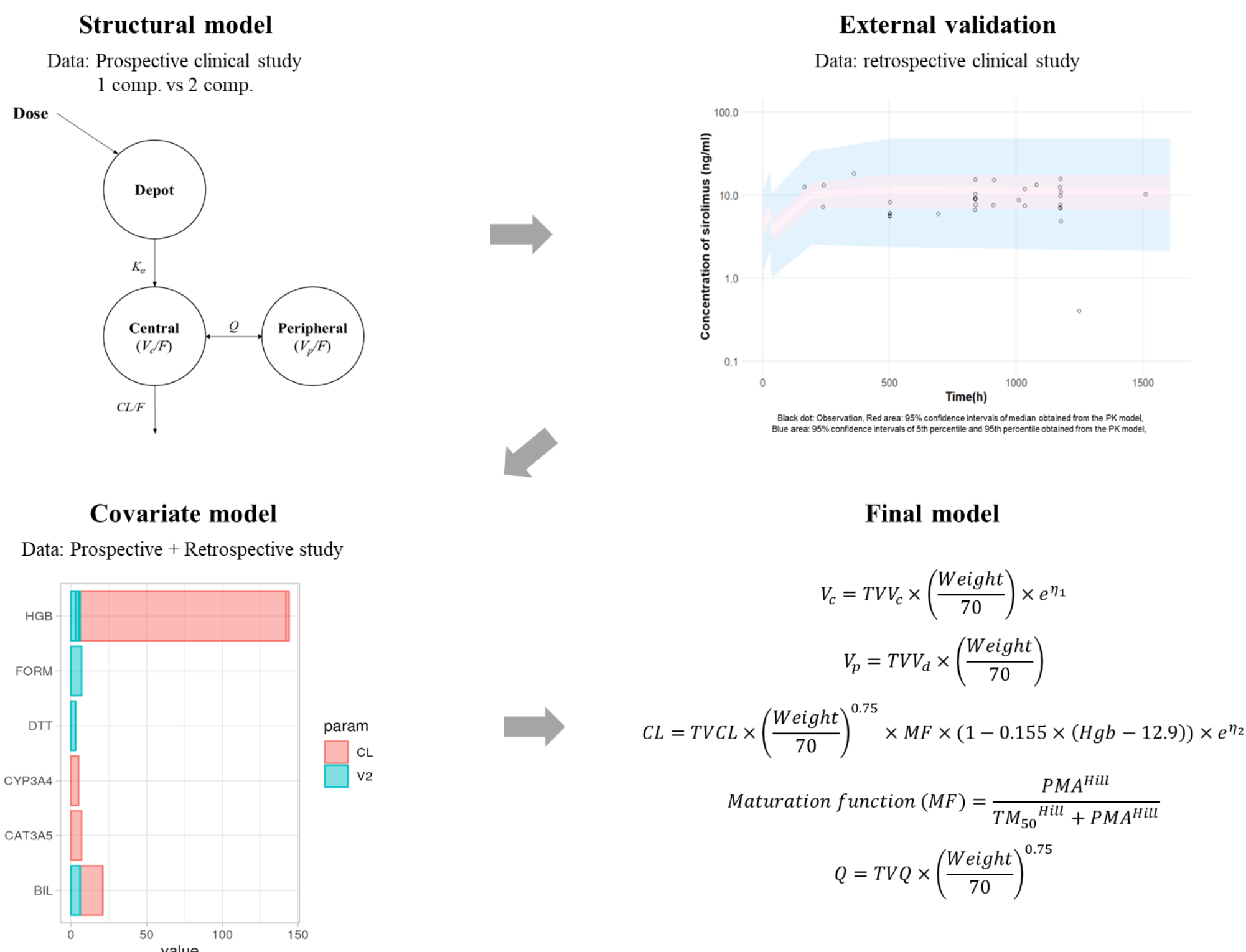
METHOD

- Systematic review of sirolimus population pharmacokinetic modeling**
 - Literature Database: Google scholar
 - Keyword: "sirolimus" OR "rapamune" AND "vascular anomalies" OR "vascular malformation" OR "vascular tumor" AND "population pharmacokinetics" AND "pediatrics“
 - Four studies were included in the systematic review following PRISMA guidelines. Their population modeling results were used to inform key model parameters as prior information.

Reference	Subject	Comp.	Model parameter
Tomoyuki Mizuno et al. (2017)	Pediatric patients with vascular anomalies (n=52, age 0.1 – 18.6 yr)	1 comp	$Cl_{pediatrics} = Cl_{adult} * \left(\frac{WT}{70}\right)^{Power} * \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}}$ $V_{pediatrics} = V_{adult} * \left(\frac{WT}{70}\right)$
Dongdong Wang et al. (2019)	Kaposiform hemangioendothelioma pediatric patients (n=17, Age 0.2 – 6 yr)	1 comp	$CL/F = \theta CL/F \times EXP(\theta AGE \times age) \times EXP(\theta ALT \times ALT) \times EXP(\theta SEX \times sex)$ $V/F = \theta V/F \times EXP(\theta DTT \times (DTT/10))$.
Taichi Miyazaki et al. (2024)	Patients with VAs, LAM, and focal cortical dysplasia (FCD) (n=215, Age 0.083 – 71.6 yr)	2comp.	$F = 1 \times 1.26 (if Granule) or 0.730 (if Solution)$ $Ka = 0.441 L/h \times 3.40 (if Granule)$ $CL/F = 14.2 L/h \times \left(\frac{TVWT}{70}\right)^{0.75} \times \frac{PMA^{2.94}}{62.9^{2.94} + PMA^{2.94}} \times (1.72 if CYP3A4 inhibitor) \times (0.930 if frozen sample) \times \left(\frac{Hgb}{133}\right)^{-1.02}$ $V/F = 191 L \times \left(\frac{TVWT}{70}\right)^{0.75}, Vp/F = 626 L \times \left(\frac{TVWT}{70}\right)^1, Q/F = 37.5 L/h \times \left(\frac{TVWT}{70}\right)^{0.75}$
Xiao Chen et al. (2020)	Paediatric kaposiform haemangioendothelioma patients (n=14, Age 1.53 ± 1.40 yr)	1comp	$Cl_{p/F} = 7.55 \times \left(\frac{WT}{70}\right)^{0.75} \times (1 - (-0.999) \times CYP3A5)$ $V_{p/F} = 1840 \times \left(\frac{WT}{70}\right)$

- Dataset: Retrospective and prospective clinical study**
 - Patient: vascular anomalies pediatric patients (n=28)
 - Inclusion criteria
 - Patients diagnosed with a vascular anomaly (vascular tumors or malformations) with at least one associated complication (coagulopathy, chronic pain, recurrent cellulitis, ulceration, visceral and/or bone involvement, organ dysfunction, or severe deformity).
 - Vascular tumors that failed to respond to or relapsed after treatment with one or more of the following: steroids, interferon-α, chemotherapeutic agents, propranolol, or surgical/localized treatments.
 - Vascular malformations that were difficult to treat surgically or locally, failed treatment, or relapsed after such interventions.
 - PK sampling point
 - Retrospective study: Trough samples collected on Day 3, Day 7, and 1 month
 - Prospective study: Post-dose 1 h (syrup) / 2 h (tablet), 4 h, and 12 h (predose) on Day 1 and Day 2; Pre-dose and post-dose 1 h (syrup) / 2 h (tablet) on the first outpatient visit.

Pharmacokinetic model development



- Simulation**
 - Scenario: 0.01 ~ 0.1 mg/kg, q.d., multiple dose during 1 month
 - Population:
 - Weight and Age: Participants were stratified into groups based on weight and postmenstrual age (PMA), using the 2017 Pediatric Growth Chart Handbook by the Korea Disease Control and Prevention Agency (n=100 per group)

WT 5~10kg, PMA 40~66 wks	WT 5~10kg, PMA 66~92 wks	WT 5~10kg, PMA 92~118 wks	WT 10~20kg, PMA 118~144 wks
WT 10~20kg, PMA>144 wks	WT 20~30kg, PMA>144 wks	WT 30~40kg, PMA>144 wks	WT 40~50kg, PMA>144 wks
WT 50~60kg, PMA>144 wks	WT 50~60kg, PMA>144 wks	WT 70~80kg, PMA>144 wks	WT 80~90kg, PMA>144 wks

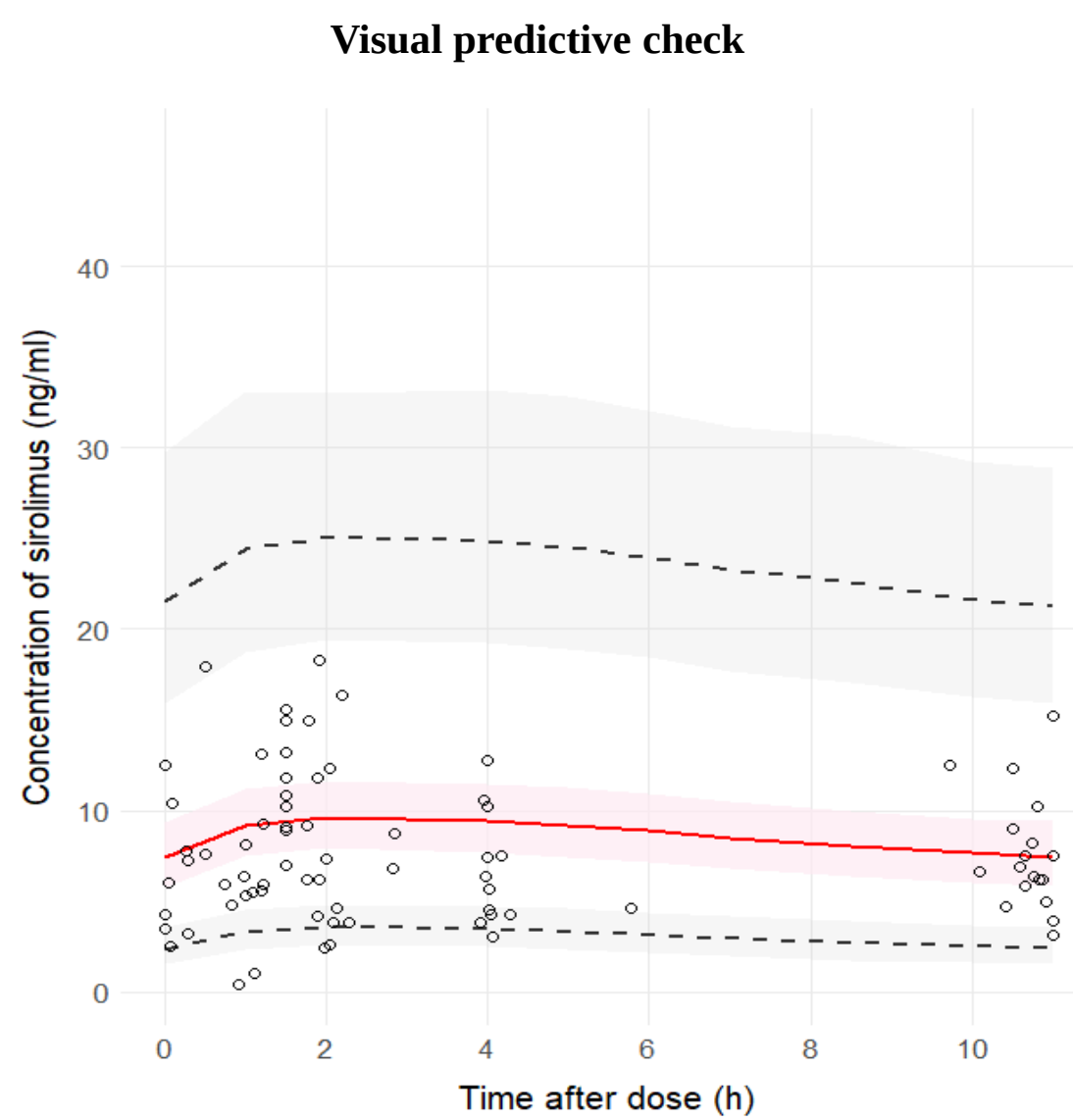
 - Hemoglobin (Hgb) : 10 ~ 11, 11 ~ 12, 12 ~ 13, 13 ~ 14, 14 ~ 15 g/dL
 - Optimal dose regimen for patients: Maintain concentration of sirolimus within 5 ~ 15 ng/mL

RESULT

Population pharmacokinetic model of sirolimus for vascular anomalies on pediatrics

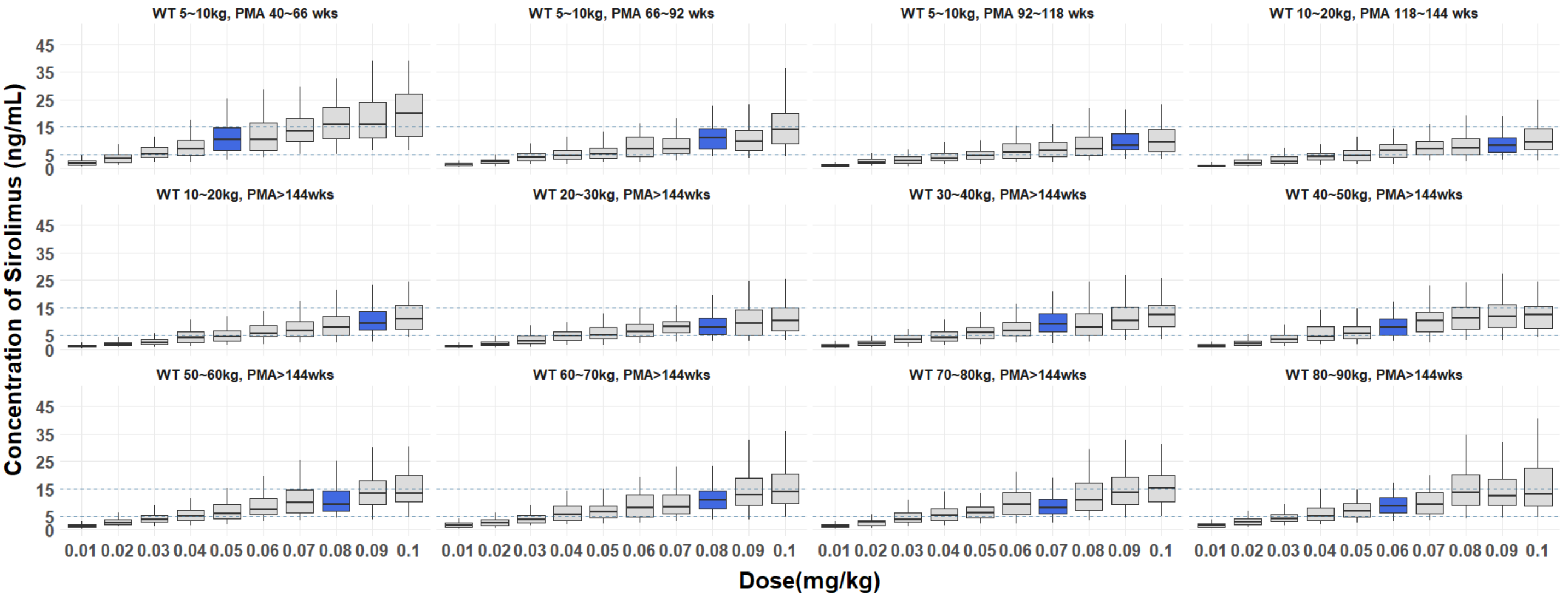
- Final model: Parameter estimates and Visual predictive check

Final model			Bootstrap	
Parameter estimate	Value	RSE(%)	Median	95%CI (2.5% CI ~ 97.5 CI)
K _a	0.149	74	0.150	0.071 ~ 0.674
V _c	79.4	115	85.2	7.0 ~ 367.6
V _p	937	45	885.6	410.2 ~ 2038
CL	13.7	12	13.9	9.9 ~ 17.9
Q	21.9	59	22.2	10.0 ~ 45.8
TM50	62.9 FIX	-	62.9 FIX	-
Hill	2.94 FIX	-	2.94 FIX	-
COVHGB	- 0.155	23	- 0.162	- 0.278 ~ -0.063
Error				
IIV_V	0.31	113	0.27	0.02 ~ 1.04
IIV_CL	1.58	89	1.60	0.13 ~ 27.61
RV (proportional)	0.11	13	0.10	0.07 ~ 0.14



Simulation

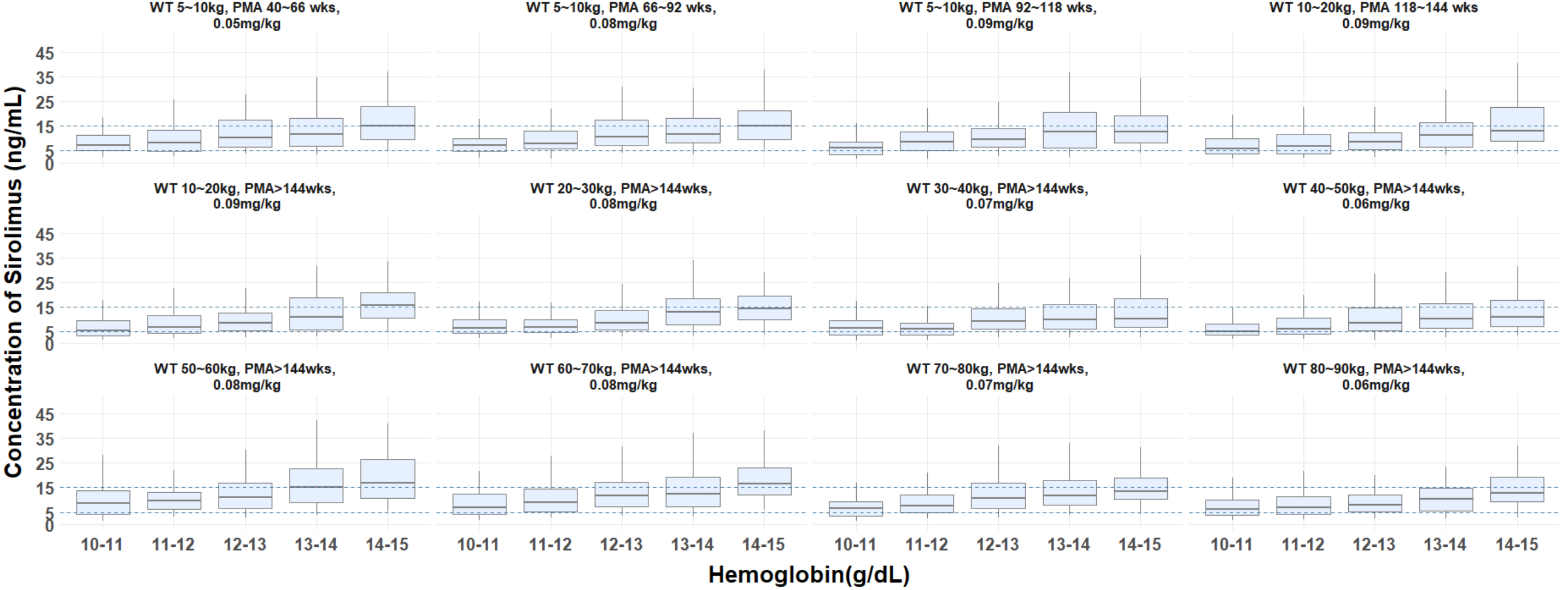
- Target Attainment by Dose Across Groups at Steady State



- Percentile of target range attainment across different doses

	0.09	0.08	0.07	0.06	0.05							
DOSE (mg/kg)	51.1	67.8	70	73.3	68.9	53.3	62.2	57.8	57.8	54.4	48.9	61.1
	47.8	72.2	55.6	64.4	64.4	74.4	57.8	62.2	72.2	73.3	48.9	47.8
	58.9	63.3	62.2	66.7	62.2	73.3	72.2	62.2	63.3	62.2	78.9	65.6
	57.8	55.6	58.9	61.1	58.9	63.3	58.9	70	78.9	53.3	62.2	77.8
	70	51.1	43.3	50	45.6	53.3	63.3	51.1	63.3	66.7	61.1	62.2
	WT 5~10kg, PMA 40~66 wks	WT 5~10kg, PMA 66~92 wks	WT 5~10kg, PMA 92~118wks	WT 10~20kg, PMA 118~144wks	WT 10~20kg, PMA>144wks	WT 20~30kg, PMA>144wks	WT 30~40kg, PMA>144wks	WT 40~50kg, PMA>144wks	WT 50~60kg, PMA>144wks	WT 60~70kg, PMA>144wks	WT 70~80kg, PMA>144wks	WT 80~90kg, PMA>144wks

- Hemoglobin-Level Stratified Target Attainment at Steady State (Best Dose Only)



CONCLUSION&DISCUSSION

- In this study, a robust and reliable pharmacokinetic model of sirolimus was developed for the pediatric patients with vascular anomalies. Optimal dosing regimens should be suggested based on individual growth of pediatrics and hemoglobin levels.

REFERENCE

[1] Triana P, Dore M, Cerezo VN, et al. Sirolimus in the Treatment of Vascular Anomalies. Eur J Pediatr Surg. 2017;27(1):86-90. doi:10.1055/s-0036-1593383

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