

SUPPLEMENTARY DATA

Title: Avelumab Dose Selection for Clinical Studies in Pediatric Patients With Solid Tumors

Journal: *Clinical Pharmacokinetics*

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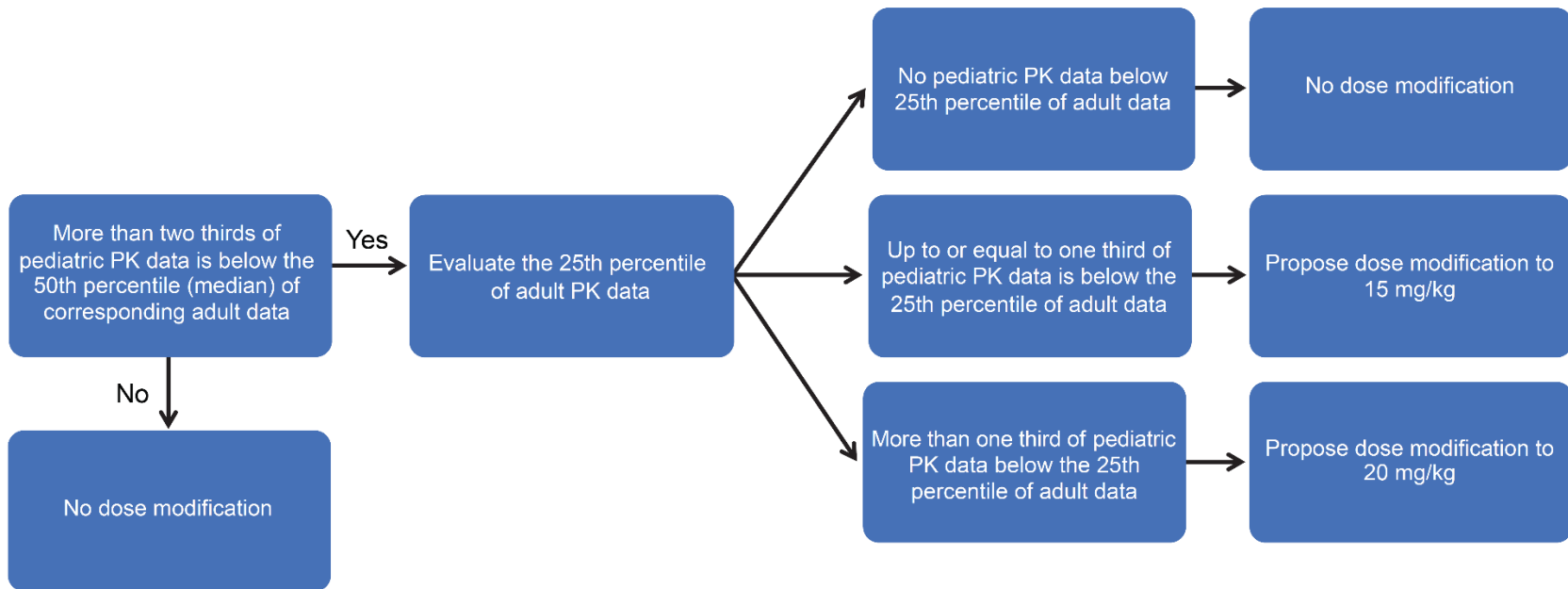
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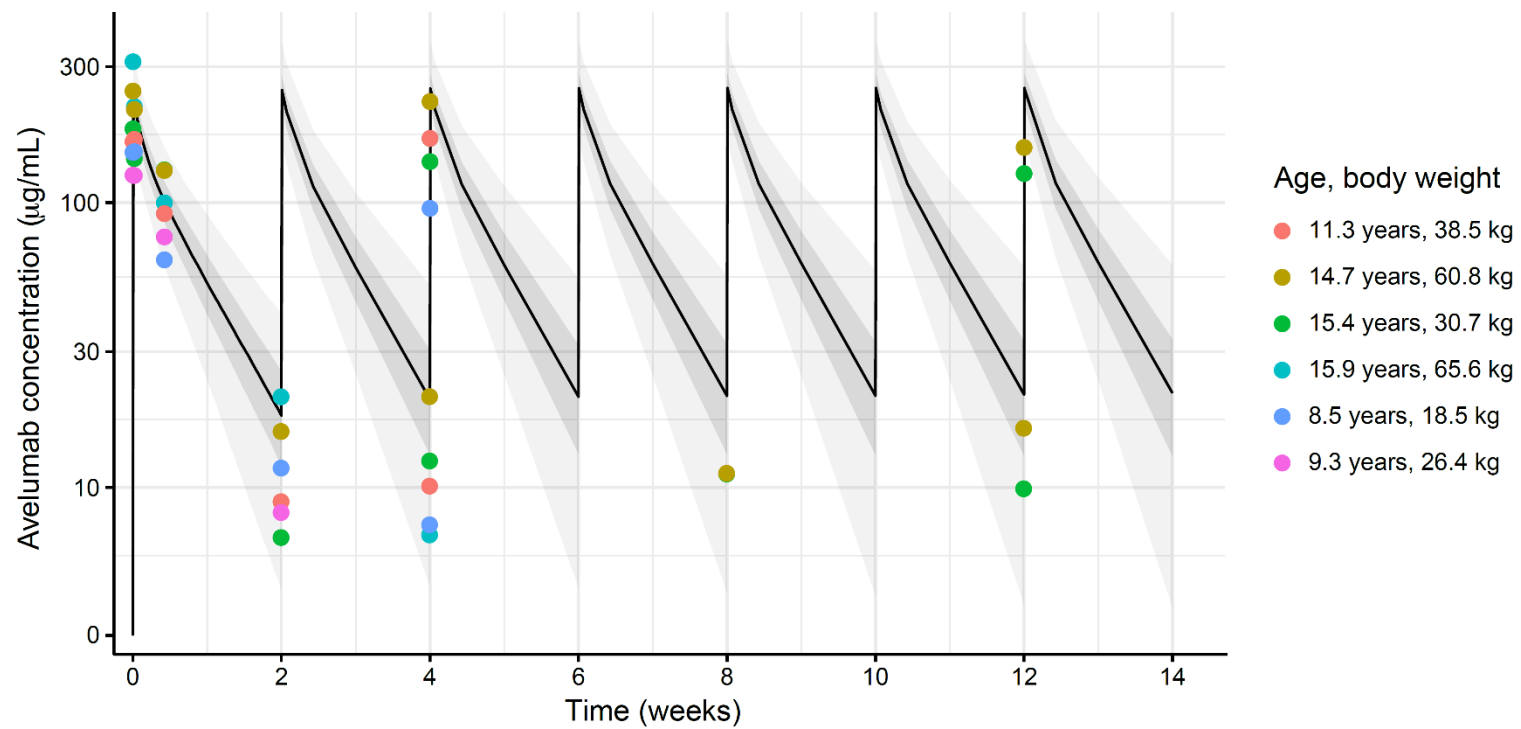
akash.khandelwal@merckgroup.com

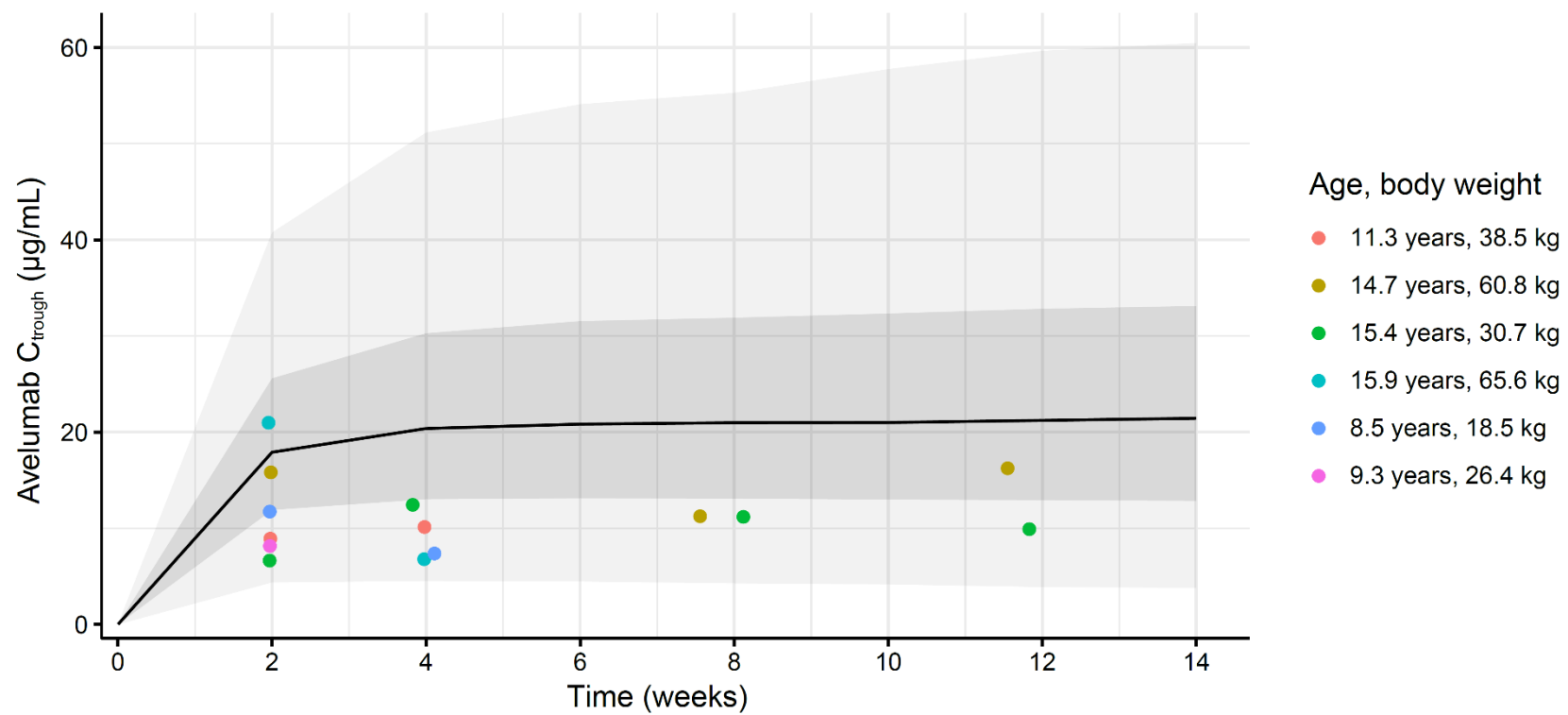
Supplementary Figure 1. Predefined criteria decision chart for real-time dose escalation in phase 1 of this trial. *PK* pharmacokinetic.



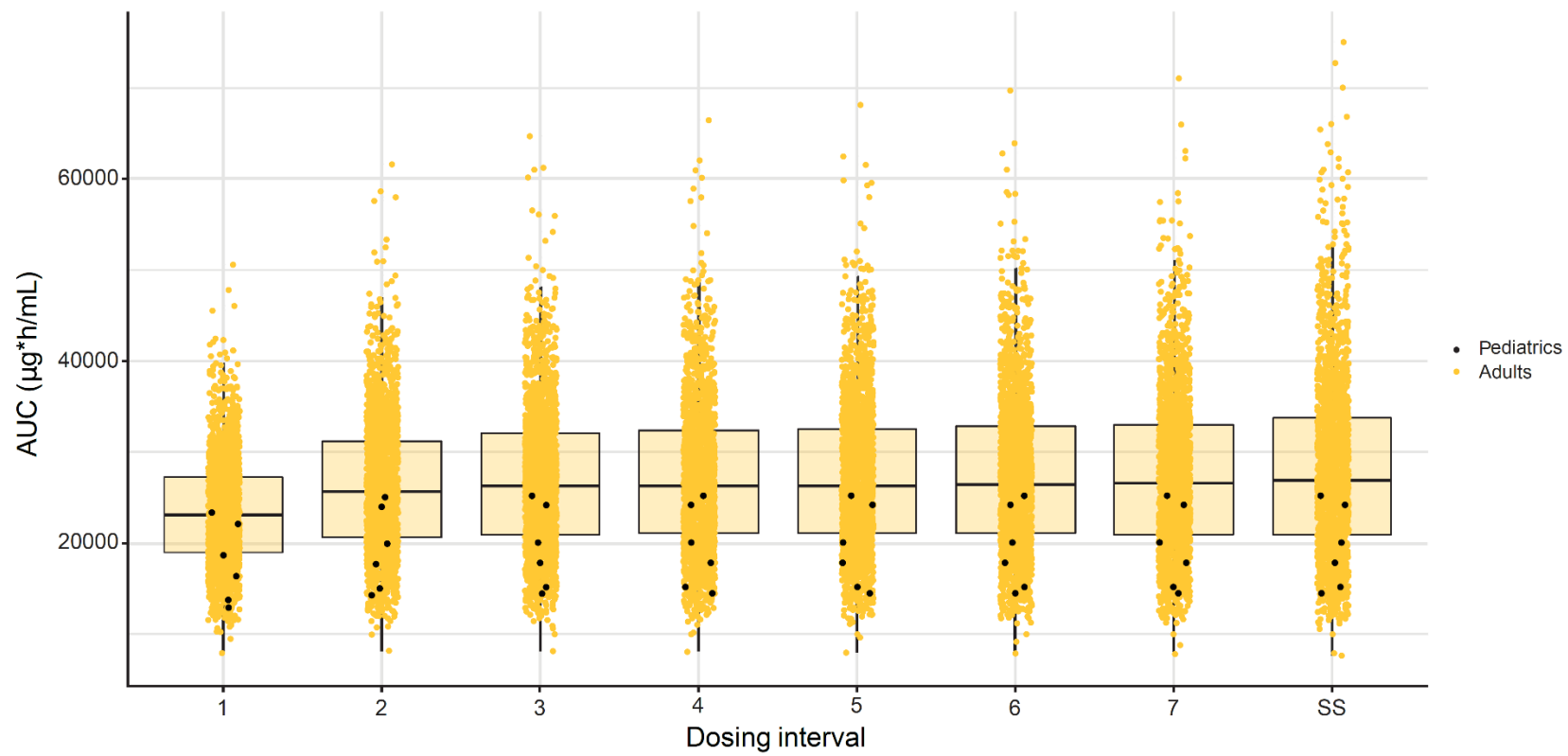
Supplementary Figure 2. Analysis of pediatric PK data from patients who received the 10 mg/kg dose compared with PK data from adults for real-time dose-escalation decisions. (A) Avelumab concentration over time. (B) C_{trough} . (C) AUC. For (A) and (B), points are individual observations, colored by patient; lines represent medians, dark gray shaded areas show 25th and 75th percentiles, and light gray shaded areas show 2.5th and 97.5th percentiles of the adult population. For (C), boxes represent interquartile range; horizontal lines are medians; whiskers extend to the most extreme point, which is no more than 1.5 times the length of the box away from the box; and points are observations that are outside 1.5 times the length of the box away from the box. *AUC* area under the concentration-time curve, *C_{trough}* trough concentration, *PK* pharmacokinetic.

A

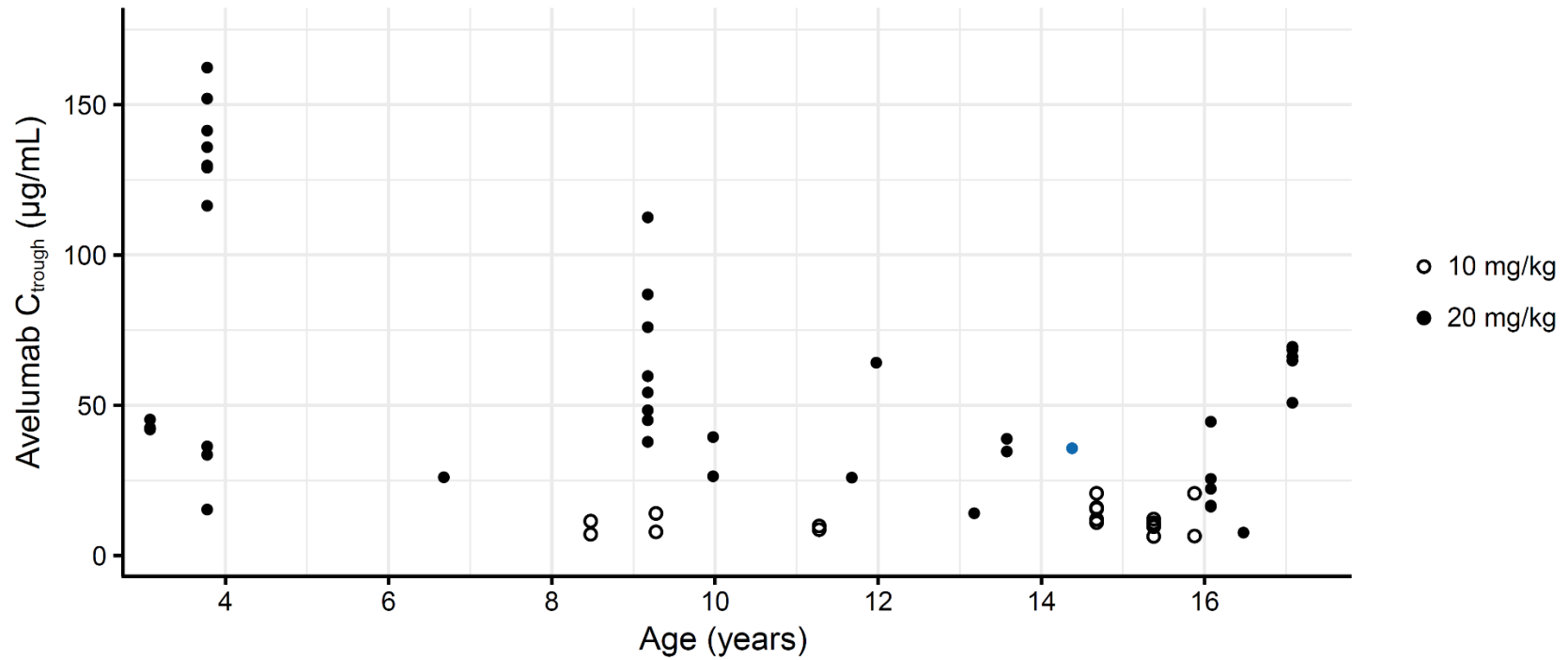


B

C

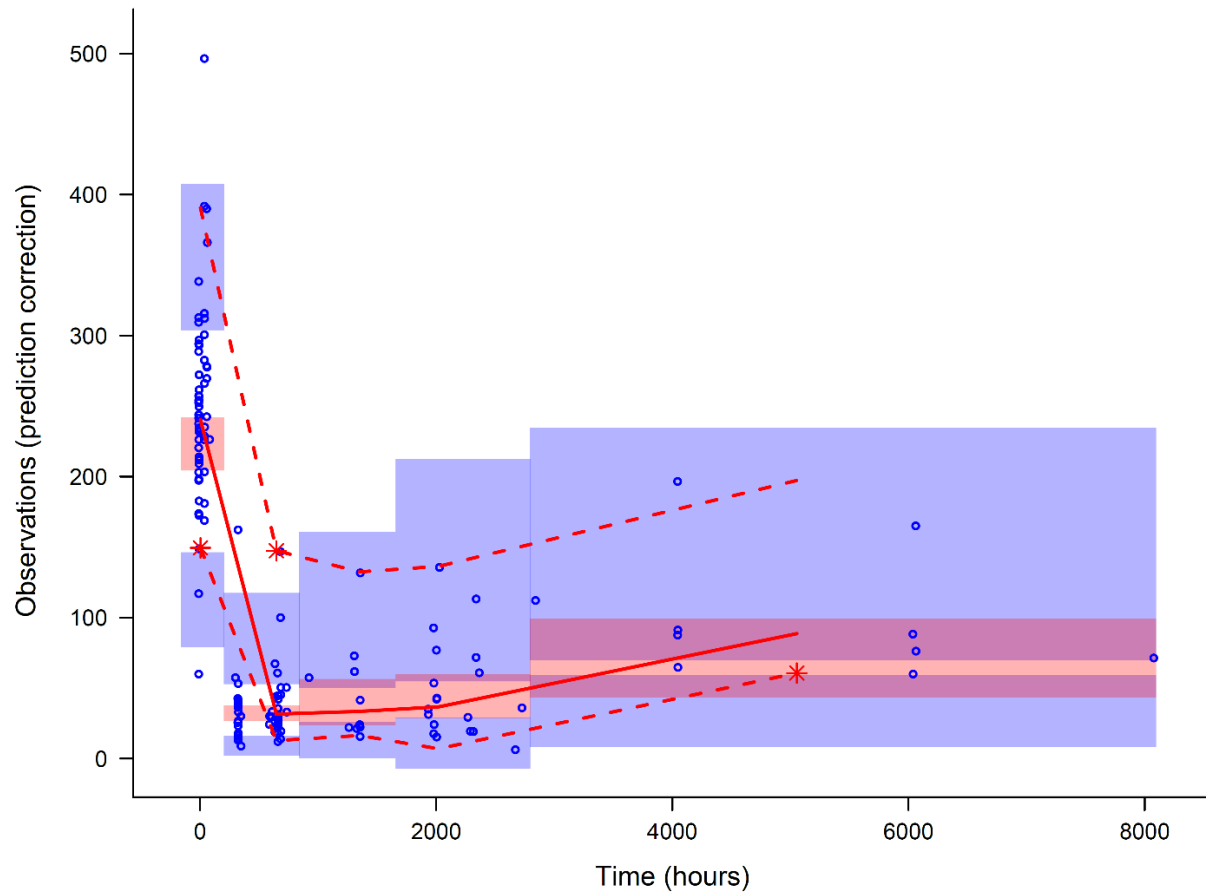


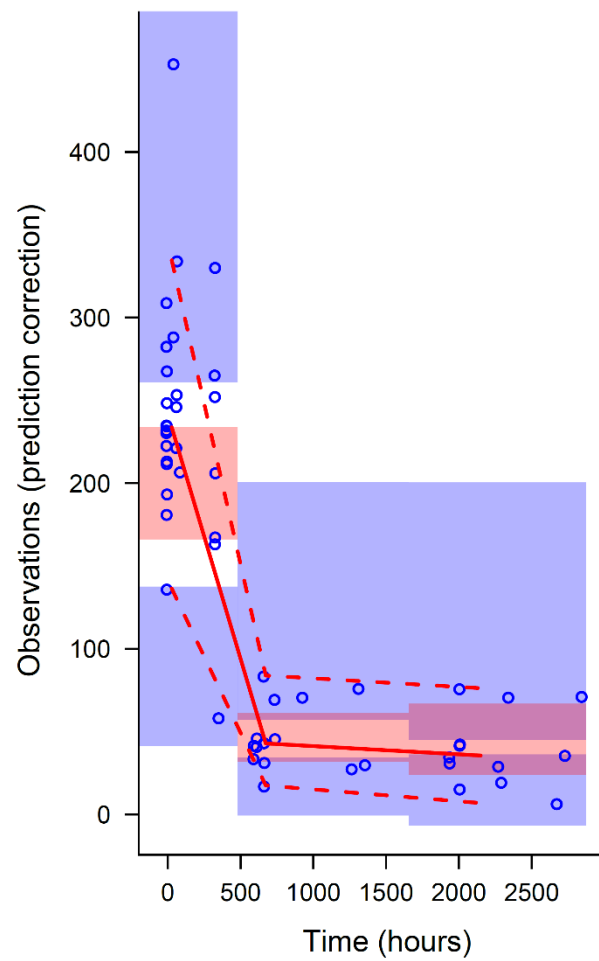
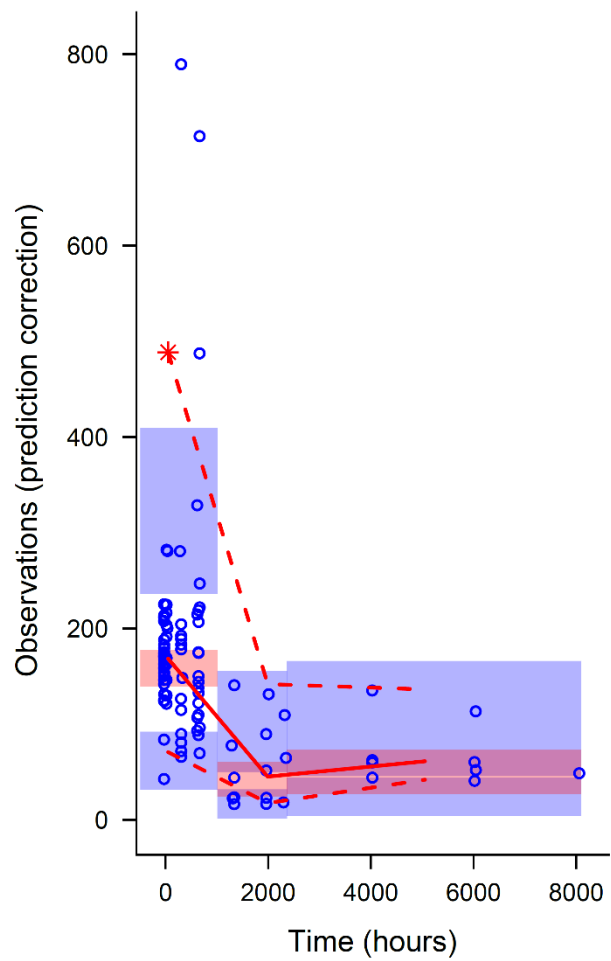
Supplementary Figure 3. Distribution of observed C_{trough} by age. The blue dot represents the patient who had a dose-limiting toxicity. C_{trough} trough concentration.



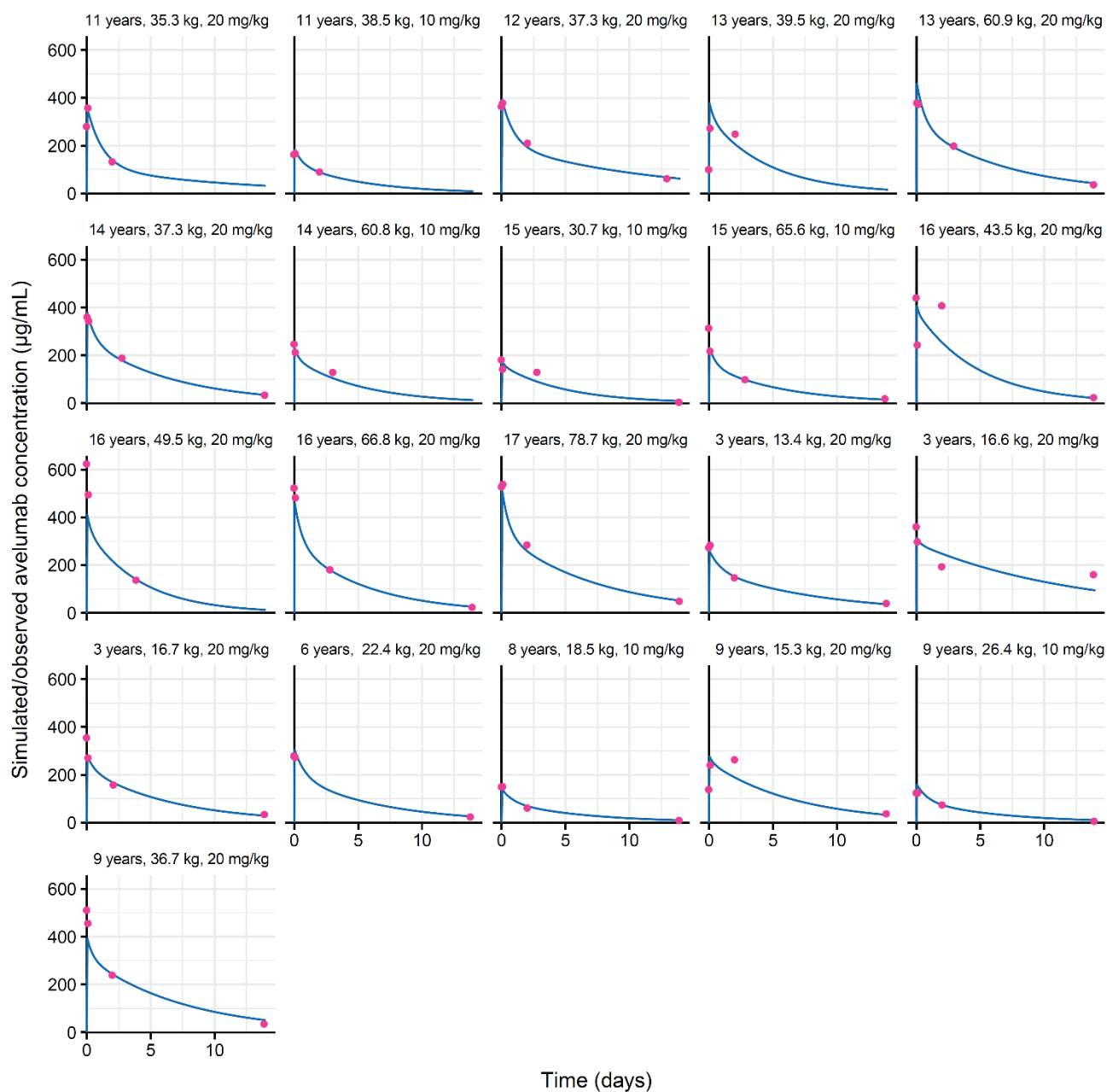
Supplementary Figure 4. Visual predictive checks for the final pediatric population pharmacokinetic model in (A) all patients and (B) in patients weighing <40 kg (left panel) and ≥ 40 kg (right panel). Points are observations, solid lines represent medians of actual data, dashed lines are the 2.5th and 97.5th percentiles of actual data, shaded areas represent the 95% CIs of the median and 2.5th and 97.5th percentiles of the simulated data, and stars show outlying percentiles.

A



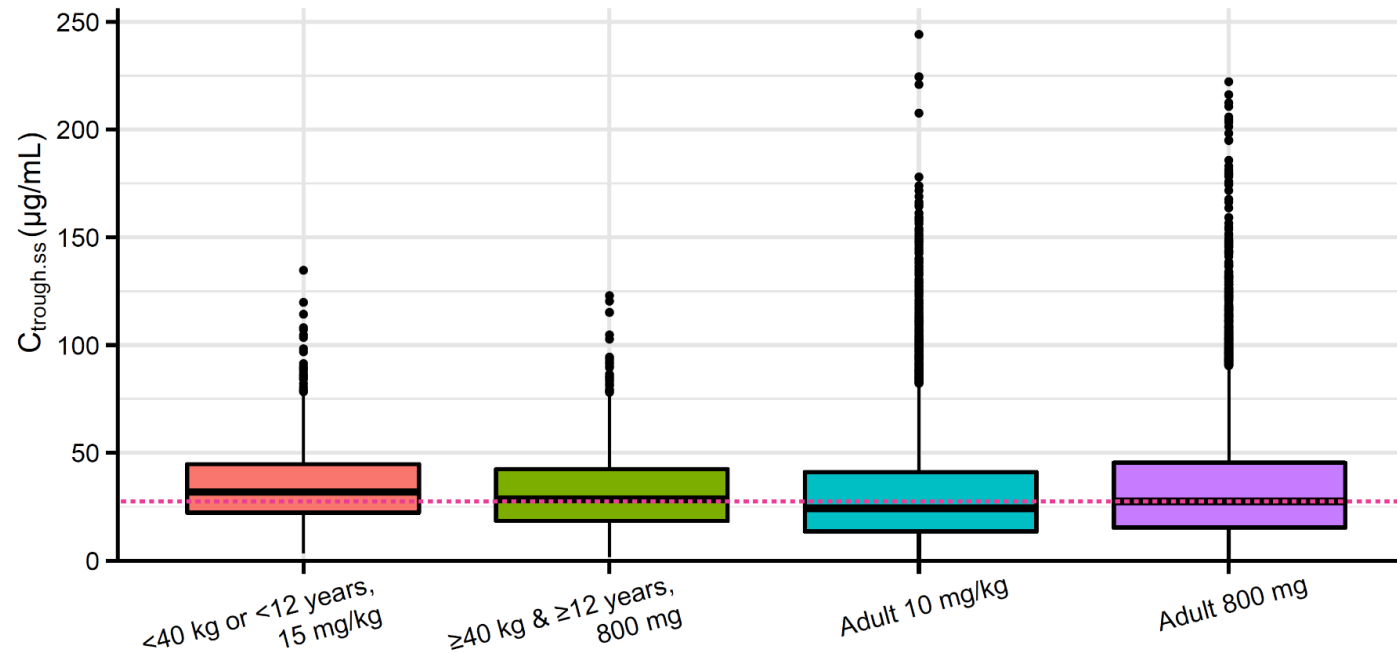
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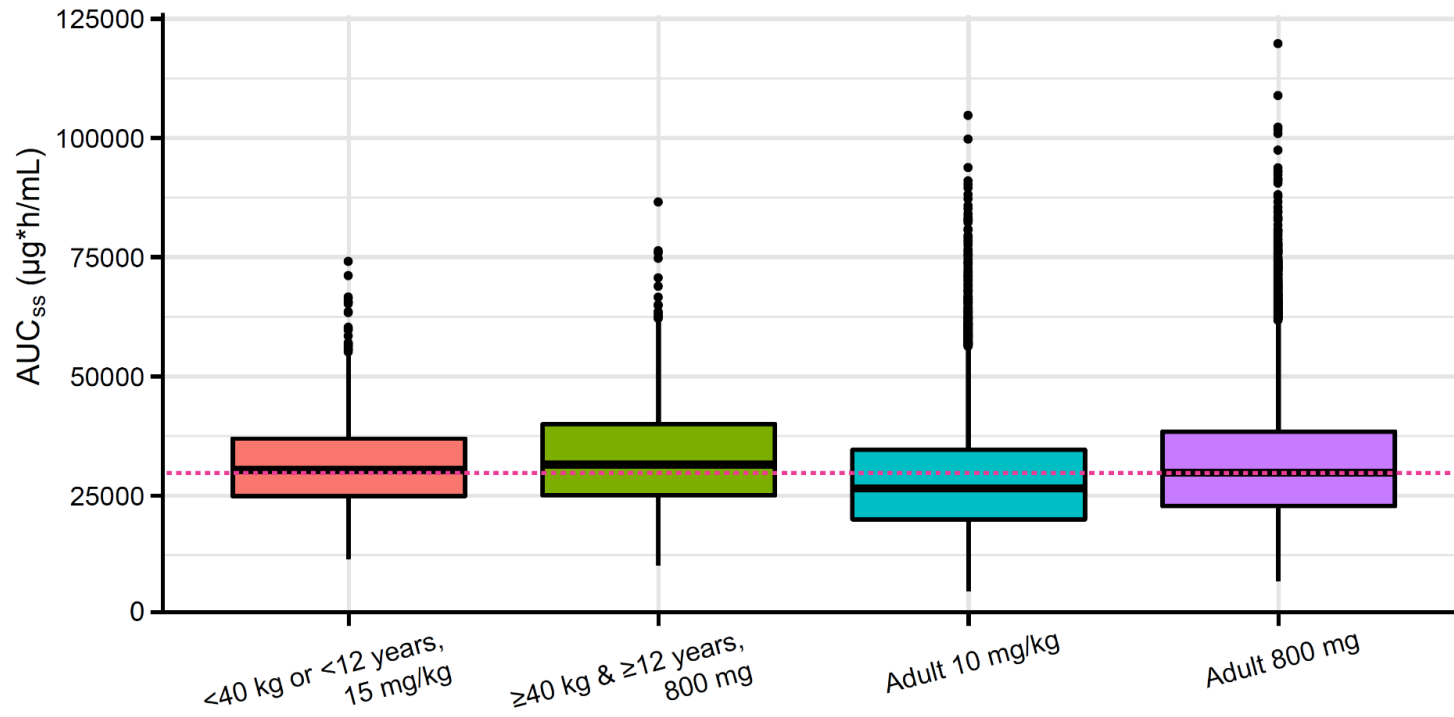
Supplementary Figure 5. Individual predicted vs observed avelumab concentration for each patient using the final population pharmacokinetic model.



Supplementary Figure 6. Simulations of (A) C_{trough} and (B) AUC at steady state for pediatric dosing regimens in subgroups defined by age and body weight and in adults. Boxes represent interquartile range; horizontal lines are medians; whiskers extend to the most extreme point, which is no more than 1.5 times the length of the box away from the box; and points are observations that are outside 1.5 times the length of the box away from the box. Pink dashed line represents the median for adult 800 mg data. AUC area under the concentration-time curve, C_{trough} trough concentration.

A



B

Supplementary Table 1. Comparison of simulated exposure distributions after a single dose at recommended doses and the highest dose tested (20 mg/kg) using the final pediatric population PK model with the adult population PK model at various dosing regimens. AUC_{ss} , area under the concentration-time curve (single dose); $C_{trough,ss}$, trough serum concentration (single dose); $C_{max,ss}$, maximum serum concentration (single dose).

Dose	PK parameter	Geometric mean: Simulated	Difference from adults: 10 mg/kg, %	Difference from adults: 800 mg, %	Difference from adults: 20 mg/kg, %
Pediatric patients aged ≥ 12 years and body weight ≥ 40 kg					
800 mg (recommended dose)	$C_{trough,sd}$	20.0	+30.6	+16.2	-34.7
	AUC_{sd}	25537	+17.2	+4.29	-41.4
	$C_{max,sd}$	309	+35.4	+20.5	-32.3
20 mg/kg	$C_{trough,sd}$	28.0	+83.2	+63.0	-8.39
	AUC_{sd}	35819	+64.4	+46.3	-17.8
	$C_{max,sd}$	433	+89.9	+69.0	-5.05
Pediatric patients aged < 12 years or body weight < 40 kg					
15 mg/kg (recommended dose)	$C_{trough,sd}$	22.2	+44.9	+28.9	-27.6
	AUC_{sd}	23870	+9.56	-2.51	-45.2

	$C_{\max, \text{sd}}$	238	+4.49	-7.03	-47.8
20 mg/kg	$C_{\text{trough}, \text{sd}}$	30.0	+93.2	+71.9	-3.40
	AUC_{sd}	31827	+46.1	+30.0	-27.0
	$C_{\max, \text{sd}}$	318	+39.3	+24.0	-30.3

Supplementary Table 2. Comparison of simulated exposure distributions at steady state at recommended doses and the highest dose tested (20 mg/kg) using the final pediatric population PK model with the adult population PK model at various dosing regimens.

AUC_{ss} , area under the concentration-time curve (steady state); $C_{trough,ss}$, trough serum concentration (steady state); $C_{max,ss}$, maximum serum concentration (steady state)

Dose	PK parameter	Geometric mean: Simulated	Difference from adults: 10 mg/kg (%)	Difference from adults: 800 mg (%)	Difference from adults: 20 mg/kg (%)
Pediatric patients aged ≥ 12 years and body weight ≥ 40 kg					
800 mg (recommended dose)	$C_{trough,ss}$	27.0	+23.9	+9.66	-38.8
	AUC_{ss}	31465	+19.8	+6.61	-40.1
	$C_{max,ss}$	339.7	+45.9	+29.8	-27.2
20 mg/kg	$C_{trough,ss}$	37.9	+73.8	+54.1	-14.1
	AUC_{ss}	44135	+68.1	+49.5	-16.0
	$C_{max,ss}$	476.5	+104.7	+82.1	+2.16
Pediatrics aged < 12 years or body weight < 40 kg					
	$C_{trough,ss}$	30.8	+41.4	+25.4	-30.1

15 mg/kg (recommended dose)	AUC _{ss}	30365	+15.6	+2.88	-42.2
	C _{max,ss}	272.5	+17.0	+4.15	-41.6
20 mg/kg	C _{trough,ss}	41.1	+88.5	+67.1	-6.86
	AUC _{ss}	40487	+54.2	+37.2	-22.9
	C _{max,ss}	363.4	+56.1	+38.9	-22.1