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Oral Abstract Session IV: Special Populations: Tailoring Current and New Interventions to Children and Elderly
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Eculizumab Dosing Strategies in Pediatric Patients with Stem Cell Transplant-Associated Thrombotic Microangiopathy (TA-TMA): PK/PD Model based assessment

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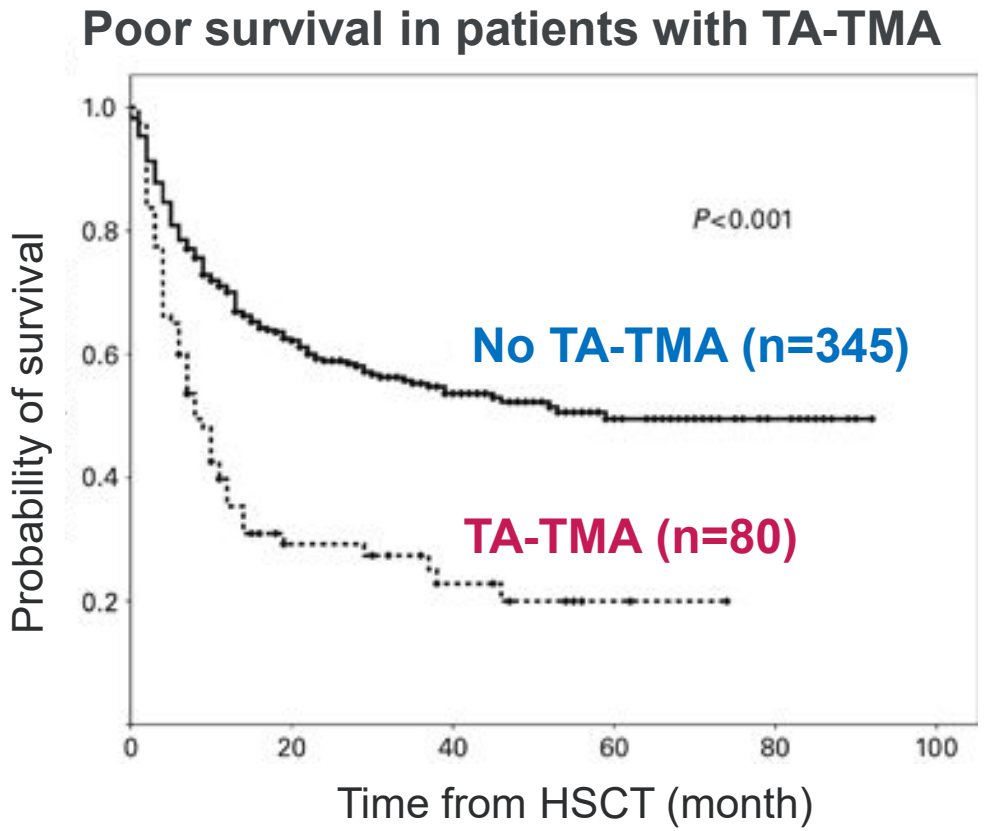
Poor survival of stem cell transplant-associated thrombotic microangiopathy (TA-TMA)

- A severe post-transplant complication with ***high-risk of death***
- Multifactorial disease with a ***20-30% incidence*** in stem cell recipients
- Low survival rates with conventional treatments such as plasma exchange, defibrotide, and/or rituximab
- ***Key for survival*** of high-risk TA-TMA is ***early intervention*** before severe multi-organ endothelial injury occurs.



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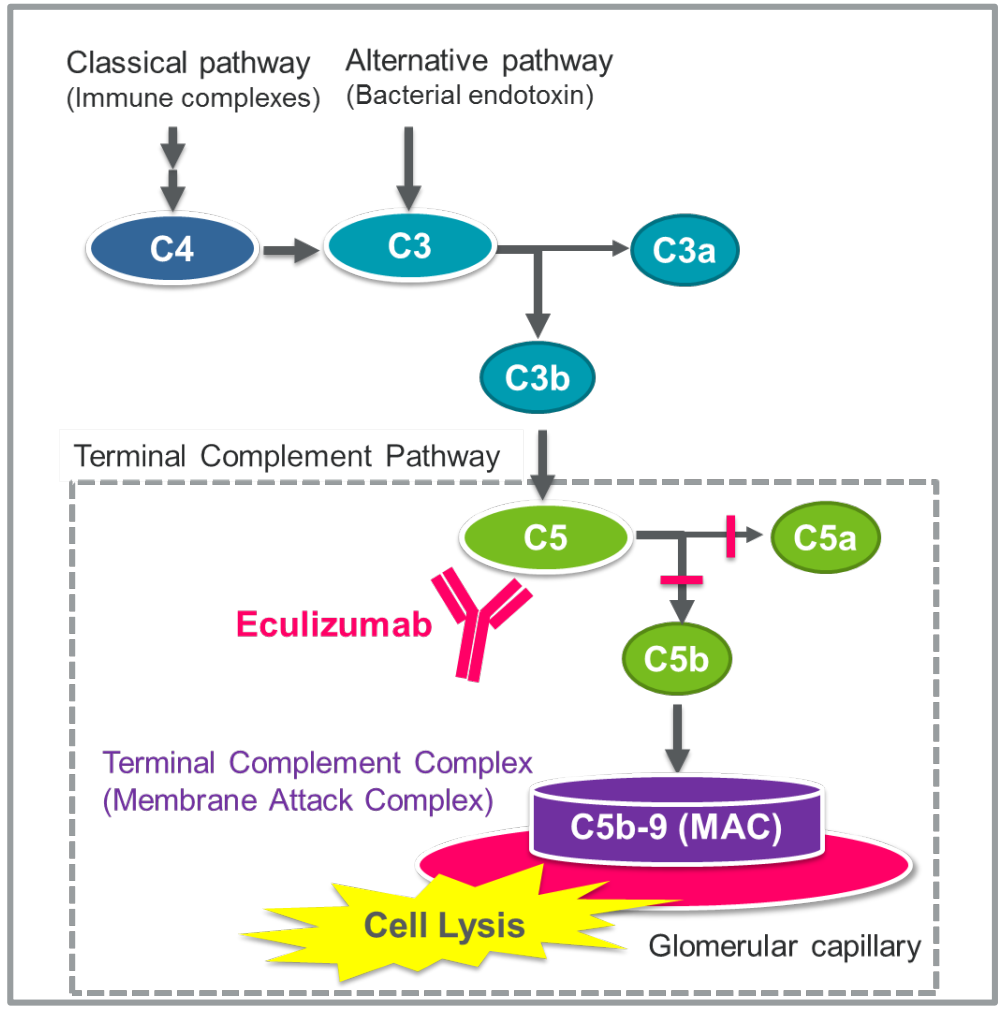
Balassa et al. *Bone Marrow Transplant.* 2015; 50(10):1321-5.

Anti-C5 monoclonal antibody Eculizumab for TA-TMA



Complement pathways

➢ **Mechanism of action:**

A monoclonal antibody (mAb) targeting complement C5

➢ **Indications:**

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Atypical Hemolytic Uremic Syndrome (aHUS)

➢ **Recommended dose**

Body weight	Induction dose	Maintenance dose
≥ 40kg	900 mg weekly	1200 mg biweekly
30 - ≤ 40kg	600 mg weekly	900 mg biweekly
20 - ≤ 30kg		600 mg biweekly
10 - ≤ 20kg		300 mg biweekly
5 - ≤ 10kg	300 mg weekly	

➢ **Cost:**

$6,143 or more for 1 vial (300 mg)

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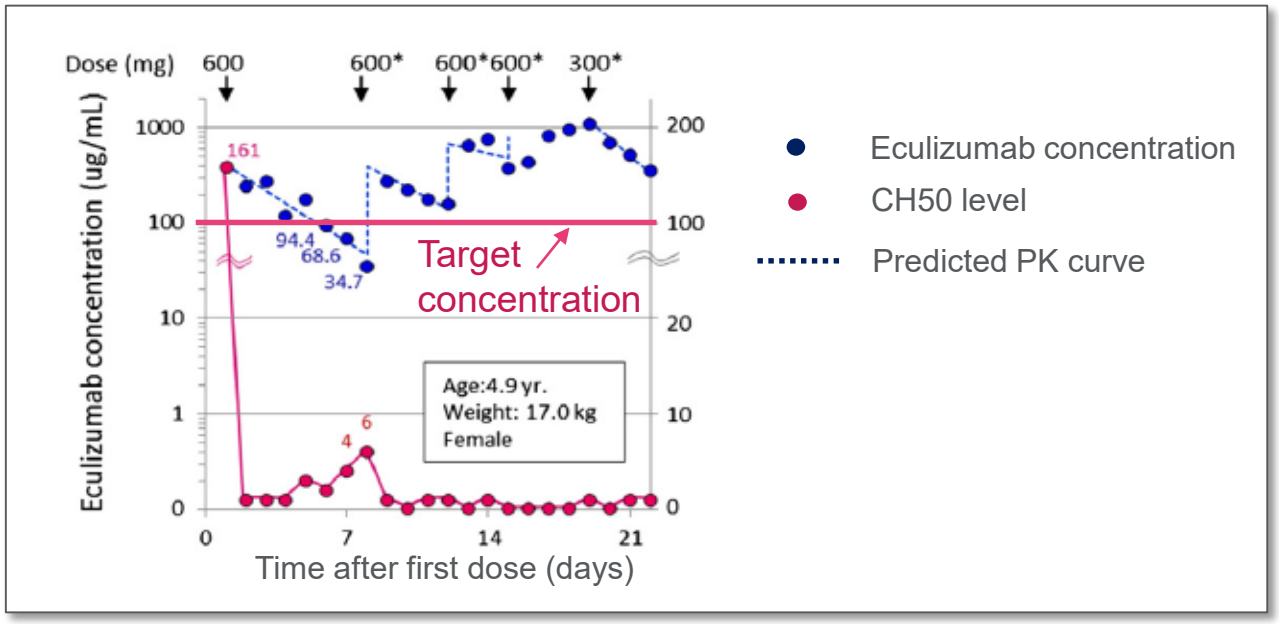
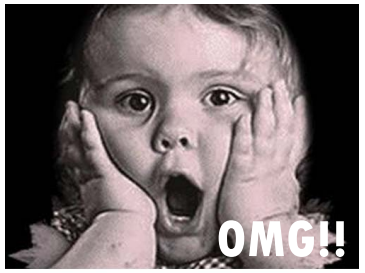
Jodele et al. *Biol Blood Marrow Transplant.* 2019; 23(12): 2172-7.

Big challenges with eculizumab dosing





- Large “between” and “within” patient variability in PK is observed!
- Current dosing strategies need to be optimized!

Jodele et al. *Biol Blood Marrow Transplant.* 2014 Apr;20(4):518-25.

PK/PD guided-precision dosing promises to increase treatment success

Monitoring biomarkers for dose adjustment	
PK:	**Eculizumab concentration**
PD:	**sC5b-9** (soluble terminal complement complex): Indicator of disease severity **CH50** (total hemolytic complement activity): Indicator of the effectiveness of complement blockade by eculizumab

Purpose

- To characterize eculizumab PK and PD over the course of treatment
- To develop a population PK model as part of a precision dosing strategy considering target mediated disposition
- To develop an optimal dosing strategy using a model-based approach to achieve higher PK target attainment resulting in better outcomes

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Methods

Sample collection

- Eculizumab serum concentrations: Once daily during induction therapy
- sC5b-9 monitoring : At least 3 times per week during therapy.

Population Pharmacokinetic Modeling

- NONMEM 7.2 with FOCE-I method
- Evaluated covariates: Body weight, sC5b-9 level, number of dosing cycles

Monte Carlo Simulations

Optimal dosing intervals to achieve high PK target attainment (C_{trough}>100 mg/mL) were explored based on the PK simulation using the developed model considering:

- Initial sC5b-9 burden (200-800 ng/mL)
- A cohort of representative patients (n=1,000; weight ranging from 3-80 kg)

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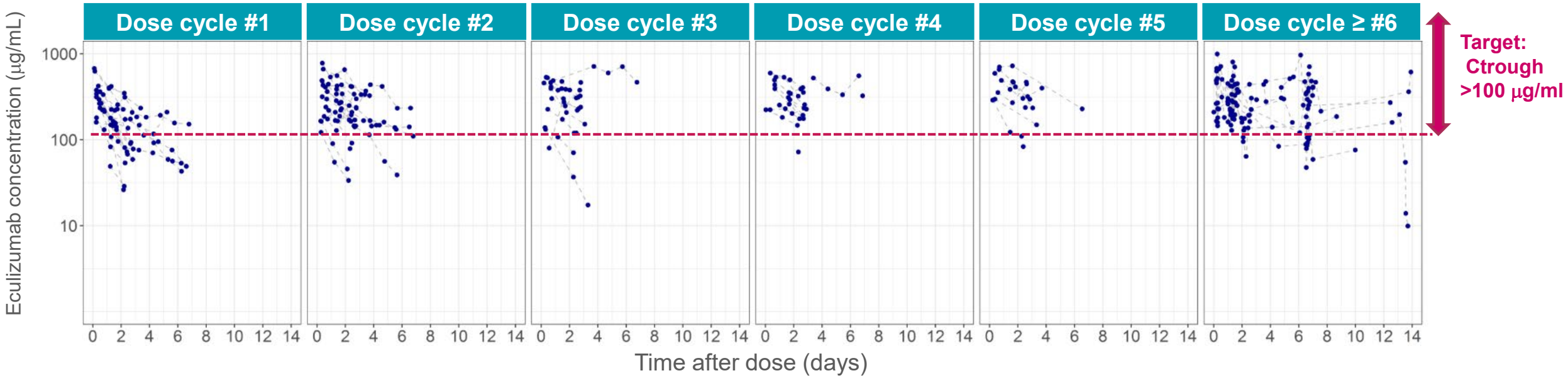
Large eculizumab target mediated PK variability during treatment



Patient demographics

Parameters	Number	Parameters	Median (range)
Number of patients	21	Time course available (weeks)	2 (0-25)
Number of observations	384	Age (years)	4.8 (1.1-29.8)
Number of dose cycles	5 (2-23)	Body weight (kg)	15.0 (5.5-80)
Induction dose: 300 mg/600 mg/900 mg	4 / 10 / 7	Pre-treatment sC5b-9 level (ng/mL) (normal<244 ng/mL)	337 (131-1700)

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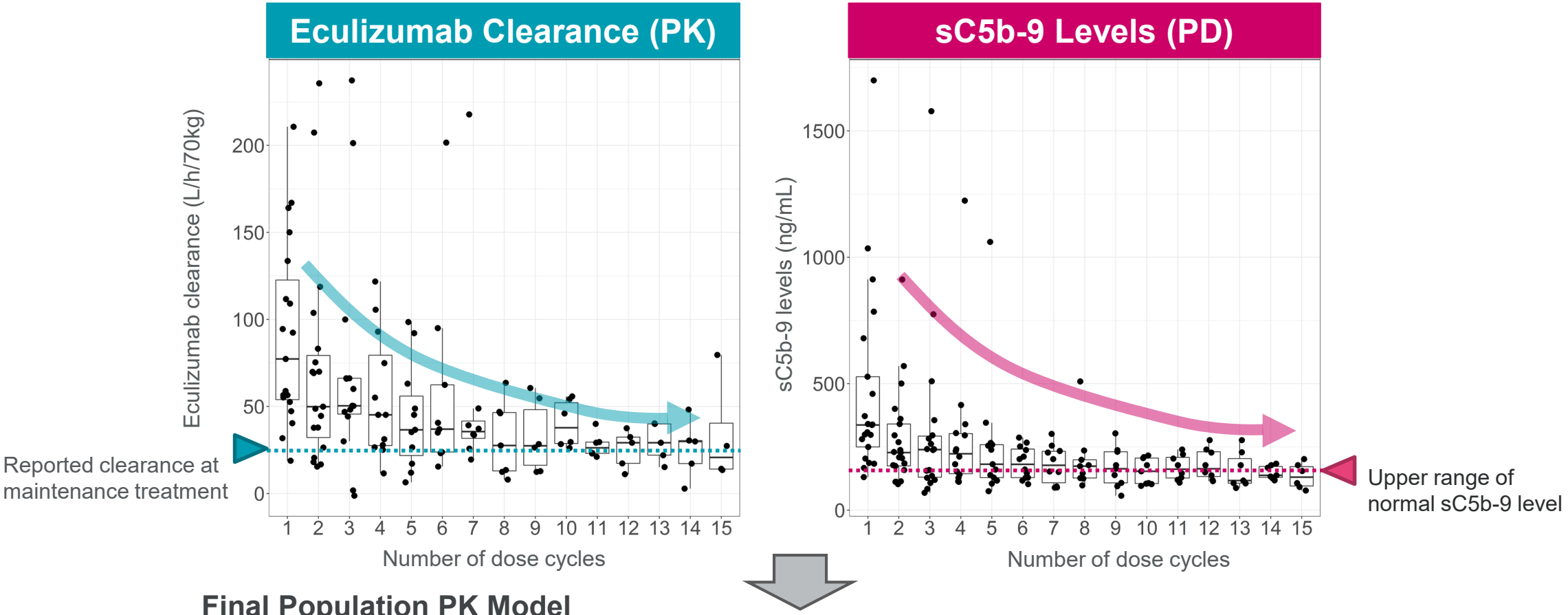
Eculizumab PD marker changes in parallel with PK



Final Population PK Model

$$CL = CLNL(nonlinear) + CLL\ (linear)$$

- $CLNL = CLNL_{pop} \times \left(\frac{predoseC5b9}{337}\right) \times e^{-\theta_{Ndose} \times (Ndose-1)} \times \left(\frac{WT}{70}\right)^{0.75}$
- $CLL = CLL_{pop} \times \left(\frac{WT}{70}\right)^{0.75}$

PD marker change over the course of treatment

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Population PK modeling and model validation

Final model

- CL=CLL (linear) +CLNL (non-linear)

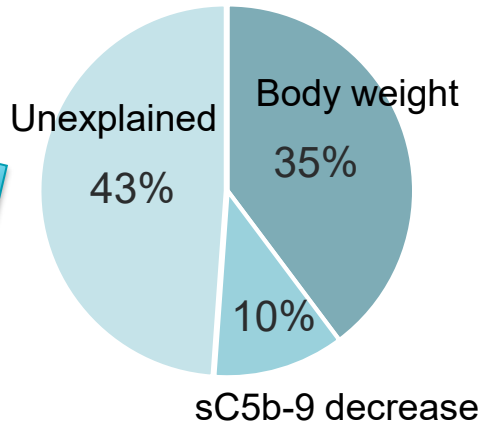
$$\mathbf{CLL}=\mathbf{CLL_{pop}}\cdot\left(\frac{\mathbf{WT}}{\mathbf{70}}\right)^{\mathbf{0.75}}$$

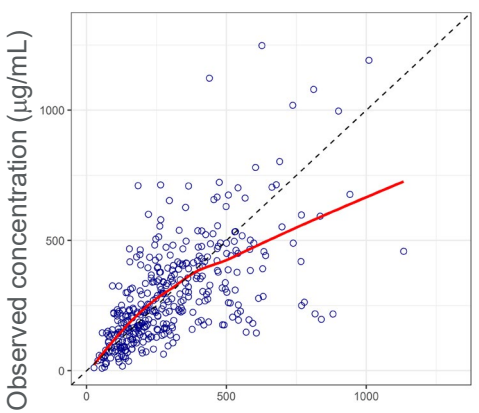
$$\mathbf{CLNL}=\mathbf{CLNL_{pop}}\cdot\left(\frac{\mathbf{predoseC5b9}}{\mathbf{337}}\right)\cdot\mathbf{e}^{-\theta_{\mathbf{Ndose}}\cdot(\mathbf{Ndose}-\mathbf{1})}\cdot\left(\frac{\mathbf{WT}}{\mathbf{70}}\right)^{\mathbf{0.75}}$$

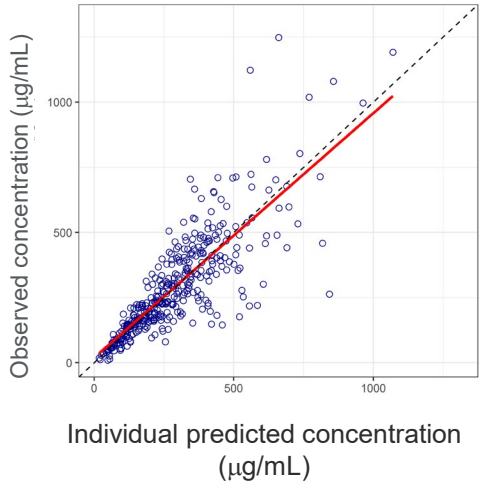
- $\mathbf{Vd}=\mathbf{Vdpop}\cdot\left(\frac{\mathbf{WT}}{\mathbf{70}}\right)^{\mathbf{1.0}}$

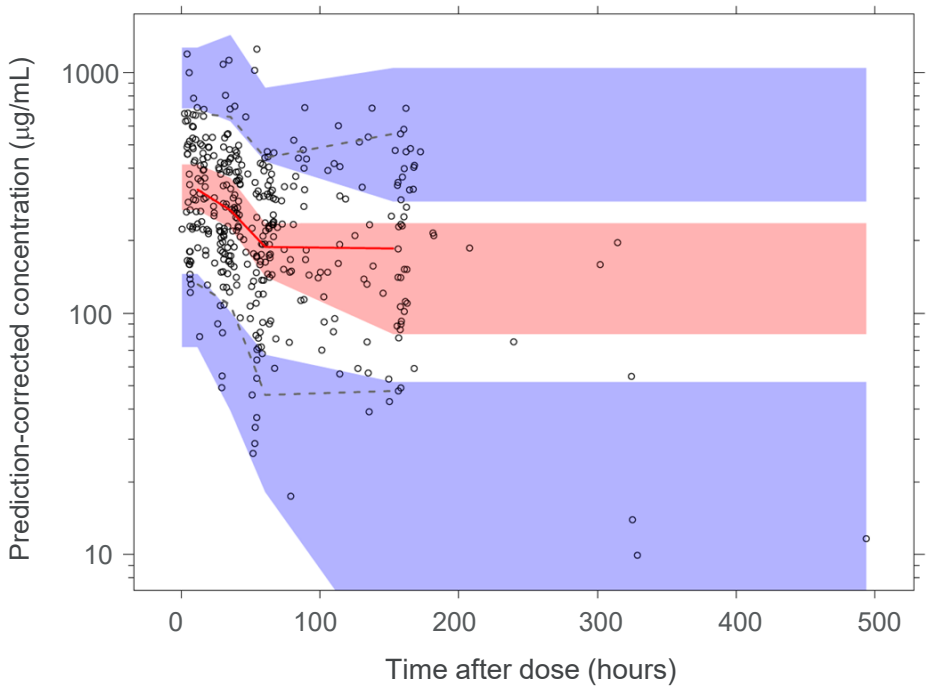
Parameter	Mean (%RSE)
Fixed effects	
CLL_{pop} (mL/h/70kg)	22.8 (17%)
Exponent of allometry for CL	Fixed to 0.75
Vd_{pop} (L/70kg)	8.15 (8%)
Exponent of allometry for Vd	Fixed to 1.0
$CLNL_{pop}$ (mL/h/70kg)	40.5 (17%)
q_{NDOSE}	0.20 (29%)
Inter-individual variability	
ω_{CL} (%CV)	43.5% (27%)
ω_{vd} (%CV)	25.3% (33%)
ω_{IOV} (%CV)	30.7% (17%)
Random residual variability	
ε_{prop}	0.104 (14%)

88% CL variability









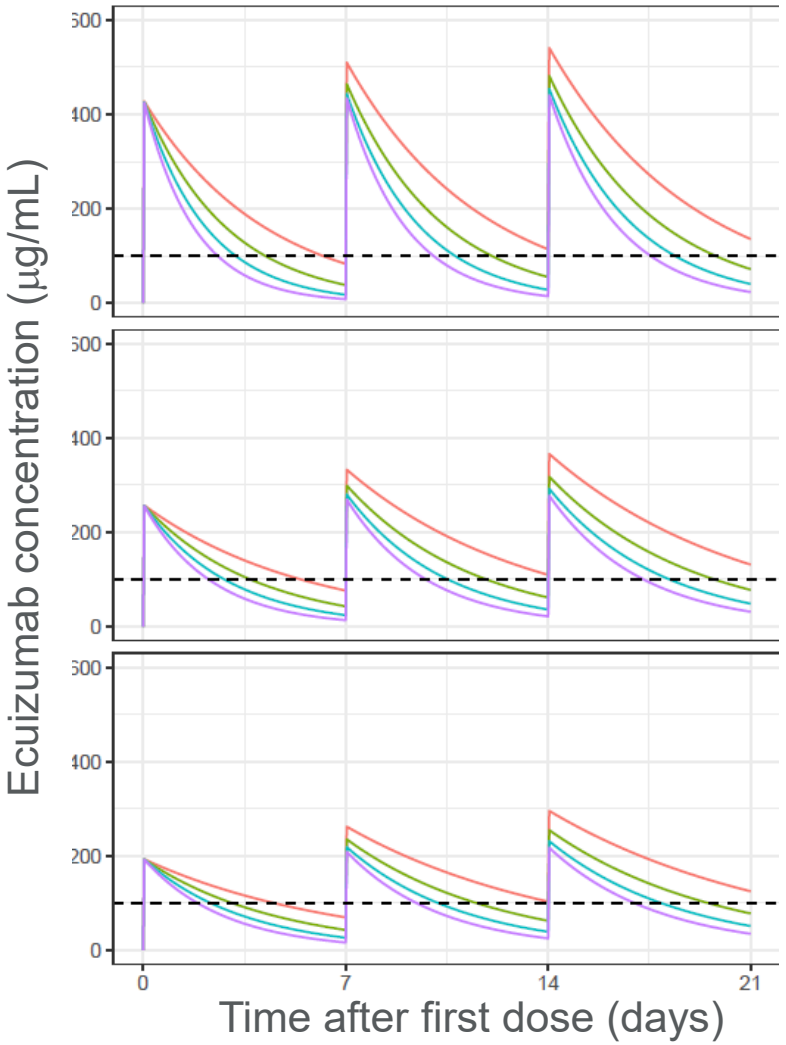
Intensifying dosing scenarios for higher target attainment

Simulation 1
Weight: 6 kg
Dose: 300mg

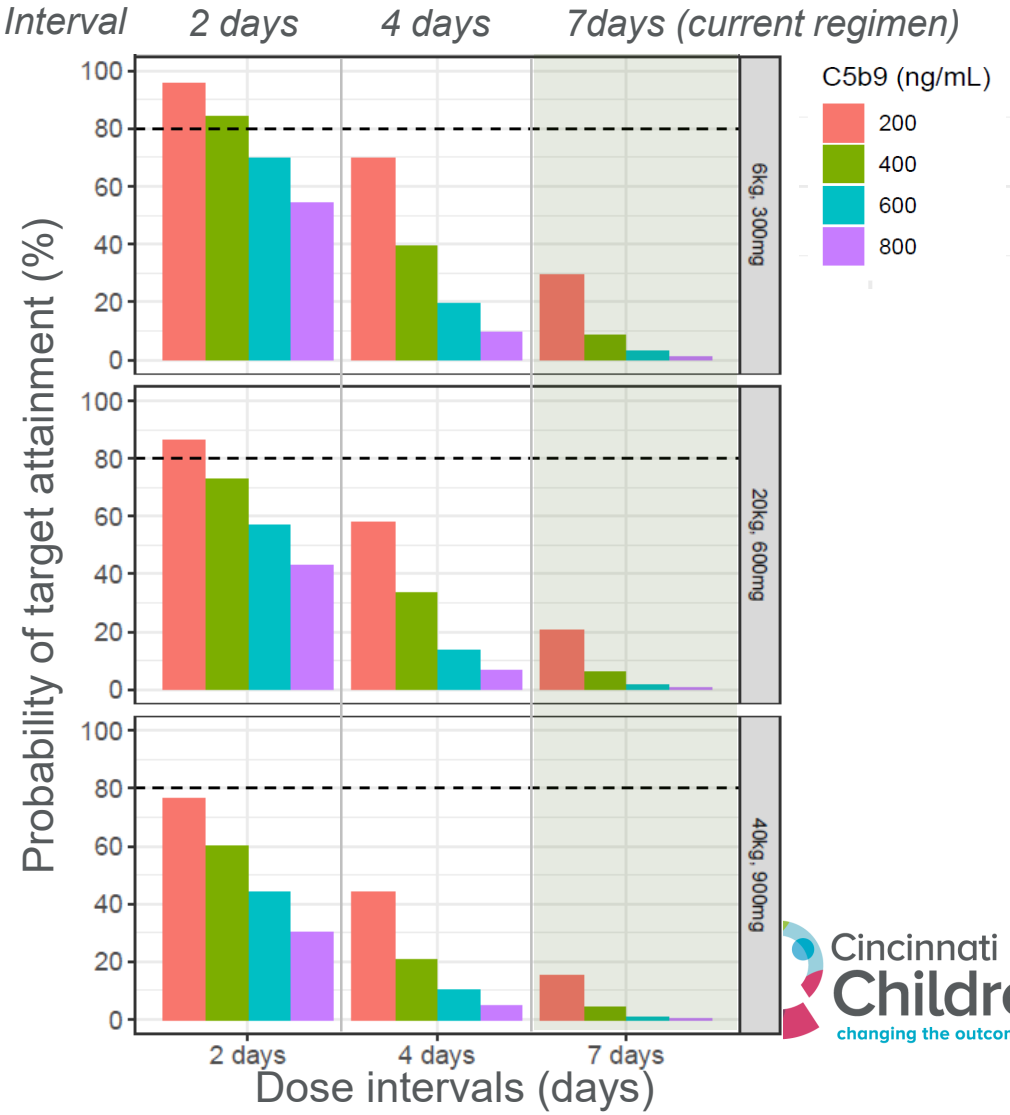
Simulation 2
Weight: 20 kg
Dose: 600mg

Simulation 3
Weight: 40 kg
Dose: 900mg

Population PK Simulation



Probability of target attainment (C_{trough}>100 µg/mL)



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Conclusion

Our PK/PD model-based optimal dosing strategy indicated that eculizumab precision dosing with consideration of body weight and sC5b-9 levels will increase the probability of PK target attainment resulting in better outcomes.

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Acknowledgements

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Patients and Families
All medical staff for patient care