

Population Pharmacokinetic and Pharmacodynamic Analysis of Sevasemten (EDG-5506) in Becker Muscular Dystrophy

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Conclusion

- The main covariate in the population PK of sevasemten is serum creatinine as a surrogate for muscle mass. Its effect on peripheral volume explains the observed difference in PK between healthy volunteers and BMD participants at Day 14
- Neither age nor body weight appears to affect the PK of sevasemten, suggesting that no change in dose is required due to age or severity of disease
- Indirect response population PK/PD models support that both CK and TNNI2 respond to sevasemten in an exposure-dependent manner

Background

- Sevasemten (EDG-5506) is an investigational, first-in-class, orally bioavailable, small molecule, allosteric, selective, fast myofiber (type II) myosin inhibitor being developed for the treatment of Becker muscular dystrophy (BMD) and Duchenne muscular dystrophy (DMD).
- BMD is a rare, serious, progressively debilitating, and potentially fatal inherited neuromuscular disorder with a high unmet medical need.
- The objectives of this analysis were to develop a population PK model to characterize the PK of sevasemten, including identification of covariates affecting PK, as well as develop population PK/PD models for two biomarkers, creatine kinase (CK) and fast troponin (TNNI2).

Methods

Population PK model development

- Clinical data from 3 studies:

- EDG-5506-001:** Phase 1 SAD/MAD Study to Evaluate the Safety, Tolerability, PK, and PD of EDG 5506 in Adult Healthy Volunteers and Adults with BMD
- EDG-5506-002:** Phase 1b, Open-label Study of the Safety and PK of EDG-5506 in Adults with BMD
- EDG-5506-201:** Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of EDG-5506 on Safety, Biomarkers, PK, and Functional Measures in Adults and Adolescents with BMD

- Doses ranged from 0.5 mg to 135 mg single dose, and 5 mg to 20 mg once daily dosing (QD) using 3 formulations: oral suspension (SS), enteric capsule (EC) and immediate release tablet (IR)
- Population PK model developed using FOCEI in NONMEM (version 7.5.1)
- Stepwise approach was used to test key covariates, which included serum creatinine as a surrogate for muscle mass

List of Covariates Evaluated in the Population PK Model

Covariate	Type	PK parameters tested
Age at baseline (years)	Continuous	All clearances and volumes
Body weight (kg)	Continuous	All clearances and volumes
Body Mass Index (BMI) (kg/m ²)	Continuous	All clearances and volumes
Sex	Categorical	All clearances and volumes
Race	Categorical	All clearances and volumes
Serum creatinine (μmol/L)	Continuous	All clearances and volumes
Healthy volunteer or BMD	Categorical	All clearances and volumes
Absolute eGFR (mL/min)	Continuous	Central clearance
AST (U/L)	Continuous	Central clearance
ALT (U/L)	Continuous	Central clearance
Total bilirubin (μmol/L)	Continuous	Central clearance

External model validation in DMD pediatric participants

- External VPCs carried out using data from two DMD studies:

- EDG-5506-210:** 2-part Phase 2 Study of Safety, PK and Biomarkers in Children with DMD
- EDG-5506-215:** Phase 2 Study to Evaluate the Effect of EDG-5506 on Safety, PK, and Biomarkers in Children and Adolescents with DMD Previously Treated with Gene Therapy

Population PK/PD models for biomarkers CK and TNNI2

- Indirect response (i.e., turnover) model with inhibition on Kin

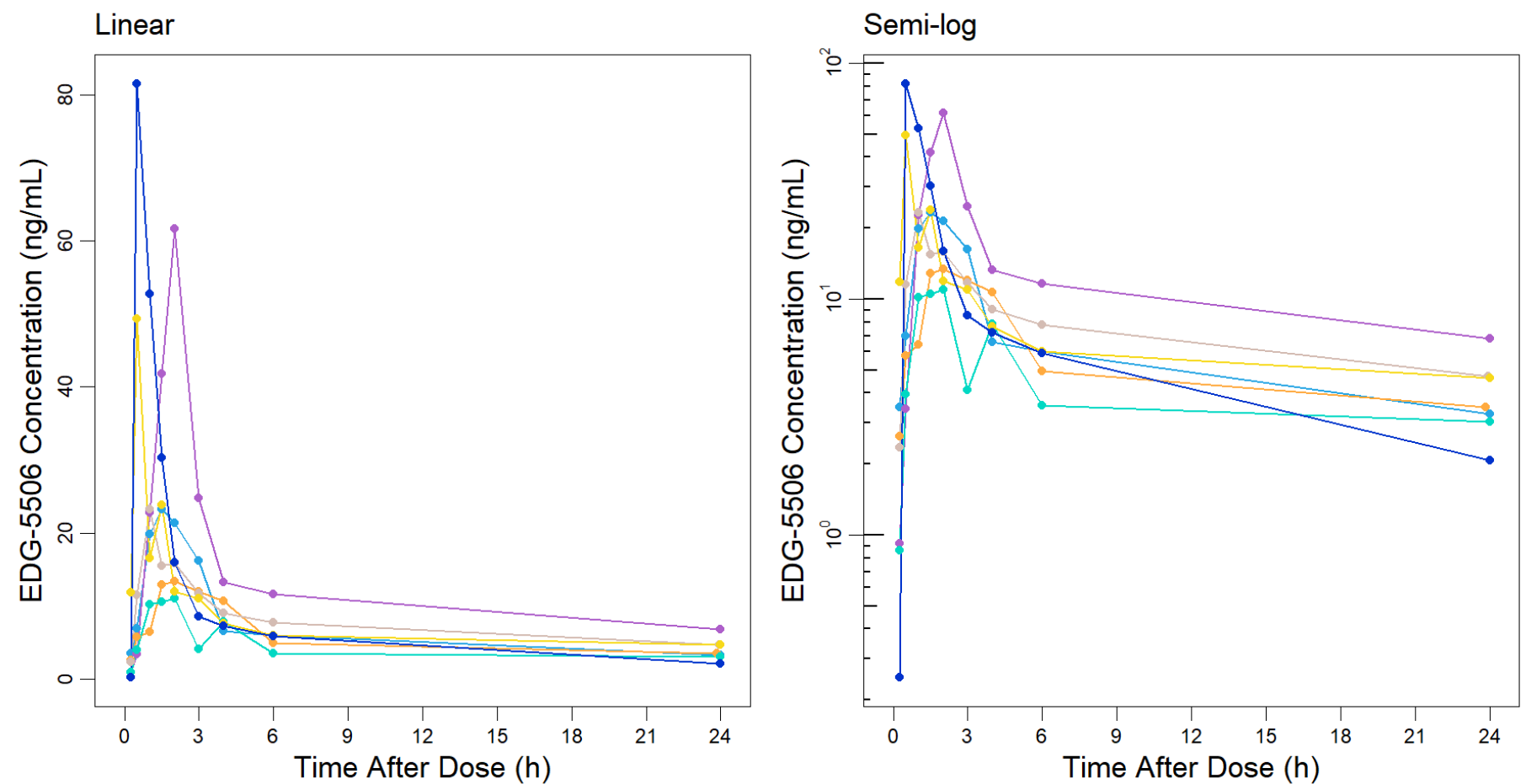
$$\frac{dR}{dt} = k_{in}(1 - I(C)) - k_{out}R \quad I(C) = I_{max} \left(\frac{C^{\gamma}}{IC_{50}^{\gamma} + C^{\gamma}} \right) \quad R_0 = \frac{k_{in}}{k_{out}}$$

Results

Exploratory data analysis

Spaghetti Plot for Intensive Pharmacokinetic Sampling on Day 1 in Study EDG-5506-002, Linear and Semi-log Scales

Study EDG-5506-002, Day 1 Intensive PK Sampling
10 mg Dose, IR Formulation (N=7)



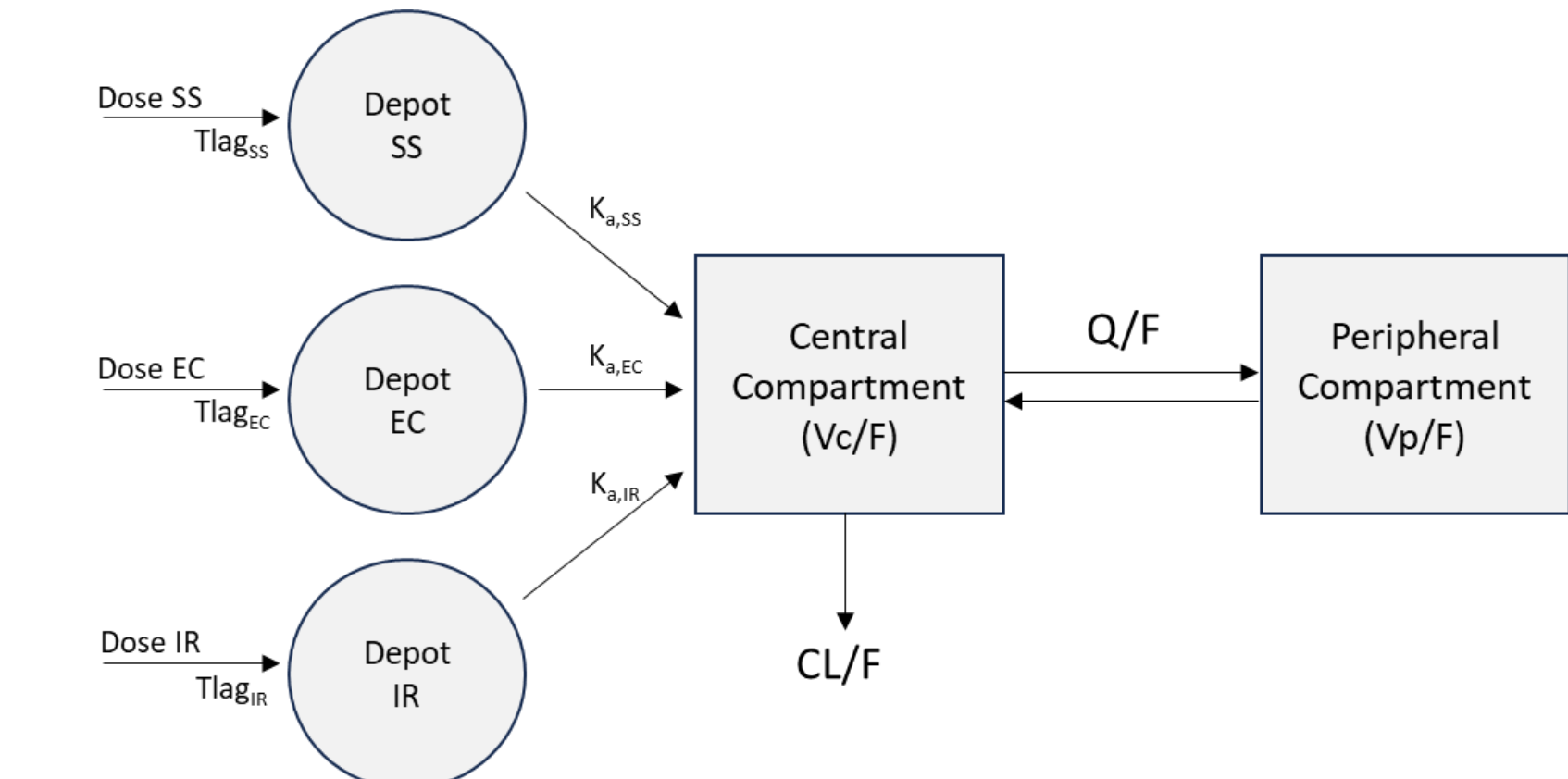
References

- Donovan J, et al. Muscle Nerve. 2025 Sep;72(3):399-407.
- Wang L, et al. BMC neurology. 2021 Sep 25;21(1):372.

Results

Population PK model fits observed data well for all studies and formulations

Schematic of the Final Pharmacokinetic Model of EDG-5506 in Adult Healthy Volunteers and Adult and Adolescent BMD Participants



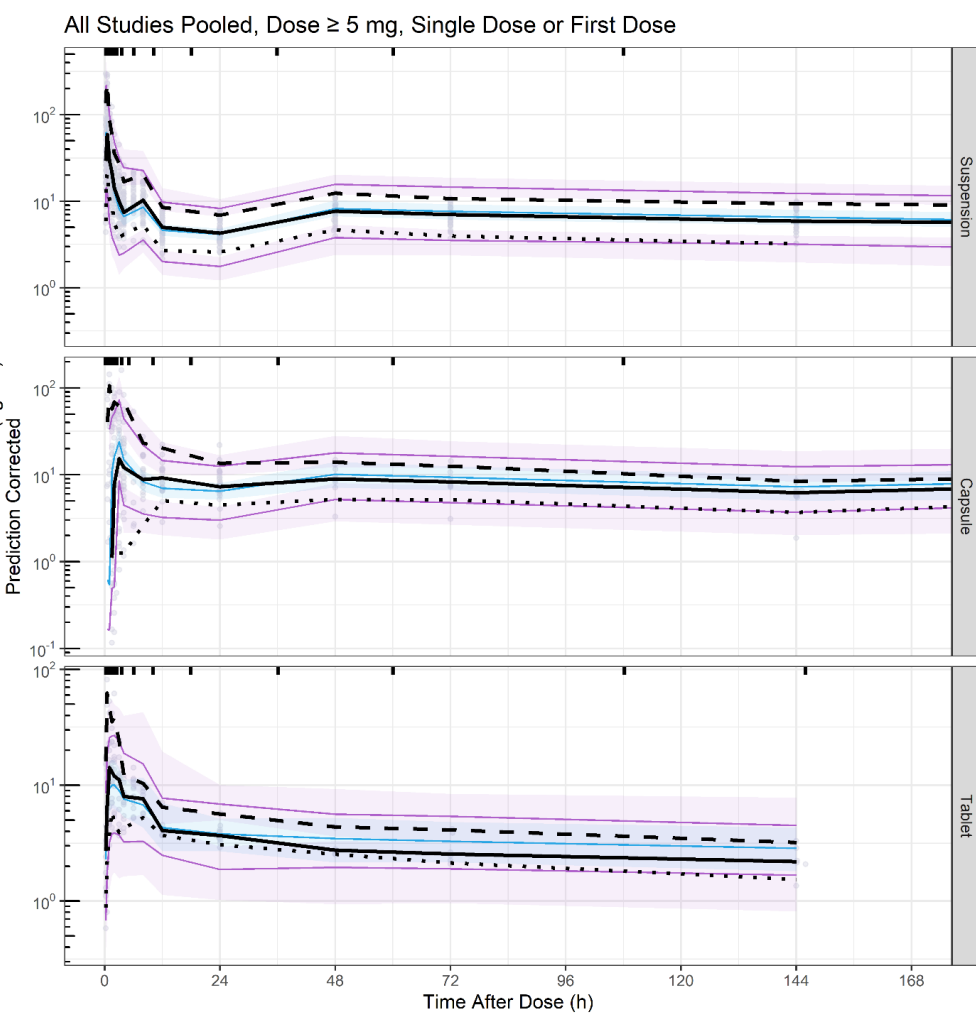
SS = suspension; EC = enteric capsule; IR = immediate release; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution; CL/F = apparent clearance; Q/F = apparent intercompartmental clearance; K₁₂ = absorption rate constant of suspension; K₁₃ = absorption rate constant of enteric capsule; K₁₄ = absorption rate constant of immediate release; Tag_{SS} = absorption lag time of suspension; Tag_{EC} = absorption lag time of enteric capsule; Tag_{IR} = absorption lag time of immediate release.

Parameter Estimates for the Final Population Pharmacokinetic Model of Sevasemten

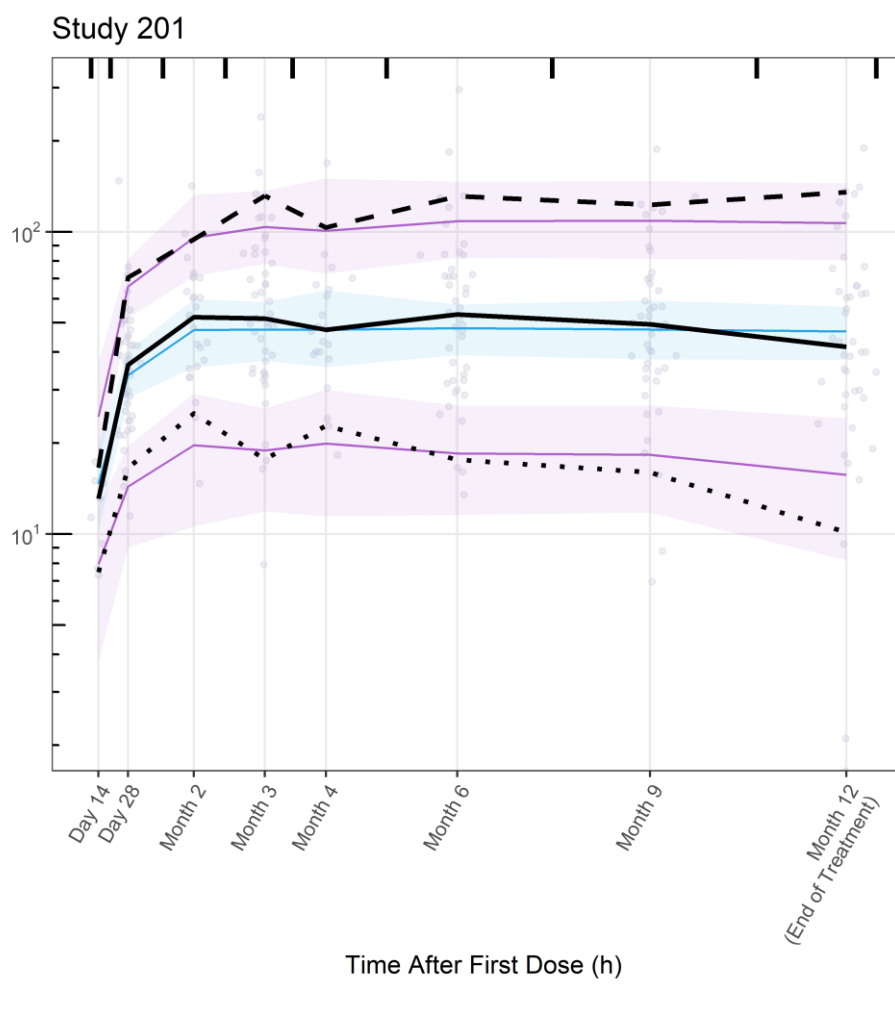
Parameter	Estimate	RSE%	Bootstrap		Shrinkage
			Median	95% CI	
Typical Values					
CL/F (L/h)	8.26	4.54	8.25	7.56 – 9.00	-
Vc/F (L)	210	10.4	208	167 – 256	-
Vp/F (L)	3472	4.48	3477	3200 – 3808	-
Q/F (L/h)	215	9.10	213	179 – 255	-
Ka for SS formulation (h ⁻¹)	13.1	20.9	12.9	9.04 – 24.5	-
Ka for EC formulation (h ⁻¹)	0.516	17.4	0.517	0.378 – 0.821	-
Ka for IR formulation (h ⁻¹)	0.603	14.0	0.608	0.439 – 0.880	-
Tag for SS formulation (h)	0.216	2.71	0.217	0.199 – 0.225	-
Tag for EC formulation (h)	0.469	5.60	0.470	0.441 – 0.608	-
Tag for IR formulation (h)	0.179	9.13	0.181	0.138 – 0.211	-
Covariate Effects					
Female sex on CL/F	0.599	14.4	0.600	0.453 – 0.813	-
Serum creatinine on Vp/F	1.03	17.8	1.02	0.668 – 1.41	-
Female sex on Vp/F	0.504	8.92	0.499	0.395 – 0.605	-
Inter-individual Variability					
On CL/F	0.446	6.77	0.441	0.389 – 0.494	12.7%
On Vc/F	1.00	8.85	1.02	0.817 – 1.30	21.5%
On Vp/F	0.367	12.6	0.362	0.279 – 0.455	22.7%
On Q/F	0.874	10.4	0.858	0.701 – 1.06	20.4%

CI = confidence interval; RSE = relative standard error; CL/F = apparent clearance; Q/F = apparent intercompartmental clearance; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution; Ka = absorption rate constant; Tag = absorption lag time; SS = suspension; EC = enteric capsule; IR = immediate release; OFV = objective function value.

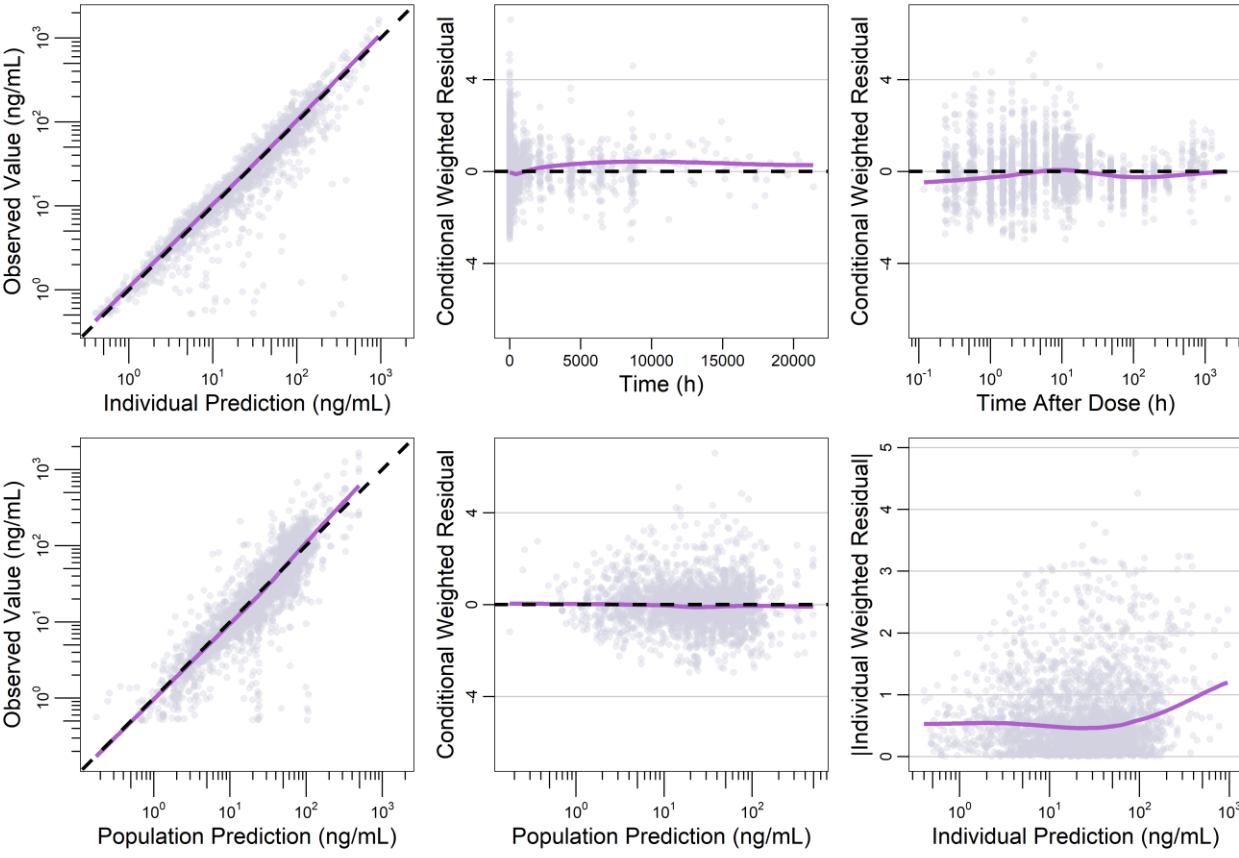
VPC for richly sampled single-dose data



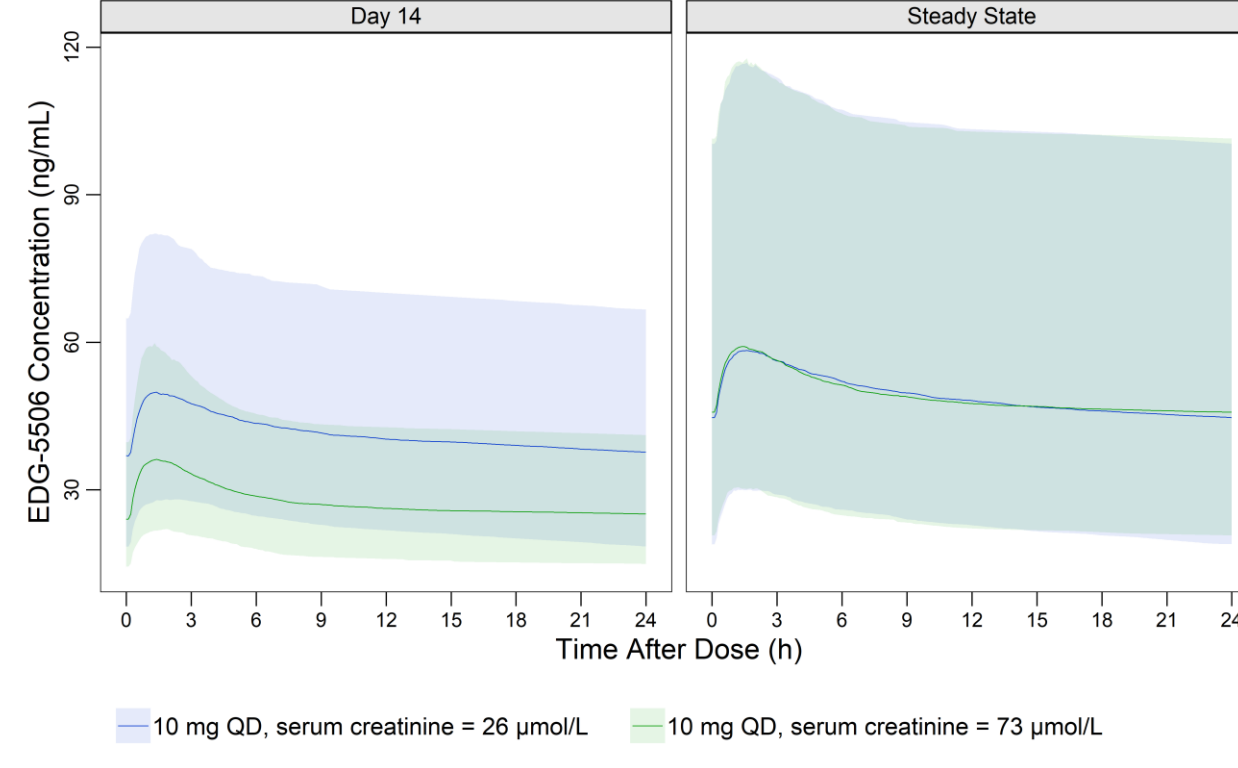
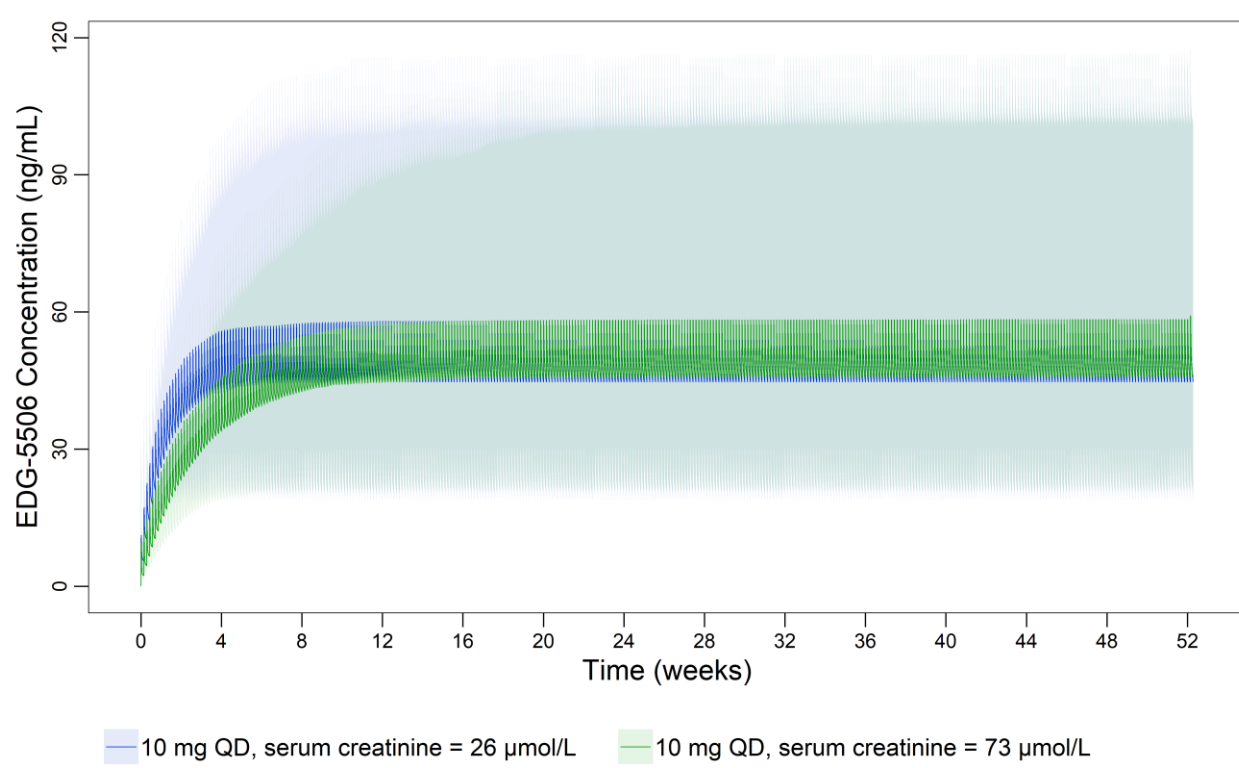
VPC for sparsely sampled multiple-dose data



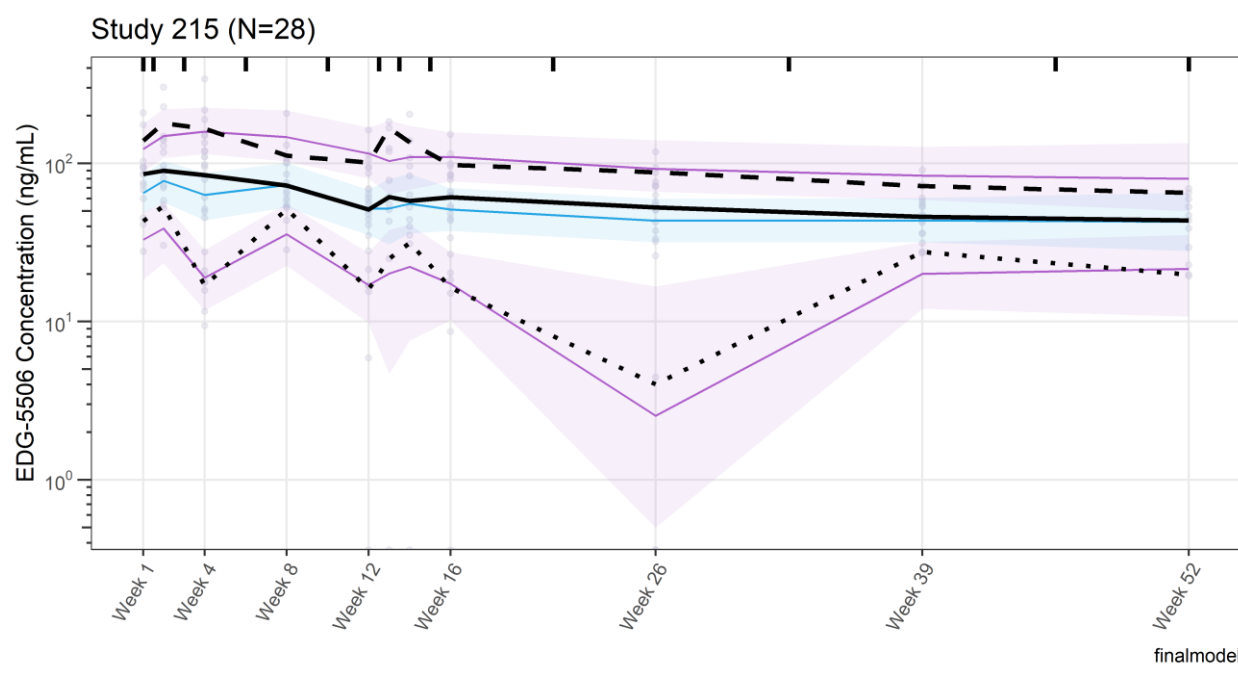
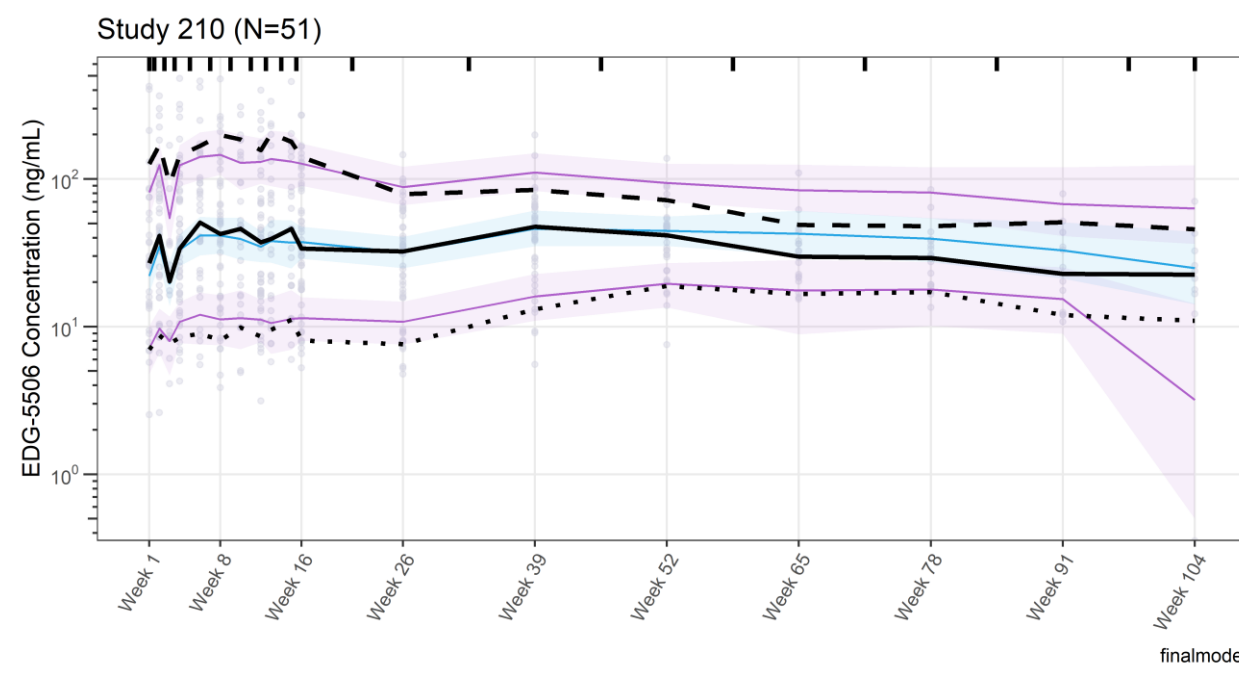
Goodness-of-fit



Simulations illustrate how the effect of serum creatinine on peripheral volume predicts the observed difference in PK between healthy volunteers and BMD participants at Day 14



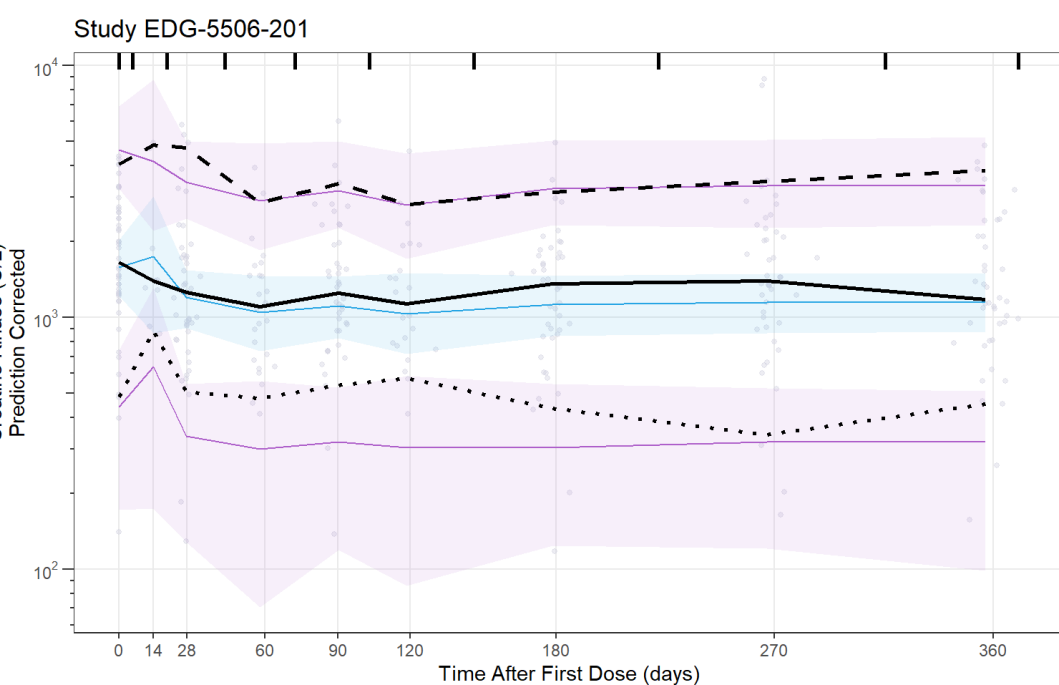
External validation demonstrates that the population PK model generalizes to DMD pediatric participants



Data were binned according to nominal time point. The tick marks at the top of each panel denote the bin limits. The black solid, dotted, and dashed lines represent the median, 10th and 90th percentile respectively in each bin of the observed data, following transformation for prediction correction, which are represented by gray points. The blue (median) and purple (upper and lower quantiles) shaded areas are the simulation-based 95% confidence intervals of the corresponding quantiles from a simulation of 500 replicates. The solid blue and purple lines are the medians across replicates in each bin.

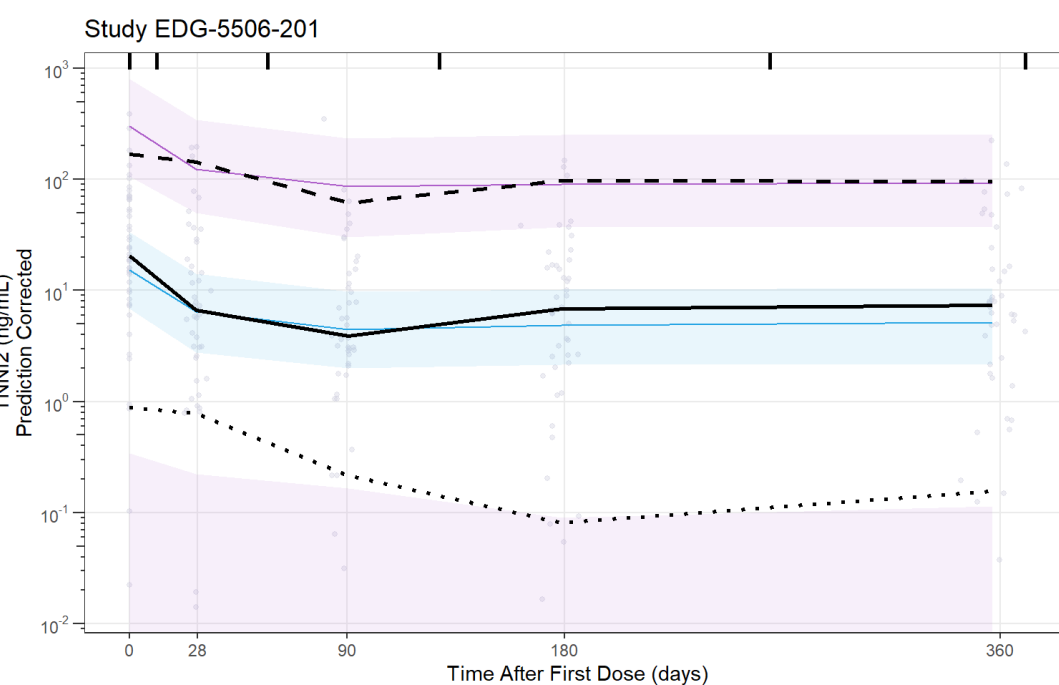
Population PK/PD models capture the dose-dependent decrease in biomarkers CK and TNNI2

Final population PK/PD model for CK



Parameter	Estimate	RSE%
Typical Values		
Baseline	1486	7.87
K _{out} (per hour)	0.0577	34.3
I _{max}	0.528	17.8
IC ₅₀ (ng/mL)	38.2	59.7
Hill factor	1.00 Fixed	-
Covariate Effects		
Body weight on baseline	-1.71	16.2
Inter-individual Variability		
On baseline	0.574	12.6
Residual Error		
Proportional Error (%)	41.0	5.45

Final population PK/PD model for TNNI2



Parameter	Estimate	RSE%
Typical Values		
Baseline	22.5	23.1
K _{out} (per hour)	1.59	50.2
I _{max}	1.00 Fixed	-
IC ₅₀ (ng/mL)	25.8	36.1
Hill factor	1.23	31.5
Inter-individual Variability		
On baseline	1.61	13.1
Residual Error		
Proportional Error (%)	93.2	5.36