

Characterization of the population dose-exposure-efficacy relationships of vamorolone, a synthetic corticosteroid drug in the treatment of Duchenne Muscular Dystrophy (DMD)

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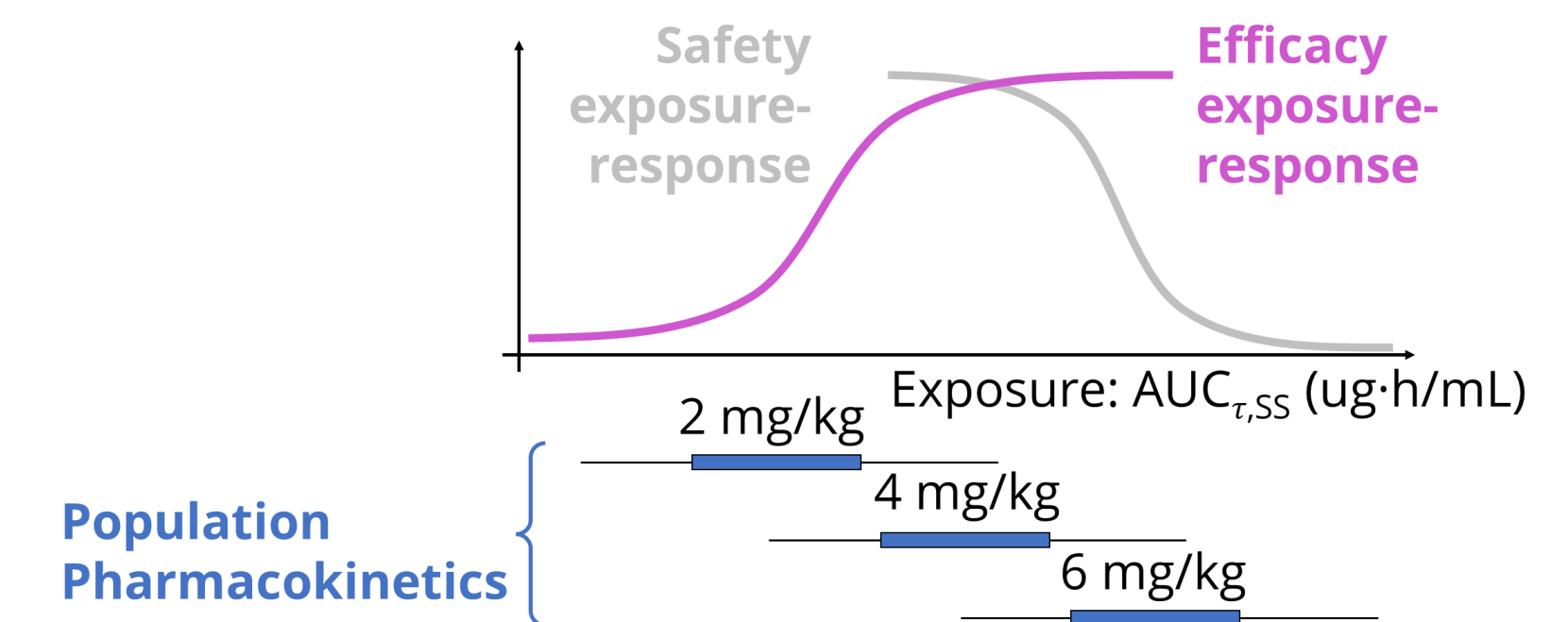
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Background

- Duchenne Muscular Dystrophy (DMD), a life-threatening genetic disease occurring in around 1:3600-6000 children (predominantly male).
- After start of physical deterioration at around five years of age by twelve years of age, most DMD patients are unable to walk.
- Vamorolone is a synthetic steroidal drug approved for the treatment of DMD to improve muscle strength and function.
- In five clinical studies a Vamorolone dose range between 0.1-20 mg/kg/day was assessed:
 - The influence of formulation, prandial state, and hepatic impairment on vamorolone pharmacokinetics (PK) was assessed.
 - The effect of vamorolone on disease progression was investigated in patients between four to seven years of age considering doses between 0.25-6 mg/kg.

Criteria Used to Identify the Optimal Clinical Dose

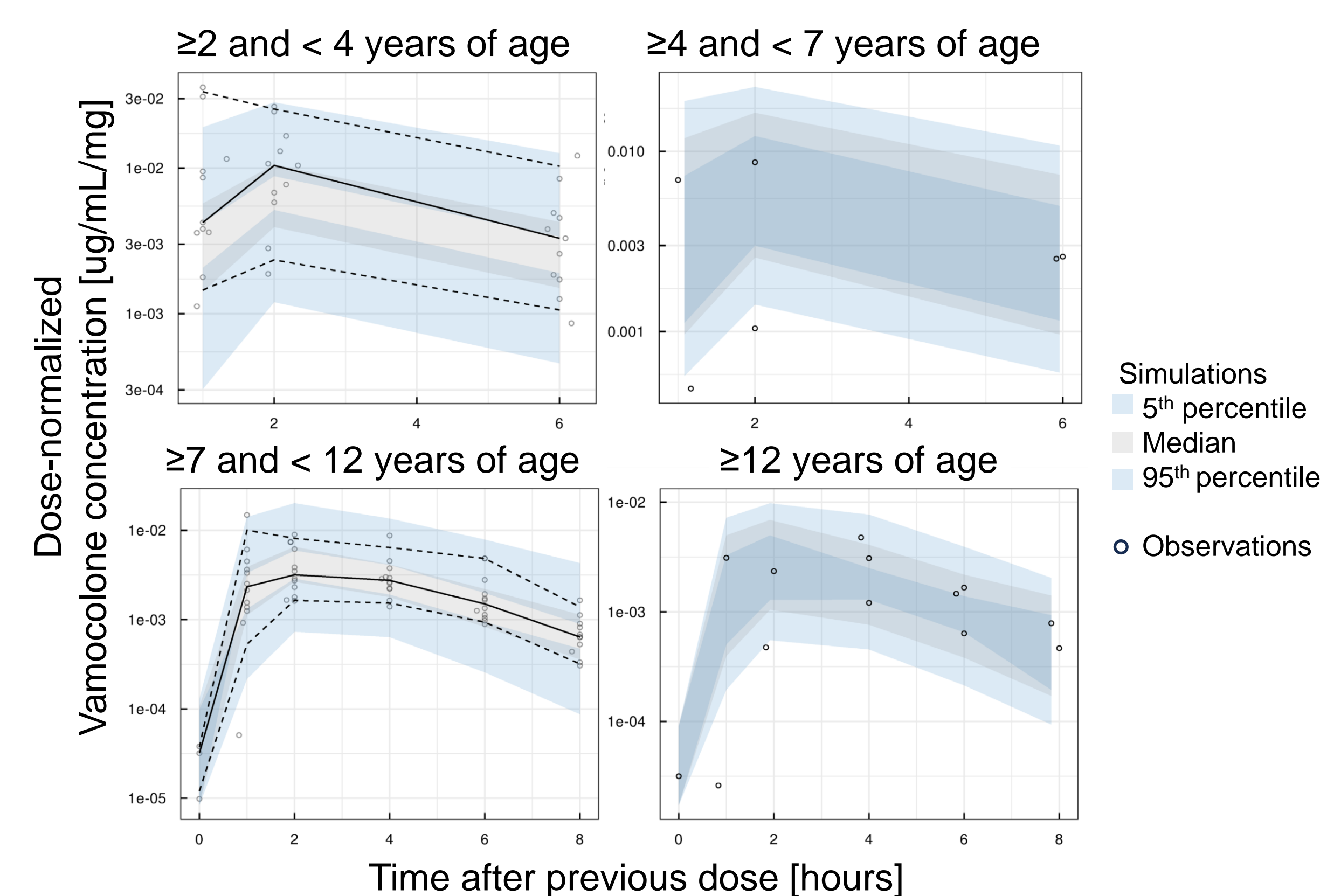
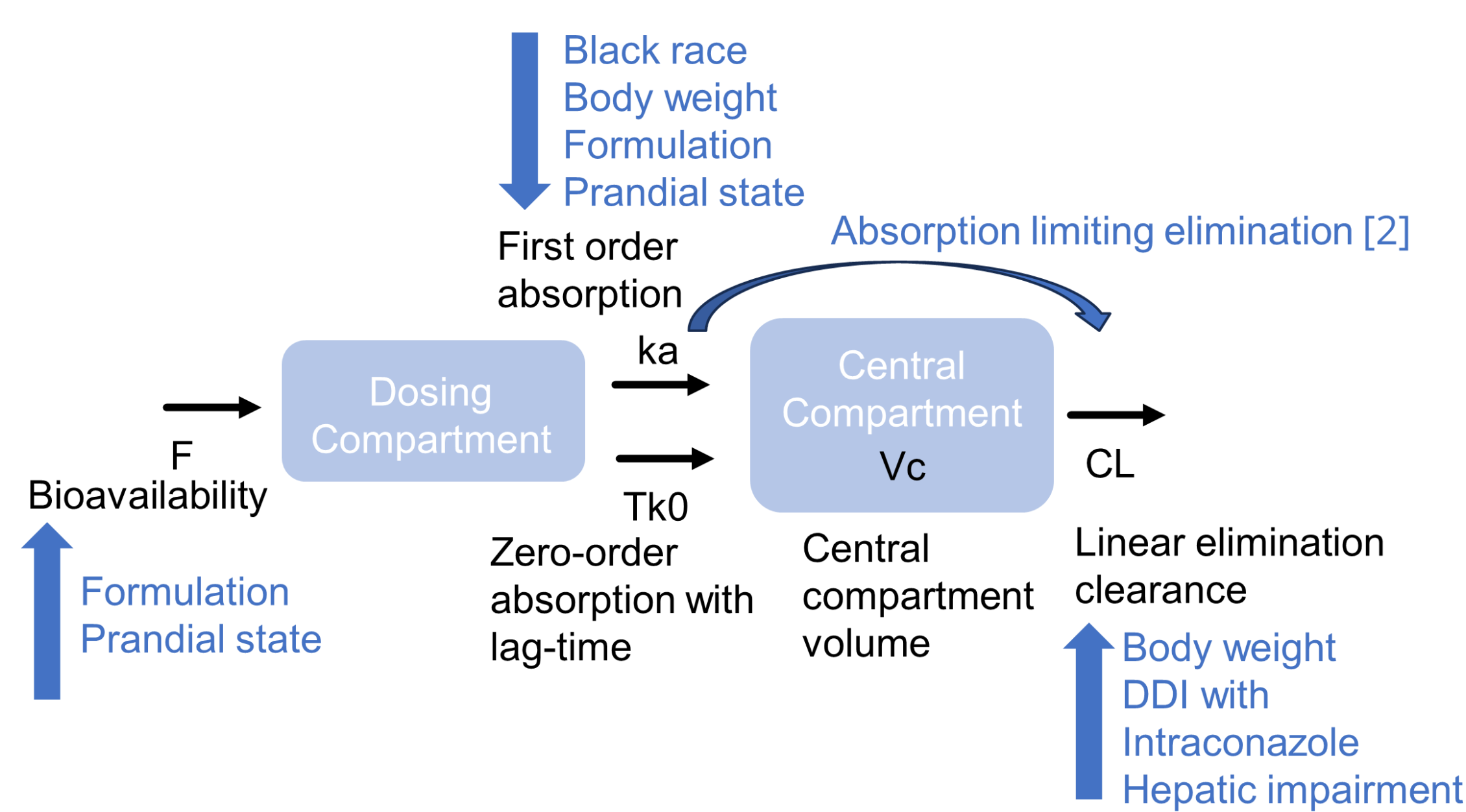
- Many different studies with different populations
- High variability in disease progression
- Transfer of insights from healthy adults to patients
- Exposure constraints by safety markers



Results

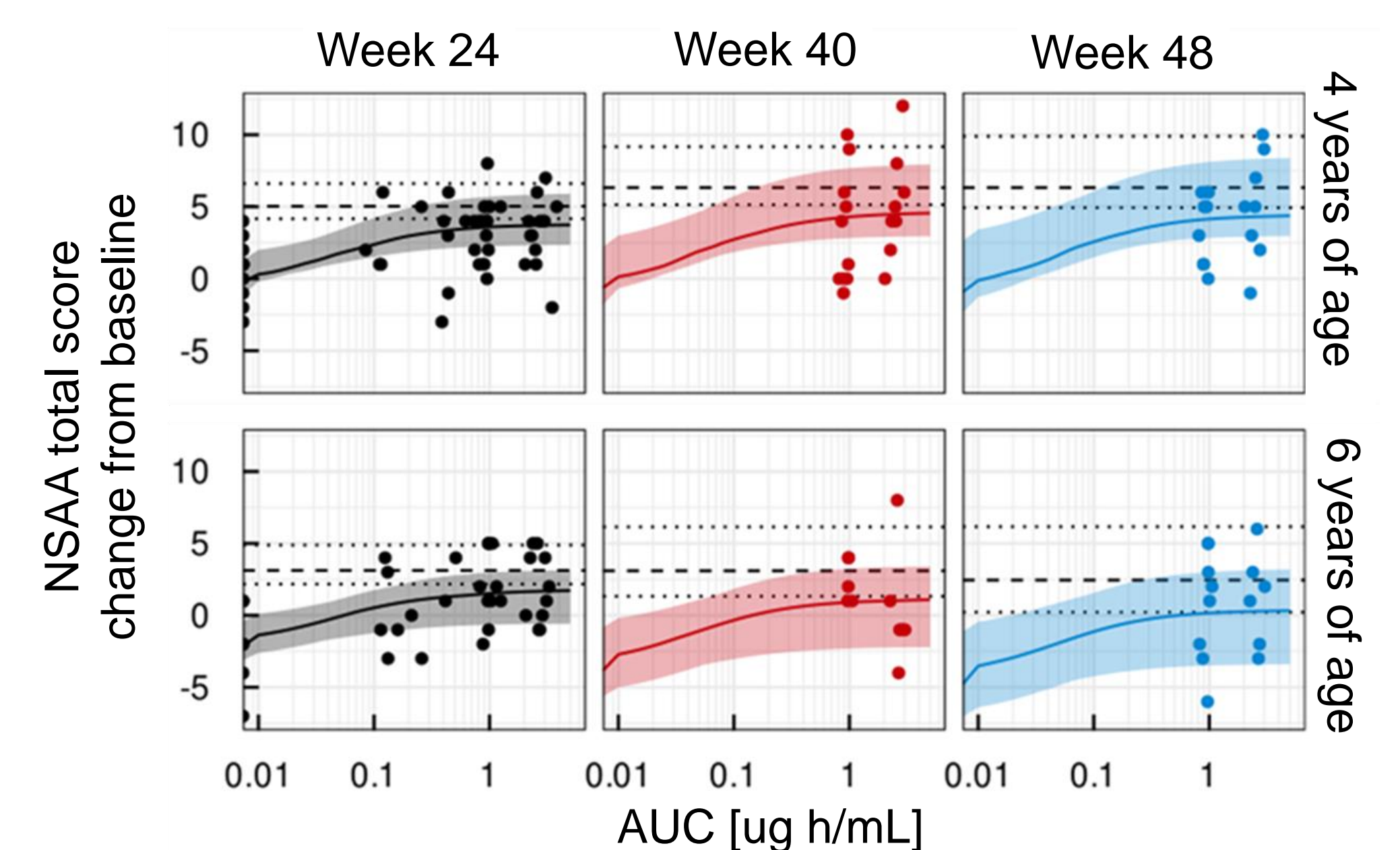
Population Pharmacokinetics

- Dose-proportional PK and no accumulation after two weeks of treatment
- Update of population PK model [1] based on 126 healthy adults, and 117 pediatric DMD patients.
- External validation was satisfactory over all age groups.



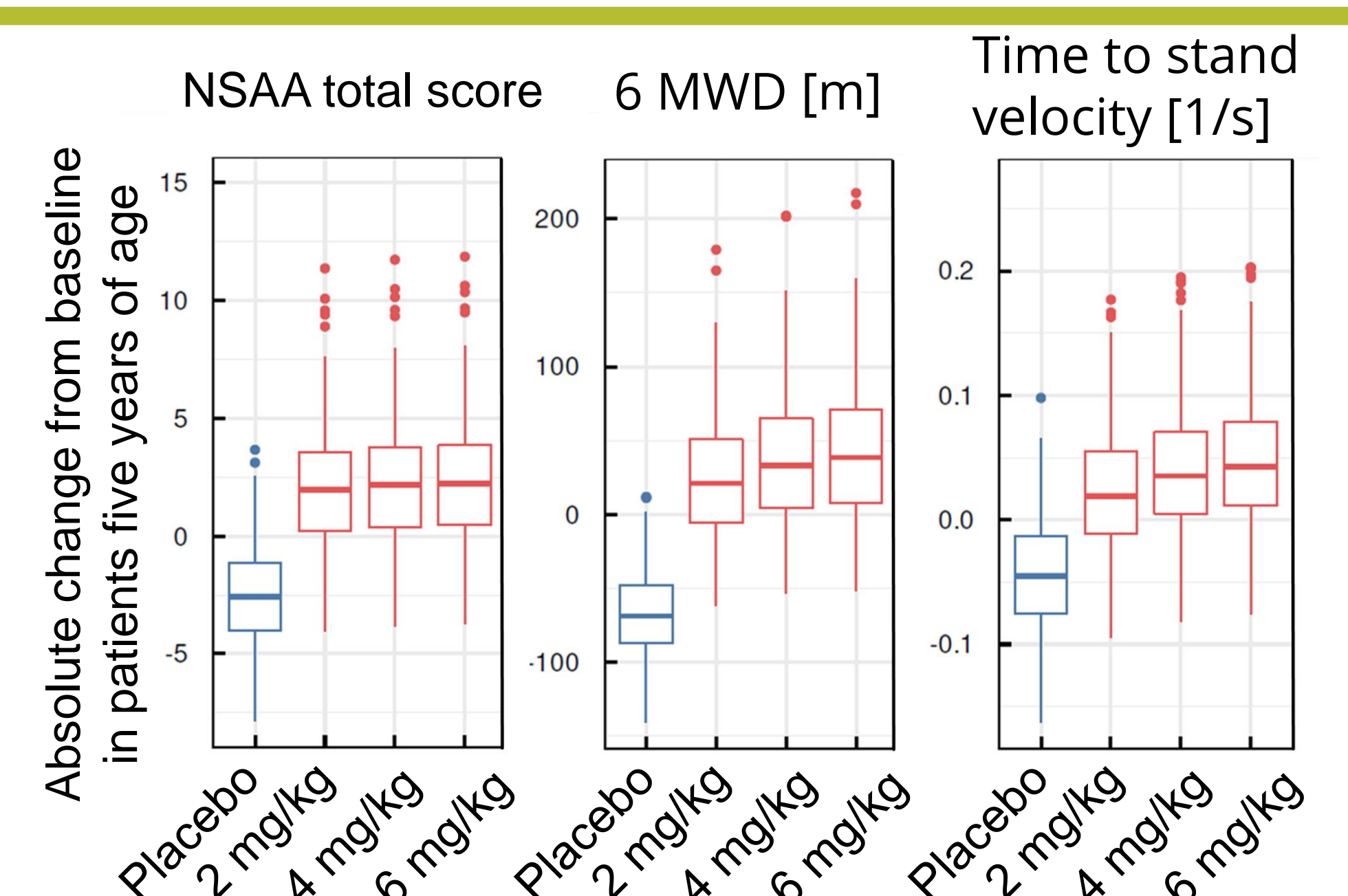
Efficacy Exposure-Response

- NSAA total score of 17-item test, six-minute walking distance (6MWD), and time to stand velocity [3] were considered to assess disease progression in DMD patients.
- Sigmoidal exposure-response models described the treatment effect including placebo response on change from baseline over 48 weeks in efficacy endpoints.
- Treatment was found to slow down disease progression and age at which the functional endpoints reached their maximum response.



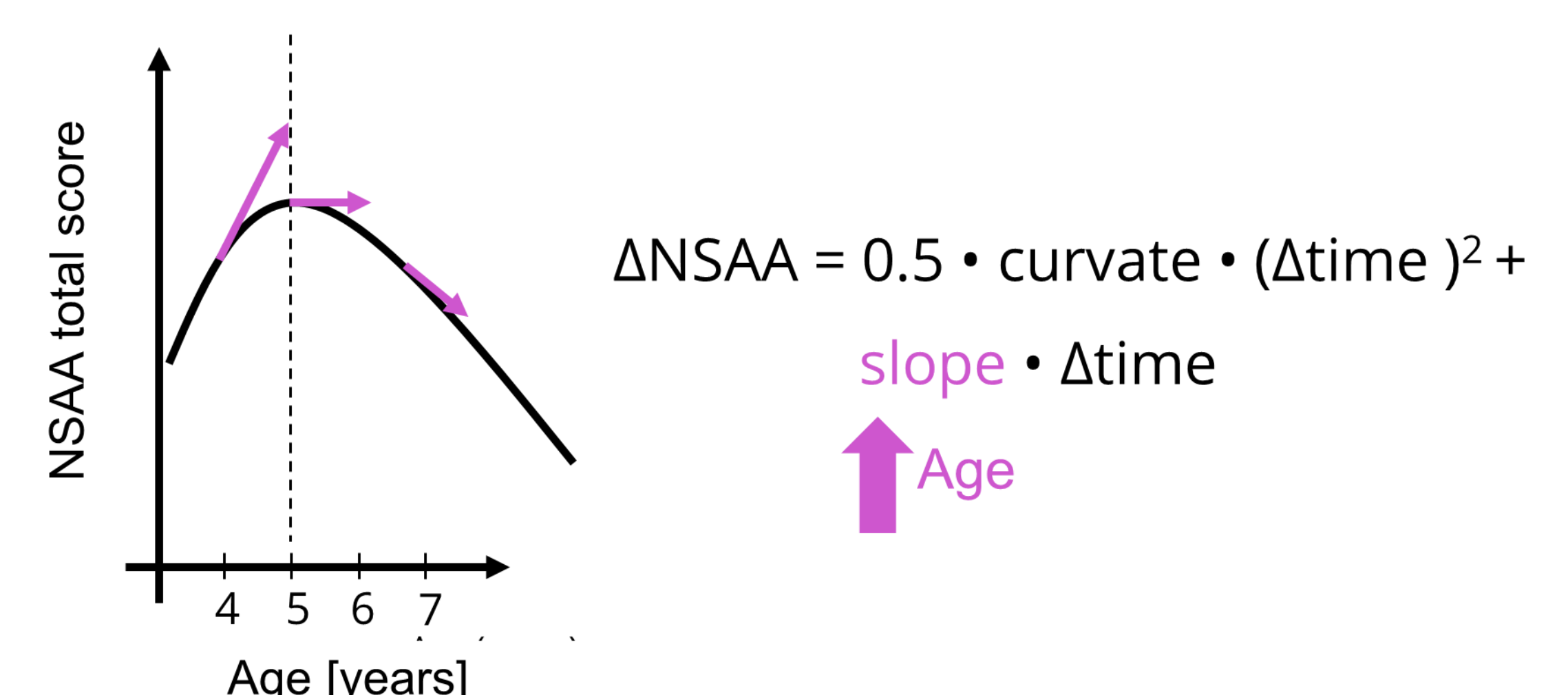
Clinical dose

- The highly individual disease progression was found to be the determining factor in the expected treatment effect.
- A similar one-year treatment effect of about 5 points in NSAA total score was to be expected for vamorolone doses of 2, 4, and 6 mg/kg/day.
- An increase in efficacy with increasing doses between 2 and 6 mg/kg/day was found for six-minute walk test and time to stand velocity.
- Overall, the analysis supported treatment with an initial dose of 6 mg/kg/day and potential down titration to 4 or 2 mg/kg/day, based on safety markers.



Methods

- The vamorolone dose-concentration relationship was assessed via a population PK approach.
- The vamorolone efficacy exposure-response relationship was assessed by a by time-dependent process, approximating disease progression by a parabola (quadratic equation).
- Covariates were identified in a step-wise covariate modelling approach and were assessed based on statistical significance and clinical relevance.
- Models were selected based on diagnostic plots, convergence, plausibility of parameter estimates, precision of parameter estimates and the Bayesian Information Criterion (BIC).
- All modeling was performed in NONMEM (V 7.5.1.) using IQRtools.



References: [1]: Mavroudis et al., 2019 [2]: Yáñez et al., 2011 [3]: Scott et al., 2012

Declaration of interests: Authors Ana de Vera and Catherine Dutreix are employed by Santhera AG. Authors Martin Fink, Daniel Kaschek, and Nils Bundgaard are employed by IntiQuan AG.

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