Abstract #235

PK/PD modeling to inform clinical development of an adeno-associated virus gene transfer therapy for Duchenne muscular dystrophy

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Acknowledgments and disclosures

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- These data are an encore of data first presented by L. East at the 27th International Annual Congress of the World Muscle Society (WMS) 2022

Disclosures

- LE, RAP, JS, AH and CW are employees of Sarepta Therapeutics and may have stock options
- LRRK is an employee of Sarepta Therapeutics, has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy, as well as financial consideration from Sarepta Therapeutics and Myonexus Therapeutics (now acquired by Sarepta Therapeutics). In addition, she is a co-inventor of AAVrh74.MHCK7.micro-dys technology

Objectives and overview

- To evaluate the PK/PD relationship between tissue vector genome exposure, biological efficacy and functional outcome in DMD^{mdx} mice following treatment with delandistrogene moxeparvovec (SRP-9001)

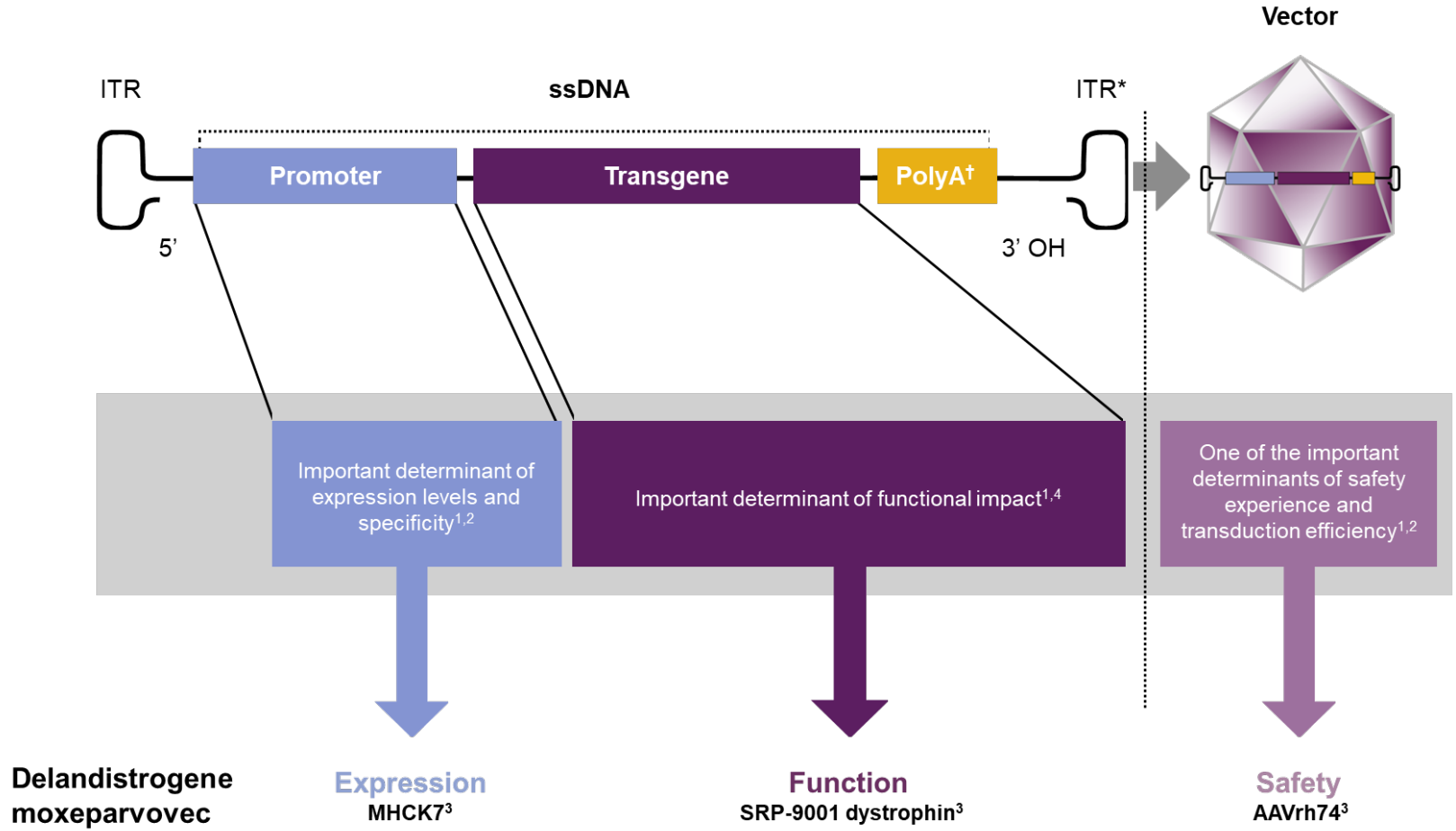
What does this study mean for the DMD community?

These findings provided foundational support for the therapeutic potential and clinical dose selection of delandistrogene moxeparvovec

DMD, Duchenne muscular dystrophy; mdx, muscular dystrophy X-linked; PD, pharmacodynamic; PK, pharmacokinetic.

Background

- Delandistrogene moxeparvovec is an investigational rAAV vector-based gene therapy designed to compensate for missing dystrophin in DMD by delivering a transgene encoding SRP-9001 dystrophin, an engineered dystrophin protein that retains key functional domains of the wild-type protein[1–4]
- Extensive dose-ranging evaluations were performed in a dystrophin-null mouse model (DMD^{mdx}), a representative model of DMD, to characterize the biodistribution and efficacy of delandistrogene moxeparvovec and support its clinical development[5–13]



*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (i.e. copies) it.
AAVrh74, adeno-associated virus rhesus isolate serotype 74; DMD, Duchenne muscular dystrophy; ITR, inverted terminal repeat; mdx, muscular dystrophy X-linked; MHCK, myosin-heavy-chain kinase; OH, hydroxyl; PolyA, polyadenylation; rAAV, recombinant adeno-associated virus; ssDNA, single-stranded DNA.
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11. Mendell JR, et al. Presented at WMS 2018; Poster #P.177; 12. Potter RA, et al. Presented at MDA 2019; Poster #P.57; 13. Nelson DM, et al. *Hum Mol Genet*. 2018; 27:2090–2100.

Methods

- Using data collected from DMD^{mdx} mice, the pharmacokinetic (PK)/pharmacodynamic (PD) relationship was evaluated, across a wide dose range (0.443, 0.7, 1.33, 2.66 and 4.01×10^{14} vg/kg) inclusive of the clinically proposed dose of 1.33×10^{14} vg/kg, between the following variables:

Dose

Tissue vector genome exposure achieved via transduction (PK endpoint)

SRP-9001 dystrophin protein expression (biological PD endpoint, immunofluorescence [IF] percent dystrophin-positive fibers [PDPF])

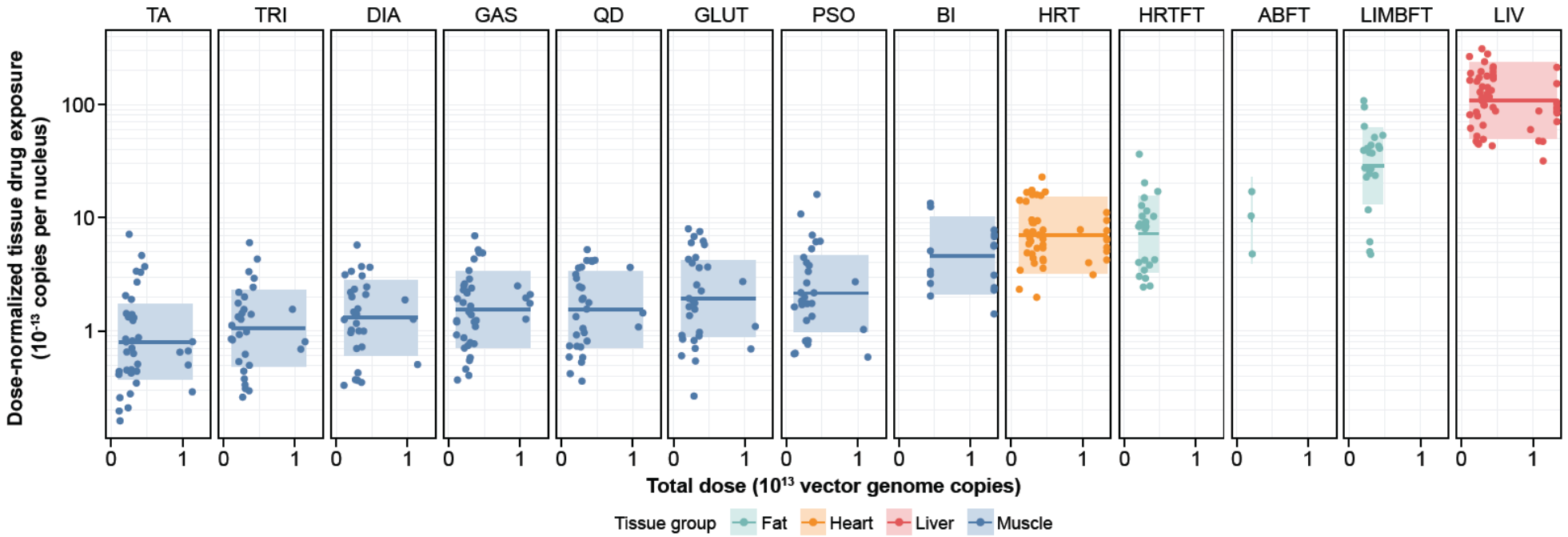
Motor function improvement (functional PD endpoint, relative specific force in the diaphragm and tibialis anterior)

- The relationship between the biomarker of biological efficacy (SRP-9001 dystrophin protein expression) and motor function improvement was also assessed

DMD, Duchenne muscular dystrophy; IF, immunofluorescence; mdx, muscular dystrophy X-linked; PD, pharmacodynamic; PDPF, percent dystrophin-positive fibers; PK, pharmacokinetic; vg, vector genome.

Biodistribution and tissue PK

Dose-normalized tissue drug exposure versus total vector genome dose across tissues*



Delandistrogene moxeparvovec exhibits dose-dependent increases in tissue drug exposure and apparent linear PK characteristics

- Results demonstrate dose-proportionality of tissue drug exposure across different tissues for intended commercial process delandistrogene moxeparvovec material

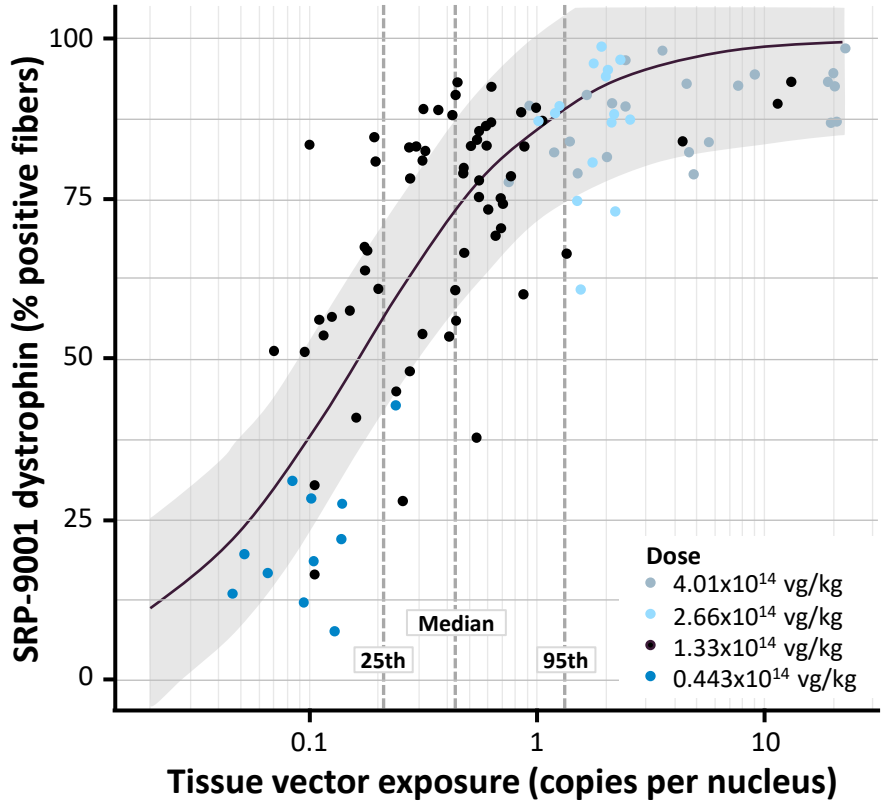
*Horizontal lines and ribbons correspond to prediction and 68% prediction interval of constant model.

ABFT, abdominal fat; BI, biceps; DIA, diaphragm; GAS, gastrocnemius; GLUT, gluteus; HRT, heart; HRTFT, heart fat; LIMBFT, limb fat; LIV, liver; PK, pharmacokinetic; PSO, psoas major; QD, quadriceps femoris; TA, tibialis anterior; TRI, triceps brachii.

PK/PD relationship with SRP-9001 dystrophin (IF PDPF)

- Tissues from TRI, GAS and QD were selected as clinically relevant muscle groups for human biopsies
- Across these tissues, the non-linear PK/PD relationship was best described by a sigmoid Emax model with Emax fixed to 100% PDPF and an EC_{50} of 0.163 vg copies/nucleus (RSE of 8.15%)
- PDPF values approached saturation at the clinically proposed dose of 1.33×10^{14} vg/kg, for which the median drug exposure was 0.438 vg copies/nucleus

Percent positive SRP-9001 dystrophin-expressing fibers versus drug exposure in TRI, GAS and QD

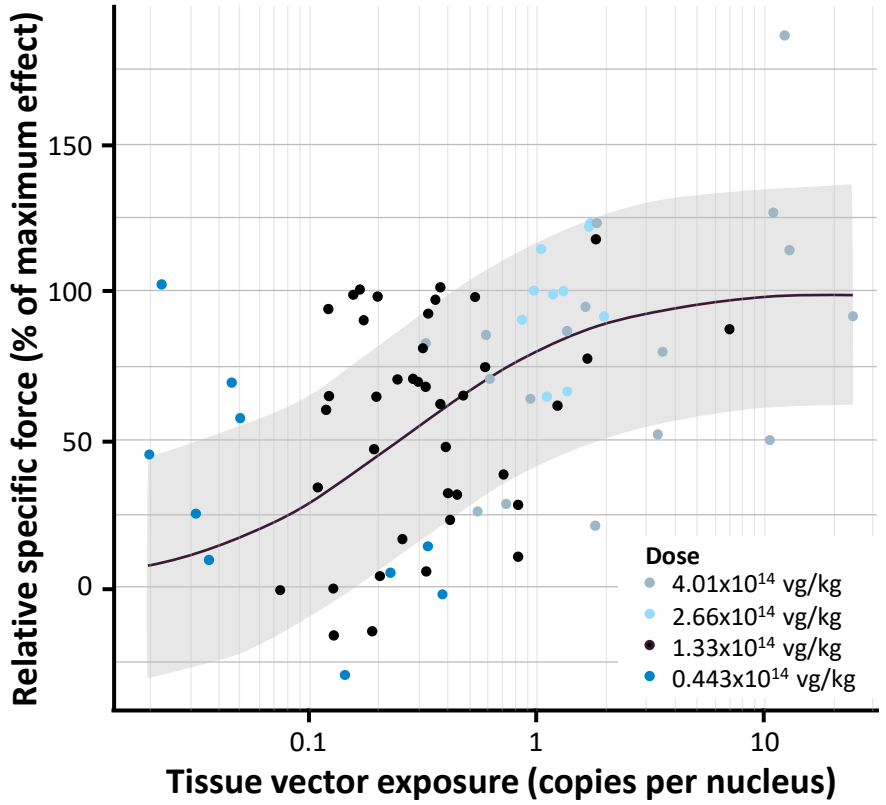


EC_{50}, half-maximal effective concentration; Emax, maximum effect; GAS, gastrocnemius; IF, immunofluorescence; PD, pharmacodynamic; PDPF, percent dystrophin-positive fibers; PK, pharmacokinetic; QD, quadriceps femoris; RSE, relative standard error; TRI, triceps brachii; vg, vector genome.

PK/PD relationship with motor function

- The PK relationship between motor function outcome (represented by relative specific force in the DIA and TA) and tissue drug exposure was:
  - Non-linear
  - Best described by an Emax model with Emax fixed to 100% relative specific force and an EC_{50} of 0.254 vg copies/nucleus (RSE of 22.3%)

Relative specific force versus drug exposure in DIA and TA



DIA, diaphragm; EC_{50}, half-maximal effective concentration; Emax, maximum effect; PD, pharmacodynamic; PK, pharmacokinetic; RSE, relative standard error; TA, tibialis anterior; vg, vector genome.

Parameter estimates of delandistrogene moxeparvovec exposure

Non-linear PK/PD relationships were quantified between delandistrogene moxeparvovec tissue vector exposure, SRP-9001 dystrophin protein expression, and motor function improvement (relative specific force)

Delandistrogene moxeparvovec parameter estimates of the drug exposure–percent SRP-9001 dystrophin-expressing fibers model in TRI, GAS and QD

Parameter	Value	RSE %	Comment
EC_{50}	0.163	8.15%	Half-maximal effective drug exposure (copies per nucleus)
Emax	100 (fixed)	–	Maximal PDPF effect (%)
Error model	14.6	–	Additive error (residual SE)

Model: PDPF ~ 100 × vg/(vg+EC_{50}). Values rounded to 3 significant digits.

Delandistrogene moxeparvovec parameter estimates of the drug exposure-relative specific force model

Parameter	Value	RSE %	Comment
EC_{50}	0.254	22.3%	Half-maximal effective drug exposure (copies per nucleus)
Emax	100 (fixed)	–	Maximal mdx relative specific force effect (%)
Error model	37.7	–	Additive error (residual SE)

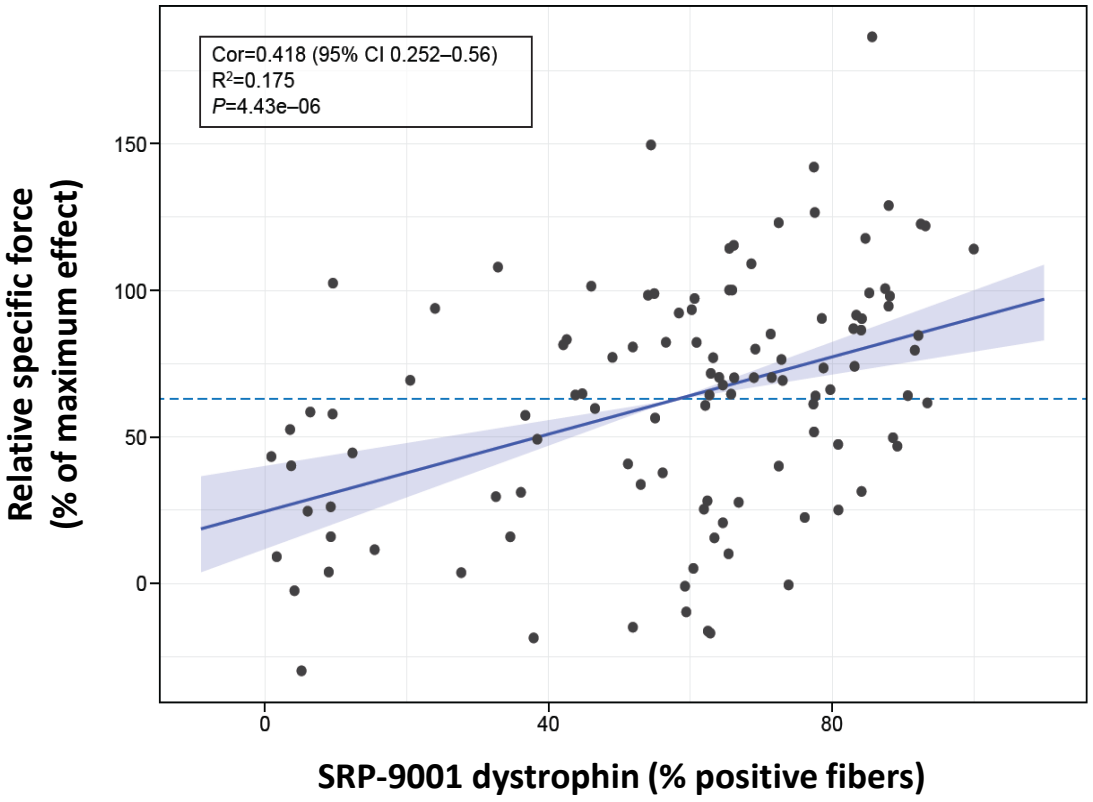
Model: MDXrelSF ~ 100 × vg/(vg+EC_{50}). Values rounded to 3 significant digits.

EC_{50}, half-maximal effective concentration; Emax, maximum effect; GAS, gastrocnemius; mdx, muscular dystrophy X-linked; MDXrelSF, mdx relative specific force; PD, pharmacodynamic; PDPF, percent dystrophin-positive fibers; PK, pharmacokinetic; QD, quadriceps femoris; RSE, relative standard error; SE, standard error; TRI, triceps brachii; vg, vector genome.

Correlation between relative specific force and protein expression

- A positive and statistically significant correlation (P=4.43×10^{-6}) was observed between functional outcome and percent positive SRP-9001 dystrophin-expressing fibers
- A strong linear correlation was not expected, as exploratory modeling of the relationship between motor function and SRP-9001 dystrophin protein expression (PDPF) indicated a non-linear relationship that was best quantified using an Emax model

Relative specific force versus percent positive SRP-9001 dystrophin-expressing fibers

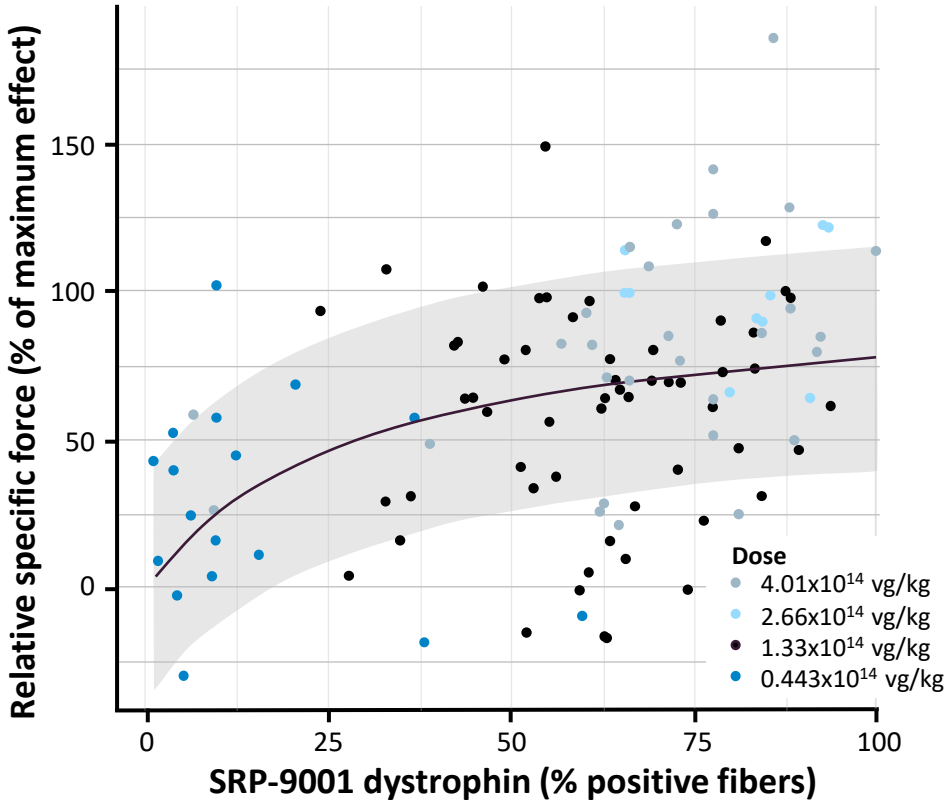


CI, confidence interval; Cor, correlation; Emax, maximum effect; PDPF, percent dystrophin-positive fibers; R^2, coefficient of determination.

Relative specific force versus PDPF

- The relationship between motor function outcome (represented by relative specific force) and PDPF appeared to be non-linear and was best described by an Emax model fixed to 100% relative specific force and an EC_{50} of 28.6% PDPF

Relative specific force versus PDPF in DIA and TA



DIA, diaphragm; EC_{50}, half-maximal effective concentration; Emax, maximum effect; PDPF, percent dystrophin-positive fibers; TA, tibialis anterior; vg, vector genome.

Conclusions

- For the first time, data from tissue vector genome expression, a biomarker of biological efficacy (measured as SRP-9001 dystrophin protein expression), and motor function efficacy were used to quantify and demonstrate PK/PD relationships for an AAV-based gene transfer therapy in an animal disease model of DMD
- Linear kinetics with a dose-proportional increase in tissue drug exposure were demonstrated across the nearly 10-fold dose range (4.43×10^{13}–4.01×10^{14} vg/kg), and in all tissues
- The non-linear PK/PD relationship characterized for SRP-9001 dystrophin protein expression (PDPF) and motor function improvement with a saturable profile suggests that the clinical dose of 1.33×10^{14} vg/kg is approaching the plateau of biological efficacy and functional improvement in the animal disease model
- The non-clinical results continue to support the therapeutic benefit observed in clinical trials as well as the clinical dose selection of delandistrogene moxeparvovec

AAV, adeno-associated virus; DMD, Duchenne muscular dystrophy; PD, pharmacodynamic; PDPF, percent dystrophin-positive fibers; PK, pharmacokinetic; vg, vector genome.