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

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Objective

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.

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 ($4.43x10^{13}$–$4.01x10^{14}$ 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 suggest that the clinical dose of $1.33x10^{14}$ 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.

BACKGROUND

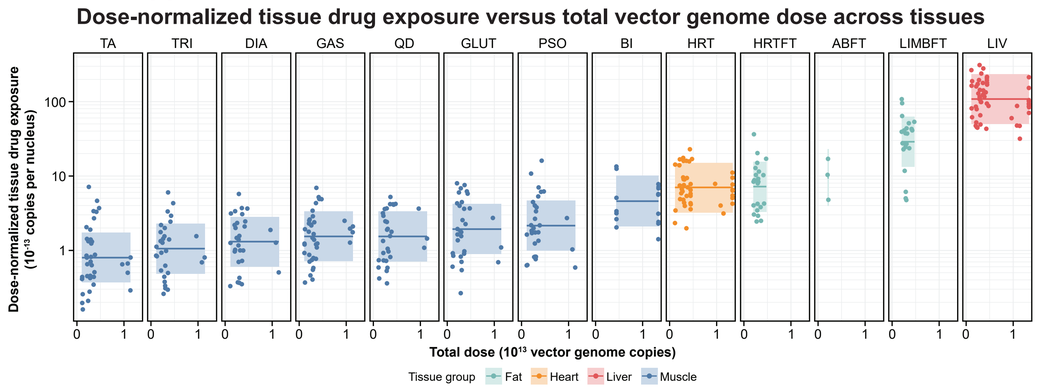
- Delandistrogene moxeparvovec is an investigational rAAV vector-based gene therapy, designed to compensate for missing dystrophin in DMD by delivering a transgene encoding SRP-9001 dystrophin, an engineered dystrophin protein that retains key functional domains of the wild-type protein.[1–4]
- Extensive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

METHODS

- The PK/PD relationship was evaluated between dose, tissue vector genome exposure (i.e. PK), SRP-9001 dystrophin protein expression (i.e. PD; analyzed via PDPF and western blot), and motor function improvement (relative specific force from DIA and TA) using data collected from DMD^{mdx} mice and 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 $1.33x10^{14}$ vg/kg.
- The relationship between the biomarker of biological efficacy (SRP-9001 dystrophin protein expression) and motor function improvement was also assessed.

RESULTS

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

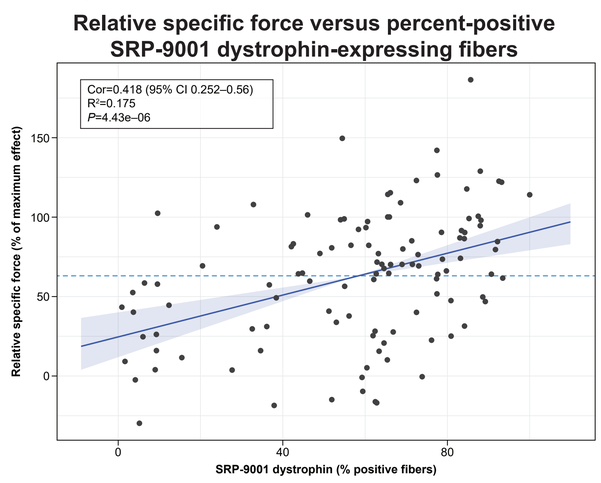


Horizontal lines and ribbons correspond to prediction and 68% prediction interval of constant model.

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

Correlation between relative specific force and protein expression in DMD^{mdx} mice following treatment with delandistrogene moxeparvovec

- 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.



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)

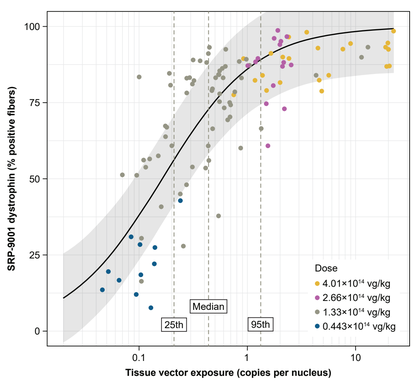
Model: PDPF ~ 100 × vg/(vg+EC_{50}). Values rounded to 3 significant digits.

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)

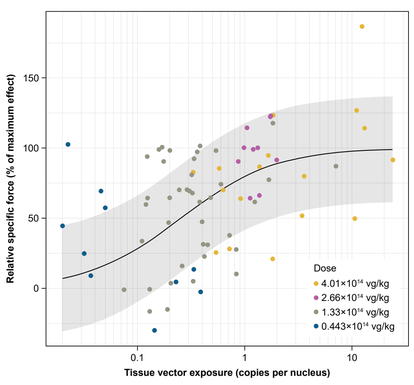
Model: MDXrelSF ~ 100 × vg/(vg + EC_{50}). Values rounded to 3 significant digits.

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



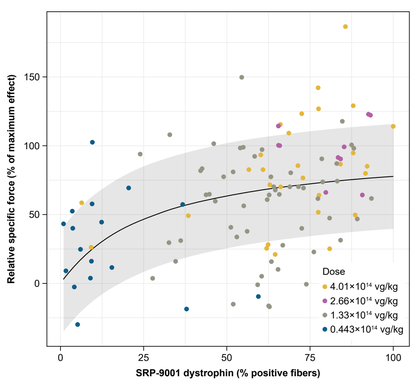
- Tissues from TRI, GAS, and QD were selected as clinically relevant muscle groups for human biopsies.
- Across these tissues, the non-linear PK/PD relationship was best described by a sigmoid Emax model with Emax fixed to 100% PDPF and an EC_{50} of 0.163 vg copies/nucleus.
- PDPF values approached 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.

Relative specific force versus drug exposure in DIA and TA



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

Relative specific force versus PDPF in DIA and TA



- 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.

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ABBREVIATIONS

AAV, adeno-associated virus; ABFT, abdominal fat; BI, biceps; CI, confidence interval; Cor, correlation; DIA, diaphragm; DMD, Duchenne muscular dystrophy; EC_{50}, half maximal effective concentration; Emax, maximum effect; GAS, gastrocnemius; GLUT, gluteus; HRT, heart; HRTFT, heart fat; LIMBFT, limb fat; LIV, liver; mdx, muscular dystrophy X-linked; MDXrelSF, mdx relative specific force; PD, pharmacodynamic; PDPF, percent dystrophin-positive fibers; PK, pharmacokinetic; PSO, psoas major; QD, quadriceps femoris; rAAV, recombinant adeno-associated virus; R^2, coefficient of determination; RSE, relative standard error; SE, standard error; TA, tibialis anterior; TRI, triceps brachii; vg, vector genome.

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