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

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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.
- The non-linear PK/PD relationship characterised for SRP-9001 dystrophin protein expression (PDPF) and motor function improvement with a saturable response support 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 AAV-based gene transfer therapy for DMD, developed for targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin — a shortened and functional dystrophin protein.[1-4]
- Extensive dose-ranging evaluations were performed in a dystrophin-null mouse model (DMD^{mdx}), representative of DMD, to characterise the biodistribution and efficacy of delandistrogene moxeparvovec and support its clinical development.[5-13]

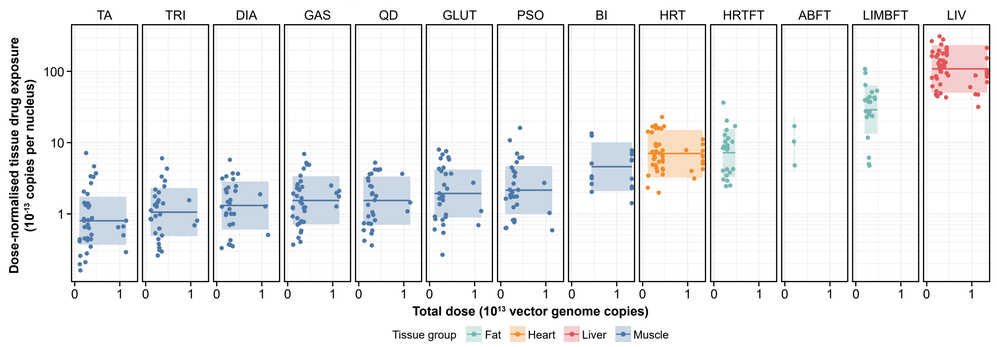
METHODS

- The PK/PD relationship was evaluated between tissue vector genome exposure (PK), PD response on SRP-9001 dystrophin protein expression (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, 4.01x10^{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 functional improvement was also assessed.

RESULTS

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

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



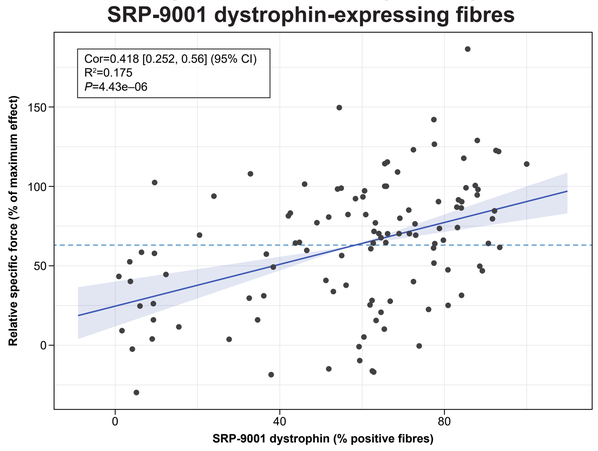
- Results demonstrate dose-proportionality of tissue drug exposure across different tissues for intended commercial process delandistrogene moxeparvovec material.

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

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 fibres.
- A strong linear correlation was not expected, as exploratory modelling 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 fibres



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 fibres 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)

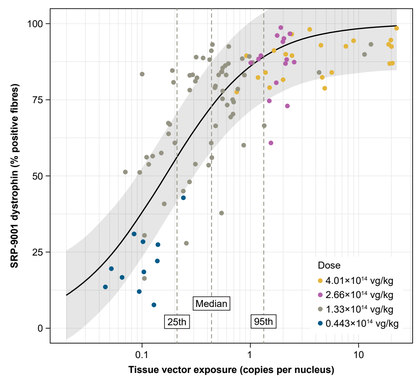
Model: PDPF ~ 100 x vg/(vg+EC_{50}). Values rounded to 3 significant digits.

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)

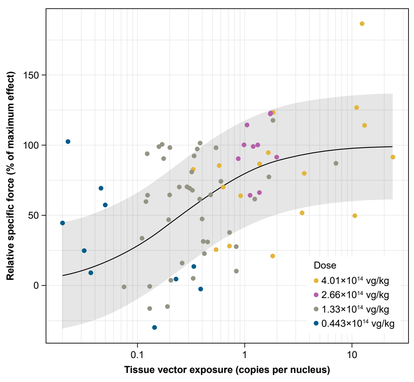
Model: MDXrelSF ~ 100 x vg/(vg + EC_{50}). Values rounded to 3 significant digits.

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



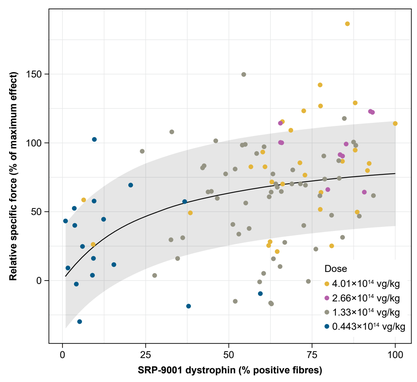
- Tissue from TRI, GAS and QD were selected as clinically relevant muscle groups for human biopsies.
- Across these tissues, the non-linear PK/PD relationship was best described by a sigmoid Emax model with Emax fixed to 100% PDPF and an EC_{50} of 0.163 vg copies/nucleus.
- PDPF values approached saturation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

ABFT, abdominal fat; AAV, adeno-associated virus; 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 fibres; PK, pharmacokinetic; PSO, psoas major; QD, quadriceps femoris; 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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