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Analysis of vector shedding following treatment with delandistrogene moxeparvovec, an investigational rAAVrh74-based gene therapy for Duchenne muscular dystrophy

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Objective

To evaluate the extent and magnitude of vector shedding following administration of delandistrogene moxeparvovec (SRP-9001).

What does this study mean for the DMD community?

Peak vector shedding generally occurs the day after infusion, then exponentially declines to insignificant levels by Week 4.

CONCLUSIONS

- Peak vector shedding generally occurs the day after infusion, then exponentially declines to insignificant levels by Week 4.
- There was considerable variability in shed vector on Day 1 following treatment, while a high proportion of observations in the terminal phase were BLOD.
- These conclusions conform with non-clinical vector shedding and biodistribution data in DMD animal models and data and literature for other AAV-based gene therapy products currently approved or in development.

BACKGROUND

- Delandistrogene moxeparvovec is an investigational gene transfer therapy developed for targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin — an engineered, shortened, functional dystrophin protein packaged in an AAV vector.[1-4]
- Due to the biological properties of viruses, vector shedding is expected following the administration of a virus-based gene therapy product, which raises theoretical possibility of exposure from treated to untreated individuals, such as patient family members and caregivers.[5]
- As a precaution, patient family members and caregivers often take great lengths to reduce the potential for exposure to the viral vector (e.g., by sequestering patient siblings from the treated patient).[5]

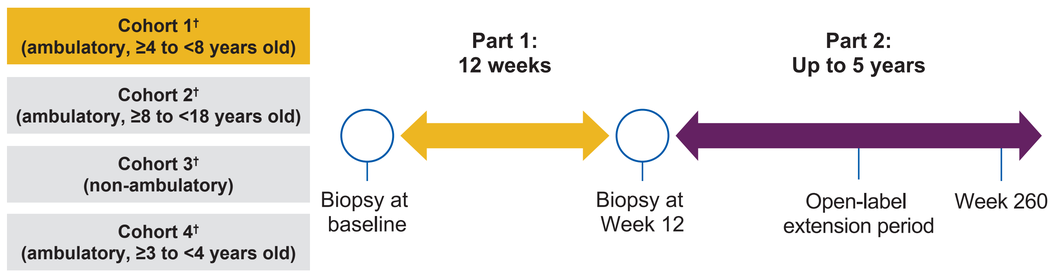
METHODS

- We evaluated the extent and magnitude of shedding and clearance from delandistrogene moxeparvovec as well as the potential for untreated individuals to be exposed to the product, using interim data from ENDEAVOR (Study 103; NCT04626674), a Phase 1 study assessing the safety and expression of intended commercial process delandistrogene moxeparvovec material in boys with DMD.
  - Delandistrogene moxeparvovec vector exposure in saliva, urine, and faeces was quantified by droplet digital polymerase chain reaction in ENDEAVOR (N=20) to characterise vector shedding (proportion of observations BLOD) in participants. This method uses a vector-specific primer probe set for sequences of the MHCK7 promoter (within the SRP-9001 dystrophin gene cassette).

RESULTS

Clinical assessment of delandistrogene moxeparvovec vector shedding in participants from ENDEAVOR

Study design: Single IV infusion dose of 1.33x10^{14} vg/kg* of intended commercial process delandistrogene moxeparvovec material



*Linear qPCR. †Only 1-year data for Cohort 1 are presented in this poster; 1-year data for other cohorts are not yet available.

- ENDEAVOR is an ongoing, open-label, single-arm, single-dose, Phase 1b study with four cohorts and a two-part follow-up period conducted at five sites in the USA using the intended commercial process material. Samples from different clinical biomaterials and at predefined time points over the course of the study (260 weeks) were collected from subjects across the four cohorts.

Baseline demographics of Cohort 1 in ENDEAVOR

Characteristic	Total for Cohort 1 (N=20) Mean (SD)
Age, years*	5.8 (1.1)
Height, cm	108.8 (7.7)
Dosing weight, kg	21.2 (4.2)
Years since DMD diagnosis	2.4 (1.4)

*Age distribution: 11 (55.0%) patients in the age category 4–5 years and nine (45.0%) patients in the age category 6–7 years. †Following the two new treatment-related SAEs observed in Cohort 2 (safety data for Cohort 2 are not presented here), inclusion criteria were amended such that mutations between or including exons 1 and 17 were not eligible.

Evaluation of vector exposure in various biomaterials after administration of delandistrogene moxeparvovec in participants from ENDEAVOR (Cohort 1)

Biomaterial	N	N samples	N BLOD samples*	N samples included in analysis	Cut-off used in data analysis, days	Time of last observation above LOD, days†
Saliva	18	132	67 (50.8%)	115 (87.1%)	100	84.17
Urine	20	172	76 (44.2%)	154 (89.5%)	200	175.96
Faeces	10	58	10 (17.2%)	54 (93.1%)	200	90.92

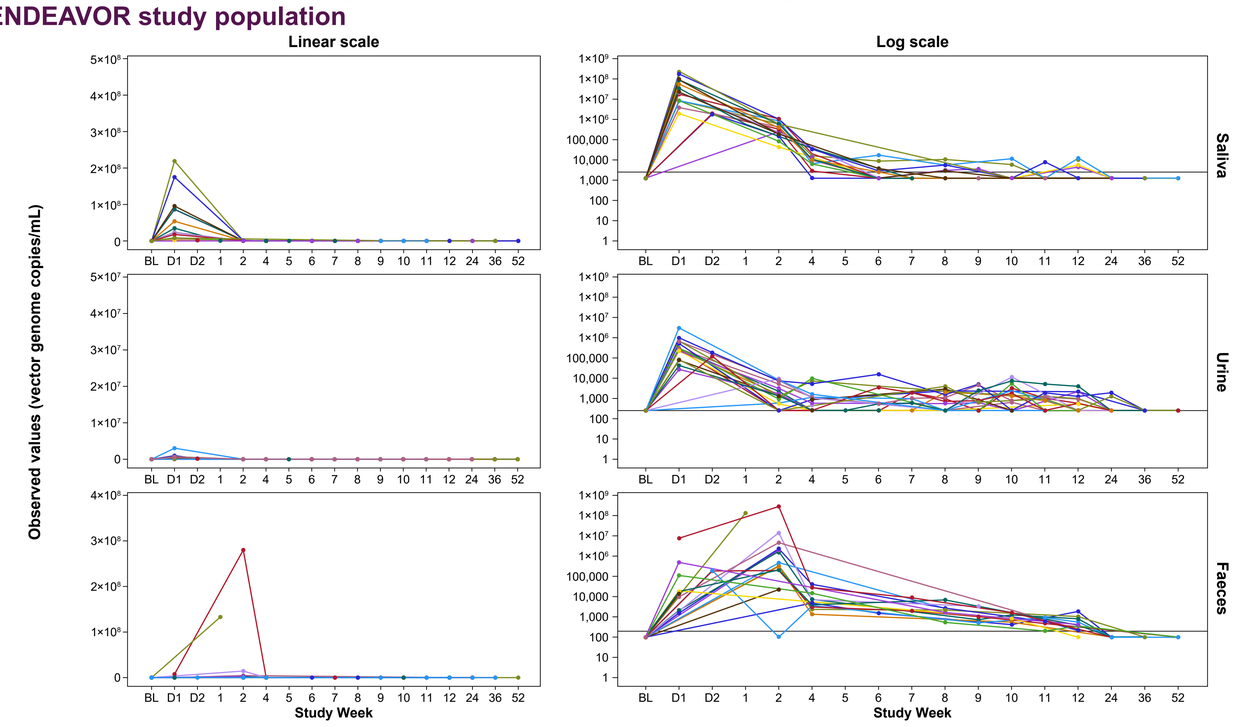
*These records were not excluded from the analysis but were set to LLOQ (M3 method) for population PK model development. For the number of BLOD samples and number of samples included in the analysis, the total number and percentage of the number of total samples is provided. †Values based on a modelling prediction.

Mean vector genome DNA at peak compared with Week 4

- The vector DNA concentration peaked roughly at Day 1 in saliva and urine, and at Week 2 in faeces. The mean concentration in all samples declined significantly by Week 4.
- The percentage decrease from peak (Day 1 for saliva and urine; Week 2 for faeces) to Week 4 was greater than 99%.

Sample	Mean peak concentration (vgc/mL)	Mean Week 4 concentration (vgc/mL)	Percentage decrease from peak to Week 4
Saliva	5.6x10^{7} (n=15; Day 1)	1.4x10^{4} (n=12)	99.97%
Urine	4.8x10^{5} (n=17; Day 1)	1.7x10^{3} (n=18)	99.64%
Faeces	2.4x10^{7} (n=13; Week 2)	1.1x10^{4} (n=11)	99.99%

Quantification of delandistrogene moxeparvovec vector shedding over time for Cohort 1 of the ENDEAVOR study population



- The horizontal line is the reference line for LOD: 2,500 for saliva samples, 500 for urine samples, and 200 for faeces samples.
- There was considerable variability in shed vector on Day 1 following treatment, while a high proportion of observations in the terminal phase were BLOD.
- A delayed rate of kinetics of vector shed was observed in faeces relative to saliva and urine samples due to the innate differences between the biomaterials. The local peak seen in vector shedding in faeces declined by >99% from Weeks 2–4.
- Results from biodistribution and vector shedding data obtained in non-clinical studies were consistent with clinical shedding results and support the clinical shedding analysis.

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ABBREVIATIONS

AAV, adeno-associated virus; BL, baseline; BLOD, below the limit of detection; D, day; DMD, Duchenne muscular dystrophy; IV, intravenous; LOD, limit of detection; LLOQ, lower limit of quantitation; MHCK7, α-myosin heavy-chain creatine kinase 7; PK, pharmacokinetics; qPCR, quantitative polymerase chain reaction; rAAVrh74, recombinant AAV rhesus isolate serotype 74; SAE, serious adverse event; SD, standard deviation; vg, vector genome; vgc, vector genome copies.

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