Model-Based Evaluation of Delandistrogene Moxeparvovec Adeno-Associated Virus Pharmacokinetics and Safety Implications

Lilly East,[1] **Stefanie Mason**,[1] **Eddie Darton**,[1] **Danielle A. Griffin**,[1] **Oliver Rogers**,[1] **Xiaolan Zhang**,[1] **Sarah Lewis**,[1] **Michael Derks**,[2] **Louise R. Rodino-Klapac**[1]

[1]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [2]Roche Pharma Research and Early Development, Roche Products Ltd, Welwyn Garden City, UK

Background

- Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disease caused by pathogenic variants in the *DMD* gene that result in the absence of functional dystrophin[1]
- Delandistrogene moxeparvovec is a recombinant adeno-associated virus rhesus isolate serotype 74 (rAAVrh74) vector-based gene transfer therapy that delivers a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered, functional form of dystrophin shown to stabilize or slow disease progression in DMD[2-5]
- Delandistrogene moxeparvovec is approved in the US and in other selected countries[6-13]
- Study 102 (NCT03769116) is a randomized, double-blind, placebo-controlled study of delandistrogene moxeparvovec in ambulatory patients with DMD aged ≥4 to <8 years[14]
- ENDEAVOR (NCT04626674) is a 2-part, open-label, phase 1b study assessing the transduction, expression, and safety of delandistrogene moxeparvovec in patients with DMD[15]

Objectives

- Use data from participants with DMD enrolled in Study 102 and ENDEAVOR (cohorts 1-3) clinical trials to
  - Characterize the pharmacokinetics (PK) of the delandistrogene moxeparvovec vector genome in serum and excreta (urine, feces, and saliva) using population PK modeling
  - Assess the relationship between delandistrogene moxeparvovec clinical safety biomarkers and the dose administered or serum drug exposure

Methods

PK and safety biomarker samples

- Serum and excreta samples were obtained from patients enrolled in ENDEAVOR (cohorts 1-3; N=33)
- Samples for clinical safety biomarker analyses were obtained from patients (N=74) enrolled in ENDEAVOR (cohorts 1-3; n=33) and Study 102 (n=41)
- Study 102 and ENDEAVOR study designs and patient populations have been previously described[1,16,17]

Delandistrogene moxeparvovec dose and drug exposure

- Dose administered was quantified as total capsid load or total vector genome copies administered
- Vector genome concentration was measured and quantified in the serum and excreta using droplet digital polymerase chain reaction
- Serum and excreta vector exposure–time data were characterized through population PK modeling
- Serum vector exposure metrics (peak concentration [C_{max}] and area under the curve [AUC] over 130 days) were determined through simulation of individual population PK model parameters obtained by empirical Bayes estimates

Clinical safety biomarkers

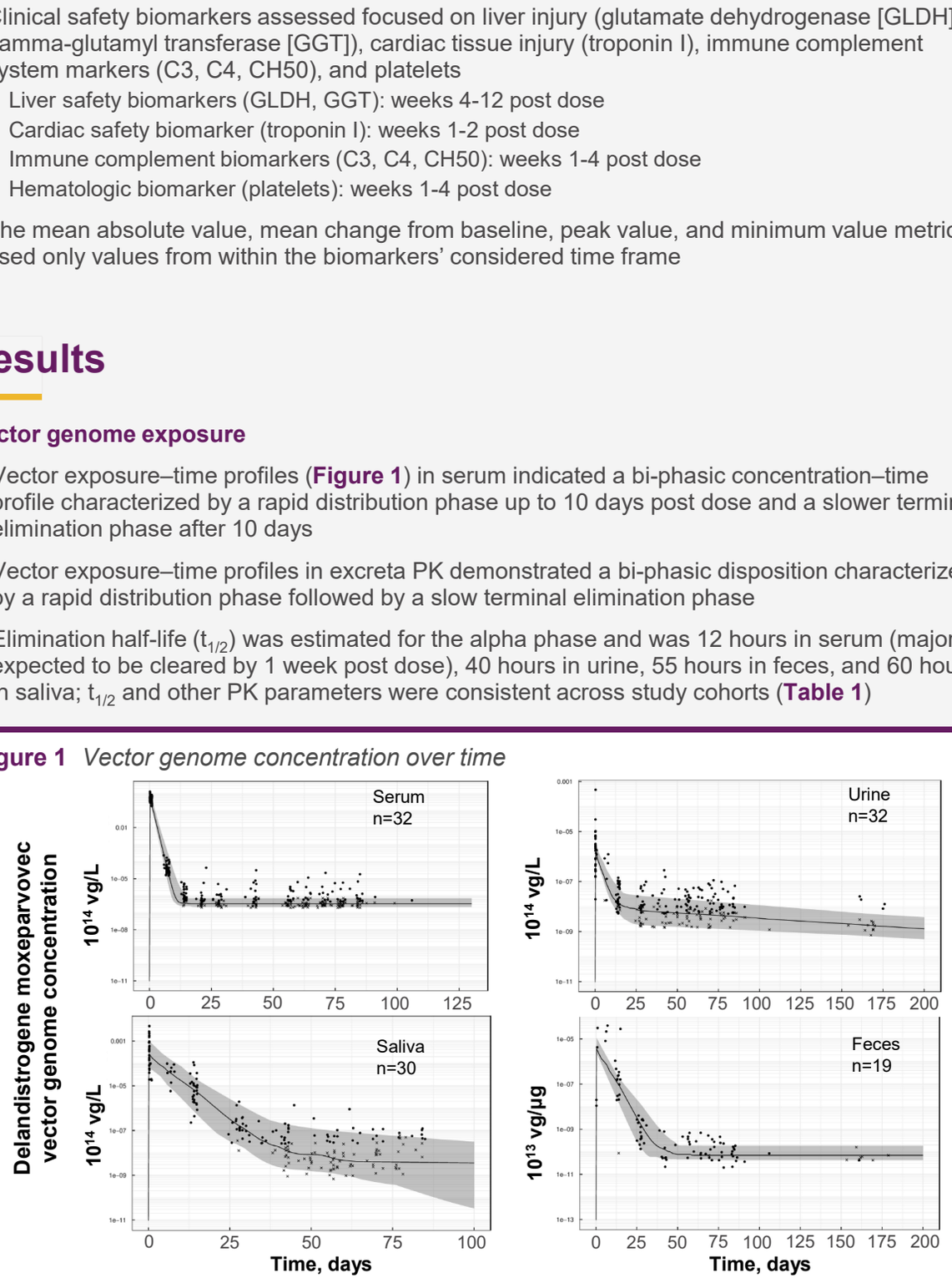
- Relationships between delandistrogene moxeparvovec clinical safety biomarker and dose administered or serum drug exposure were assessed
- Clinical safety biomarkers assessed focused on liver injury (glutamate dehydrogenase [GLDH], gamma-glutamyl transferase [GGT]), cardiac tissue injury (troponin I), immune complement system markers (C3, C4, CH50), and platelets
  - Liver safety biomarkers (GLDH, GGT): weeks 4-12 post dose
  - Cardiac safety biomarker (troponin I): weeks 1-2 post dose
  - Immune complement biomarkers (C3, C4, CH50): weeks 1-4 post dose
  - Hematologic biomarker (platelets): weeks 1-4 post dose
- The mean absolute value, mean change from baseline, peak value, and minimum value metrics used only values from within the biomarkers' considered time frame

Results

Vector genome exposure

- Vector exposure–time profiles (**Figure 1**) in serum indicated a bi-phasic concentration–time profile characterized by a rapid distribution phase up to 10 days post dose and a slower terminal elimination phase after 10 days
- Vector exposure–time profiles in excreta PK demonstrated a bi-phasic disposition characterized by a rapid distribution phase followed by a slow terminal elimination phase
- Elimination half-life ($t_{1/2}$) was estimated for the alpha phase and was 12 hours in serum (majority expected to be cleared by 1 week post dose), 40 hours in urine, 55 hours in feces, and 60 hours in saliva; $t_{1/2}$ and other PK parameters were consistent across study cohorts (**Table 1**)

Figure 1 *Vector genome concentration over time*



Simulations were performed with individual parameter estimates. The curves represent the median of simulated data with the range (as the 5th and 95th percentile of the simulated data). Points indicate individual data points. Crosses indicate below (lower) limit of detection/quantification (BLOD/BLOQ) observations imputed by individual predictions.

Table 1 *Summary statistics of population PK parameters for serum vector genome exposure by ENDEAVOR study cohort*

Parameter, geometric mean (CV%)[a]	Cohort 1 Ambulatory 4-7 years of age n=20	Cohort 2 Ambulatory 8-12 years of age n=6[b]	Cohort 3 Non-ambulatory 9-20 years of age n=6
T_{max}, median (min-max), h	2.4 (2.4-2.4)	2.4 (2.4-3.1)	2.9 (2.4-3.8)
Total CL, L/h	0.79 (10.2)	1.06 (10.8)	1.04 (27.8)
$t_{1/2,\alpha}$, h	12.4 (11.1)	12.2 (16.8)	11.8 (9.0)
Central volume, L	45.4 (8.7)	44.7 (12.4)	45.6 (12.3)
Peripheral volume, L	3.8×10^7 (17.0)	5.3×10^7 (9.7)	4.7×10^7 (37.0)

[a]All parameters are reported as geometric mean (CV%) except for T_{max}, which is reported as median (min-max).
[b]One patient was removed from the analysis as <4 observations were available after restricting the time frame to 130 days.
CL, clearance; CV%, geometric coefficient of variation; PK, pharmacokinetic; $t_{1/2,\alpha}$, distribution half-life; T_{max}, time to maximum serum vector exposure.

Clinical safety biomarkers

Troponin I (Figure 2A-B)

- Peak troponin I levels were mostly within the normal range (0-0.04 µg/L)
- Some patients had higher troponin I levels (0.05-0.23 µg/L), but these remained below the highest baseline values
- There was no apparent relationship between troponin I levels and capsid load or vector genome exposure (C_{max}, AUC)

C3 (Figure 2C)

- C3 levels decreased post dose but remained within the normal range (86-184 mg/dL) for most patients
- There was a trend for greater C3 reduction with increasing capsid load and vector genome exposure (C_{max}), which was influenced by 1 patient in cohort 3
- Overall, there was no apparent relationship between drug exposure and C3 change from baseline

C4 (Figure 2D)

- C4 levels decreased post dose
- There was no clinically relevant association between variations in C4 levels and drug exposure

Figure 2 *Summary of clinical safety biomarkers: troponin I (**A-B**), C3 (**C**), and C4 (**D**)*

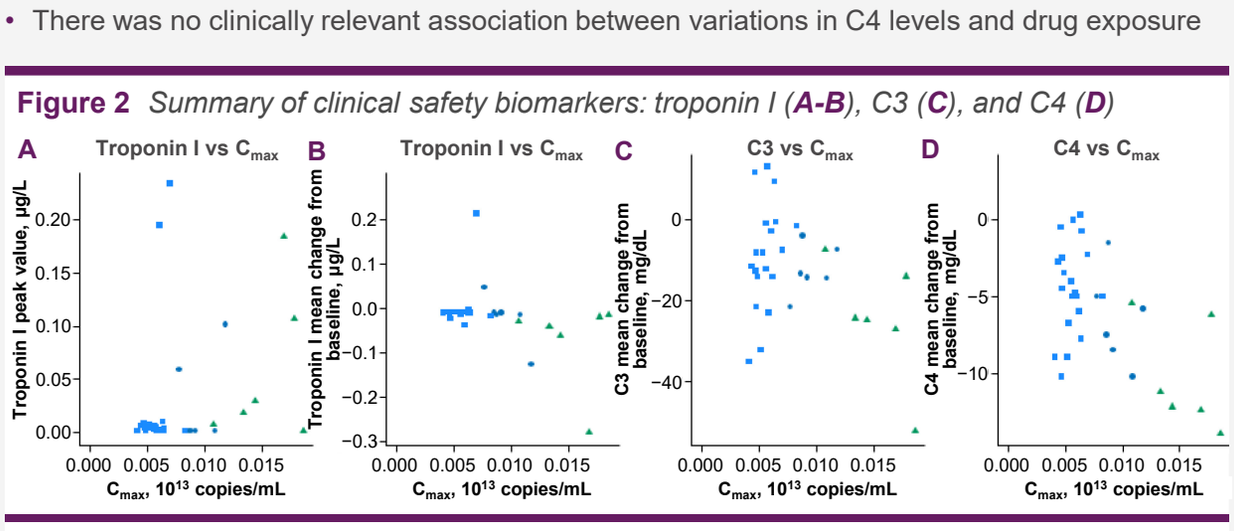
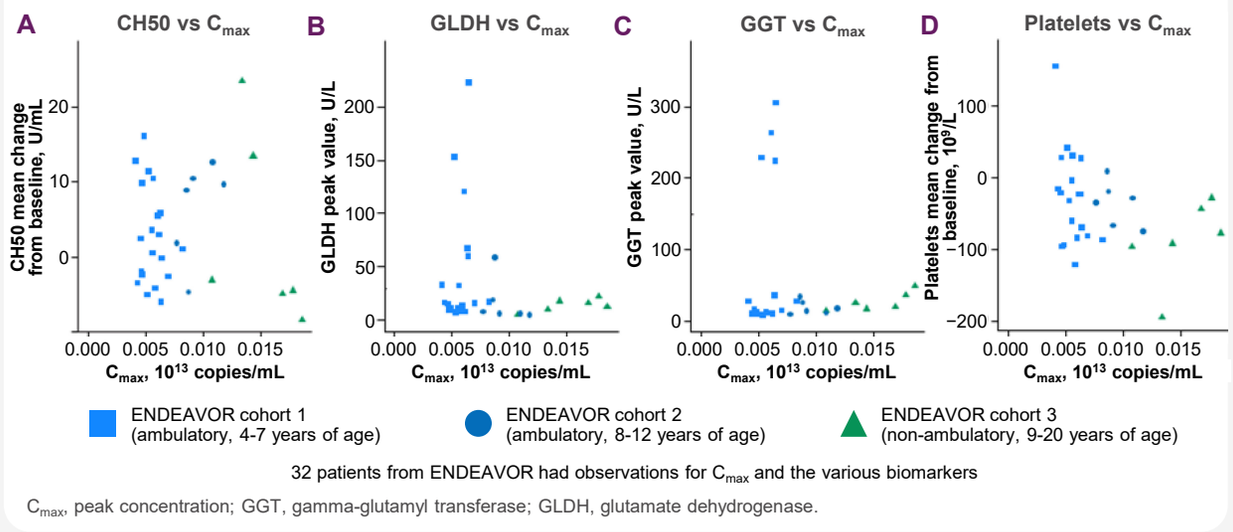


Figure 3 *Summary of clinical safety biomarkers: CH50 (**A**), GLDH (**B**), GGT (**C**), and platelets (**D**)*



32 patients from ENDEAVOR had observations for C_{max} and the various biomarkers

C_{max}, peak concentration; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase.

CH50 (Figure 3A)

- CH50 levels changed between −10 and +10 U/mL for most patients
- No trends were observed between CH50 minimum values or change from baseline and vector genome exposure (C_{max}, AUC)

GLDH (Figure 3B)

- GLDH peak levels did not increase with increasing capsid load and there were no associations with vector genome exposure (C_{max}, AUC)

GGT (Figure 3C)

- For most patients, GGT peak levels were within the normal range (1-94 U/L)
- GGT peak levels did not increase with increasing capsid load and there were no associations with vector genome exposure (C_{max}, AUC)

Platelets (Figure 3D)

- A transient reduction in platelet levels was observed; values remained within the normal range ($150\text{-}350\times10^9$/L) for about 50% of patients (for others: $50\text{-}150\times10^9$/L)
- No trends were observed between minimum values or change from baseline with higher vector genome exposure (C_{max}, AUC)
- Representative figures show the relationships between delandistrogene moxeparvovec drug exposure, in terms of C_{max}, and clinical safety biomarkers (**Figures 2** and **3**); consistent findings were observed for other measures of exposure such as AUC and dose metrics (total viral capsid and total vector genome)

Conclusions

- Delandistrogene moxeparvovec rapidly distributes via systemic circulation and widely distributes into target muscle tissues followed by elimination in the urine and feces
- Serum and excreta PK characteristics were consistent across a broad DMD population regardless of ambulatory status
- There was a lack of relationship between any of the liver, cardiac, immune complement, and hematologic clinical safety biomarkers assessed and vector genome exposure
- This is the first report on the population PK characterization of an AAV-based drug modality in humans
- Consistent PK across a broad DMD population and unremarkable safety biomarker findings support the weight-based dosing regimen for delandistrogene moxeparvovec

Acknowledgments and Disclosures

Acknowledgments: This study was sponsored and funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA. ENDEAVOR was also funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Medical writing and editorial assistance was provided by Deborah Lew, PhD, of Envision 90TEN, an Envision Medical Communications agency, a part of Envision Pharma Group, in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022) and was funded by Sarepta Therapeutics, Inc., Cambridge, MA, USA. Previously presented at the American Society for Clinical Pharmacology & Therapeutics (ASCPT) Annual Meeting; May 28-31, 2025; Washington, DC, USA. Poster PII-075.

Disclosures: LE, **SM**, **ED**, **DAG**, **OR**, **XZ**, **SL**, and **LRR-K** are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. **LRR-K** is a co-inventor of AAVrh74.MHCK7.micro-dys technology. **MD** is an employee of Roche Products Ltd. and may own stock/options in F. Hoffmann-La Roche Ltd.

References

1. Zaidman CM, et al. *Ann Neurol*. 2023;94(5):955-968. **2**. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-274. **3**. Zheng C, Baum BJ. *Methods Mol Biol*. 2008;434:205-219. **4** Mendell JR, et al. *JAMA Neurol*. 2020;77(9):1122-1131. **5**. Mendell JR, et al. Presented at: MDA Clinical and Scientific Conference; March 3-6, 2024; Orlando, FL. Poster M164. **6**. Elevidys. Prescribing information. Sarepta Therapeutics, Inc; 2025. **7**. Qatar Ministry of Public Health. Accessed January 23, 2026. https://www.moph.gov.qa/english/OurServices/advancedsearch/Pages/servicesdetails.aspx?serviceId=234 **8**. United Arab Emirates Ministry of Health and Prevention. Accessed January 23, 2026. https://mohap.gov.ae/en/registered-medical-product-directory **9**. Kuwait Ministry of Health. Accessed January 23, 2026. https://e.gov.kw/sites/kgoenglish/Pages/eServices/MOH/DrugFoodSupplementPrices.aspx **10**. National Health Regulatory Authority Bahrain. Accessed January 23, 2026. https://www.nhra.bh/Departments/PPR/ **11**. Oman Ministry of Health. Accessed January 23, 2026. https://moh.gov.om/en/hospitals-directorates/directorates-and-centers-at-hq/drug-safety-center/#Resources **12**. Ministry of Health Israel. Accessed January 23, 2026. https://israeldrugs.health.gov.il/#!/byDrug **13**. Brazilian Ministry of Health. Accessed January 23, 2026. https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/anvisa-aprova-registro-de-primeiro-produto-de-terapia-genica-para-distrofia-muscular-de-duchenne-dmd **14**. ClinicalTrials.gov identifier: NCT03769116. Updated November 14, 2024. Accessed January 23, 2026. https://clinicaltrials.gov/study/NCT03769116?term=NCT03769116&rank=1 **15**. ClinicalTrials.gov identifier: NCT04626674. Updated December 29, 2025. Accessed January 23, 2026. https://clinicaltrials.gov/study/NCT04626674?term=NCT04626674&rank=1 **16**. Proud C, et al. Presented at: WMS 2024; October 8-12, 2024; Prague, Czechia. Poster 424P. **17**. Mendell JR, et al. *Front Cell Dev Biol*. 2023;11:1167762.