Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

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References, abbreviations and acknowledgements ›

Objectives and overview

Objectives of the integrated analyses:

- To evaluate functional data from patients with DMD (≥4 to ≤8 years old) who have participated in delandistrogene moxeparvovec clinical trials
- To compare these clinical trial data with a control cohort of propensity-score-weighted external control patients
- To provide updated safety data from the delandistrogene moxeparvovec clinical development program

What does this study mean for the DMD community?

This functional comparison of data from three delandistrogene moxeparvovec studies with an external control cohort contextualizes the findings from these clinical trials, some of which lacked a placebo arm

DMD, Duchenne muscular dystrophy.

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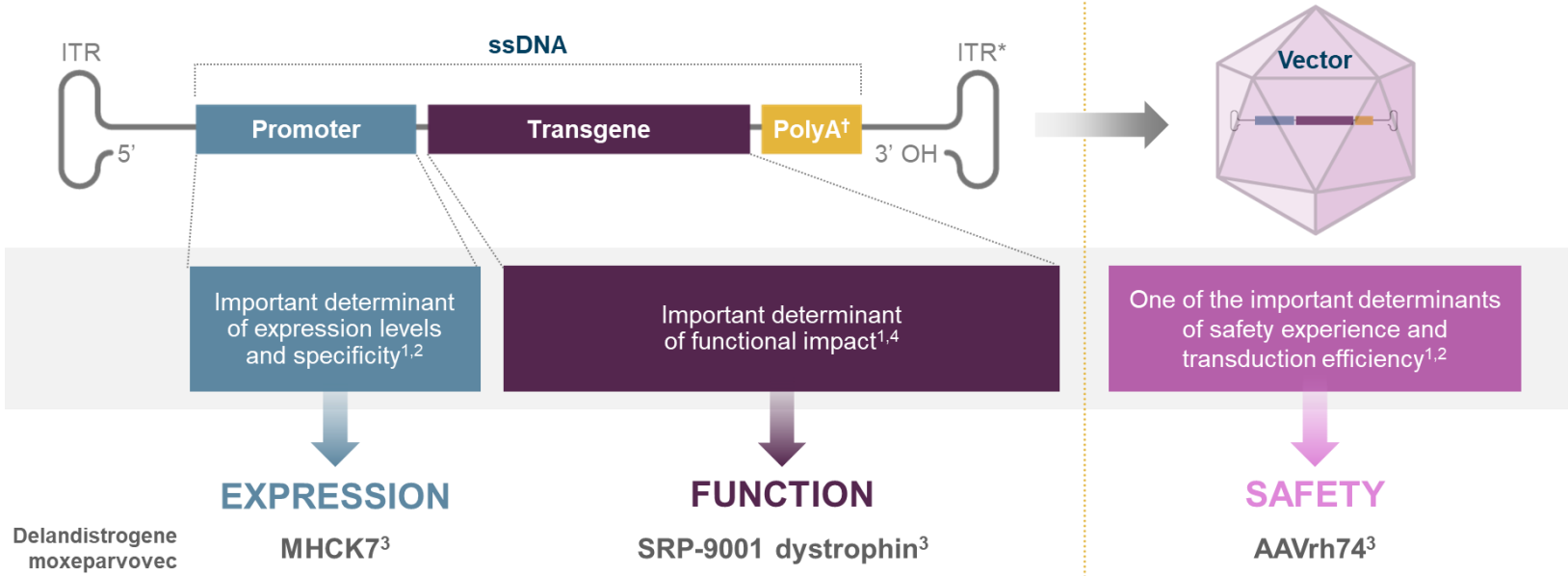
Background

- Delandistrogene moxeparvovec (SRP-9001) is an investigational gene transfer therapy developed for targeted skeletal and cardiac muscle expression of SRP-9001 dystrophin—an engineered, shortened, functional dystrophin protein[1-3]
- Delandistrogene moxeparvovec is being studied in patients with DMD



*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.
AAV, adeno-associated virus; AAVrh74, AAV rhesus isolate serotype 74; DMD, Duchenne muscular dystrophy; ITR, inverted terminal repeat; MHCK, myosin-heavy-chain kinase; OH, hydroxide; PolyA, polyadenylation; ssDNA, single-stranded DNA.

1. Asher DR, et al. *Expert Opin Biol Ther*. 2020; 20:263–74; 2. Zheng C and Baum BJ. *Methods Mol Biol*. 2008; 434:205–19; 3. Mendell JR, et al. *JAMA Neurol*. 2020; 77:1–10; 4. Chandler RJ and Venditti CP. *Transl Sci Rare Dis*. 2016; 1:73–89;

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Study design

We present **an integrated analysis of functional data** from 52 patients from:

- Study 101 [NCT03375164] (n=4)[1]
- Patients with one-year functional assessment who received the target dose* in Study 102 [NCT03769116] (n=28)[2]
- Patients from Cohort 1 of ENDEAVOR [NCT04626674] (n=20)[3]

Collective safety data from all patients in Study 101, Study 102, and all cohorts of ENDEAVOR (N=84) are also presented

Integrated analysis: primary endpoint
1-year change from baseline in NSAA total score

Integrated analysis: exploratory endpoints
1-year change from baseline in timed function tests (Time to Rise, 10MWR)

*1.33×10^{14} vg/kg by linear qPCR of delandistrogene moxeparvovec.
10MWR, 10-metre walk/run; NSAA, North Star Ambulatory Assessment; qPCR, quantitative polymerase chain reaction.
1. ClinicalTrials.gov. NCT03375164 (Accessed June 2022); 2. ClinicalTrials.gov. NCT03769116 (Accessed June 2022); 3. ClinicalTrials.gov. NCT04626674 (Accessed June 2022).

Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in Duchenne muscular dystrophy (DMD)

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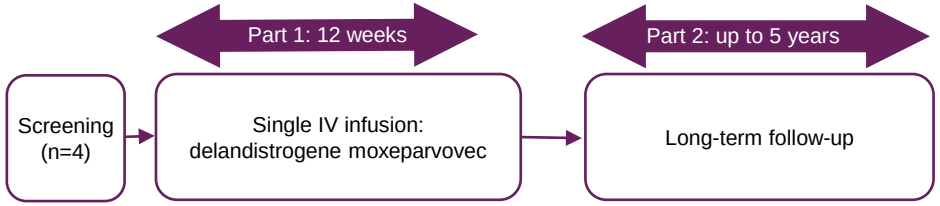
Functional data were pooled from three studies

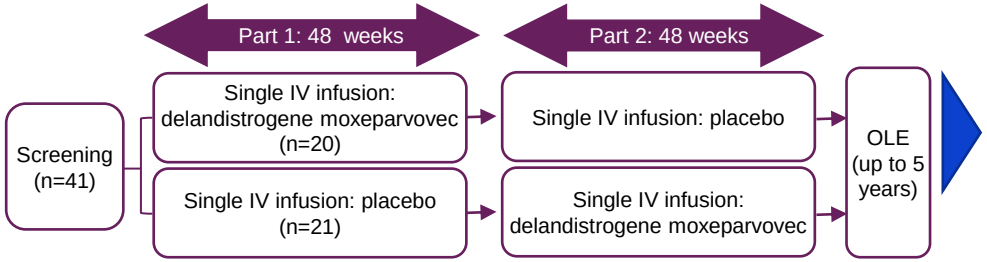
- Study 101

An ongoing Phase 1/2 study evaluating the safety, efficacy and tolerability of a single IV dose of delandistrogene moxeparvovec*



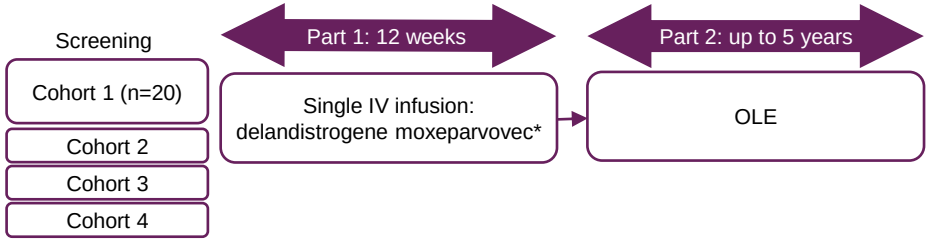
- Study 102

An ongoing Phase 2 study evaluating the safety, efficacy and tolerability of a single IV dose of delandistrogene moxeparvovec†, compared with placebo



- ENDEAVOR/Study 103

An ongoing open-label, Phase 1b study to assess the expression and safety of commercially representative delandistrogene moxeparvovec material



*The dose of delandistrogene moxeparvovec in Study 101 was 2.0×10^{14} vg/kg determined by supercoiled qPCR method (equivalent to 1.33×10^{14} vg/kg using qPCR with linear standard). †The intended target dose in Study 102 was 1.33×10^{14} vg/kg delandistrogene moxeparvovec IV infusion compared with placebo infusion. The 1.33×10^{14} vg/kg dose in Study 102 is the same as the 2.0×10^{14} dose previously used in Study 101. The difference is due to changes in PCR quantification methods.
IV, intravenous; OLE, open-label extension; PCR, polymerase chain reaction; qPCR, quantitative PCR.

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- Study 101

An ongoing Phase 1/2 study evaluating the safety, efficacy and tolerability of a single IV dose of delandistrogene moxeparvovec*

Study N=4
Analysis N=4

Ambulatory boys with DMD aged ≥4 to <8 years

Clinical process material

- Study 102

An ongoing Phase 2 study evaluating the safety, efficacy and tolerability of a single IV dose of delandistrogene moxeparvovec†, compared with placebo

Study N=41
Analysis n=28‡

Boys with DMD aged ≥4 to <8 years

Clinical process material

- ENDEAVOR/Study 103

An ongoing open-label, Phase 1b study to assess the expression and safety of a single IV dose of delandistrogene moxeparvovec

Study N=40
Analysis n=20§

Boys with DMD
- Cohort 1 (ambulatory, ≥4 to <8 years old)
- Cohort 2 (ambulatory, ≥8 to <18 years old)
- Cohort 3 (non-ambulatory)
- Cohort 4 (ambulatory, ≥3 to <4 years old)

Commercially representative material

*The dose of delandistrogene moxeparvovec in Study 101 was 2.0×10^{14} vg/kg determined by supercoiled qPCR method (equivalent to 1.33×10^{14} vg/kg using qPCR with linear standard). †The intended target dose in Study 102 was 1.33×10^{14} vg/kg delandistrogene moxeparvovec IV infusion compared with placebo infusion. The 1.33×10^{14} vg/kg dose in Study 102 is the same as the 2.0×10^{14} dose previously used in Study 101. The difference is due to changes in PCR quantification methods. ‡The 28 patients who received the target dose and had 1-year NSAA data in Study 102 were analyzed. §The 20 patients in Cohort 1 were analyzed. One-year data from Cohorts 2-4 are not yet available and will be presented at the next update.
IV, intravenous; NSAA, North Star Ambulatory Assessment PCR, polymerase chain reaction; qPCR, quantitative PCR.

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External control cohort pool (N=131*)

The control cohort includes natural history and external clinical trial data from†:

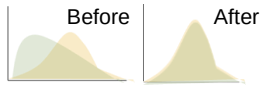
- CINRG/DNHS[1,2] (n=16)
- FOR-DMD[3] (n=86)
- Lilly Study (H6D-MC-LVJJ)[4] (n=29)

Prespecified analysis

Propensity score weighting was performed to ensure maximum comparability between this external cohort and the delandistrogene moxeparvovec groups, based on:

- Age
- NSAA
- Time to Rise results
- 10MWR results

Example EC before and after propensity weighting§



Based on their ability to predict disease trajectory, the following criteria were used to identify external control patients who were similar to patients enrolled in the delandistrogene moxeparvovec studies‡:

Age
≥4 to ≤8 years old

NSAA score
≥13 and ≤30

Time to Rise
≤10.4 seconds

10MWR
≤9.1 seconds

Stable dose or dose equivalent of oral corticosteroids for ≥12 weeks pre-baseline§

*N=131 before propensity-score-weighting. After excluding external control subjects with non-overlapping propensity scores, N=105 for NSAA, N=103 for 10MWR, and N=101 for TTR. †CINRG was a prospective natural history study of patients with DMD. FOR-DMD was a double-blind study comparing three corticosteroid regimens widely used for DMD. Patients on the daily regimen (prednisone or deflazacort) were included as external control patients for the analysis. The Lilly study was a Phase 3, randomized, placebo-controlled trial of tadalafil in patients with DMD. Only placebo patients were included as external control patients for the analysis. ‡Criteria ranges represent the ranges of values measured in the pool of patients treated with delandistrogene moxeparvovec. §Pre-baseline = prior to first functional assessment.

10MWR, 10-metre walk/run; CINRG, Cooperative International Neuromuscular Research Group; DNHS, Duchenne Natural History Study; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; NSAA, North Star Ambulatory Assessment; TTR, Time to Rise.

1. https://cinrgresearch.org/ (Accessed June 2022); 2. Thangarajh M, et al. PLoS Curr. 2018; 10:ecurrents.md.4cdeb6970e54034db2bc3dfa54b4d987; 3. https://for-dmd.org/en/ (Accessed June 2022); 4. ClinicalTrials.gov. NCT01865084 (Accessed June 2022).

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	Delandistrogene moxeparvovec functional analysis (N=52)	Propensity-score-weighted EC (N=105)
Age in years, mean (SD)	6.44 (1.32)	6.67 (0.68)
NSAA total score, mean (SD)	22.1 (3.8)	21.4 (3.1)
Time to Rise in seconds, mean (SD)	4.48 (1.83)	4.49 (1.15)
Time of 10MWR in seconds, mean (SD)	5.14 (1.10)	5.17 (0.70)

10MWR, 10-metre walk/run; EC, external control; NSAA, North Star Ambulatory Assessment.

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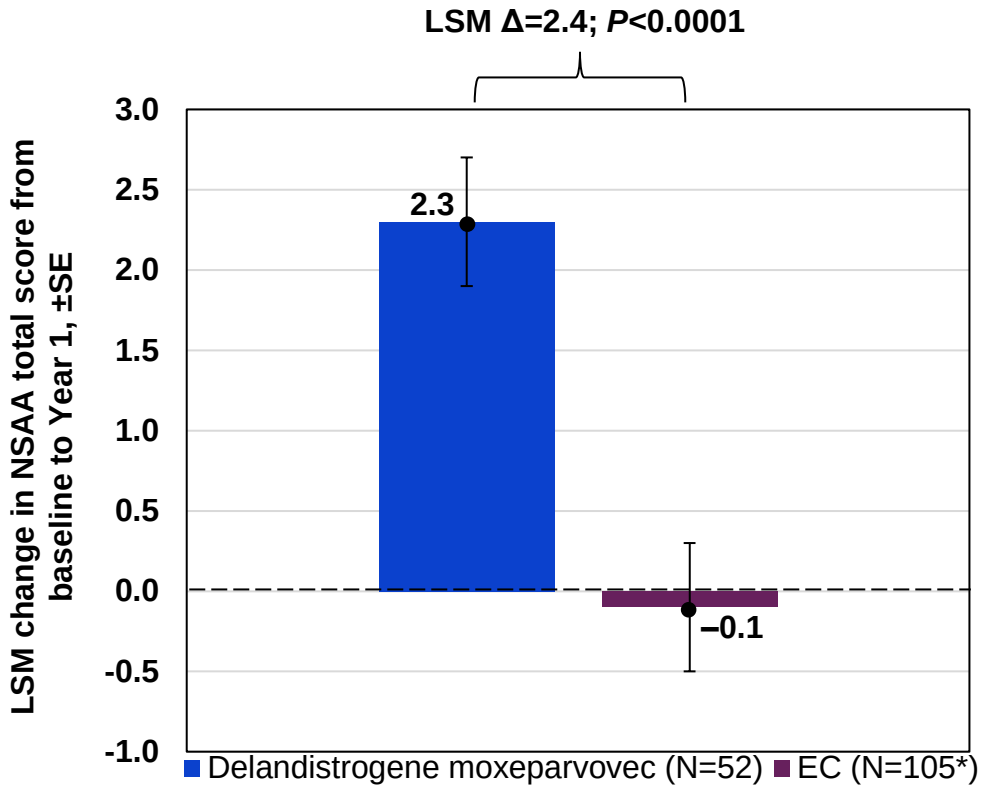
Functional results: Change from baseline in NSAA total score over 1 year



*131 EC participants were used to derive the propensity scores. After the propensity scores were derived, 26 participants were removed because their propensity scores were outside the range of the treated patients. Therefore, in the comparative analysis, only 105 patients were included.
EC, external control; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error.

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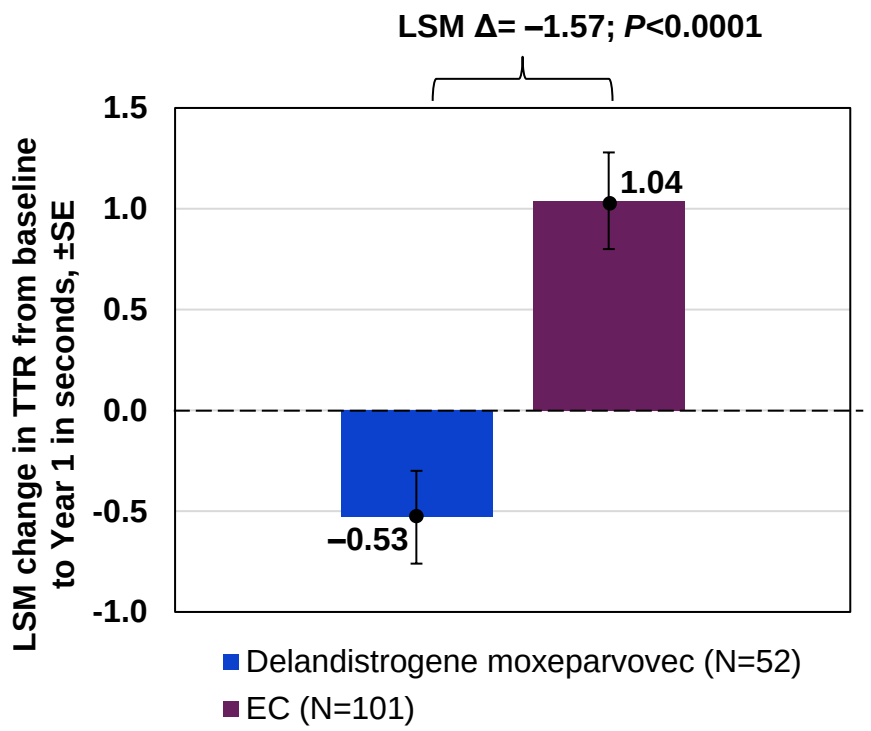
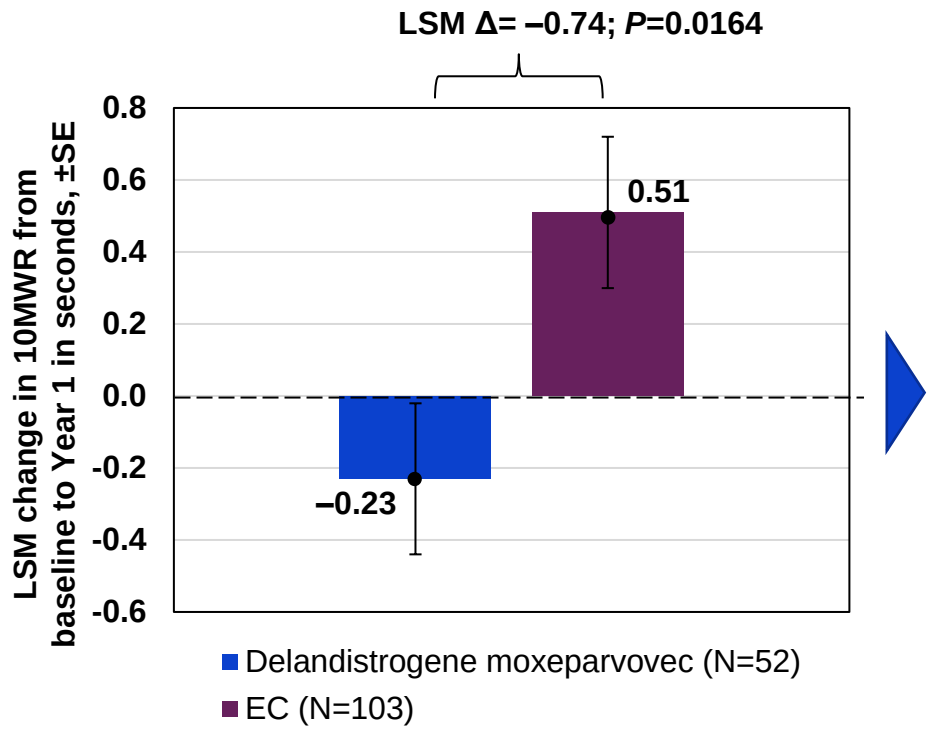
Functional results: timed function tests*





*Note that reductions in TTR and 10MWR signify improvement, while increases signify deterioration.
10MWR, 10-metre walk/run; EC, external control; LSM, least-squares mean; SE, standard error; TTR, Time to Rise.

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Safety results

	Target dose* (N=72)	All† (N=84)
Number of AEs	865	1,190
Number of TEAEs	826	1,139
Number of treatment-related TEAEs	326	364
Number of SAEs	7	12
Number of treatment-related SAEs	6	9
Patients with any AEs, n (%)	70 (97.2)	82 (97.6)
Patients with any TEAEs, n (%)	70 (97.2)	82 (97.6)
Patients with any treatment-related TEAEs, n (%)	63 (87.5)	73 (86.9)
Deaths, n (%)	0	0
Patients with any SAEs, n (%)	6 (8.3)	10 (11.9)
Patients with any treatment-related SAEs, n (%)	5 (6.9)	7 (8.3)
Patients with any AEs leading to discontinuation, n (%)	0	0

*1.33×10^{14} vg/kg. †For the integrated safety data, the clinical cut-off dates were April 26, 2022 for Study 101, April 1, 2022 for Study 102, and April 6, 2022 for ENDEAVOR.
AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE.

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Safety results: TEAEs occurring in at least 25% of all participants

TEAE	Target dose* (N=72)	All (N=84)
Vomiting, n (%)	45 (62.5)	52 (61.9)
Decreased appetite, n (%)	35 (48.6)	40 (47.6)
Nausea, n (%)	31 (43.1)	34 (40.5)
Upper respiratory tract infection, n (%)	23 (31.9)	34 (40.5)
Pain in extremity, n (%)	16 (22.2)	24 (28.6)
Abdominal pain upper, n (%)	18 (25.0)	23 (27.4)
Irritability, n (%)	17 (23.6)	23 (27.4)
Procedural pain, n (%)	14 (19.4)	22 (26.2)

*1.33×10^{14} vg/kg.
TEAE, treatment emergent adverse event.

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Treatment-related SAEs

- Seven patients (8.3%) experienced treatment-related SAEs
- Treatment-related SAEs included:
  - Vomiting (2)
  - Increased transaminases (2)
  - Rhabdomyolysis (2)
  - Liver injury (1)
  - Immune-mediated myositis (1)
  - Myocarditis (1)

In ENDEAVOR (Cohort 2), there were 2 new treatment-related SAEs

1. Immune-mediated myositis in one 9-year-old boy with a large mutation in exons 3-43*
- The patient experienced muscle weakness, including severe impairment of moving limbs and problems breathing and swallowing
- The heart was not involved; the patient received plasmapheresis and tacrolimus and returned to pre-event status
- The cellular immune response detected was specific to the patient's mutation and informed a protocol amendment excluding mutations between exons 1-17
- No other events of immune-mediated myositis have been observed in any ENDEAVOR cohort **or in other delandistrogene moxeparvovec studies**

2. Myocarditis in one 11-year-old boy initially admitted to treat nausea and vomiting
- Raised troponin was noted incidentally during his hospitalization, with no symptoms/signs of systolic dysfunction
- Function was preserved on ECHO and cardiac MRI, but MRI findings were consistent with myocarditis superimposed on DMD cardiomyopathy
- The patient received 3 days of IV methyl-prednisolone
- Post event: additional chronic cardiac medications added, cardiac MRI (1 month) showed normal function and partial resolution of myocarditic changes, and ECHO (4 months) showed normal systolic function

*This event has been disclosed previously.
ECHO, echocardiogram; IV, intravenous; MRI, magnetic resonance imaging; SAE, serious adverse event; SUSAR, suspected unexpected serious adverse reaction.

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Conclusions (one-year data)

EC cohort

- Comparison of functional data from patients who received the target dose of delandistrogene moxeparvovec and the propensity-score-weighted EC cohort suggested treatment-induced changes in disease trajectory:
  - NSAA total score improved in treated patients relative to EC patients (LSM Δ=2.4 [*P*<0.0001])
  - 10MWR and TTR also improved in patients treated with delandistrogene moxeparvovec relative to ECs (10MWR LSM Δ from baseline was –0.23 in treated patients and 0.51 in EC patients; TTR LSM Δ from baseline was –0.53 in treated patients and 1.04 in EC patients)

Safety

Across the delandistrogene moxeparvovec clinical trials:

- There were no deaths
- No AEs led to study discontinuation
- 7 patients (8.3%) experienced treatment-related SAEs
- The most frequently observed TEAE was vomiting
- No clinically relevant complement activations were observed

10MWR, 10-metre Walk/Run; AE, adverse event; EC, external control; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SAE, serious AE; SD, standard deviation; TEAE, treatment-emergent AE; TTR, Time to Rise.

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Abbreviations

10MWR, 10-metre walk/run; AAV, adeno-associated virus; AAVrh74, AAV rhesus isolate serotype 74; AE, adverse event; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; DNHS, Duchenne Natural History Study; EC, external control; ECHO, echocardiogram; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; ITR, inverted terminal repeat; IV, intravenous; LSM, least squares mean; MHCK, myosin-heavy-chain kinase; MRI, magnetic resonance imaging; NSAA, North Star Ambulatory Assessment; OH, hydroxide; OLE, open-label extension; polyA, polyadenylation; PCR, polymerase chain reaction; qPCR, quantitative PCR; rAAVrh74, recombinant AAVrh74; SAE, serious AE; SE, standard error; ssDNA, single-stranded DNA; SUSAR, suspected unexpected serious adverse reaction; TEAE, treatment emergent AE; TTR, Time to Rise.

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Disclosures

CZ receives research support from Biogen and Novartis, serves on an advisory board for Biogen, receives speaker fees from Sarepta, and was a paid consultant for Optum.

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SM, LH, LY, ED, JR, JM, and TS are employees of Sarepta Therapeutics and may have stock options.

MG and CW are employees of F. Hoffmann-La Roche Ltd and have nothing to disclose.

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