Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in DMD

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What does this study mean for the DMD community?

- This functional comparison of data from three delandistrogene moxeparvovec (SRP-9001) studies with an EC cohort contextualises the findings from these clinical trials, some of which lacked a placebo arm.

Conclusions

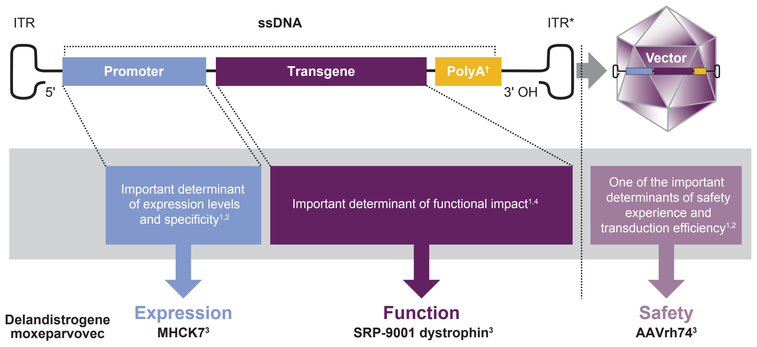
- Comparison of functional data from patients who received the target dose of delandistrogene moxeparvovec and the propensity-score-weighted EC cohort suggested treatment-induced changes in disease trajectory:
  - NSAA total score, 10MWR and TTR improved in treated patients relative to EC patients.
- 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.

Objective

- 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 cohort of propensity-score-weighted EC patients.
- To provide updated safety data from the delandistrogene moxeparvovec clinical development programme.

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.[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.

Methods

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

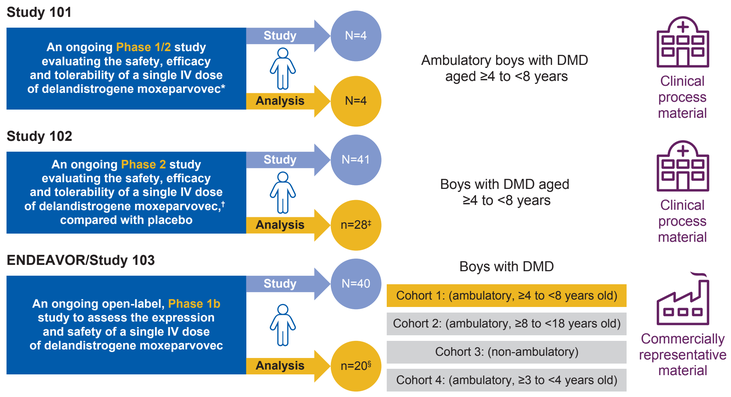
- Study 101 (NCT03375164; N=4)[5]
- patients with a 1-year functional assessment who received the target dose (1.33x10^{14} vg/kg by linear qPCR) of delandistrogene moxeparvovec in Study 102 (NCT03769116; n=28)[6]
- patients from Cohort 1 of ENDEAVOR (NCT04626674; n=20).[7]

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

Integrated analysis: Exploratory endpoints
1-year change from baseline in TFTs (TTR, 10MWR)

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

Functional data were pooled from three studies:



*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 1.33x10^{14} vg/kg delandistrogene moxeparvovec IV infusion compared with placebo infusion. The 1.33x10^{14} vg/kg dose in Study 102 is the same as the 2.0x10^{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 analysed. §The 20 patients in Cohort 1 were analysed. One-year data from Cohorts 2–4 are not yet available and will be presented at the next update.

Methods (Contd.)

EC cohort pool (N=131*)

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

- CINRG/DNHS[8,9] (NCT00468832;[10] n=16)
- FOR-DMD[11] (NCT01603407;[12] n=86)
- Lilly study (H6D-MC-LVJJ; NCT01865084;[13] n=29).

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

Age
≥4 to ≤8 years old

NSAA score
≥13 and ≤30

TTR
≤10.4 seconds

10MWR
≤9.1 seconds

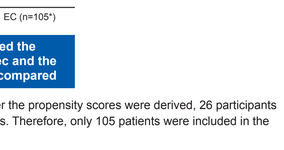
Stable dose or dose equivalent of oral corticosteroids
for ≥12 weeks pre-baseline§

Pre-specified analysis

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

- age
- NSAA
- TTR
- 10MWR.

Example EC before and after propensity-score weighting‖



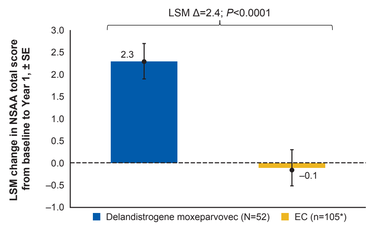
*N=131 before propensity-score weighting. After excluding EC subjects with non-overlapping propensity scores, n=105 for NSAA, n=103 for 10MWR and n=101 for TTR. †CINRG was a prospective natural history study of patients with DMD. FOR-DMD was a double-blind study comparing three corticosteroid regimens widely used for DMD. Patients on the daily regimen (prednisone or deflazacort) were included as EC patients for the analysis. The Lilly study was a Phase 3, randomised, placebo-controlled trial of tadalafil in patients with DMD. Only placebo patients were included as EC 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. ‖Propensity-score weighting involves taking an EC group with similar age and function, but unequal distribution, and ensuring overlap after propensity-score weighting. Example ECs before and after propensity-score weighting are shown in the example graphs.

Results

Demographics

	Delandistrogene moxeparvovec functional analysis (N=52)	Propensity-score-weighted EC (n=105)
Age, years, mean (SD)	6.44 (1.32)	6.67 (0.68)
NSAA total score, mean (SD)	22.1 (3.8)	21.4 (3.1)
TTR, seconds, mean (SD)	4.48 (1.8)	4.49 (1.2)
10MWR, seconds, mean (SD)	5.14 (1.1)	5.17 (0.7)

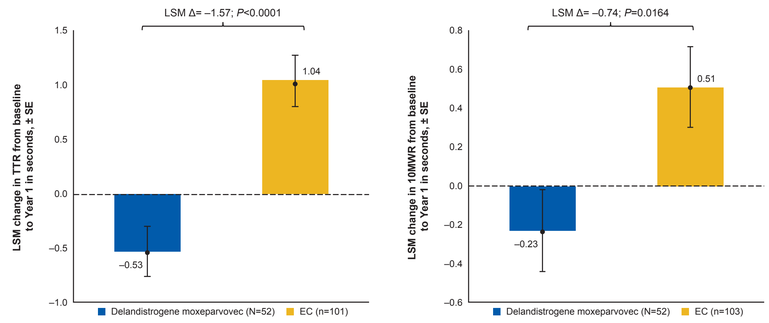
Functional results: Change from baseline in NSAA total score over 1 year



Functional data from patients who received the target dose of delandistrogene moxeparvovec and the propensity-score-weighted EC cohort were compared

*One hundred and thirty-one 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, only 105 patients were included in the comparative analysis.

Functional results: TFTs*



*Note that reductions in TTR and 10MWR signify improvement, while increases signify deterioration.

Results (Contd.)

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 26 Apr 2022 for Study 101, 1 Apr 2022 for Study 102, and 6 Apr 2022 for ENDEAVOR.

TEAEs occurring in at least 25% of all participants

	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.

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 two 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 any 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 hospitalisation, 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 methylprednisolone.
- 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.

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Abbreviations

10MWR, 10-metre walk/run; AAVrh74, adeno-associated virus 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; PCR, polymerase chain reaction; PolyA, polyadenylation; qPCR, quantitative PCR; SAE, serious AE; SD, standard deviation; SE, standard error; ssDNA, single-stranded DNA; TEAE, treatment-emergent AE; TFT, timed function test; TTR, Time to Rise; vg, vector genome.

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