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Phase 1/2a trial of delandistrogene moxeparvovec in patients with DMD: 4-year update

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What does this study mean for the DMD community?

- Findings from this study demonstrated that the single-dose gene transfer therapy delandistrogene moxeparvovec (SRP-9001) generally led to improvements in functional measures over 4 years in patients with DMD and reinforce that delandistrogene moxeparvovec has a long-term acceptable safety profile.
  - The current study provides proof-of-concept support for the continuation of clinical trials to assess the safety and efficacy of delandistrogene moxeparvovec in patients with DMD.

Conclusions

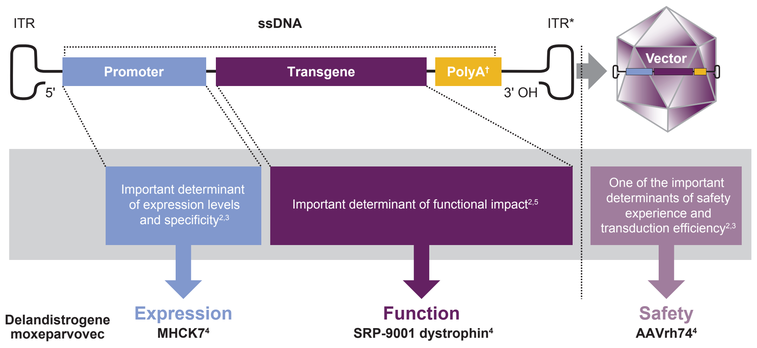
- Four-year data from Study 101 reinforced that delandistrogene moxeparvovec is well tolerated, with no new safety signals; safety data were consistent with the wider delandistrogene moxeparvovec clinical trial programme.
  - TRAEs mostly occurred in the first 90 days post-infusion, and all resolved.
  - Four-year safety data reinforced an overall long-term acceptable safety profile.
- NSAA showed long-term overall improvements in motor function from baseline that were maintained over 4 years, which demonstrated a durable response and provided evidence of stabilisation of function.
  - NSAA improvements were generally accompanied by improvement in TFTs over 4 years.
- In a post hoc analysis, there was a significant difference in NSAA total score in treated patients relative to EC patients; this difference is clinically meaningful.
- The safety profile and durable response provide proof-of-concept support for continued clinical trials to assess delandistrogene moxeparvovec in patients with DMD.

Objective

- This Phase 1/2a, open-label clinical trial (Study 101; NCT03375164)[1] evaluated the safety of systemic delivery of delandistrogene moxeparvovec in patients with DMD (≥4 to <8 years old).
  - Here we provide a 4-year update on long-term safety, and functional data from four patients treated with delandistrogene moxeparvovec.
  - To put the results into context, a post hoc analysis was conducted to compare the 4-year data from Study 101 with data from a propensity-score-weighted EC cohort.

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.[2–4]



*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.

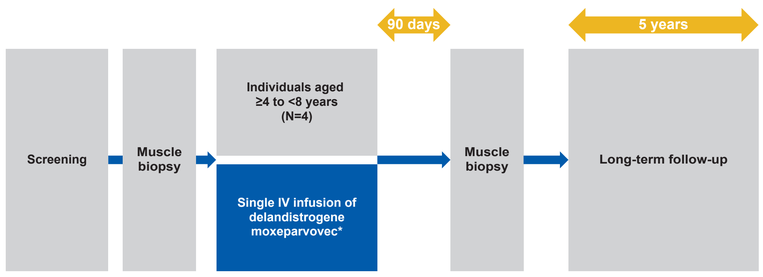
Study design and baseline characteristics

Primary outcome measure:

- safety based on the number of participants with AEs.

Key additional outcome measures:

- SRP-9001 dystrophin expression in pre- and post-muscle biopsy at 12 weeks post-infusion (Day 90): IF and WB
- change in NSAA and TFTs: 100MWR, 4-stair Climb, 10MWR and TTR.



*All patients received one IV infusion in the peripheral limb vein at the dose 2.0×10^{14} vg/kg determined by supercoiled qPCR method (1.33×10^{14} vg/kg linear qPCR equivalent), and prednisone (1 mg/kg/day) 1 day pre- to 30 days post-gene delivery.

Study 101 baseline demographics[4]	Patient 1	Patient 2	Patient 3	Patient 4
Age at screening, years	5	4	6	4
Height, cm	109.9	104.3	110.0	95.7
Weight, kg	18.4	18.9	21.4	13.7
BMI	15.2	17.4	17.7	15.0
NSAA	18	19	26	19

Results

Study 101: 4-year data

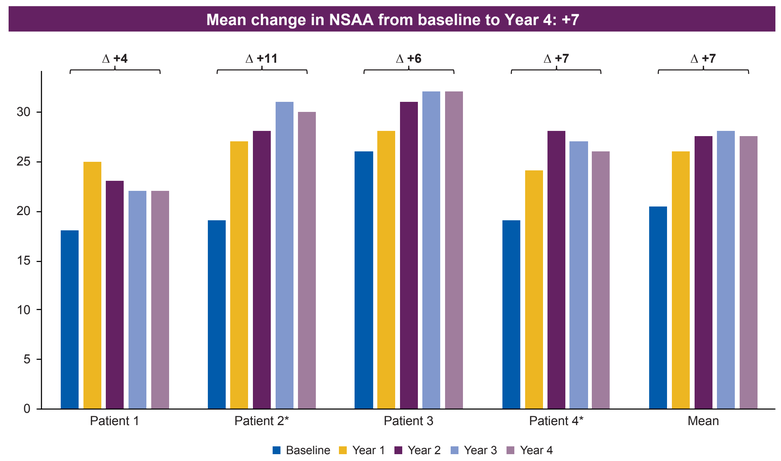
Primary endpoint: Safety*

- There were no SAEs or discontinuations from the study.
- TRAEs were mild or moderate and all resolved.
  - TRAEs occurred mostly within the first 90 days of treatment.
  - No TRAEs occurred from the second to the fourth year post-infusion.
  - The most common TRAE was vomiting (9 of 18 TRAEs).
    - Patients had transient vomiting generally within the first week post-infusion.
    - TRAEs of vomiting did not correlate with liver enzyme elevations or any other abnormalities.
- There were no serious abnormalities observed in haematological and chemistry panels.
  - Three patients had elevated γ-glutamyl transpeptidase in the first 3 months post-treatment, which resolved with oral steroid treatment.
    - These changes were asymptomatic, and no patients were hospitalised.
- None of the AEs were associated with clinical complement activation.
- No other clinically significant laboratory findings were reported.

*Up to data cut-off: 26 Apr 2022.

Functional outcome: NSAA total scores over 4 years after treatment with delandistrogene moxeparvovec

Mean change in NSAA from baseline to Year 4: +7



Age (years)	Patient 1	Patient 2	Patient 3	Patient 4	Mean
At baseline†	5.7	4.8	6.0	4.0	5.1
At Year 1	6.8	5.8	7.1	5.1	6.2
At Year 2	7.7	6.8	8.0	6.3	7.2
At Year 3	8.7	7.8	9.1	7.1	8.2
At Year 4	9.7	8.8	10.1	8.1	9.2

*Three-year NSAA value (Patient 2) and 2-year NSAA value (Patient 4) were from a remote assessment due to COVID-19-related restrictions at the site. †Age at baseline NSAA assessment.

Functional outcome: Summary of 4-year TFTs

	Change from baseline to Year 4				Mean
	Patient 1	Patient 2	Patient 3	Patient 4	All patients
Age at Year 4, years	9.7	8.8	10.1	8.1	**9.2**
NSAA total score	+4	+11	+6	+7	**+7.0**
TTR, seconds*	+0.7	–0.3	–0.7	0	**–0.1**
4-stair Climb, seconds*	–0.7	–1.7	+0.7	–2.6	**–1.1**
100MWR, seconds*	–4.1	–10.1	–0.1	–13.5	**–7.0**
10MWR, seconds*	–0.7	–0.8	+0.3	–0.1	**–0.3**

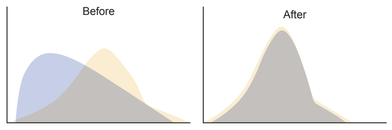
*Negative values show an improvement in the time taken to achieve this endpoint.

Post hoc analysis: Study 101 4-year data versus propensity-score-weighted EC

Propensity-score-weighted EC cohort pool (N=36*)

- A post hoc analysis was conducted to contextualise the 4-year data from Study 101 with data from a propensity-score-weighted EC cohort.
- The control cohort includes external clinical trial data from the FOR-DMD[6†] study (NCT01603407[7]; N=36).
- Similar methodology to the ENDEAVOR study[8] and integrated analyses[9] was used to identify EC patients for this post hoc analysis.
- Propensity-score weighting[‡] was based on:
  - age
  - NSAA
  - TTR
  - 10MWR.

Example EC before and after propensity-score weighting[‡]



*N=36 before propensity-score weighting. After excluding subjects with non-overlapping propensity scores, n=21. †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. ‡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.

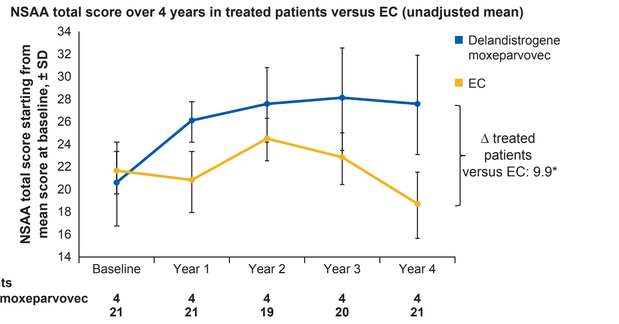
Baseline comparison of delandistrogene moxeparvovec-treated patients versus propensity-score-weighted EC cohort

	Statistics	Delandistrogene moxeparvovec-treated patients (N=4)	EC (n=21)*
Age, years†	Mean (SD) Min–Max	5.1 (0.9) 4.0–6.0	6.4 (0.3) 4.9–7.7
NSAA total score	Mean (SD) Min–Max	21 (3.7) 18–26	22 (1.9) 13–30
TTR, seconds	Mean (SD) Min–Max	3.7 (0.5) 3.0–4.1	3.9 (0.4) 2.6–7.4
10MWR, seconds	Mean (SD) Min–Max	4.9 (0.5) 4.3–5.4	5.0 (0.3) 3.6–6.7

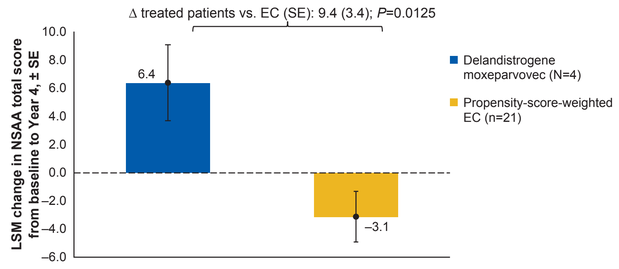
*N=36 before propensity-score weighting. After excluding subjects with non-overlapping propensity scores, n=21. †Age at first assessment.

NSAA total score over 4 years after treatment with delandistrogene moxeparvovec versus propensity-score-weighted EC cohort

NSAA total score over 4 years in treated patients versus EC (unadjusted mean)



Change in NSAA total score from baseline to Year 4 in treated patients versus EC (LSM)



*NSAA change from baseline to Year 4 in treated patients versus EC calculated using unadjusted means.

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Abbreviations

10MWR, 10-metre walk/run; 100MWR, 100-metre walk/run; AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; BMI, body mass index; COVID-19, coronavirus disease of 2019; DMD, Duchenne muscular dystrophy; EC, external control; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; IF, immunofluorescence; ITR, inverted terminal repeat; IV, intravenous; LSM, least squares mean; MHCK, myosin-heavy-chain kinase; NSAA, North Star Ambulatory Assessment; OH, hydroxide; PolyA, polyadenylation; qPCR, quantitative polymerase chain reaction; SAE, serious AE; SD, standard deviation; SE, standard error; ssDNA, single-stranded DNA; TFT, timed function test; TRAE, treatment-related AE; TTR, Time to Rise; vg, vector genome; WB, western blot.

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