Poster 97

A Phase 2 clinical trial evaluating the safety and efficacy of delandistrogene moxeparvovec in patients with DMD

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What does this study mean for the DMD community?

- Findings from Study 102 (SRP-9001-102; NCT03769116)[1] support a favorable benefit–risk profile of delandistrogene moxeparvovec (SRP-9001), with no new safety signals observed.
- Overall stabilization of motor function was observed up to 2 years following treatment with delandistrogene moxeparvovec.

Conclusions

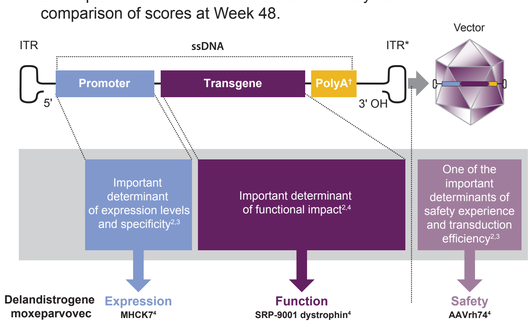
- The safety profile of patients treated in Part 2 was consistent with that seen in Part 1, supporting that delandistrogene moxeparvovec has a favorable benefit–risk profile. Most treatment-related TEAEs occurred within the first 60 days of treatment, and all resolved.
- SRP-9001 dystrophin protein expression at 12 weeks post-treatment was achieved in patients treated with delandistrogene moxeparvovec in both Parts 1 and 2, and patients treated in Part 1 continued to express SRP-9001 dystrophin protein after 60 weeks.
- Overall maintenance of motor function was observed over 2 years following delandistrogene moxeparvovec treatment, when functional decline is expected based on natural history.
- Patients treated in Part 1 demonstrated a higher mean NSAA score 2 years post-treatment than the propensity-score-weighted EC cohort, although this was not statistically significant. However, given that there was one outlier with a significant 17-point drop, reanalysis using the median NSAA score demonstrated a statistically significant difference.
- Patients treated in Part 2 demonstrated improved change in motor function as measured by the NSAA score compared with the propensity-score-weighted EC cohort.
- Further investigations to assess the efficacy of delandistrogene moxeparvovec are ongoing.

Objective

- To evaluate the safety and efficacy of delandistrogene moxeparvovec, compared with placebo, in patients with DMD aged ≥4 to <8 years.
  - Here we present safety, biological, and functional data for patients who have been treated with delandistrogene moxeparvovec up to 2 years post-infusion.
  - To put the Part 2 results into context, a post hoc analysis was conducted to compare the functional Study 102 data with data from a propensity-score-weighted EC cohort.

Background

- Delandistrogene moxeparvovec is an investigational rAAV vector-based gene therapy, designed to compensate for missing dystrophin in DMD by delivering a transgene encoding SRP-9001 dystrophin, an engineered dystrophin protein that retains key functional domains of the wild-type protein.[2–4]
- In Part 1 of Study 102 (previously presented), for the primary endpoint, change in NSAA total score from baseline, the difference between patients treated with delandistrogene moxeparvovec versus placebo was not statistically significant (see Supplementary Materials).[5]
  - Discrepancies in NSAA scores at baseline may have confounded the comparison of scores at Week 48.

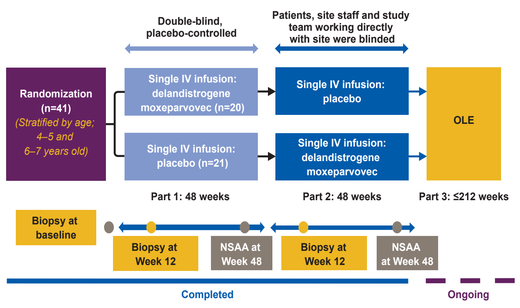


*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (i.e. copies) it.

Study design

Study design[1]

- Study 102 is a Phase 2, randomized, double-blind, placebo-controlled, crossover clinical trial evaluating the safety and efficacy of a single IV dose of delandistrogene moxeparvovec compared with placebo in patients with DMD aged ≥4 to <8 years.[1,5]



All patients in Part 1 received the delandistrogene moxeparvovec dose $2.0x10^{14}$ vg/kg as determined by the supercoiled standard qPCR method specified in the protocol at the time. The dose $2.0x10^{14}$ vg/kg was estimated by supercoiled qPCR and is equivalent to $1.33x10^{14}$ vg/kg using the linear qPCR method. Retrospective analysis using the linear qPCR method indicates that 60% of the patients in Part 1 received a lower dose than $1.33x10^{14}$ vg/kg based on the new method. All patients dosed in Part 2 received the delandistrogene moxeparvovec dose $1.33x10^{14}$ vg/kg as determined by the linear qPCR method.

EC cohort pool*

The EC comparator was composed of data from the following studies:†

- CINRG/DNHS[6,7] (NCT00468832[8])
- FOR-DMD[9] (NCT01603407[10])
- Lilly study (H6D-MC-LVJJ; NCT01865084[11]).

Inclusion criteria‡

- Age matched at baseline
- On a stable dose or dose equivalent of oral corticosteroids for ≥12 weeks before baseline (patients on 10-day on/10-day off regimen were excluded)
- NSAA score: ≥13 and ≤30 at baseline
- TTR: ≤10.4 seconds at baseline
- 10MWR: ≤9.1 seconds at baseline.

*After excluding EC subjects with non-overlapping propensity scores, N=103. †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, randomized, placebo-controlled trial of tadalafil in patients with DMD. Only patients receiving placebo 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.

Results

Baseline demographics: Intent-to-treat population[5,12]

Characteristic	Statistics	Patients treated in Part 1* (delandistrogene moxeparvovec/ placebo) (n=20)	Patients treated in Part 2† (placebo/ delandistrogene moxeparvovec) (n=21)
Age, years	Mean (SD) Min–Max	6.3 (1.2) 4.47–7.85	6.2 (1.1) 4.34–7.98
Years since corticosteroid treatment started	Mean (SD) Min–Max	1.0 (1.1) 0.2–3.8	1.3 (1.2) 0.2–5.1
Corticosteroid type, deflazacort	n (%)	7 (35.0)	7 (33.3)
Dosing weight, kg	Mean (SD) Min–Max	23.3 (4.4) 18.0–34.5	21.6 (3.5) 15.0–30.0
NSAA total score at baseline	Mean (SD) Min–Max	19.8 (3.3) 13–26	22.6 (3.3) 15–29
TTR results at baseline, seconds	Mean (SD) Min–Max	5.1 (2.2) 3.2–10.4	3.6 (0.7) 2.7–4.8
10MWR results at baseline, seconds	Mean (SD) Min–Max	5.4 (1.1) 4.1–8.9	4.8 (0.7) 4.0–7.2

*Patients who received delandistrogene moxeparvovec in Part 1 and placebo in Part 2. †Patients who received placebo in Part 1 and delandistrogene moxeparvovec in Part 2.

- NSAA scores were not well matched at baseline between the treated group and placebo group.

Functional baseline characteristics of treated patients versus EC

	Patients treated in Part 1		Placebo crossover (patients treated in Part 2)	
Parameter	Delandistrogene moxeparvovec (N=19)	EC (N=51)	Delandistrogene moxeparvovec (N=20)	EC (N=103)
Age, years				
Mean (SD)	6.21 (1.17)	6.20 (0.45)	7.24 (1.12)	7.03 (0.42)
Median	6.49	6.10	7.07	6.97
Q1–Q3	5.12–7.24	5.59–6.81	6.28–8.49	6.17–8.00
Min–Max	4.47–7.85	4.75–7.73	5.27–8.89	5.13–8.92
NSAA total score				
Mean (SD)	19.9 (3.4)	19.7 (1.9)	23.8 (3.7)	23.5 (1.9)
Median	20.0	20.0	24.5	24.0
Q1–Q3	17.0–21.0	17.0–22.0	22.0–26.5	20.0–27.0
Min–Max	13–26	15–28	13–30	13–30
TTR, seconds				
Mean (SD)	5.17 (2.21)	5.22 (1.05)	4.02 (1.34)	3.92 (0.59)
Median	4.60	4.70	3.80	3.70
Q1–Q3	3.60–5.90	4.20–6.10	2.95–4.70	3.00–4.60
Min–Max	3.20–10.40	1.90–9.20	2.40–7.20	1.90–10.20
10MWR, seconds				
Mean (SD)	5.39 (1.16)	5.39 (0.58)	4.84 (1.15)	4.83 (0.40)
Median	5.10	5.50	4.65	4.90
Q1–Q3	4.60–5.80	4.70–6.40	4.20–5.00	4.10–5.50
Min–Max	4.10–8.90	3.03–7.50	3.80–9.10	3.03–8.00

- Due to the lack of a placebo group in Part 2, the EC was propensity-score weighted to the patients in Study 102 and used to contextualize the Part 2 results.

Safety summary[12]

- For patients treated in Part 1, most treatment-related TEAEs occurred within the first 60 days of treatment; these patients generally did not report treatment-related TEAEs in Part 2.
- No new safety signals or clinically relevant complement activation was observed.
- There were no deaths and no patient study discontinuations due to an AE.
- No treatment-related SAEs were reported during Part 2 of the study (see Supplementary Materials).
- Five treatment-related SAEs were reported in Part 1: Four in the group that received delandistrogene moxeparvovec and one in the placebo group.
  - Three instances of rhabdomyolysis (two in patients who received delandistrogene moxeparvovec and one in the placebo group) that resolved.
  - Increased transaminases in one patient and liver injury in another (both in patients who received delandistrogene moxeparvovec).

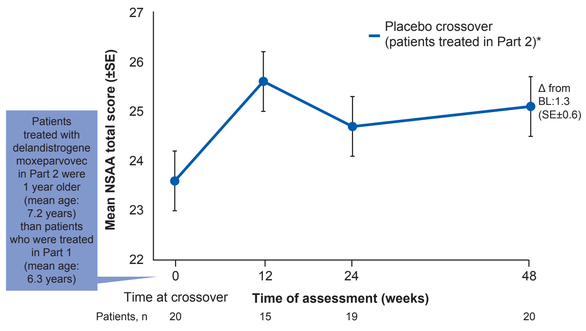
Most common treatment-related TEAEs: Study 102 safety population

	Patients treated in Part 1* BL to Week 48 (n=20)[12]	Patients treated with placebo in Part 1† BL to Week 48 (n=21)	Patients treated in Part 1* Weeks 48–96 (n=20)[12]	Patients treated in Part 2† Weeks 48–96 (n=21)[12]
Patients with any treatment-related TEAE	17 (85.0)	9 (42.9)	4 (20.0)	20 (95.2)
Most common treatment-related TEAEs,‡ n (%)				
Vomiting	12 (60.0)	4 (19.0)	0	16 (76.2)
Decreased appetite	6 (30.0)	0	0	15 (71.4)
Nausea	6 (30.0)	2 (9.5)	1 (5.0)	10 (47.6)
Gamma-glutamyl transferase increased	5 (25.0)	0	0	6 (28.6)
Abdominal pain upper	3 (15.0)	1 (4.8)	1 (5.0)	8 (38.1)
Abdominal pain	3 (15.0)	0	0	1 (4.8)
Pyrexia	1 (5.0)	0	0	4 (19.0)
Thrombocytopenia	0	0	0	5 (23.8)
Glutamate dehydrogenase increased	0	0	0	3 (14.3)

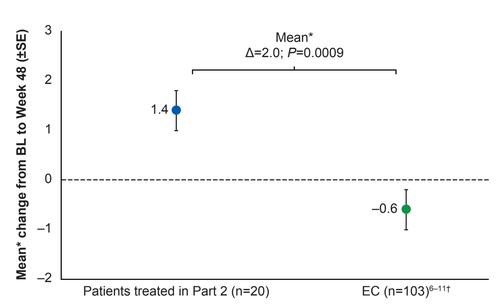
*Patients who received delandistrogene moxeparvovec in Part 1 and placebo in Part 2. †Patients who received placebo in Part 1 and delandistrogene moxeparvovec in Part 2. ‡Treatment-related TEAEs reported in at least three patients in Part 1 or Part 2.

Patients treated in Part 2: NSAA total score at Week 48

- At Week 48, the change in NSAA total score from BL was +1.3 points (SE=0.6) in patients treated in Part 2* 1 year after treatment with delandistrogene moxeparvovec.[12]
- In a post hoc analysis, a statistically significant difference in mean NSAA total score change from BL was observed in patients treated in Part 2 versus the EC (P=0.0009).



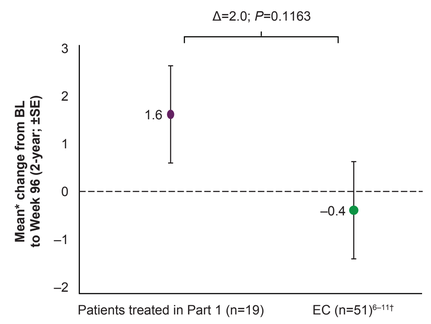
*Patients who received placebo in Part 1 and delandistrogene moxeparvovec in Part 2. Includes 20 patients who had BL and Week 48 results.

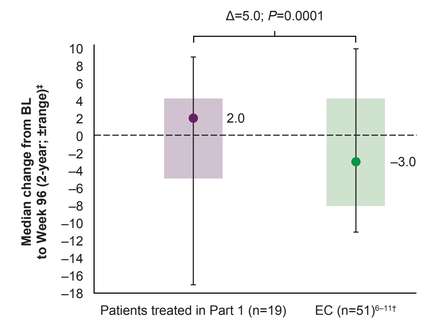


*LSM from weighted linear regression. †For the 48-week (1-year) comparator group, EC data were available for 103 participants.

Post hoc analyses: 2-year analysis of patients treated in Part 1 versus EC: Mean and median change from BL in NSAA total score

- The difference in mean* change from BL in NSAA total score in Part 1-treated patients 2 years after treatment with delandistrogene moxeparvovec versus the EC was not statistically significant (Δ=2.0; P=0.1163).
- A data point (17-point decrease) was observed, which skewed the mean estimate; therefore, an analysis was carried out to test the equality of the median, which demonstrated a statistically significant difference (Δ=5.0; P=0.0001).





*LSM from weighted linear regression. †For the 96-week (2 year) comparator group, EC data were only available for 51 participants. ‡Boxes represent IQR.

Summary of change from baseline biological results for all patients

		All patients treated in Part 1*			All patients treated in Part 2†	
		BL (n=20)	Change from BL to Week 12 (n=20)	Change from BL to Week 60 (n=18)	BL (n=21)	Change from BL to Week 12 (n=21)
Western blot adjusted for muscle content, % normal	Mean	4.23	23.82	19.10	1.91	39.64
	Min–Max	0.39–30.18	–0.64 to 131.67	–9.93 to 147.79	0.15–5.75	–1.13 to 90.43
Vector genome copy number	Mean	0.00	1.56	0.94	0.00	3.43
	Min–Max	0.00–0.00	0.48–6.61	0.05–5.07	0.00–0.00	0.33–7.34
Fiber intensity, % control	Mean	37.90	25.81	38.30	34.27	74.09
	Min–Max	22.62–105.40	–7.67 to 189.17	–8.31 to 252.85	20.05–57.21	1.15–138.09
PDPF, %	Mean	9.07	23.88	57.12	9.81	78.92
	Min–Max	0.35–22.85	–7.29 to 85.51	8.55–97.12	1.75–29.35	4.82–96.10

*Patients who received delandistrogene moxeparvovec in Part 1 and placebo in Part 2. †Patients who received placebo in Part 1 and delandistrogene moxeparvovec in Part 2.

- SRP-9001 dystrophin protein expression at 12 weeks post-treatment was achieved in patients treated with delandistrogene moxeparvovec in both Parts 1 and 2.
- Patients treated in Part 1 continued to express SRP-9001 dystrophin protein after 60 weeks of treatment.

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Abbreviations

10MWR, 10-meter Walk/Run; AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; BL, baseline; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; DNHS, Duchenne Natural History Study; EC, external control; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; IQR, interquartile range; ITR, inverted terminal repeat; IV, intravenous; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; OH, hydroxyl; OLE, open-label extension; PDPF, percent dystrophin-positive fibers; polyA, polyadenylation; qPCR, quantitative polymerase chain reaction; rAAV, recombinant adeno-associated virus; SAE, serious adverse event; SD, standard deviation; SE, standard error; ssDNA, single-stranded DNA; TEAE, treatment-emergent adverse event; TTR, Time to Rise.

References

1. ClinicalTrials.gov. NCT03769116 (Accessed February 2023);
2. Asher DR, et al. *Expert Opin Biol Ther*. 2020; 20:263–274;
3. Zheng C and Baum BJ. *Methods Mol Biol*. 2008; 434:205–219;
4. Mendell JR, et al. *JAMA Neurol*. 2020; 77:1122–1131;
5. Mendell JR, et al. Presented at MDA 2021;
6. https://cinrgresearch.org/ (Accessed February 2023);
7. Thangarajh M, et al. *PLoS Curr*. 2018; 10:ecurrents.md.4cdeb6970e54034db2bc3dfa54b4d987;
8. ClinicalTrials.gov. NCT00468832 (Accessed February 2023);
9. https://for-dmd.org/en/ (Accessed February 2023);
10. ClinicalTrials.gov. NCT01603407 (Accessed February 2023);
11. ClinicalTrials.gov. NCT01865084 (Accessed February 2023);
12. Mendell JR, et al. Presented at MDA 2022.

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