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 (NCT03769116)[1] reinforce that delandistrogene moxeparvovec (SRP-9001) has a favourable benefit-risk profile, with no new safety signals observed.
- Overall maintenance of motor function was observed over 2 years following treatment with delandistrogene moxeparvovec.

Conclusions

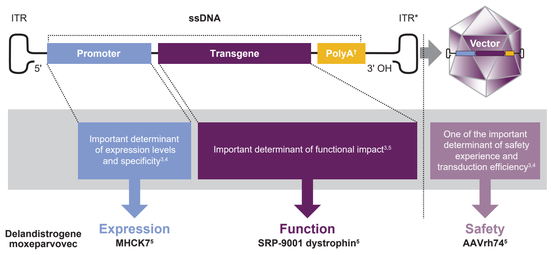
- The safety profile of patients treated in Part 2 was consistent with that seen in Part 1, reinforcing that delandistrogene moxeparvovec has a favourable benefit-risk profile.
- Patients treated in Part 2 demonstrated improved change in motor function as measured by the NSAA compared with a matched EC group.
- In the poster, we also show two-year data on NSAA for the patients treated in Part 1.
  - The mean NSAA score for patients treated in Part 1 was higher than the EC, 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.
- 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.
- Further investigations to assess the efficacy of delandistrogene moxeparvovec are ongoing.

Objective

- Study 102 is a Phase 2, randomised, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of delandistrogene moxeparvovec in patients with DMD aged ≥4 to <8 years.[1,2]
  - 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 102 data 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.[3–5]
- 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).[2]
  - Discrepancies in NSAA scores at baseline may have confounded the comparison of scores at Week 48.

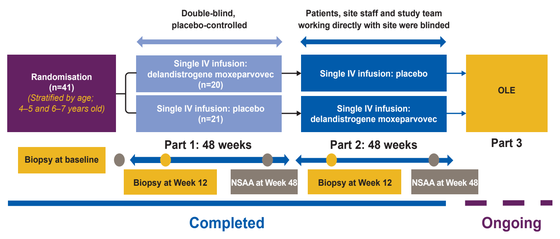


*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (i.e. copies) it.

Study design

Study design[1]

- Study 102 is a Phase 2, randomised, double-blind, placebo-controlled 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.[1,2]



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 will be excluded)
- NSAA score: ≥13 and ≤ 30 at baseline
- Rise from the floor: ≤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, 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.

Results

Baseline demographics: Intent-to-treat population[2,12]

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
Time to Rise 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

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

- 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 contextualise Part 2 results.

Safety summary[12]

- For patients treated in Part 1, most treatment-related TEAEs occurred within the first 90 days of treatment; these patients generally did not report treatment-related TEAEs in Part 2.
- No new safety signals or clinically relevant complement activation were 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).

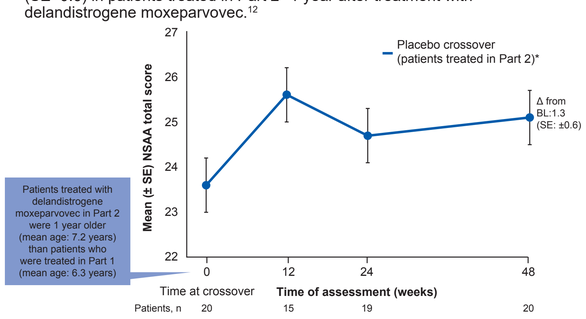
Most common treatment-related TEAEs: 102 safety population

	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 increase	0	0	0	3 (14.3)

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

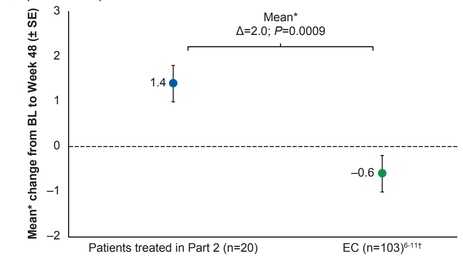
Patients treated in Part 2: NSAA total score at Week 48

- 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]



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

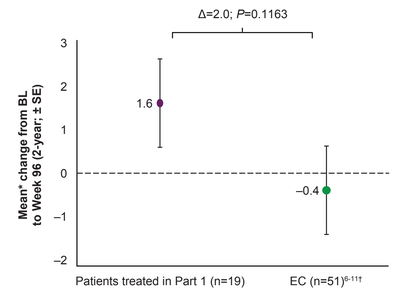
- In a post hoc analysis, a statistically significant difference in mean NSAA total score change from baseline was observed in patients treated in Part 2 versus the EC (P=0.0009).



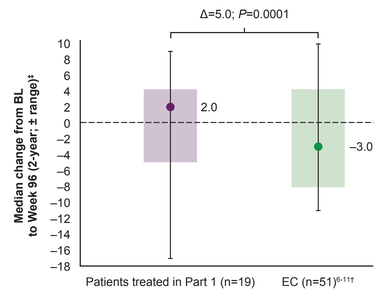
*LSM from weighted linear regression. †For the 48-week (1-year) comparator group, EC data were available for 103 participants.

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

- The difference in mean* change in NSAA total score from baseline 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
	Range	0.39 to 30.18	–0.64 to 131.67	–9.93 to 147.79	0.15 to 5.75	–1.13 to 90.43
Vector genome copy number	**Mean**	0.00	1.56	0.94	0.00	3.43
	Range	0.00 to 0.00	0.48 to 6.61	0.05 to 5.07	0.00 to 0.00	0.33 to 7.34
Fibre intensity, % control	**Mean**	37.90	25.81	38.30	34.27	74.09
	Range	22.62 to 105.40	–7.67 to 189.17	–8.31 to 252.85	20.05 to 57.21	1.15 to 138.09
PDPF, %	**Mean**	9.07	23.88	57.12	9.81	78.92
	Range	0.35 to 22.85	–7.29 to 85.51	8.55 to 97.12	1.75 to 29.35	4.82 to 96.10

- 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.

*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.

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Abbreviations

10MWR, 10-metre Walk/Run; AAVrh74, adeno-associated virus rhesus isolate serotype 74; 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; MHCK, myosin-heavy-chain kinase; NSAA, North Star Ambulatory Assessment; OH, hydroxyl; OLE, open-label extension; PDPF, percent dystrophin positive fibres; polyA, polyadenylation; qPCR, quantitative polymerase chain reaction; SAE, serious adverse event; SD, standard deviation; SE, standard error; ssDNA, single-stranded DNA; TEAE, treatment-emergent adverse event.

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12. Mendell JR, et al. Presented at MDA 2022.

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Presented at the 27th International Annual Congress of the World Muscle Society (WMS), Halifax, Canada, October 11–15, 2022

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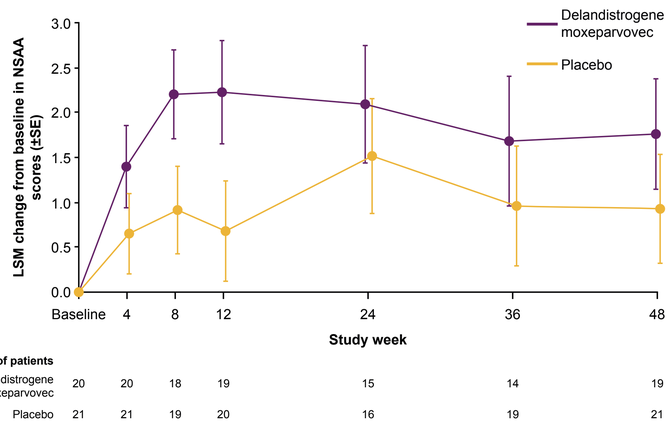
Supplementary material

NSAA primary functional endpoint: Part 1: Change from baseline in NSAA total score at Week 48[1]*

- At Week 48, the change in NSAA total score from baseline was +1.7 points in the delandistrogene moxeparvovec-treated group and +0.9 points in the placebo group, which was not statistically different (*P*=0.37).



Part 1: Discrepancies in NSAA scores at baseline may have confounded comparison of scores at Week 48[1,2]*

- Analysis of the 4- to 5-year-old subgroup, with well-matched functional measures at baseline, showed a statistically significant difference in NSAA scores; however, in 6- to 7-year-olds, NSAA scores were not well matched at baseline, and the difference was not statistically significant.

NSAA change from baseline

Age subgroup	Treatment	BL	LSM change at 48 weeks (SE)	*P*-value
4- to 5-year-olds	Delandistrogene moxeparvovec	20.1	4.3 (0.6)	<0.0001
	Placebo	20.4	1.9 (0.6)	0.0126
	Delandistrogene moxeparvovec vs placebo	–	2.5 (0.9)	0.0172
6- to 7-year-olds	Delandistrogene moxeparvovec	19.6	–0.2 (0.7)	0.7807
	Placebo	24.0	0.5 (0.7)	0.5003
	Delandistrogene moxeparvovec vs placebo	–	–0.7 (1.1)	0.5384

*The analyses of 4- to 5-year-olds and 6- to 7-year-olds were pre-specified, but there was no multiplicity control. The baseline imbalances in the 6- to 7-year-old age group may have confounded the analysis.

Overview of AEs: Study 102 safety population

		Patients treated in Part 1* BL to Week 48 (n=20)[2]	Patients treated with placebo in Part 1† BL to Week 48 (n=21)	Patients treated in Part 1* Weeks 48 to 96 (n=20)[2]	Patients treated in Part 2† Weeks 48 to 96 (n=21)[2]
Total number of AEs		308	230	157	278
Total number of TEAEs		285	209	131	262
Total number of treatment-related TEAEs		63	11	8	115
Total number of SAEs		4	2	2	1
Total number of treatment-related SAEs		4	1	0	0
Total number of deaths		0	0	0	0
Total number of patients with at least 1, n (%)	AE	20 (100.0)	21 (100.0)	19 (95.0)	21 (100.0)
	TEAE	20 (100.0)	21 (100.0)	19 (95.0)	21 (100.0)
	SAE	3 (15.0)	2 (9.5)	2 (10.0)	1 (4.8)
	Treatment-related TEAE	17 (85.0)	9 (42.9)	4 (20.0)	20 (95.2)
	Treatment-related SAEs	3 (15.0)	1 (4.8)	0	0
	AEs leading to study discontinuation	0	0	0	0

*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.

Abbreviations

AE, adverse event; BL, baseline; LSM, least-squares mean; NSAA, North Star Ambulatory Assessment; SAE, serious adverse event; SE, standard error; TEAE, treatment-emergent adverse event.

Reference

1. Mendell JR, et al. Presented at MDA 2021;
2. Mendell JR, et al. Presented at MDA 2022.

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