A Phase 2 clinical trial evaluating the safety and efficacy of delandistrogene moxeparvovec (SRP-9001) in patients with Duchenne muscular dystrophy

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- Delandistrogene moxeparvovec (SRP-9001) is an investigational therapy and has not been reviewed or approved by the FDA
- Trial registration: NCT03769116
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- ZS, KJL, MAI, BP, JDW, CLS, HCM and LAS report no conflicts of interest
- NFR reports receiving salary support from Sarepta Therapeutics for Clinical Evaluator training for ongoing and upcoming clinical trials
- LPL and LNA reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials
- RAP, DAG, SL, LH, SU, TS and LRR-K are employees of Sarepta Therapeutics and may have stock options
- LRR-K is a co-inventor of AAVrh74.MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics
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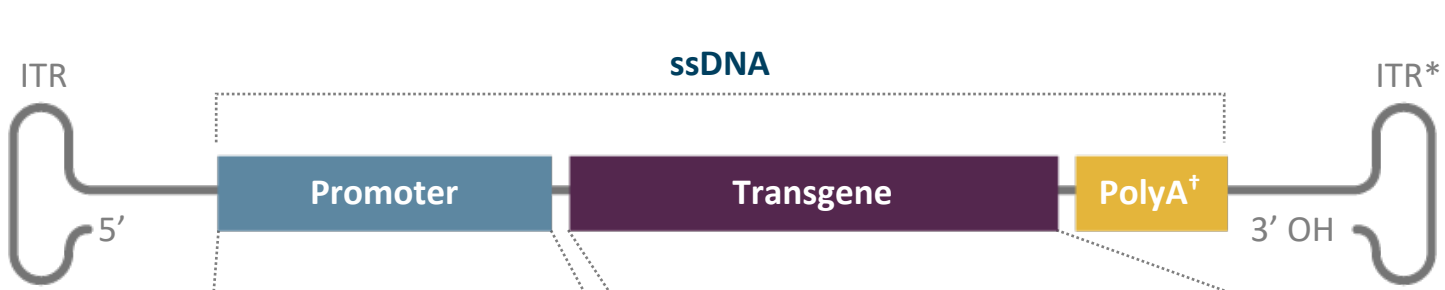
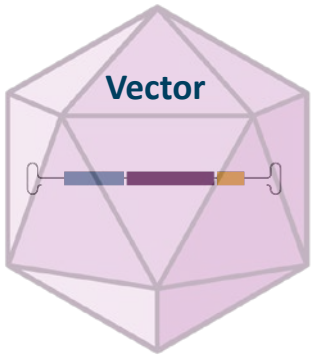
Delandistrogene moxeparvovec (SRP-9001; rAAVrh74.MHCK7.micro-dystrophin) is an investigational AAV gene transfer therapy for the treatment of DMD[1–3]





Important determinant of expression levels and specificity[1,2]

Important determinant of functional impact[1,4]

One of the important determinants of safety experience and transduction efficiency[1,2]

EXPRESSION

FUNCTION

SAFETY

Delandistrogene moxeparvovec

MHCK7[3]

Micro-dystrophin[3]

AAVrh74[3]

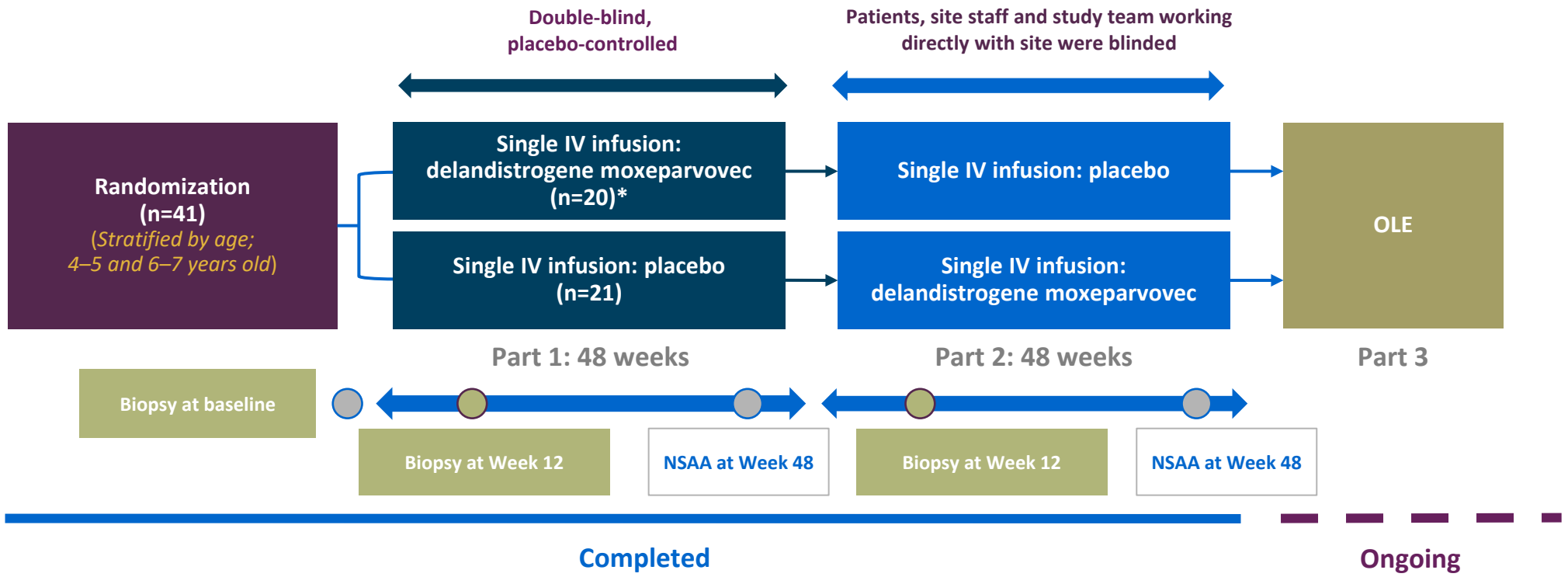
*ITRs are required for genome replication and packaging. †PolyA signals the end of the transgene to the cellular machinery that transcribes (i.e., copies) it.

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; rAAVrh74, recombinant AAVrh74; 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.

Study design

A **randomized, double-blind, placebo-controlled** clinical trial to evaluate 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.

DMD, Duchenne muscular dystrophy; IV, intravenous; NSAA, North Star Ambulatory Assessment; OLE, open-label extension; qPCR, quantitative polymerase chain reaction.

1. Clinicaltrials.gov. NCT03769116 (Accessed March 2022); 2. Mendell JR, et al. Presented at MDA 2021.

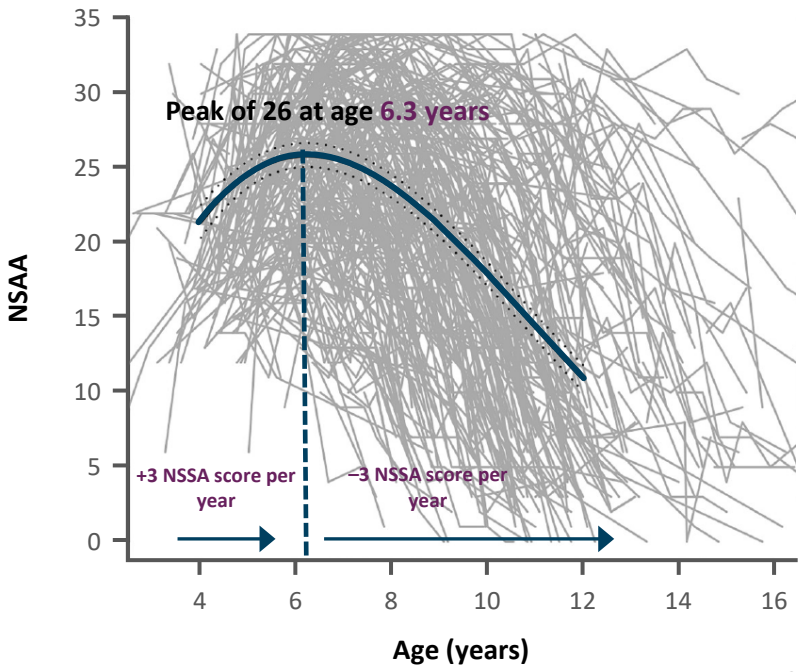
Baseline demographics: Intent-to-treat population

Characteristic	Statistics	Patients treated in Part 1* (Delandistrogene moxeparvovec/ placebo) (n=20)	Patients treated in Part 2† (Placebo/ delandistrogene moxeparvovec) (n=21)
Age (years)[1]	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[1]	Mean (SD) Min, Max	1.0 (1.1) 0.2, 3.8	1.3 (1.2) 0.2, 5.1
Corticosteroid type, deflazacort[1]	n (%)	7 (35.0)	7 (33.3)
Dosing weight (kg)[1]	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[2]	Mean (SD) Min, Max	19.8 (3.3) 13, 26	22.6 (3.3) 15, 29
Time to Rise results at baseline (seconds)[2]	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)[2]	Mean (SD) Min, Max	5.4 (1.1) 4.1, 8.9	4.8 (0.7) 4.0, 7.2

The majority of patients (61%) were ≥6 years of age at baseline, and age was the only stratification factor for randomization

*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.
10MWR, 10-meter Walk/Run; NSAA, North Star Ambulatory Assessment; SD, standard deviation.
1. Mendell JR, et al. Presented at MDA 2021; 2. Sarepta data on file.

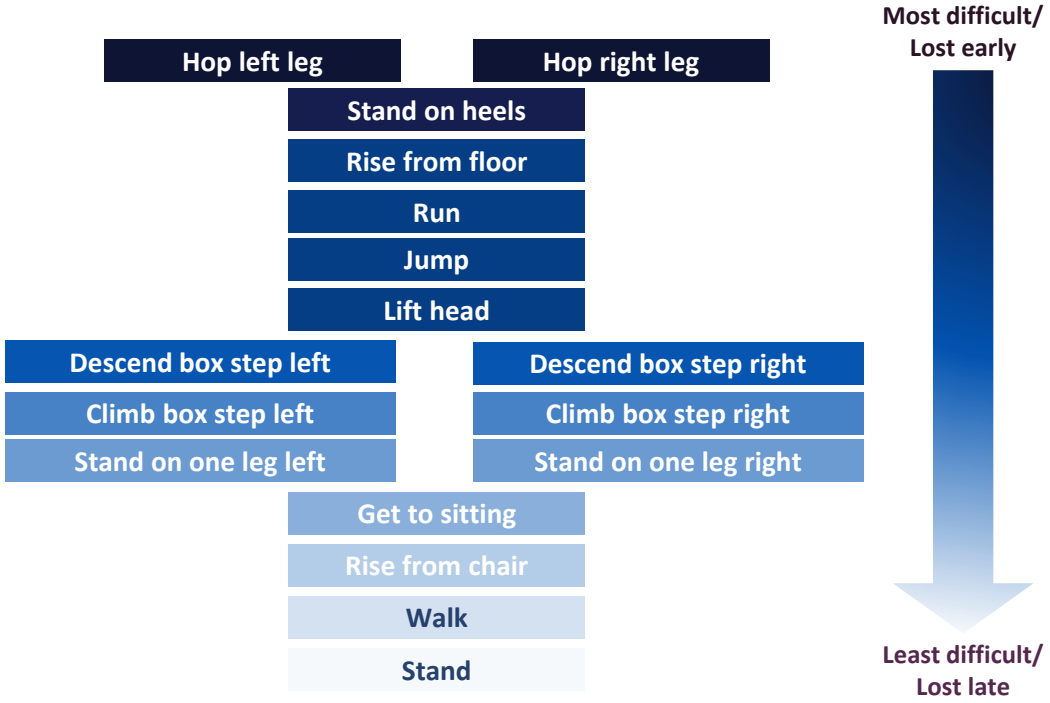
Evolution of NSAA in a natural history cohort – DMD is heterogeneous



NSAA total score trajectories for individual patients

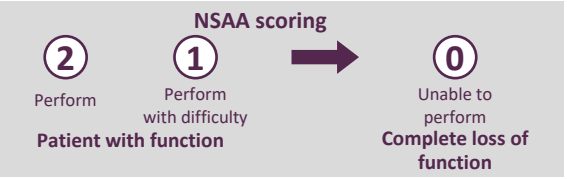
Fitted mean and 95% confidence interval

Figure adapted from Muntoni F, et al 2019[1]



Mean total NSAA score declines after the age of 6 years in patients with DMD[1]

Total possible score: **34 points[2]**

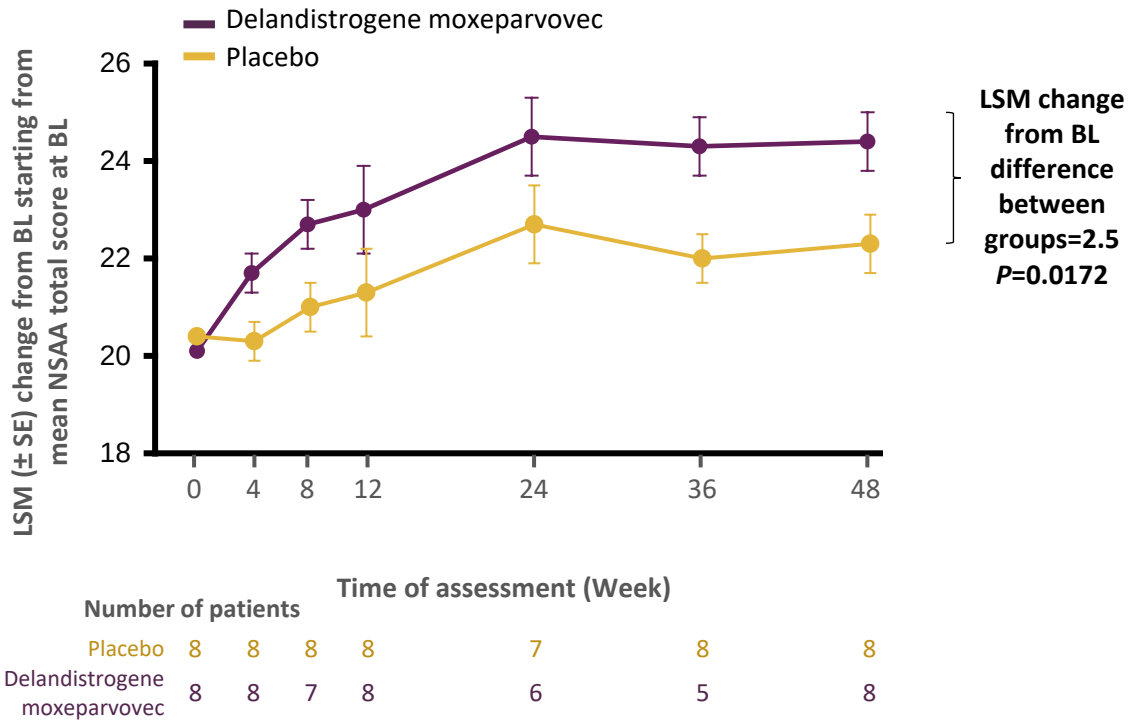


DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment.

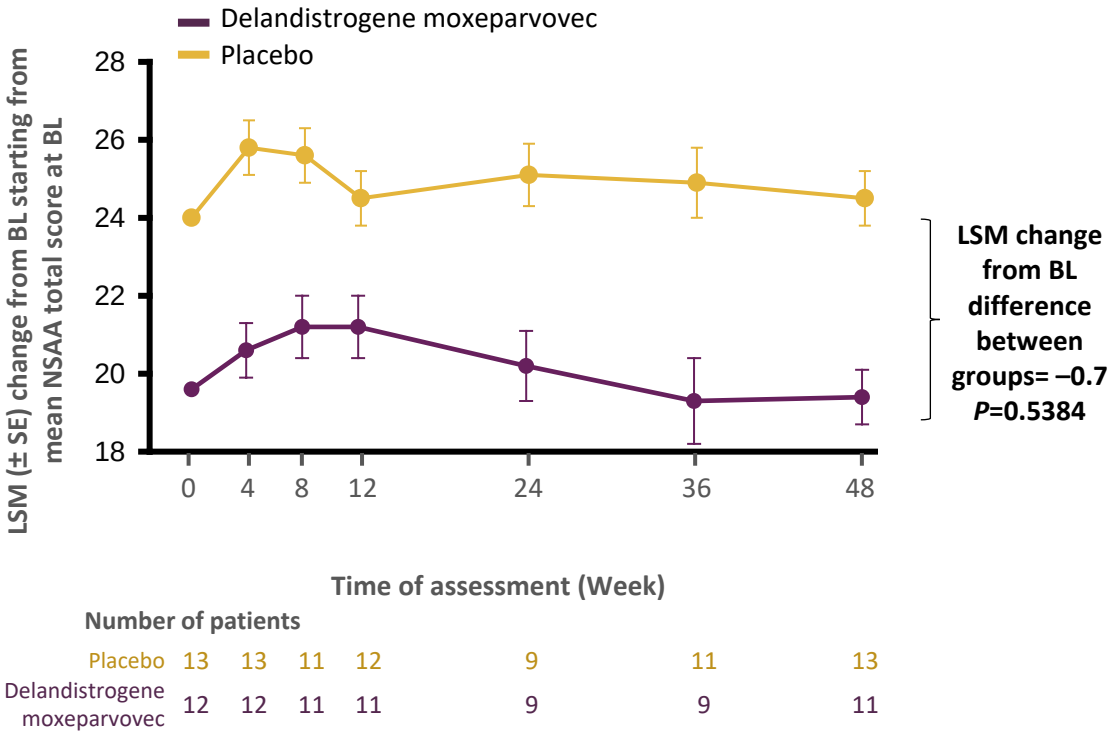
1. Muntoni F, et al. PLoS One. 2019; 14:e0221097; 2. Muscular Dystrophy UK, NSAA assessment: https://www.musculardystrophyuk.org/static/s3fs-public/2021-08/NSAA%20_Manual_%2015102020.pdf?VersionId=BaPGDWk5TxA3rtF2DDipAVYlOJ5Eoumo. (Accessed March 2022).

Part 1: Discrepancies in NSAA scores for placebo and treatment groups at baseline confounded comparison of scores at Week 48

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 in NSAA scores was not statistically significant



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 group may have confounded the analysis.
BL, baseline; LSM, least squares mean; NSAA, North Star Ambulatory Assessment; SE, standard error.
1. Mendell JR, et al. Presented at MDA 2021.

External control comparator

The external control comparator was comprised of data from the following studies:

- CINRG Duchenne Natural History Study (DNHS; NCT00468832)[1,2]
- Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD; NCT01603407)[3]
- Eli Lilly and Company Study (H6D-MC-LVJJ; NCT01865084)[4,5]

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**
- **Time to Rise: ≤10.4 seconds at baseline**
- **10MWR: ≤9.1 seconds at baseline**

Min — **Max**

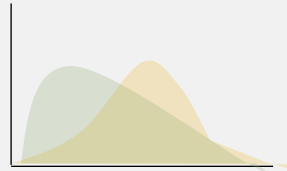
Creates a standard range across functional outcome measures for treatment and external control groups

Analysis method

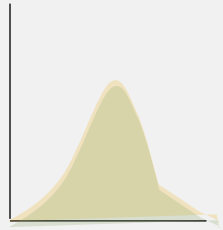
- Propensity score weighting based on:
  - Age
  - NSAA
  - Time to Rise results
  - 10MWR results

Prognostic factors in DMD that are known to impact function

Theoretical example



Before propensity weighting, the ranges are the same but with unequal distribution



After propensity weighting, the two populations completely overlap

10MWR, 10-meter Walk/Run; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; DNHS, Duchenne Natural History Study; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; NSAA, North Star Ambulatory Assessment.

1. Spurney C, et al. Muscle Nerve. 2014; 50:250–256; 2. ClinicalTrials.gov. NCT00468832 (Accessed March 2022); 3. ClinicalTrials.gov. NCT01603407 (Accessed March 2022); 4. Victor RG, et al. Neurology. 2017; 89:1811–1820; 5. ClinicalTrials.gov. NCT01865084 (Accessed March 2022).

A propensity-weighted external control matched the delandistrogene moxeparvovec group at baseline

	Patients treated in Part 2* (Placebo/delandistrogene moxeparvovec)	External control[1–3‡]	
Parameter	Baseline (n=20)[†]	Before propensity weighting (N=126)	After propensity weighting (n=103)
Age			
Mean (SD)	**7.2 (1.1)**	6.8 (1.0)	**7.0 (0.4)**
NSAA total score			
Mean (SD)	**23.8 (3.7)**	23.9 (4.4)	**23.5 (1.9)**
Time to Rise			
Mean (SD)	**4.0 (1.3)**	5.0 (2.0)	**3.9 (0.6)**
Time of 10MWR			
Mean (SD)	**4.8 (1.2)**	5.4 (1.1)	**4.8 (0.4)**

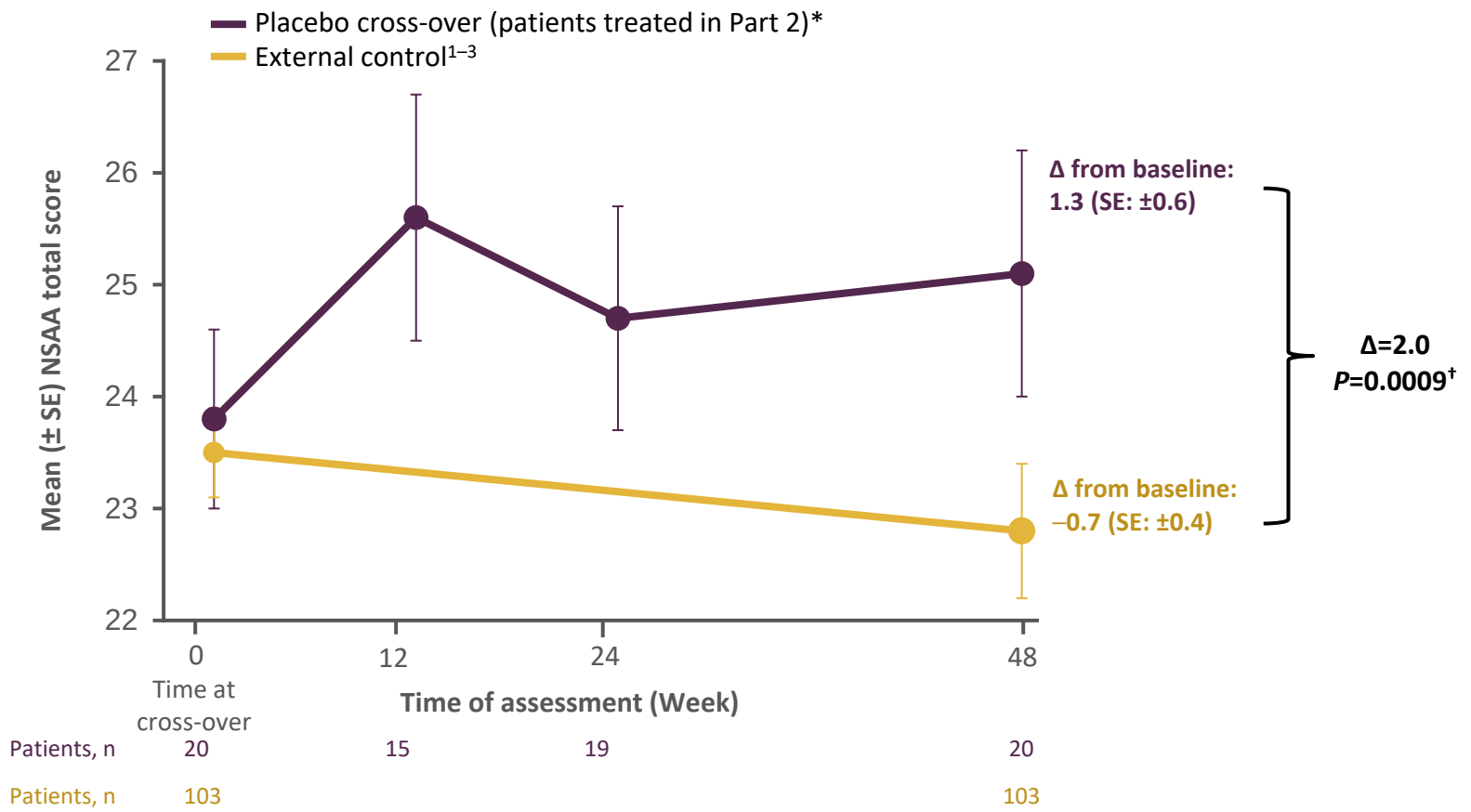
- **Propensity weighting allows simultaneous matching across multiple variables that are known to impact function in DMD**
- **After propensity weighting, the external comparator group was well matched to the patients in Study 102**

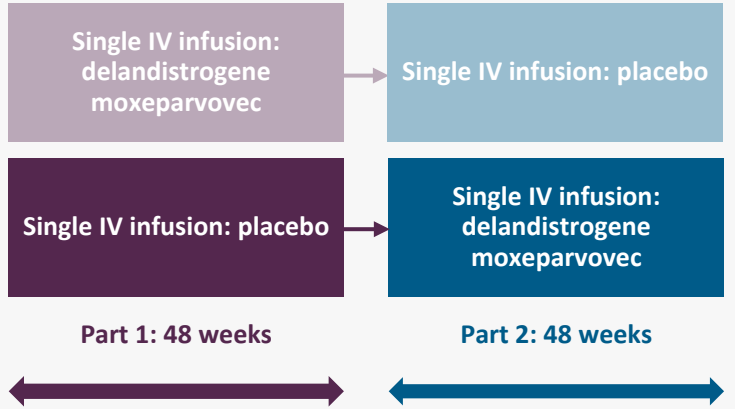
*Patients who received placebo in Part 1 and delandistrogene moxeparvovec in Part 2. †There were 21 participants in the Study 102 placebo cross-over cohort. In the analysis versus external controls, one participant was unable to perform the 48-week assessment in Part 2, due to recovery from a medical concern unrelated to the trial. ‡External control data sources: CINRG (NCT00468832); FOR-DMD (NCT01603407); Eli Lilly and Company study (NCT01865084).[1–3]

10MWR, 10-meter Walk/Run; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; FOR-DMD, Finding the Optimum Regimen for Duchenne Muscular Dystrophy; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

1. ClinicalTrials.gov. NCT00468832 (Accessed March 2022); 2. ClinicalTrials.gov. NCT01603407 (Accessed March 2022); 3. ClinicalTrials.gov. NCT01865084 (Accessed March 2022).

Placebo cross-over analysis: Mean NSAA total score 1 year after delandistrogene moxeparvovec treatment versus external control





An increase in mean NSAA total score change from baseline was observed in placebo cross-over patients 1 year after treatment with delandistrogene moxeparvovec compared with the external control: Δ=2.0

*Includes 20 patients who had baseline and Week 48 results. There were 21 participants in the Study 102 placebo cross-over cohort. In the analysis versus external controls, one participant was unable to perform the 48-week assessment in Part 2, due to recovery from a medical concern unrelated to the trial. †The *P* value was calculated based on weighted ANCOVA adjusted for age and baseline NSAA.

ANCOVA, analysis of covariance; IV, intravenous; NSAA, North Star Ambulatory Assessment; SE, standard error.

1. ClinicalTrials.gov. NCT00468832 (Accessed March 2022); 2. ClinicalTrials.gov. NCT01603407 (Accessed March 2022); 3. ClinicalTrials.gov. NCT01865084 (Accessed March 2022).

Overview of AEs: Safety population

		Patients treated in Part 1* Baseline to Week 48 (n=20)	Patients treated in Part 1* Weeks 48–96 (n=20)	Patients treated in Part 2† Weeks 48–96 (n=21)
Total number of AEs, n		306	157	278
Total number of TEAEs, n		283	131	262
Total number of treatment-related TEAEs, n		62	8	115
Total number of SAEs, n		4	2	1
Total number of treatment-related SAEs, n		4	0	0
Total number of deaths, n		0	0	0
Total number of patients with at least one, n (%)	AE	20 (100.0)	19 (95.0)	21 (100.0)
	TEAE	20 (100.0)	19 (95.0)	21 (100.0)
	SAE	3 (15.0)	2 (10.0)	1 (4.8)
	Treatment-related TEAE	17 (85.0)	4 (20.0)	20 (95.2)
	Treatment-related SAE	3 (15.0)	0	0
	AE leading to study discontinuation	0	0	0

- **There were no deaths and no patient study discontinuations due to an AE**
- **The safety profile of patients treated in Part 2 is consistent with that seen in Part 1**

*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.
AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE.

Most common treatment-related TEAEs: Safety population

		Patients treated in Part 1* Baseline to Week 48 (n=20)	Patients treated in Part 1* Weeks 48–96 (n=20)	Patients treated in Part 2† Weeks 48–96 (n=21)
Patients with any treatment-related TEAE		17 (85.0)	4 (20.0)	20 (95.2)
Most common treatment-related TEAEs‡ n (%)	Vomiting	12 (60.0)	0	16 (76.2)
	Decreased appetite	6 (30.0)	0	15 (71.4)
	Nausea	6 (30.0)	1 (5.0)	10 (47.6)
	Gamma-glutamyl transferase increased	5 (25.0)	0	6 (28.6)
	Abdominal pain upper	3 (15.0)	1 (5.0)	8 (38.1)
	Abdominal pain	3 (15.0)	0	1 (4.8)
	Blood bilirubin increased	2 (10.0)	0	2 (9.5)
	Pain in extremity	2 (10.0)	0	0
	Rhabdomyolysis	2 (10.0)	0	0
	Pyrexia	1 (5.0)	0	4 (19.0)
	Thrombocytopenia	0	0	5 (23.8)
	Glutamate dehydrogenase increased	0	0	3 (14.3)
	Fatigue	0	0	2 (9.5)
	Headache	0	0	2 (9.5)
	Ketonuria	0	1 (5.0)	1 (4.8)
	Lethargy	0	0	2 (9.5)
	Myalgia	0	0	2 (9.5)
	White blood cell count decreased	0	0	2 (9.5)

- **For patients treated with delandistrogene moxeparvovec 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 activations were observed in Part 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. ‡Treatment-related TEAEs reported in at least two patients in Part 1 or Part 2.
TEAE, treatment-emergent AE.

Study 102 conclusions

Safety summary

No new safety signals or clinically relevant complement activations were observed in Part 2

The safety profile of patients treated in Part 2 is consistent with that seen in Part 1

No new safety signals emerged for patients treated for 2 years in Part 1

Functional outcomes summary

Due to the lack of a placebo group in Part 2, an external comparator that was propensity matched to the patients in Study 102 was used to provide context to Part 2 results

An increase in mean NSAA total score change from baseline was observed in cross-over patients 1 year after treatment with delandistrogene moxeparvovec compared with the external control

- The Study 102 Part 2 results reinforce that delandistrogene moxeparvovec has a favorable benefit-risk profile
- In the external control analyses, the placebo cross-over patients had a statistically significant and clinically important increase in NSAA scores compared with the matched external control group after 1 year, indicating a potential change in DMD disease trajectory

DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment.