EP.139

Phase 1/2a trial of SRP-9001 in patients with Duchenne muscular dystrophy: 3-year safety and functional outcomes

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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 rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) generally led to improvements in functional assessments over 3 years in patients with DMD and reinforced that SRP-9001 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 SRP-9001 in patients with DMD.**

Conclusions

- Three-year data from Study 101 reinforce that SRP-9001 is well tolerated, with no new safety signals and data are consistent with safety data from the wider SRP-9001 clinical trial program.
  - Treatment-related safety events in Study 101 mostly occurred in the first 90 days post-infusion, and all resolved.
- Long-term functional assessment measured by the NSAA demonstrated overall improvements in motor abilities compared to baseline that were maintained over three years, demonstrating a durable response.
- All four patients in the SRP-9001-101 open-label trial demonstrated general improvements in functional measures compared to baseline that appear to be maintained 3 years after SRP-9001 administration.
- Motor improvements in the NSAA scale are generally associated with improvements in ambulation over 3 years compared with the decline generally expected to be observed in untreated patients from natural history.
- The safety profile and durable response in Study 101 provides proof-of-concept support for the continuation of clinical trials to assess SRP-9001 gene transfer in patients with DMD.

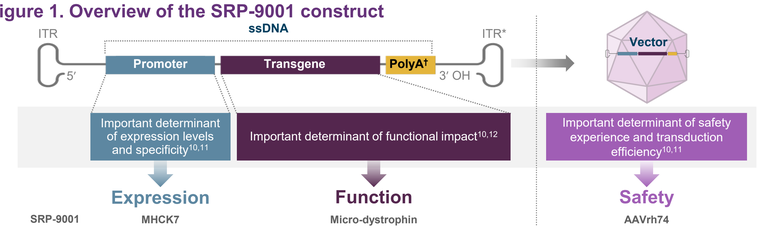
Objective

- The objective of this Phase 1/2a clinical trial ("Study 101"; NCT03375164) was to evaluate the safety of a single dose of an investigational, AAV-based gene transfer therapy, SRP-9001, in patients with DMD, aged 4 to 7 years old.[1]
  - Here we report, for the first time, the long-term (3-year) functional data from the four patients treated with SRP-9001.

Background

- DMD is an X-linked, progressive neuromuscular disease caused by mutations in the *DMD* gene that disrupt the production of functional dystrophin protein, leading to loss of muscle function and premature death.[2–4]
- We developed the AAV-based gene transfer therapy, SRP-9001, which aims to deliver a shortened functional dystrophin transgene (micro-dystrophin) through a single IV dose for targeted expression in skeletal and cardiac muscle (**Figure 1**).[5,6]
- To date, SRP-9001 has demonstrated an acceptable safety profile, successful delivery of the micro-dystrophin transgene, resulting in expression and correct localisation of the micro-dystrophin protein in the target tissues and functional improvements in outcome measures (NSAA and TFTs) over 2 years (compared to BL).[6,7]
- Here we report, for the first time, the long-term (3-year) functional and safety data from four patients with DMD enrolled in Study 101.
  - To put the results into context, NSAA total scores and 100m timed test values in patients treated with SRP-9001 are presented alongside data from natural history cohorts published by Muntoni F, et al (2019) and Alfano LN, et al (2017), respectively.[8,9]

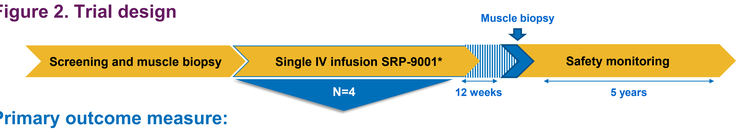
Figure 1. Overview of the SRP-9001 construct



*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

Figure 2. Trial design



Primary outcome measure:

- **Safety based on the number of participants with AEs**

Key additional outcome measures:

- **Micro-dystrophin expression in pre- and post-muscle biopsy at 12 weeks post-infusion (Day 90) (IF and WB)**
- **Change in NSAA and TFTs (100m Timed Test, 4-Stair Climb, 10m Timed Test and Time to Rise)**

*All patients received one IV infusion in the peripheral limb vein at the target dose $2.0x10^{14}$ vg/kg determined by supercoiled qPCR method ($1.33x10^{14}$ vg/kg linear qPCR equivalent), and prednisone (1 mg/kg/day) 1 day pre- to 30 days post-gene delivery.

Results

Table 1. Baseline demographics[6]

	Patient 1	Patient 2	Patient 3	Patient 4
Age (yrs)	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

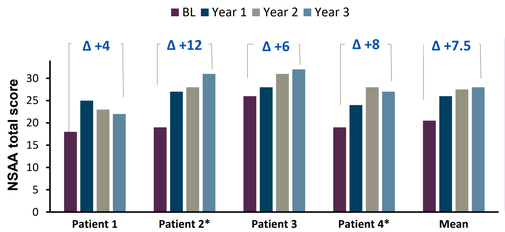
Primary endpoint: Safety*

- 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 within the second- or third-year post-infusion.
- 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 admitted.
  - No other clinically significant laboratory findings were reported.
- 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 abnormality.
- None of the AEs were associated with clinical complement activation.

*Up to data cut-off: 15 Jun 2021,

Functional outcomes

Figure 3. NSAA total scores over 3 years after treatment with SRP-9001



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

- **In a natural history study, the mean NSAA total score increased at a rate of approximately 3 units per year and peaked at 6.3 years of age with a mean score of 26.[8]**
- **This was followed by a rate of decline of approximately 3 units per year.[8]**

*Patient 2: 3-year NSAA value and Patient 4: 2-year NSAA value was from a remote assessment due to COVID-19-related restrictions at the site.

Results (cont.)

- Overall NSAA scores improved in all four patients from baseline to Year 3 (**Figure 3**).
  - All four patients demonstrated a clinically meaningful improvement on NSAA, with a **mean change from baseline to Year 3 of +7.5 (3.42 SD)**.
    - In a natural history study, the mean NSAA total score trajectory peaked at 6.3 years of age with a mean NSAA score of 26, this was followed by a rate of decline of approximately 3 units per year.[8]
- Overall, patients generally maintained muscle strength (Time to Rise and 4-Stair Climb, **Table 2**), from baseline to Year 3.*
- Patients treated with SRP-9001 generally showed improvement in ambulation ability from baseline to Year 3 (100m walk test; **Figure 4**). The natural history study shows that these patients would have been generally expected to decline.[9]

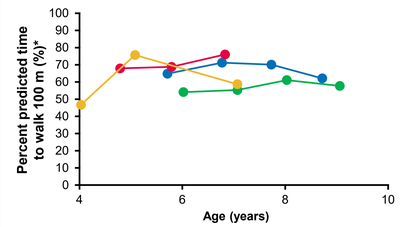
*Year 3 data are missing for one patient.

Table 2. Summary of 3-year timed function tests

	Change from baseline to Year 3				Mean
	Patient 1	Patient 2*	Patient 3	Patient 4	All patients
NSAA total score	+4	+12	+6	+8	**+7.5**
Time to Rise (sec)†	+0.6	-0.2	-1.1	+0.3	**-0.1**
4-Stair Climb (sec)†	-0.9	–	+0.1	-2.6	**-1.1**
100 m (sec)†	-3.9	–	-10.5	-16.5	**-10.3**
100 m (% predicted)	-2.7	–	+3.6	+12	**+4.3**
10 m run (sec)†	-0.5	-1.5	+0.1	-1.1	**-0.8**

*Patient 2: 3-year functional assessment values were from a remote assessment due to COVID-19-related restrictions at the site, values for the time to ascend 4 stairs, to walk 100m, and the predicted time to walk 100m are not available. †Negative values show an improvement in the time taken to achieve this endpoint.

Figure 4. Percent predicted time* to walk 100m over 3 years after treatment with SRP-9001



- **The percent predicted time can determine if a boy is nearing closer or falling behind the predicted value for his age group**
- **In a natural history study, the mean percent predicted 100m score for patients with DMD (aged 4–14 years) was 43.5% ± 13.7% (range: 17.8–74.9%).[9]**

*Percentage predicted time = (predicted time/actual time)*100. This is used to standardise the performance of patients by determining whether patients are getting closer to the percentage predicted value for their age group or falling further behind their age-matched healthy controls. †Patient 2: 3-year functional assessment value was from a remote assessment due to COVID-19-related restrictions at the site. ‡Patient 4 did not have 2-year timed function tests assessed due to COVID-19-related restrictions at the site;18-month data are presented.

Acknowledgements and Disclosures

We would like to thank the patients and their families for participation in this study, as well as the investigators and trial staff involved in Study 101. This study was funded by Sarepta Therapeutics, Inc, Cambridge, Massachusetts, USA. Writing and editorial assistance was provided by Ana Rondelli, PhD, of MediTech Media, USA, in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3) and was funded by Sarepta Therapeutics Inc.
JRM has received study funding from Sarepta Therapeutics for the current publication and has a service agreement with Sarepta to provide training on ongoing studies. In addition, he is a co-inventor of AAVrh74.MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics. ZS has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy. KJL has received an institutional grant from Sarepta Therapeutics. CN has received grant support (research) from Sarepta Therapeutics. LPP reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials and licensing fees for natural history data. NFR reports receiving salary support from Sarepta for Clinical Evaluator training for ongoing and upcoming clinical trials. MAI has nothing to disclose. 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. JVis an employee of Nationwide Children's Hospital. SL, RA, DAG, ERP, LH and KG are employees of Sarepta Therapeutics and may have stock options. KC, RS and MH have nothing to disclose. Louise R. Rodino-Klapac is an employee of Sarepta Therapeutics, has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy, as well as financial consideration from Sarepta Therapeutics and Myonexus Therapeutics (now acquired by Sarepta Therapeutics). In addition, she is a co-inventor of AAVrh74.MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics.

Abbreviations

AAV, adeno-associated virus; AE, adverse event; BL, baseline; BMI, body mass index; DMD, Duchenne muscular dystrophy; IF, immunofluorescence; ITR, inverted terminal repeat; IV, intravenous; MHCK7, myosin heavy chain kinase 7; NSAA, North Star Ambulatory Assessment; OH, hydroxide; polyA, polyadenylation; qPCR, quantitative polymerase chain reaction; rAAVrh74, recombinant AAV rhesus isolate serotype 74; SAE, serious AE; SD, standard deviation; ssDNA, single-stranded DNA; TFTs, timed function tests; TRAE, treatment-related AE; WB, Western blot.

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Presented at the World Muscle Society Virtual Congress, 20–24 September, 2021