EP.254a

A Phase 2 clinical trial evaluating the safety and efficacy of SRP-9001 for treating patients with Duchenne muscular dystrophy

Jerry R. Mendell,[1,2] Perry B. Shieh,[3] Zarife Sahenk,[1,2] Kelly J. Lehman,[1] Linda P. Lowes,[1,2] Natalie F. Reash,[1] Megan A. Iammarino,[1] Lindsay N. Alfano,[1,2] Brenna Powers,[1] Jeremy D. Woods,[3] Christy L. Skura,[3] Howard C. Mao,[3] Loretta A. Staudt,[3] Rachael A. Potter,[1,4] Danielle A. Griffin,[1,4] Sarah Lewis,[1,4] Larry Hu,[4] Sameer Upadhyay,[4] Teji Singh,[4] Louise R. Rodino-Klapac[4]

[1]Center for Gene Therapy, Nationwide Children's Hospital, Columbus, OH, USA; [2]The Ohio State University, Columbus, OH, USA; [3]UCLA Medical Center, Los Angeles, CA, USA; [4]Sarepta Therapeutics, Inc., Cambridge, MA, USA.

What does this study mean for the DMD community?

Findings from this study suggest that rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) has a biological effect that may be clinically relevant to people with DMD.

Conclusions

- Findings from Part 1 of SRP-9001 Study 102 reinforce an acceptable safety profile, consistent with previous studies.
- Study 102 achieved the primary biological endpoint of change in micro-dystrophin expression (baseline to 12 weeks post-treatment).
- Change in NSAA total score of patients who received SRP-9001 did not achieve statistical significance compared with that of patients who received placebo.
  - Analysis of the 4- to 5-year-old subgroup, with well-matched functional measures at baseline, showed a statistically significant difference between patients who received SRP-9001 and those who received placebo at Week 48.
- These results provide important information for ongoing clinical development.

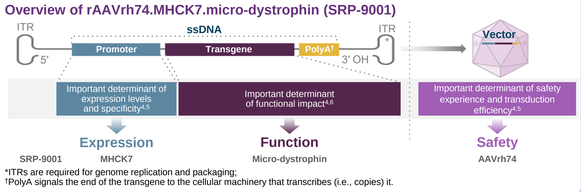
Objective

This clinical trial ("Study 102"; NCT03769116) tested the safety, efficacy, and tolerability of a single dose of an investigational gene transfer therapy, SRP-9001, for treating boys with DMD aged 4 to 7 years old.[1]

Background

- AAV-mediated gene transfer therapy has shown potential as a treatment for DMD.
- Earlier findings, including those from preclinical studies and a Phase 1/2a clinical trial (Study 101; NCT03375164), warrant further investigation of gene transfer therapy in DMD.
- We designed an AAV vector (rAAVrh74) containing a codon-optimised human micro-dystrophin transgene driven by a muscle-specific promoter with a cardiac enhancer (MHCK7).[2,3]

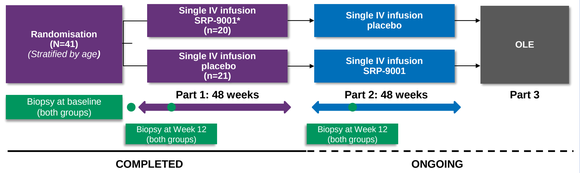
Overview of rAAVrh74.MHCK7.micro-dystrophin (SRP-9001)



*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

Randomisation was only stratified by age group at baseline (4–5 vs. 6–7 years)



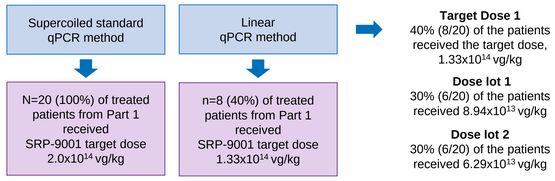
*All patients received the target dose as determined by the supercoiled standard qPCR method specified in the protocol at the time. Subsequent retrospective analysis using the new linear qPCR method indicated that 60% of the patients received a dose lower than the target dose based on the new method. Target 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. All patients going forward will receive the target dose as determined by the new method.

We tested SRP-9001 in a three-part, multicentre, Phase 2 clinical trial ("Study 102")

- Part 1 is a 48-week, randomised, double-blind, placebo-controlled period.
- Part 2 is an ongoing 48-week period, in which placebo patients from Part 1 received SRP-9001 in a crossover blinded fashion.
- Part 3 is a planned open-label follow-up period lasting up to 212 weeks.

Retrospective analysis using different titration methods showed differences between the dose titres

- The **target dose** specified in the study protocol was **2.0x10^{14} vg/kg (qPCR supercoiled standard; equivalent to 1.33x10^{14} vg/kg [qPCR with linear standard]*).**
- Retrospective analysis using the linear qPCR method indicates that 40% of patients received the target dose and 60% of patients received a dose lower than the target dose based on the new method.



- All patients dosed in Part 2 (N=21) received the target dose as determined by the new method (linear qPCR); this method will also be used for future studies.

*Method developed by Nationwide Children's Hospital and used previously in Study 101. For patients who received a dose in this study based on Nationwide Children's Hospital qPCR method, the dose used was 2.0×10^{14} vg/kg which corresponds to 1.33×10^{14} vg/kg as measured by the Sponsor's qPCR method using a linear standard. Note that both numbers (i.e., 2.0×10^{14} and 1.33×10^{14} vg/kg) refer to the same quantity of drug given to the patients; only the effective scale for the two methods is different.

Results

Safety endpoints: TEAEs and SAEs*

Most common treatment-related TEAEs	SRP-9001 (n=20) n (%)	Placebo (n=21) n (%)
Patients with any TEAE	17 (85.0)	9 (42.9)
Vomiting	12 (60.0)	4 (19.0)
Nausea	6 (30.0)	2 (9.5)
Decreased appetite	6 (30.0)	0
γ-Glutamyltransferase increased	5 (25.0)	0
Abdominal pain upper	3 (15.0)	1 (4.8)
Abdominal pain	3 (15.0)	0
Pain in extremity	2 (10.0)	1 (4.8)
Rhabdomyolysis	2 (10.0)	1 (4.8)
Blood bilirubin increased	2 (10.0)	0

*Data cut-off: December 2020.

- TEAEs were transient and manageable.
- 82% of patients with treatment-related TEAEs had only mild or moderate treatment-related TEAEs.
- No clinically relevant complement activation was observed.
- There were four patients with five treatment-related SAEs; four treatment-related SAEs were reported in the SRP-9001-treated group and one was reported in the placebo group.
  - There were three instances of rhabdomyolysis (two in the SRP-900-treated group and one in the placebo group); all were resolved.
  - In the SRP-9001 group, one patient had hepatic enzymes increased and one had liver injury.
- There were no deaths or discontinuations in Part 1 of Study 102.

Results

Biological endpoints

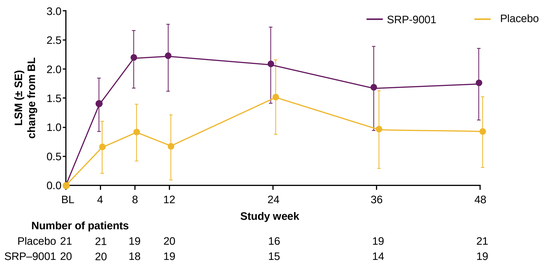
- Patients expressed micro-dystrophin at 12 weeks post-SRP-9001 treatment.

Micro-dystrophin expression and vector genome copies	
Micro-dystrophin expression by WB, mean ± SD	Percentage of normal, %*
Week 12 (n=20) Baseline (n=20) Change from baseline†	28.1 ± 40.1 4.2 ± 6.8 23.8 ± 39.8
Micro-dystrophin expression by IF, mean ± SD	PDPF, %‡
Week 12 (n=20) Baseline (n=20) Change from baseline	32.9 ± 28.1 9.1 ± 6.9 23.9 ± 25.6
Vector genome copy number, mean ± SD	Copies per nucleus
Week 12 (n=20)	1.6 ± 1.5

*WB contained some BLOQ values and non-specific protein signals; †Primary biological endpoint; ‡PDPF levels at baseline include background staining and revertant fibres.

Primary functional endpoint: change in NSAA

- At Week 48, the change in NSAA total score from baseline was +1.7 points in the SRP-9001-treated group and +0.9 points in the placebo group, which was not statistically different (*P*=0.37).



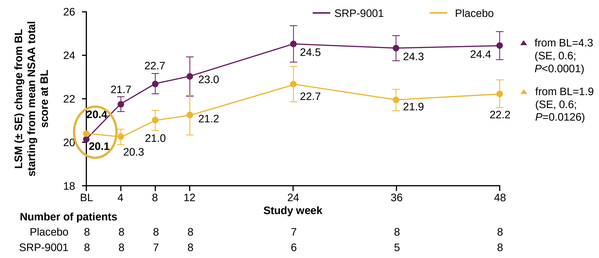
Improvements in NSAA scores reached statistical significance in a subgroup analysis of 4- to 5-year-olds*

- In 4- to 5-year-olds, the NSAA change from baseline at Week 48 was +4.3 points in the SRP-9001-treated group and +1.9 points in the placebo group (*P*=0.0172).
  - Age was a stratification factor at randomisation.

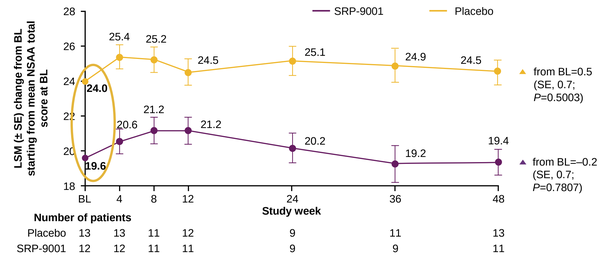
NSAA change from baseline				
Age subgroup	**Treatment**	**Baseline**	**LSM change at Week 48 (SE)**	***P***
4- to 5-year-olds	SRP-9001	20.1	4.3 (0.6)	<0.0001
	Placebo	20.4	1.9 (0.6)	0.0126
	SRP-9001 vs. placebo	–	2.5 (0.9)	0.0172
6- to 7-year-olds	SRP-9001	19.6	–0.2 (0.7)	0.7807
	Placebo	24.0	0.5 (0.7)	0.5003
	SRP-9001 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 group may have confounded the analysis.

In 4- to 5-year-olds, functional measures were well matched at baseline



However, in 6- to 7-year-olds, NSAA scores were not well matched at baseline



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 102. This study was sponsored by Sarepta Therapeutics, Inc., Cambridge, Massachusetts, USA, and funded by Sarepta Therapeutics, Inc. Writing and editorial assistance was provided by Ana Rondelli, PhD, of MediTech Media, UK, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3) and was funded by Sarepta Therapeutics Inc. and F. Hoffmann-La Roche Ltd, Basel Switzerland.

Perry B. Shieh reports being a consultant/independent contractor (AveXis, Biogen, Cytokinetics, and Sarepta Therapeutics, Inc.) and receiving grants/research support (AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Sanofi Genzyme, and Sarepta Therapeutics, Inc.). Linda P. Lowes 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. Natalie F. Reash reports receiving salary support from Sarepta for Clinical Evaluator training for ongoing and upcoming clinical trials. Lindsay N. Alfano reports receiving salary support from Sarepta Therapeutics through Nationwide Children's Hospital to support training and quality control activities for their ongoing clinical trials. Rachael A. Potter, Danielle A. Griffin, Sarah Lewis, Larry Hu, Sameer Upadhyay and Teji Singh are employees of Sarepta Therapeutics and may have stock options. Louise R. Rodino-Klapac is an employee of Sarepta Therapeutics and may have stock options. In addition, she is a co-inventor of AAVrh74.MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics. Jerry R. Mendell, Zarife Sahenk, Kelly J. Lehman, Megan A. Iammarino, Brenna Powers, Jeremy D. Woods, Christy L. Skura, Howard C. Mao, and Loretta A. Staudt report no conflicts of interest.

Abbreviations

AAV, adeno-associated virus; BL, baseline; BLOQ, below limit of quantification; DMD, Duchenne muscular dystrophy; IF, immunofluorescence; ITR, inverted terminal repeat; IV, intravenous; LSM, least squares mean; MHCK7, myosin heavy chain kinase 7; NSAA, North Star Ambulatory Assessment; OLE, open-label extension; PDPF, percentage dystrophin-positive fibres; polyA, polyadenylation; qPCR, quantitative polymerase chain reaction; rAAVrh74, recombinant AAV rhesus isolate serotype 74; SAE, serious AE; SD, standard deviation; SE, standard error; ssDNA, single-stranded DNA; TEAE, treatment-emergent AE; vg, vector genomes; WB, western blot.

References

1. ClinicalTrials.gov. NCT03769116 (Accessed August 2021);
2. Duan D. *Mol Ther*. 2018;26(10):2337–2356;
3. Mendell JR, et al. *JAMA Neurol*. 2020;77(9):1–10;
4. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3): 263–274;
5. Zheng C, Baum BJ. *Methods Mol Biol*. 2008;434:205–219;
6. Chandler RJ, Venditti CP. *Transl Sci Rare Dis*. 2016;1(1):73–89.

To access the full presentation on your mobile device, including any supplementary materials, please scan using your QR reader application. NB: there may be associated costs for downloading data. These costs may be high if you are using your smartphone abroad. Please check your mobile data tariff or contact your service provider for more details.

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