EP.152

ENDEAVOR: A gene delivery study to evaluate the safety of and expression from SRP-9001 in Duchenne muscular dystrophy

Craig Zaidman,[1] Crystal Proud,[2] Craig McDonald,[3] Kathryn Giblin,[4] Larisa Collins,[4] Shufang Wang,[4] Sameer Upadhyay,[4] Sarah Lewis,[4] Jyoti Malhotra,[4] Danielle A. Griffin,[4,5] Rachael A. Potter,[4] Maitea Guridi,[6] Louise R. Rodino-Klapac,[4] Jerry R. Mendell[5,7]

[1]Department of Neurology, WUSTL, Washington, MO, USA; [2]Children's Hospital of the King's Daughters, Norfolk, VA, USA; [3]UC Davis Health, Sacramento, CA, USA; [4]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [5]Center for Gene Therapy, Nationwide Children's Hospital, Columbus, OH, USA; [6]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [7]The Ohio State University, Columbus, OH, USA.

What does this study mean for the DMD community?

- This is the first study to assess safety and micro-dystrophin expression following treatment with commercially representative SRP-9001 material in patients with DMD.
- The safety and expression results were consistent with those from studies using SRP-9001 clinical process material (Study 101 and Study 102).[1,2]
  - These findings provide preliminary confirmation of the manufacturing and analytics of commercially representative SRP-9001 material, which will enable building capacity to supply the DMD population.

Conclusions

- Study 103, the first clinical study using commercially representative SRP-9001 material, provides preliminary evidence that the commercially representative material demonstrates safety and expression consistent with previous studies.
- The safety profile was consistent with prior studies, with no new safety signals identified.
  - Treatment-related AEs were transient and manageable.
  - No clinically relevant complement activation was observed.

Objective

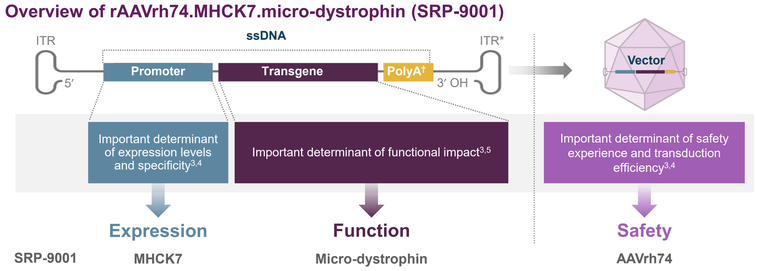
The aim of ENDEAVOR (Study 103; NCT04626674), an open-label, Phase 1b study, is to assess the expression and safety of commercially representative SRP-9001 material in patients with DMD.

Background

rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) is an investigational gene transfer therapy being developed to achieve targeted expression of a shortened functional micro-dystrophin protein in skeletal and cardiac muscle.

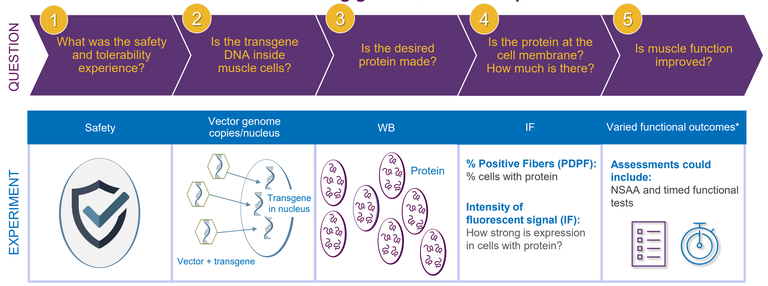
- Initial findings from ongoing Phase 1 and 2 trials, in which patients with DMD received SRP-9001 clinical process material, reported micro-dystrophin expression following gene transfer and suggested the potential for SRP-9001 to provide clinical benefit to patients with DMD.

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.

Questions to consider when evaluating gene transfer therapies



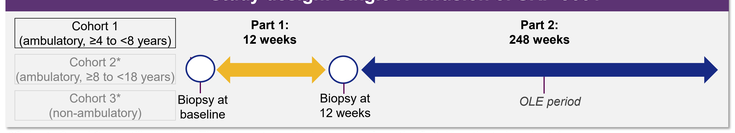
*Functional assessment data and other 48-week results are forthcoming.

Methods

Study 103 is an ongoing, Phase 1b, open-label study using commercially representative SRP-9001 material

- Trial participants in cohort 1 were given a single IV dose of 1.33×10^{14} vg/kg (linear qPCR) of commercially representative SRP-9001 material.
- The follow-up period consists of two parts: Part 1, from post-infusion through Week 12; and Part 2, post-Week 12 through Week 260.
- Twenty patients are enrolled; descriptive statistics (such as mean, SD, minimum, maximum, and percentage) by baseline age group are provided for the first 11 patients in cohort 1 who completed Part 1.

Study design: Single IV Infusion of SRP-9001



*Cohorts 2 and 3 are still enrolling. This presentation includes data from the first 11 patients in cohort 1.

Baseline demographics of the first 11 subjects in cohort 1

Characteristic	Statistics	Ages 4–5 (n=2)	Ages 6–7 (n=9)	Total (n=11)
Age (years)	Mean (SD) Min, Max	5.5 (0.6) 5.1, 5.9	6.9 (0.7) 6.0, 7.9	6.6 (0.9) 5.1, 7.9
Height (cm)	Mean (SD) Min, Max	110.5 (5.7) 106.5, 114.5	115.4 (3.9) 107.7, 121.0	114.5 (4.4) 106.5, 121.0
Weight (kg)	Mean (SD) Min, Max	24.5 (0.3) 24.3, 24.7	23.4 (4.4) 18.0, 33.1	23.6 (4.0) 18.0, 33.1
Years since DMD diagnosis	Mean (SD) Min, Max	2.3 (0.7) 1.8, 2.8	2.8 (1.8) 0.9, 6.7	2.7 (1.7) 0.9, 6.7

Key inclusion criteria (cohort 1)

- Ambulatory, male patients ≥4 to <8 years of age at the time of screening
- Definitive diagnosis of DMD based on documented clinical findings and prior genetic testing
- 3 months on stable weekly dose of oral corticosteroids
- Negative for AAVrh74 antibodies
- NSAA score of >17 and ≤26

Primary endpoint

- Change from baseline in quantity of micro-dystrophin protein expression at Week 12, as quantified by WB

Key secondary endpoints

- Safety
- Change from baseline in quantity of micro-dystrophin protein expression, as measured by IF fiber intensity at Week 12
- Change from baseline in quantity of micro-dystrophin expression, as measured by IF PDPF at Week 12

Results

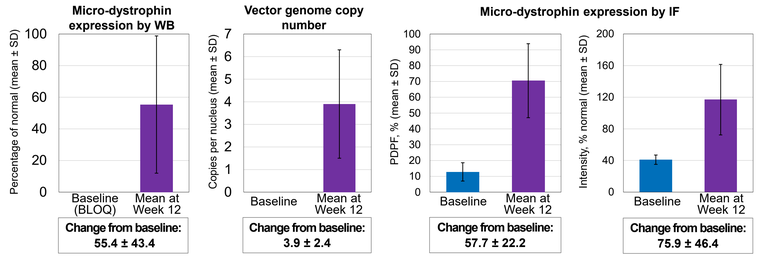
Safety results from Part 1 in the first 11 patients in cohort 1

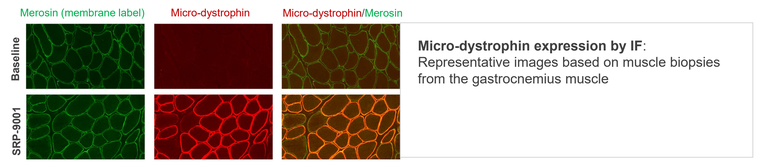
- Safety of the commercially representative SRP-9001 material was consistent with previous experience with SRP-9001. No new safety signals were identified.
- Seventy-nine TEAEs occurred.
  - As seen in previous studies, vomiting was the most common TEAE (64% of patients).
- No clinically relevant complement activation was observed.
- A total of two patients experienced three treatment-related SAEs.
  - One patient had increased transaminases that required corticosteroid treatment.
  - One patient experienced both nausea and vomiting that required intravenous treatment.
- No deaths were observed.

Safety summary	Ages 4–5 (n=2)	Ages 6–7 (n=9)	All patients (n=11)
Total number of AEs, n Patients with at least one AE, n (%)	13 2 (100)	67 9 (100)	80 11 (100)
Total number of TEAEs, n Patients with at least one: TEAE, n (%) Treatment-related TEAE, n (%)	13 2 (100) 2 (100)	66 9 (100) 9 (100)	79 11 (100) 11 (100)
Total number of SAEs, n Patients with at least one: SAE, n (%) Treatment-related SAE, n (%)	0 0 0	3 2 (22) 2 (22)	3 2 (18) 2 (18)
Patients with an AE leading to study discontinuation, n	0	0	0
Deaths, n	0	0	0

Micro-dystrophin expression and vector genome copies in the first 11 patients in cohort 1

- Treatment with SRP-9001 resulted in robust levels of micro-dystrophin protein expression localised to the sarcolemma, as shown by IF.
- Demonstration of micro-dystrophin expression was associated with vector genome copies, confirming successful delivery of SRP-9001 to target cells.





Micro-dystrophin expression by IF: Representative images based on muscle biopsies from the gastrocnemius muscle

Acknowledgements and Disclosures

We would like to thank the patients and their families for participating in this study, as well as the investigators and trial staff involved in Study 103. This study was sponsored by Sarepta Therapeutics, Inc., Cambridge, Massachusetts, USA and funded by Sarepta Therapeutics, Inc. and F. Hoffmann-La Roche Ltd., Basel, Switzerland. Writing and editorial assistance was provided by Jen Ciarochi, PhD, of MediTech Media, USA, in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3) and was funded by Sarepta Therapeutics, Inc. and F. Hoffmann-La Roche Ltd. CZ receives research support from and serves on an advisory board for Biogen, and was a paid consultant for Optum. CP participates on an advisory board and is a consultant for Biogen, Sarepta, AveXis/Novartis Gene Therapies, Genentech/Roche and Scholar Rock; serves as a speaker for Biogen; is PI of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, Fibrogen, PTC, Pfizer, Sarepta, and Scholar Rock. CM reports grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and other from Capricor, Catabasis, PTC therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics. KG, LC, SW, SU, SL, JM, DAG, and RA are employees of Sarepta Therapeutics and may have stock options. MG has nothing to disclose. LRK is an employee of Sarepta Therapeutics, has received grant support from Sarepta Therapeutics and the Parent Project Muscular Dystrophy, and financial consideration from Sarepta Therapeutics and Myonexus Therapeutics. LRK is a co-inventor of AAVrh74.MHCK7.micro-dys technology, which is exclusively licensed to Sarepta Therapeutics. 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. JRM is a co-inventor of AAVrh74.MHCK7.micro-dys technology.

Abbreviations

AE, adverse event; BLOQ, below limit of quantification; 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; OLE, open-label extension; PDPF, percentage dystrophin-positive fibers; polyA, polyadenylation; qPCR, quantitative polymerase chain reaction; rAAVrh74, recombinant AAV rhesus isolate serotype 74; SAE, serious AE; SD, standard deviation; ssDNA, single-stranded DNA; TEAE, treatment-emergent AE; WB, western blot; vg, vector genomes.

References

1. ClinicalTrials.gov. NCT03375164 (Accessed August 2021);
2. ClinicalTrials.gov. NCT03769116 (Accessed August 2021);
3. Asher DR, et al. *Expert Opin Biol Ther*. 2020;20(3):263-274;
4. Zheng C, Baum BJ. *Methods Mol Biol*. 2008;434:205-219;
5. Chandler RJ, Venditti CP. *Transl Sci Rare Dis*. 2016;1(1):73-89.

To access the full poster 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