Management Of Patients Following Investigational Delandistrogene Moxeparvovec Gene Therapy For Duchenne Muscular Dystrophy: Delphi Panel Consensus Considerations Based on Clinical Trial Experience

Natalie L Goedeker,[1*] Amal A Aqul,[2] Russell J Butterfield,[3] Anne M Connolly,[4] Ronald G Crystal,[5] Kara E Godwin,[6] Kan N Hor,[4] Katherine D Mathews,[7] Crystal M Proud,[8] Elizabeth Smyth,[6] Aravindhan Veerapandiyan,[9] Paul B Watkins,[10] Craig M Zaidman,[1] Jerry R Mendell[4]

[1]Washington University School of Medicine and St Louis Children's Hospital, St Louis, MO; [2]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [3]University of Utah School of Medicine, Salt Lake City, UT; [4]Center for Gene Therapy, The Abigail Wexner Research Institute, Nationwide Children's Hospital, Columbus, OH; Departments of Pediatrics and Neurology, Ohio State University, Columbus, OH; [5]Department of Genetic Medicine, Weill Cornell Medical College, New York, NY; [6]Sarepta Therapeutics, Cambridge, MA; [7]Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, IA; [8]Children's Hospital of the King's Daughters, Norfolk, Virginia.; [9]Division of Neurology, Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, AR; [10]Eshelman School of Pharmacy, University of North Carolina Institute for Drug Safety Sciences, Chapel Hill, NC.

***Presenter**

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Overview and objective of the Delphi panel project

- **Delandistrogene moxeparvovec** is an investigational rAAVrh74 vector-based gene therapy designed for targeted expression of SRP-9001 dystrophin protein[1-2]
- **Safety data from the delandistrogene moxeparvovec** clinical development program[3-5] identified treatment-related adverse events (TRAEs) requiring medical intervention[6-7]:
  - Vomiting
  - Myocarditis
  - Acute liver injury
  - Immune-mediated myositis
- **Literature analysis** revealed a paucity of available guidance for managing patients who experience these TRAEs following gene therapy
- **Objective:** Report the findings of a Delphi panel that was convened to develop consensus considerations for the evaluation and management of TRAEs following gene therapy

What do these findings mean for healthcare providers in the DMD community?

AAVrh74, adeno-associated virus rhesus isolate serotype 74; DMD, Duchenne muscular dystrophy; SRP-9001, delandistrogene moxeparvovec; TRAE, treatment-related adverse event.

1. Mendell JR, et al. JAMA Neurol. 2020; 77(9):1122-31; 2. Mendell J, et al. Neuromuscular Disorders. 2022;32:S102-S3. 3. ClinicalTrials.gov. NCT03375164 (Accessed January 2023); 4. ClinicalTrials.gov. NCT03769116 (Accessed January 2023); 5. ClinicalTrials.gov. NCT04626674 (Accessed January 2023); 6. Zaidman C, et al. Poster presented at: The World Muscle Society Congress, October 11-15, 2022; [P.129]; 7. Sarepta/Roche data on file.

Delandistrogene moxeparvovec* clinical development program

STUDY 101	STUDY 102	STUDY 103	STUDY 301[5]	STUDY 303[6]
Safety and proof of concept **n=4**	**Double-blind placebo-controlled safety and efficacy** **n=41**	**Safety and efficacy (expression) of scalable commercially representative material** **n=40†**	**Double-blind placebo-controlled efficacy confirmation in 4–7 year old ambulatory patients**	**Double-blind placebo-controlled safety and efficacy in non-ambulatory patients**
TRIAL 1 NCT03375164 *Nationwide Children's Hospital*	**TRIAL 2** NCT03769116	ENDEAVOR NCT04626674	EMBARK NCT05096221	ENVISION
• Goals included safety, proof-of-concept • One-year results published in *JAMA Neurology*[1] • 4-year functional data presented in October 2022[2]	• 4–7 years of age • Goals included safety, function • Data reported from Part 1[3] • Data from Part 2 presented in October 2022[2]	• Ambulant and non-ambulant • Clinical study using commercially representative material • Data reported from 20 patients Part 1, Cohort 1 (ambulant 4–7 years of age)[4]	• 4–7 years of age • Global study • NSAA (primary endpoint)	• Non-ambulatory patients (no age restriction) and ambulatory patients (8-17 years of age) • Global study • Primary endpoint PUL

*Single IV administration at a dose equivalent of 1.33E14 vg/kg using a linear standard-based PCR titration method. †40 patients included in 120-day safety report (through April 6, 2022); currently study includes 52 patients

1. Mendell JR, et al. *JAMA Neurol*. 2020; 77(9):1122-31; 2. Mendell JR, et al. Poster presented at: The World Muscle Society Congress; October 11-15,2022; [LSP36] 3. Mendell JR, et al. Poster presented at: The 2021 MDA Virtual Clinical & Scientific Conference; March 15-18, 2021. [Virtual format] 4. Zaidman C, et al. Poster presented at: The World Muscle Society Congress, October 11-15, 2022; [P.129]; 5. ClinicalTrials.gov Identifier: NCT05096221; 6 Sarepta/Roche data on file.

Delandistrogene moxeparvovec safety results (studies 101, 102, 103)[1-4]

	Treated Patients* (N=85)
Number of AEs	1,282
Number of TEAEs	1,230
Number of treatment-related TEAEs	366
Number of SAEs	13
Number of treatment-related SAEs	9
Patients with any AEs, n (%)	82 (96.5)
Patients with any TEAEs, n (%)	82 (96.5)
Patients with any treatment-related TEAEs, n (%)	73 (85.9)
Deaths, n (%)	0
Patients with any SAEs, n (%)	11 (12.9)
Patients with any treatment-related SAEs, n (%)	7 (8.2)
Patients with any AEs leading to discontinuation, n (%)	0

Safety profile was consistent, monitorable and manageable

- A total of 366 TRAEs were reported by 73/85 (85.9%) patients
- Most AEs were mild to moderate in severity
- Most TRAEs occurred within 90 days of treatment and resolved

*The integrated safety data clinical cut-off dates were October 17, 2022 for SRP-9001-101; April 1, 2022 for SRP-9001-102 (Part 1); and September 19, 2022 for SRP-9001-103.
AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE; TRAE, treatment-related AE.
1. ClinicalTrials.gov Identifier: NCT03375164; 2. ClinicalTrials.gov Identifier:NCT03769116; 3. ClinicalTrials.gov identifier: NCT04626674; 4. Sarepta/Roche data on file.

Summary of adverse events in the clinical trial safety population[1-4]

Most common TEAEs Occurring in >25% of patients[1]	Treated Patients* (N=85)
Vomiting, n (%)	52 (61.2)
Decreased appetite, n (%)	40 (47.1)
Nausea, n (%)	34 (40.0)
Upper respiratory tract infection, n (%)	36 (42.4)
Pain in extremity, n (%)	28 (32.9)
Abdominal pain upper, n (%)	23 (27.1)
Irritability, n (%)	22 (25.9)
Procedural pain, n (%)	23 (27.1)
Other selected TEAEs of special interest	
Acute liver injury, n (%)†	31 (36.5%)
Immune-mediated myositis, n (%)	1 (1.2%)
Myocarditis, n (%)	1 (1.2%)

Treatment-related SAEs

- Seven patients (8.2%) experienced treatment-related SAEs
- Treatment-related SAEs included:
  - Vomiting (2 events)
  - Increased transaminases (2 events)
  - Rhabdomyolysis (2 events)
  - Liver injury (1 events)
  - Immune-mediated myositis (1 event)
  - Myocarditis (1 event)

*The integrated safety data clinical cut-off dates were October 17, 2022 for SRP-9001-101; April 1, 2022 for SRP-9001-102 (Part 1); and September 19, 2022 for SRP-9001-103.

†Acute liver injury is a combination of multiple preferred terms and biochemical/lab-based observations that have been aggregated to represent ALI and is therefore not included among the TEAEs occurring in >25% of patients.

SAE, serious adverse event; TEAE, treatment-emergent adverse event. 1.ClinicalTrials.gov Identifier: NCT03375164; 2.ClinicalTrials.gov Identifier:NCT03769116; 3. ClinicalTrials.gov identifier: NCT04626674 ; 4.Sarepta/Roche data on file

Observed timeline of adverse events following treatment with delandistrogene moxeparvovec [1-2]

WEEKS 1 – 2

- **Vomiting:** occurred in 52/85 (61.2%) of patients[1]
  - Vomiting was observed as early as the day of the infusion and in some cases persisted over several weeks
- **Myocarditis:** occurred in 1/85 (1.2%) of patients[1]
  - Elevated troponin I observed within 4 days after infusion
    - Patient experienced serious vomiting requiring hospitalization; troponin was elevated
    - Cardiac status remained stable
  - With treatment, myocarditis resolved with sequelae over 4 weeks

WEEKS 4 – 8

- **Acute liver injury:** occurred in 31/85 patients (36.5%)[1]
  - Most ALI cases were asymptomatic and mild to moderate in severity
  - Among patients in the safety set, 3 ALI events were reported as an SAE
    - Increased transaminases (2 events)
    - Liver injury (1 event)
  - Cases of ALI resolved with treatment over 4 weeks
- **Immune-mediated myositis:** occurred in 1/85 (1.2%) of patients[1]
  - IMM occurred 1 month post infusion
  - With treatment, IMM case resolved with sequelae (residual weakness) over 30 days

ALI, acute liver-injury; IMM, immune-mediated myositis; SAE, serious adverse event.

1. Sarepta/Roche data on file.

A consensus approach based on a modified Delphi panel

Literature Review

- Paucity of literature with guidance for management of selected TRAEs following gene therapy

Assemble Delphi Panel

- Multidisciplinary panel of 12 US-based experts with gene therapy experience

Delphi Questionnaire 1

- Telephone interviews to collect free-text responses on management of selected TRAEs
  - 146 unique responses collected

Delphi Questionnaire 2

- Telephone interviews to assess agreement with Questionnaire 1 responses using a Likert scale
- Consensus defined as 7/12 (≥58%) of experts either agreeing or disagreeing
  - 100 responses achieved consensus agreement; 46 responses did not achieve consensus

In-person Meeting

- Convene Delphi panelists to discuss consensus statements

Final Consensus Statements

- Panelists approve final consensus statements

TRAE, treatment-related adverse event.

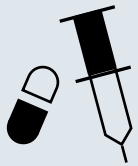
Consensus considerations for management of vomiting

Clinical trial experience

Vomiting was the most common AE (reported in 61.2%) [1]
Vomiting started as early as the day of infusion
Vomiting was transient, resolving within weeks

General Consensus Considerations

- Patient/caregiver should follow up immediately if post-treatment vomiting occurs



- An antiemetic may be provided as needed
- Switch to IV steroids if oral steroids are not tolerated/retained due to vomiting

AE, adverse event; IV, intravenous.
1. Sarepta/Roche data on file.

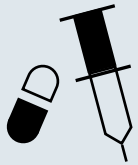
Consensus considerations for management of acute liver injury

Clinical trial experience

Acute liver injury* was reported by 36.5% of patients[1]
Acute liver injury occurred within 4-8 weeks post infusion
Observed cases resolved within 2 months

General Consensus Considerations

- Patient/caregiver should follow up immediately to report symptoms such as jaundice or abdominal pain
- Closely monitor liver function and increase frequency as clinically indicated



- Treatment considerations should be based on timing of onset and severity of symptoms
- Optimize steroid regimen

- A consultation with a hepatologist may be considered

*Acute liver injury is a combination of multiple preferred terms and biochemical/lab-based observations that have been aggregated to represent ALI and is therefore not included among the TEAEs occurring in >25% of patients.

1.Sarepta/Roche data on file.

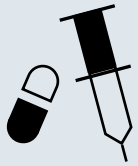
Consensus considerations for management of myocarditis

Clinical trial experience

Myocarditis reported by 1 (1.2%) patient[1]
During the trial, elevated troponin I was observed within first week following infusion
Most cases resolved over 4 weeks

General Consensus Considerations

- Patient/caregiver should follow up immediately to report symptoms such as chest pain and shortness of breath
- Closely monitor troponin levels and increase frequency as clinically indicated



- Treatment considerations should be based on duration and severity of troponin elevation and presence of symptoms
- Optimize steroid regimen and consider ECG, ECHO, and cMRI as clinically indicated

- A consultation with a cardiologist may be considered

cMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; ECHO, echocardiogram.

1. Sarepta/Roche data on file.

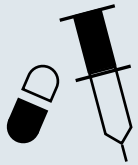
Consensus considerations for management of immune-mediated myositis

Clinical trial experience

Immune-mediated myositis occurred in 1 (1.2%) of patients[1]
Immune-mediated myositis occurred 4 weeks post infusion
Observed case resolved (with sequelae, residual muscle weakness) over 30 days

General Consensus Considerations

- Patient/caregiver should follow up immediately to report symptoms such as severe muscle weakness, hypophonia, dysphagia, and/or dyspnea
- Increase physical and laboratory monitoring as clinically indicated



- Treatment considerations may include targeted immunosuppressant therapy, steroid regimen optimization, and other interventions as clinically appropriate

- A consultation with an immunologist may be considered

1.Sarepta/Roche data on file.

Conclusions: Delphi panel consensus considerations based on delandistrogene moxeparvovec clinical trial experience

- In clinical trials, the safety profile of delandistrogene moxeparvovec, informed by 85 patient exposures, has been consistent, monitorable, and manageable
  - Significant adverse events included vomiting, myocarditis, acute liver injury, and immune-mediated myositis
- In view of the lack of available data regarding management of select treatment-related SAEs that may arise following a gene therapy, a Delphi panel developed consensus considerations based on delandistrogene moxeparvovec clinical trials
- The Delphi panel findings provide considerations for patient management, diagnostic testing and evaluation, and treatments
  - Delphi process limitations include potential bias based on the selection of panel members, exclusion of global perspectives, and absence of the patient/caregiver viewpoint
- These consensus considerations address the lack of available data and provide additional insight on patient management of potential adverse events that may arise following gene therapies

SAE, serious adverse event.