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

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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?

*Delandistrogene moxeparvovec is an investigational product under FDA review for the treatment of Duchenne muscular dystrophy

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 data on file.

Delandistrogene moxeparvovec* clinical development program

STUDY 101	STUDY 102	STUDY 103	STUDY 301[5]
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**
TRIAL 1 NCT03375164 *Nationwide Children's Hospital*	**TRIAL 2** NCT03769116	ENDEAVOR NCT04626674	EMBARK NCT05096221
• 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)

*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.

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 within the studies 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 data on file.

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

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 serious AEs

- 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 event)
  - 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 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]
  - Among patients in the safety set, 2 vomiting events were reported as an SAE
  - Vomiting was observed as early as the evening of the infusion and in some cases persisted over several weeks
    - A small number of patients experienced a vomiting described as morning sickness 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 or non-serious
  - 3 ALI events were reported as treatment-related 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
  - IMM case resolved with sequelae (residual weakness) over 30 days with continued treatment

***Acute Liver Injury Definition Based on CIOMS (Council for International Organizations of Medical Sciences) Working Group and FDA definitions**

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

1. Mendell JR, et al. Assessment of Systemic Delivery of rAAVrh74.MHCK7.micro-dystrophin in Children With Duchenne Muscular Dystrophy: A Nonrandomized Controlled Trial. JAMA Neurol. 2020;77(9):1122-1131. 2. Sarepta data on file.

A consensus approach based on a modified Delphi panel[1-3]

Literature Review

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

Assemble Delphi Panel

- Multidisciplinary panel* of 12 US-based clinicians 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

***The panel included immunologists, cardiologists, hepatologists, neurologists, a gastroenterologist/toxicologist, and a nurse-practitioner selected based on their experience using gene transfer therapy**

1. Diamond IR, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol.* 2014;67(4):401-409; 2.Hasson F, et al. Research guidelines for the Delphi survey technique. *J Adv Nurs.* 2000;32(4):1008-1015; 3. Niederberger M, Spranger J. Delphi Technique in Health Sciences: A Map. *Front Public Health.* 2020;8:457.

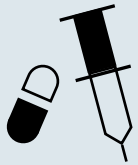
TRAE, treatment-related adverse event.

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

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

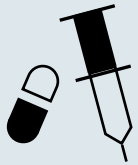
Consensus considerations for management of acute liver injury

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 could 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 data on file.

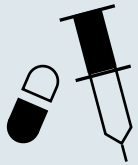
Consensus considerations for management of myocarditis

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-I levels and increase frequency as clinically indicated



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

- A consultation with a cardiologist could be considered

cMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; ECHO, echocardiogram.
1. Sarepta data on file.

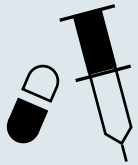
Consensus considerations for management of immune-mediated myositis

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 could be considered

*Specific mutations may place patients at increased risk for IMM. Delphi considerations were developed post identification of clinical trial adverse event.
1. Sarepta 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
  - Treatment-related SAEs 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 rAAVrh74 vector-based 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

*Delandistrogene moxeparvovec is an investigational product under FDA review for the treatment of Duchenne muscular dystrophy
SAE, serious adverse event.