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Poster #53

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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Objective

A Delphi panel was convened to develop consensus considerations for the evaluation and management of selected treatment-related adverse events reported in delandistrogene moxeparvovec clinical studies

CONCLUSIONS

- 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 these 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

INTRODUCTION

- Duchenne muscular dystrophy (DMD), is a rare, X-linked devastating neuromuscular disease with a predictable disease course that is progressive and ultimately fatal
- DMD is caused by the absence of functional dystrophin protein in skeletal, cardiac, gastrointestinal, and respiratory muscle due to mutations in the DMD gene; this absence leads to progressive muscle degeneration, loss of ambulation, respiratory weakness, and cardiomyopathy[1,2]
- Delandistrogene moxeparvovec is an investigational rAAVrh74-based gene transfer therapy designed for targeted expression of SRP-9001 dystrophin protein, a shortened dystrophin retaining key functional domains of the wild-type protein in skeletal and cardiac muscle[3,4]
- Safety data from the delandistrogene moxeparvovec clinical development program[5-7] (**Figure 1, Tables 1 and 2**) demonstrates that the safety profile in clinical trials is consistent, monitorable, and manageable (**Figure 2**)
  - A total of 366 treatment-related adverse events (TRAEs) were reported by 73/85 (85.9%) patients (**Table 1**)
  - Most were mild to moderate in severity
  - Most TRAEs occurred within 90 days of treatment and resolved
- A small number of treatment-related serious adverse events (SAEs) requiring medical intervention were identified (**Table 1**)[8,9]
  - Vomiting
  - Myocarditis
  - Acute liver injury (ALI)
  - Immune-mediated myositis (IMM)
- Literature analysis revealed a paucity of available guidance for managing patients who experience TRAEs following administration of gene therapy
- A multidisciplinary panel of 12 US-based experts with gene therapy experience utilized a modified Delphi process to reach consensus considerations for management of vomiting, myocarditis, ALI, and IMM following treatment with delandistrogene moxeparvovec in the clinical setting

Figure 1. Delandistrogene Moxeparvovec* Clinical Development Program

STUDY 101	STUDY 102	STUDY 103	STUDY 301[12]	STUDY 303[9]
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*[9] • 4-year functional data presented in October 2022[10]	• 4-7 years of age • Goals included safety, function • Data reported from Part 1[11] • Part 2 data presented in October 2022[10]	• 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)[8]	• 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.
NSAA, North Star Ambulatory Assessment; PUL, Performance of Upper Limb.

Table 1. Delandistrogene Moxeparvovec Safety Results (Studies 101, 102, 103)[5-7,9]

	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

*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; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

Table 2. Most Common TEAEs Occurring in >25% of Patients[5-7,9]

	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)

*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 acute liver injury and is therefore not included among the TEAEs occurring in >25% of patients.
TEAE, treatment-emergent adverse event.

Figure 2. Observed Timeline of Adverse Events Following Treatment With Delandistrogene Moxeparvovec[9]

WEEKS 1-2

- **Vomiting:** occurred in 52/85 (61.2%) of patients[9]
  - 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[9]
  - 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

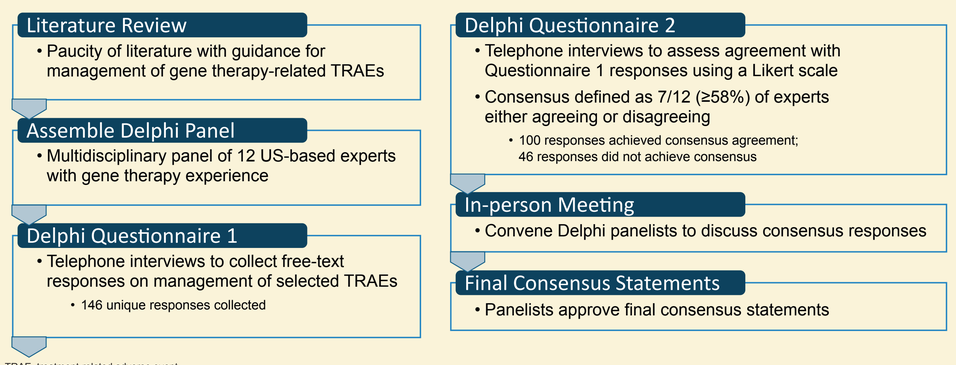
- **Acute liver injury:** occurred in 31/85 patients (36.5%)[9]
  - Most ALI cases were asymptomatic and mild to moderate in severity
  - Among patients in the safety set, 3 ALI events were reported as an SAE
    - Increased transaminases (2 events)
    - Liver injury (1 event)
  - Cases of ALI resolved with treatment over 4 weeks
- **Immune-mediated myositis:** occurred in 1/85 (1.2%) of patients[9]
  - 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.

METHODS

- Conducted a literature search to retrieve published clinical studies, case series, and retrospective analyses reporting data and treatment strategies for vomiting, myocarditis, ALI, and IMM following gene therapy
- A multidisciplinary panel of 12 US-based experts with gene therapy experience utilized a modified Delphi process to reach consensus guidance on gene therapy-related consensus guidance on management of TRAEs following gene therapy (**Figure 3**)
- The Delphi process included 2 rounds of telephone surveys and 1 in-person meeting
- Experts rated their agreement using a 5-point Likert scale (1=strongly disagree; 5=strongly agree)
  - Consensus was defined as ≥58% of experts either agreeing (rating a statement 4 or 5) or disagreeing (rating a statement 1 or 2) with management decisions relating to case-based questions

Figure 3. Summary of Delphi Process



TRAE, treatment-related adverse event.

RESULTS

- The Delphi panel created consensus considerations for the evaluation and management of vomiting, myocarditis, ALI, and IMM following treatment with delandistrogene moxeparvovec in the clinical setting (**Tables 3, 4, 5, 6**)

Table 3. Consensus Considerations for Management of Vomiting

Clinical trial experience
Vomiting was the most common AE (reported in 61.2%)[9] 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.

Table 4. Consensus Considerations for Management of Acute Liver Injury

Clinical trial experience
Acute liver injury* was reported by 36.5% of patients[9] 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 • Monitor liver function weekly and increase or continue monitoring 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 livery injury is a combination of multiple preferred terms and biochemical/lab-based observations that have been aggregated to represent acute liver injury and is therefore not included among the TEAEs occurring in >25% of patients.

Table 5. Consensus Considerations for Management of Myocarditis

Clinical trial experience
Myocarditis reported by 1 (1.2%) patient[9] Elevated troponin I 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 • Monitor troponin weekly and increase or continue monitoring 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.

Table 6. Consensus Considerations for Management of Immune-Mediated Myositis

Clinical trial experience
Immune-mediated myositis occurred in 1 (1.2%) of patients[9] 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

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DISCLOSURES

NLG: consultancy/advisory role with and speakers' bureau for Novartis. **AAA, KDM, and PBW:** No relevant disclosures. **KNH:** consultancy/advisory role with Bristol-Myers Squibb, Capricor Therapeutics, Catabasis Pharmaceuticals, Daiichi Sankyo, PTC Therapeutics, Revidia Therapeutics, Sarepta Therapeutics, Stealth Biotherapeutics, Vertex Pharmaceuticals, and Wave Life Science; research funding from Sarepta Therapeutics; speakers' bureau for NS Pharma and PTC Therapeutics; other relationship(s) with Blade Therapeutics (DSMB) and FibroGen (DSMB). **RGC:** equity interest in and consultancy/advisory role with LEXEO Therapeutics and XyloCor Therapeutics. **AV:** consultancy/advisory role with AMO Pharma, AveXis, Biogen, Edgewise Therapeutics, Fibrogen, Novartis, Pfizer, PTC Therapeutics, Sarepta Therapeutics, and Scholar Rock; research funding from AMO Pharma, Capricor Therapeutics, Edgewise Therapeutics, Fibrogen, Muscular Dystrophy Association, Novartis, Parent Project Muscular Dystrophy, Pfizer, RegenxBio, and Sarepta Therapeutics; other relationship(s) with Medlink Neurology for editorial services. **KEG and ES:** employment with Sarepta Therapeutics. **RJB:** consultancy/advisory role with Aavanti, Biogen, Reata, Sarepta Therapeutics, and Scholar Rock. **AMC:** consultancy/advisory role with Biohaven, Edgewise, Sarepta Therapeutics, and Scholar Rock; research funding from Biohaven, Edgewise, Fibrogen, MDA, Sarepta Therapeutics, and Scholar Rock. **CMP:** consultancy/advisory role with AveXis/Novartis Gene Therapies, Biogen, Genentech/Roche, Sarepta Therapeutics, and Scholar Rock; research funding from AveXis/Novartis Gene Therapies, Astellas, Biogen, CSL Behring, Fibrogen, PTC, Pfizer, Sarepta, and Scholar Rock; speakers' bureau for Biogen. **CMZ:** consultancy/advisory role with Biogen, Optum; research funding from Biogen, Novartis; speakers' bureau for Sarepta. **JRM:** research funding from Sarepta Therapeutics; patents, royalties, or other intellectual property as co-inventor of AAVrh74.MHCK7.SRP-9001-dys technology.

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