Practical considerations for delandistrogene moxeparvovec gene therapy in patients with Duchenne muscular dystrophy

JR Mendell,[1,2] C Proud,[3*] C Zaidman,[4] S Mason,[5] E Darton,[5] C Wandel,[6] AP Murphy,[7] E Mercuri,[8] F Muntoni,[9] C McDonald[10]

[1]Center for Gene Therapy, Nationwide Children's Hospital, Columbus, OH, USA; [2]The Ohio State University, Columbus, OH, USA; [3]Children's Hospital of the King's Daughters, Norfolk, VA, USA; [4]Department of Neurology, WUSTL, Washington, MO, USA; [5]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [6]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [7]Roche Products Ltd, Welwyn Garden City, UK; [8]Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy; [9]The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust, London, UK; [10]UC Davis Health, Sacramento, CA, USA

*Presenting on behalf of the authors (email address: medinfo@sarepta.com)

What does this study mean for the DMD community?

- Evaluation of clinical trial experience with delandistrogene moxeparvovec from three studies of patients with DMD informed the outline of several practical considerations for administration of delandistrogene moxeparvovec gene therapy.

Conclusions

- Clinical trial experience has led to important learnings and practical considerations that may mitigate the risk of AEs following administration of delandistrogene moxeparvovec.
- Although the safety profile of delandistrogene moxeparvovec to date has been consistent, monitorable, and manageable, appropriate mitigation of potential risks can help to ensure patient safety.

Objective

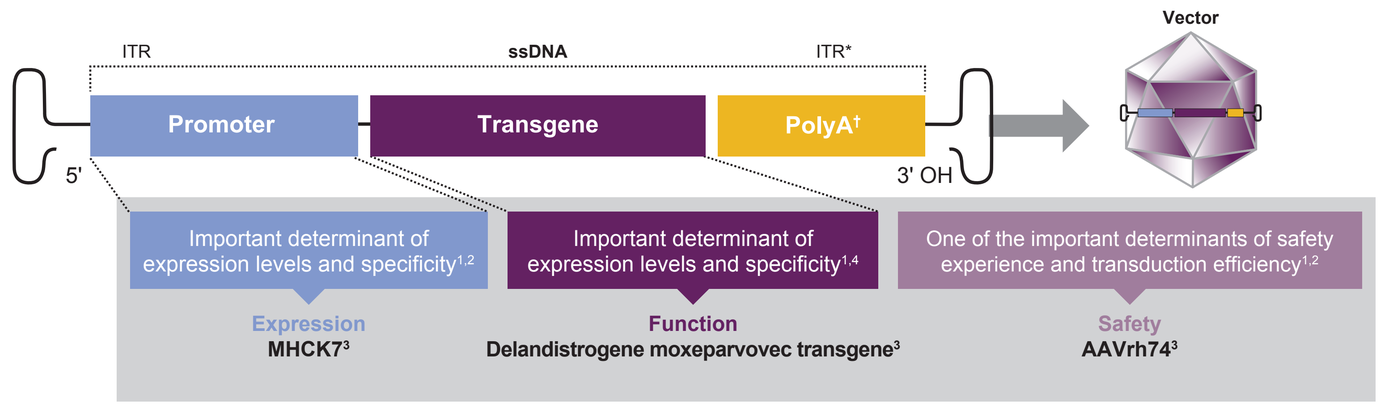
- To outline several practical considerations for the administration of delandistrogene moxeparvovec based on learnings from clinical trial experience.

Background

- Delandistrogene moxeparvovec is an rAAV vector-based gene therapy, designed to compensate for the absence of functional dystrophin in DMD by delivering a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered protein that retains key functional domains of the wild-type protein (**Figure 1**).[1–3]
- Delandistrogene moxeparvovec is approved in the USA and UAE for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the *DMD* gene.[5,6,*†]
- Delandistrogene moxeparvovec gene therapy shows promise in clinical trials of patients with DMD and offers the potential to compensate for the absence of functional dystrophin in DMD.
- The safety and efficacy of delandistrogene moxeparvovec have been assessed in patients who participated in Study 101 (SRP-9001-101; NCT03375164),[7,8] Study 102 (SRP-9001-102; NCT03769116),[9,10] or the ongoing ENDEAVOR study (SRP-9001-103; NCT04626674).[11,12]

*Delandistrogene moxeparvovec is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.
†As of August 2023.

Figure 1. Overview of delandistrogene moxeparvovec



*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

- Practical considerations for administration of delandistrogene moxeparvovec were based on clinical trial experience in 85 patients who participated in Study 101, Study 102, or the ongoing ENDEAVOR study.[7–12] Clinical cut-off dates were October 17, 2022 for Study 101, April 1, 2022 for Study 102 (Part 1 only), October 3, 2022 for Study 102 (all available data), and September 19, 2022 for ENDEAVOR.
- The observed time course of events, monitoring for and management of AEs, and mitigation strategies are described.
- This poster outlines several key learnings and practical considerations from clinical trial experience.

Learnings from clinical trials of delandistrogene moxeparvovec

Patient selection

Screening patients for pre-existing antibodies

- Patients with elevated anti-AAVrh74 total binding antibody titers (≥1:400) were not recommended for treatment with delandistrogene moxeparvovec.
  - Patients with elevated anti-AAVrh74 total binding antibodies prior to infusion may experience potential transduction inhibition and/or AEs associated with an immune response to the viral capsid.

- Prior to administration of delandistrogene moxeparvovec, patients were screened for anti-AAVrh74 total binding antibodies

Monitoring and management

- Even in the absence of pre-existing antibodies, immune responses to the AAVrh74 vector are expected following delandistrogene moxeparvovec infusion.
- To reduce the risk of an adverse immune response, corticosteroids were either initiated or the dose was increased prior to infusion (**Table 1**).
  - This regimen was maintained for a minimum of 60 days post-infusion, unless earlier tapering was clinically indicated.

- Corticosteroids were started 1 day prior to infusion (for patients already on corticosteroids) and the corticosteroid regimen maintained for a minimum of 60 days post-infusion

Table 1. Pre- and post-infusion corticosteroid dosing

Baseline patient corticosteroid dosing*	Peri-infusion corticosteroid dose (prednisone equivalent)†	Recommended maximum total daily dose	Recommended corticosteroid regimen taper duration
Daily or intermittent dose	Start **1 day** prior to infusion: 1 mg/kg/day (and continue baseline dose)	60 mg/day	2 weeks‡ if tapering from added corticosteroids back to baseline dose
High dose for 2 days per week	Start **1 day** prior to infusion:1 mg/kg/day taken on days without high-dose corticosteroid treatment (and continue baseline dose)	60 mg/day	2 weeks‡ if tapering from added corticosteroids back to baseline dose
Not on corticosteroids	Start **1 week** prior to infusion: 1.5 mg/kg/day	60 mg/day	4 weeks‡ if tapering from added corticosteroids back to no corticosteroids

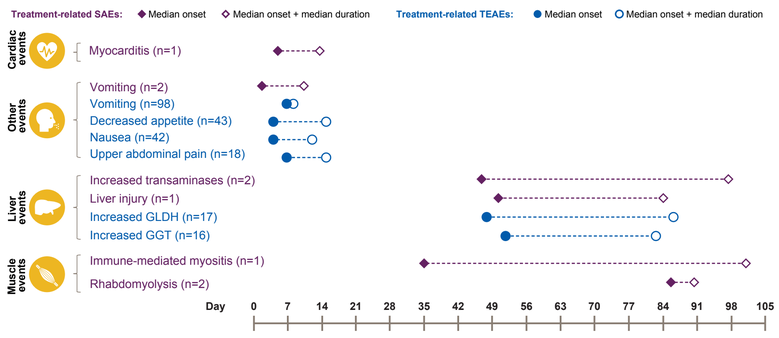
*Patient continues to receive this dose. †Deflazacort is not recommended for use as a peri-infusion corticosteroid. ‡Or longer, as needed.
To lower the risk of an adverse immune response, corticosteroids should be considered starting 1 day prior to delandistrogene moxeparvovec infusion if the patient is already on corticosteroids at baseline, and 1 week prior to infusion if the patient is not on corticosteroids at baseline.

Safety experience in clinical trials of delandistrogene moxeparvovec

AEs

- The overall safety profile has been monitorable and manageable, following a predictable time course (**Figure 2**).
- AEs of vomiting were observed as early as the day of infusion. Other common adverse reactions (incidence ≥5%), including nausea, thrombocytopenia, and pyrexia, occurred within the first 2 weeks following infusion.
- 73 out of 85 patients experienced a total of 366 treatment-related TEAEs, most of which were mild to moderate in severity and began within 90 days of treatment.
- Seven patients experienced nine treatment-related SAEs: Vomiting (n=2), increased transaminases (n=2), rhabdomyolysis (n=2), liver injury (n=1), immune-mediated myositis (n=1), and myocarditis (n=1).

Figure 2. Time course of the safety profile of delandistrogene moxeparvovec (N=85)



Acute serious liver injury

- In clinical studies, elevations in liver enzymes (AST, ALT, GGT, GLDH, hepatic enzymes, transaminases, blood bilirubin) were very common, typically occurring within 8 weeks following infusion.
- Most cases were generally asymptomatic and resolved without clinical sequelae and within 60 days, either spontaneously or following a temporary increase in systemic corticosteroids.

- Careful consideration should be given when administering AAV-based therapies in patients with pre-existing liver impairment* or a chronic hepatic condition, as they may be at a higher risk of acute serious liver injury
- Baseline liver function tests should be performed prior to administration of delandistrogene moxeparvovec
- Monitor liver function weekly for 3 months following infusion and, if clinically indicated, continue monitoring until results are unremarkable (normalized, or near baseline levels)

*Pre-existing liver impairment is defined as having metabolic, structural, genetic, or infectious variants of liver disease, any of which could be active or could be triggered by gene transfer.

Cardiac function

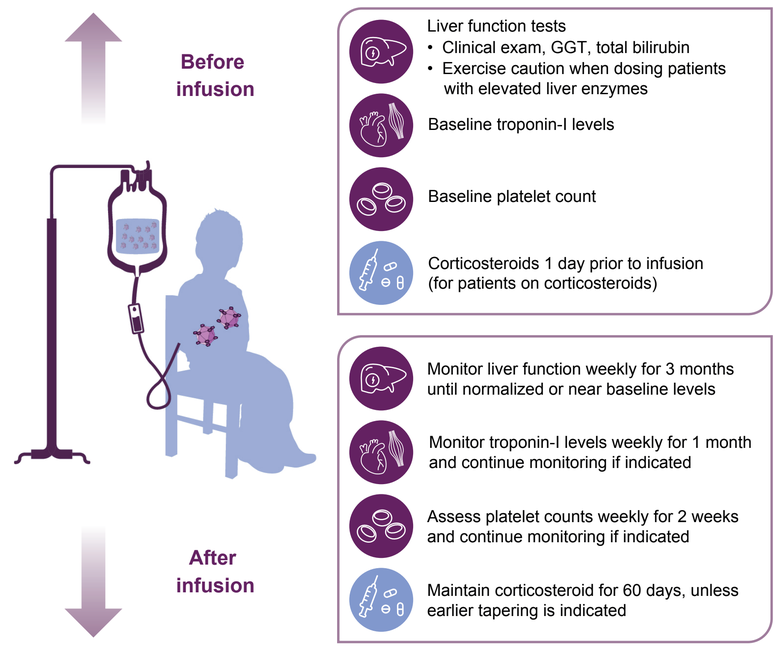
- Troponin-I elevations, including one serious case of myocarditis, have been observed in clinical trials of delandistrogene moxeparvovec.

- Assess baseline troponin-I prior to administration of delandistrogene moxeparvovec
- Monitor troponin-I levels weekly for the first month and continue monitoring if clinically indicated

Treatment preparation

- Practical considerations to support physicians initiating delandistrogene moxeparvovec gene therapy in patients with DMD include (**Figure 3**):
  - Screening patients for anti-AAVrh74 total binding antibody levels <1:400 with the specific, manufacturer-approved assay
  - Avoiding co-administering with vaccinations
  - Postponing dosing if patients have a viral or bacterial infection.

Figure 3. Considerations for initiating delandistrogene moxeparvovec gene therapy in patients with DMD



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Abbreviations

AAV, adeno-associated virus; AAVrh74, adeno-associated virus rhesus isolate serotype 74; AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; DMD, Duchenne muscular dystrophy; GLDH, glutamate dehydrogenase; GGT, gamma-glutamyl transferase; ITR, inverted terminal repeat; OH, hydroxyl; PolyA, polyadenylation; SAE, serious adverse event; ssDNA, single-stranded DNA; TEAE, treatment-emergent adverse event; UAE, United Arab Emirates.

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