Acute Liver Injury Mitigation and Management in Patients with Duchenne Muscular Dystrophy Following Administration of Delandistrogene Moxeparvovec: Expert Committee Considerations

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Disclosure

I have the following conflicts of interest to declare:

- Dr. Shieh reports being a consultant for Novartis, Biogen, Roche, Pfizer, Sarepta, argenx, Alexion, UCB, Catalyst, Grifols, and CSL Behring, and is receiving grants/research support from Novartis, Biogen, Solid, Pfizer, Sarepta Therapeutics, Avidity, Dyne, UCB, Abcuro, Arcellx, and Astellas

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Background

- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene transfer therapy for DMD approved in the USA and other select countries[1–9]
- ALI is an identified risk following AAV-based gene therapies, including delandistrogene moxeparvovec
- There have been two fatal cases of ALI in non-ambulatory patients that progressed into ALF ~3-months post-treatment with delandistrogene moxeparvovec
  - There was one fatal case of treatment-related ALF in a 51-year-old non-ambulatory patient with LGMD 2D/R3 following treatment with SRP-9004[b] (first sign of liver enzyme elevation, Day 21 [~3 weeks post-infusion]; time of death was ~12 weeks post-infusion)

ALI in Delandistrogene Moxeparvovec Clinical Trials[10a]	
n (%)	**All Patients N = 156**
ALI, n (%)	**65 (42)**
GGT >3× ULN	25 (16)
GLDH >2.5× ULN[c]	55 (35)
ALP >2× ULN	1 (0.6)
ALT >3× BL[d]	22 (14)
Total bilirubin >2× ULN, n (%)	**4 (3)**

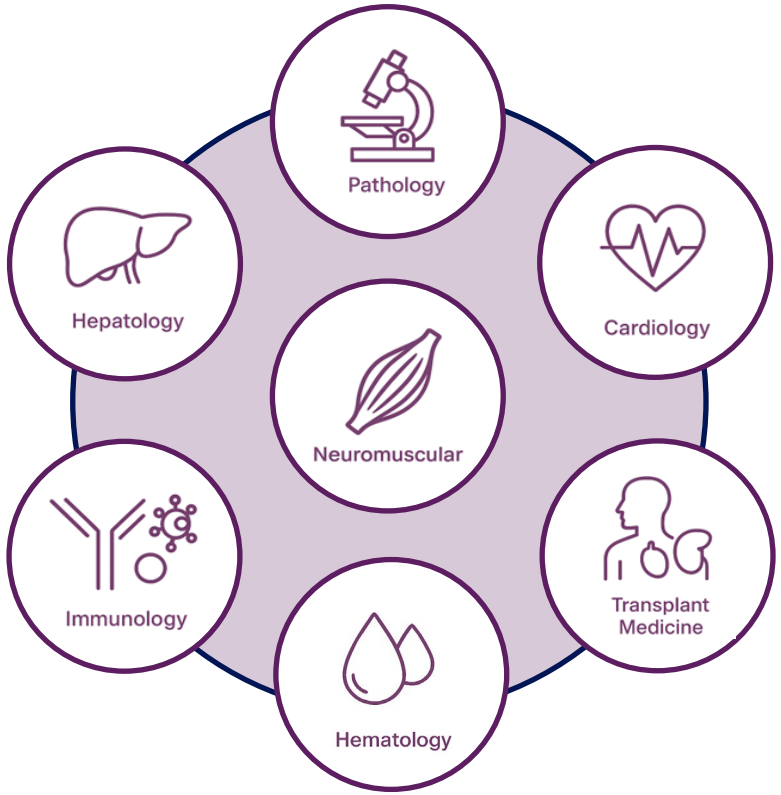
Delandistrogene Moxeparvovec Treatment-related ALF Cases in DMD					
	Setting	**Ambulatory status**	**Age**	**1st sign of LE elevation**	**Time of death**
Case 1	Commercial setting	Non-ambulatory	16 years	Day 28 (4 weeks post-infusion)	12 weeks post-infusion
Case 2	ENVISION clinical trial (NCT05881408)	Non-ambulatory	15 years	Day 33 (5 weeks post-infusion)	11 weeks post-infusion

[a]Includes Study 101 (cutoff date, June 8, 2023), Study 102 (cutoff date, September 29, 2023), Study 103 and Study 301 Part 1 (cutoff date, January 15, 2024).
ALF, acute liver failure; ALI, acute liver injury; ALP, alkaline phosphatase; ALT, alanine transaminase; BL, baseline; DMD, Duchenne muscular dystrophy; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; LE, liver enzyme; LGMD 2D/R3, limb girdle muscular dystrophy 2D/R3; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; ULN, upper limit of normal.
[b]SRP-9004 is an investigational treatment. [c]GLDH was not collected in Study 102 Part 1. GLDH is not a commercially available assay. [d]Excluding elevations from muscle. 1. US Food and Drug Administration. ELEVIDYS® Highlights of prescribing information. https://www.fda.gov/media/169679/download (Accessed March 2025). 2. Qatar Ministry of Public Health Update, 26 July 2024. Roche data on file. 3. UAE Ministry of Health & Prevention. https://mohap.gov.ae/en/services/registered-medical-product-directory (Accessed March 2025). 4. Kuwait Ministry of Health Update, 19 February 2024. Roche data on file. 5. National Health Regulatory Authority Bahrain. Pharmacy & Pharmaceutical Products Regulation. https://www.nhra.bh/Departments/PPR/ (Accessed March 2025). 6. Ministry of Health Oman, Registration Certificate, 25 March 2024. Roche data on file. 7. Ministry of Health Israel, Registration Certificate. 27 June 2024. Roche data on file. 8. Ministry of Health Brazil. https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/anvisa-aprova-registro-de-primeiro-produto-de-terapia-genica-para-distrofia-muscular-de-duchenne-dmd (Accessed March 2025). 9. Japanese Ministry of Health, Labour, and Welfare, 13 May, 2025. Roche data on file. 10. Proud C, et al. Poster presented at the 29th Annual Congress of the World Muscle Society; October 8-12, 2024; Prague, Czechia and virtual

Interdisciplinary expert committee objectives

Following the two fatal ALF cases associated with delandistrogene moxeparvovec, three interdisciplinary expert committees were convened

- Composed of globally recognized medical specialists, each bringing extensive domain expertise and decades of clinical and academic leadership, including neuromuscular physicians with delandistrogene moxeparvovec treatment experience, hepatologists, and specialists experienced in immunosuppressive therapies



Expert Committee Objectives

- Analyze and review ALF safety data to identify **early indicators** of ALI and define populations **at elevated risk** for ALF
- Evaluate and recommend strategies to **prevent and mitigate ALI and ALF**, emphasizing early risk recognition and patient stratification
  - Focus on interventions, clinical pathways, and risk-based management
- Discuss **optimized clinical management approaches** for ALI and ALF, including prophylactic immunosuppression and monitoring parameters
  - Focus on clinical care, protocols, and monitoring

ALF, acute liver failure; ALI, acute liver injury.

Expert committee members

Name	Specialty
Jawad Ahmad, MD	Transplant Hepatology
Diana Bharucha-Goebel, MD	Neuromuscular
Carsten Bönnemann, MD	Neuromuscular
John Brandsema, MD	Neuromuscular
Barry J. Byrne, MD, PhD	Immunology, Cardiology
Catherine Chapin, MD, MS	Transplant Hepatology, Gastroenterology
Tamir Diamond, MD	Transplant Hepatology, Gastroenterology
Susan Matesanz, MD	Neuromuscular

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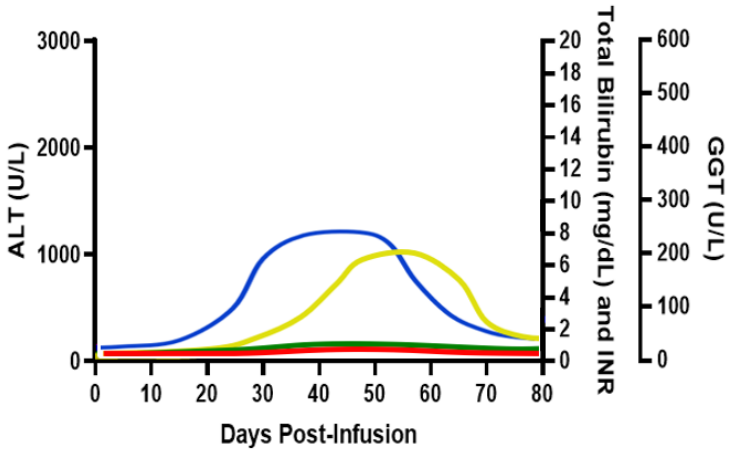
Benjamin Samelson-Jones, MD, PhD	Hematology, Oncology
Perry Shieh, MD, PhD	Neuromuscular
Jonathan Soslow, MD	Cardiology
Aravindhan Veerapandiyan, MD	Neuromuscular
Benjamin Wilkins, MD, PhD	Pathology

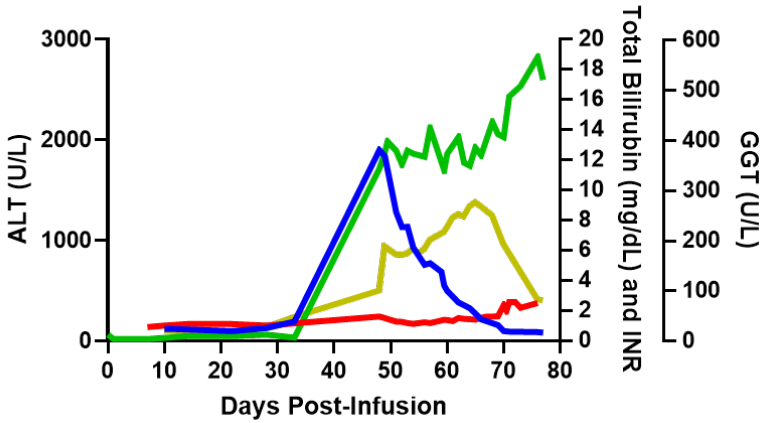
Expert Committee Sponsor Attendees: Damon Asher, Stefanie Mason, Marianne Gerber

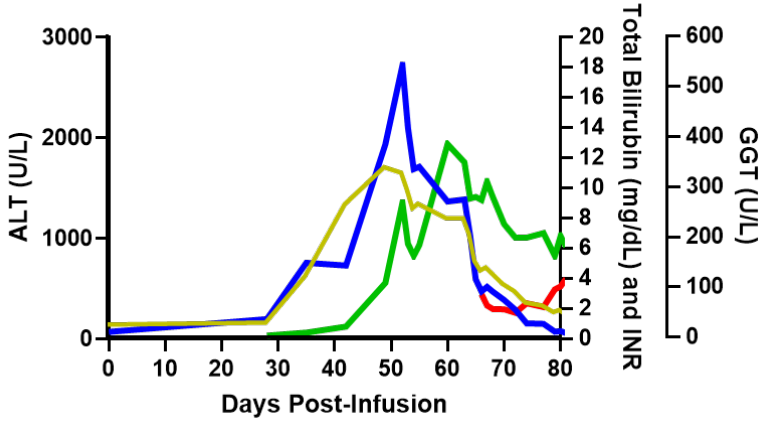
Representative hepatic biomarker trends following delandistrogene moxeparvovec administration

Representative ALI[a]
n=65/156[b]



Treatment-related ALF Cases Following Delandistrogene Moxeparvovec
n=2





ALT GGT Total Bilirubin INR

- Time of onset in two treatment-related ALF cases was similar to that observed in general ALI cases
- Most ALI cases resolved with appropriate management
- Declining ALT and AST with persistently elevated or declining GGT with elevated bilirubin was seen in the two ALF cases

[a]Representative image only. Administration of delandistrogene moxeparvovec may result in elevations of liver enzymes (e.g., GGT, ALT) and total bilirubin, typically seen within 8 weeks.
[b]Includes Study 101 (cutoff date, June 8, 2023), Study 102 (cutoff date, September 29, 2023), Study 103 and Study 301 Part 1 (cutoff date, January 15, 2024).
ALF, acute liver failure; ALI, acute liver injury; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio.

ALI detection challenges and observations in two patients with ALF

Clinical Trial ALI Definition:[1]

- GGT >3× ULN *or*
- GLDH >2.5× ULN *or*
- ALP >2× ULN *or*
- ALT >3× BL when BL is elevated

ELEVIDYS Prescribing Information[2]

ELEVIDYS Prescribing Information recommends a corticosteroid dose modification based on abnormal hepatic laboratory monitoring as follows:

- GGT ≥150 U/L and/or other clinically significant liver function abnormalities (e.g., total bilirubin >2× ULN) following infusion

Discussion of Current Limitations in ALI Detection

Expert committee commented on the limitation with the current ALI treatment threshold and suggested to lower hepatic thresholds as currently they **may not fully capture severity**:

- GGT threshold alone may be too high
- GGT changes may lag behind ALT and AST

Observations in Two Patients with ALF

- ALT and AST levels declined while INR, bilirubin, and fibrinogen worsened in ALF
- Advisors highlighted abnormalities in clotting factors and persistent low fibrinogen
- Advisors raised the possibility of consumptive coagulopathy based on elevated VWF and mean platelet volume

ALF, acute liver failure; ALI, acute liver injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Bl, baseline; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; INR, international normalized ratio; ULN, upper limit of normal; VWF, von Willebrand factor.

1. Data on File. Sarepta Therapeutics. 2. US Food and Drug Administration. ELEVIDYS® Highlights of prescribing information. https://www.fda.gov/media/169679/download (Accessed March 2025).

Potential approaches for earlier detection of ALI

Overarching theme: Hepatic biomarker thresholds should be modified to facilitate timely intervention

Earlier Intervention Before or When Approaching Hepatic Biomarker Thresholds

Advisors highlighted a need for earlier intervention

- Advisors agreed that GGT thresholds should be based on patient's baseline values
  - Using baseline values may help mitigate assay variability given the wide range of ULN values between laboratories and the age-dependent differences in ULN thresholds
- Some advisors suggested intervening before or when GGT levels reach 3× baseline value
- Advisors largely suggested thresholds for bilirubin of >ULN

ALI, acute liver injury; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

1. Data on File. Sarepta Therapeutics.

Potential approaches for the capturing risk

Overarching theme: No single risk factor was identified that consistently predicted progression from ALI to ALF

Potential for evaluating steatosis risk:

- Non-ambulatory patients often experience significant weight gain and elevated BMI[1]
- Moderate to severe hepatic steatosis has been reported in approximately two-thirds of non-ambulatory patients[2]
- Corticosteroid treatment can contribute to insulin resistance and steatosis risk[2]
- At present, advisors found insufficient data to label steatosis as an ALF risk factor

Capturing Risk

Advisors recommended considering enhancing baseline liver characterization:

- ✓ Lipid panels
- ✓ Transient elastography
- ✓ Ultrasound

Advisors emphasized need for **identifying predisposing factors** and **populations at highest risk** for developing ALF

Advisors suggested that ambulatory status may represent a **surrogate for disease severity**, but it is likely not a direct risk factor

Advisors indicated that **weight and dose** were **not** considered contributing **risk factors**

ALF, acute liver failure; ALI, acute liver injury; BMI, body mass index.

1. Houwen-van Opstal SLS, et al. Neuromuscul Disord. 2022;32(3):236-244. 2. Tang YC, et al. Nutrients. 2022;14(4):727.

Potential approaches for improved ALI prevention

Overarching Theme: Addition of prophylactic sirolimus[a] to the current corticosteroid regimen was preferred to escalating corticosteroid doses for the prevention of ALI

Prophylactic Immunosuppression Strategies Considered
Increasing the corticosteroid regimen without adding additional prophylactic agents
Current corticosteroid regimen[b] PLUS prophylactic sirolimus
Increased corticosteroid regimen PLUS addition of either prophylactic sirolimus or tacrolimus

Most advisors favored adding sirolimus to the current corticosteroid regimen

- Initiate sirolimus 1 – 2 weeks prior to infusion with a target trough of 2 – 4 ng/mL
  - Some advisors advocated for a wider target trough range of 2 – 8 ng/mL
- Maintain sirolimus for 8 – 12 weeks post-infusion
- Discontinue based on clinical and lab parameters

Although some advisors initially supported universal prophylaxis, most ultimately favored trialing prophylactic immunosuppression in high-risk subgroups first due to limited mechanistic data and potential for overtreatment.

[a]Not FDA approved for combination use with delandistrogene moxeparvovec
[b]Current corticosteroid regimen includes prednisone equivalent of 1 mg/kg/day starting 1 day prior to infusion in addition to baseline daily or intermittent corticosteroid dosing for DMD or 1 mg/kg/day taken on days without high-dose corticosteroid treatment starting 1 day prior to infusion in addition to high-dose corticosteroids for 2 days/week for DMD. For those not receiving baseline corticosteroids, treat with prednisone equivalent of 1.5 mg/kg/day starting 1 week prior to infusion.
ALI, acute liver injury; IV, intravenous
1. US Food and Drug Administration. RAPAMUNE (sirolimus) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021083s059,021110s076lbl.pdf (Accessed March 2025).

Potential approaches for improved management of ALI

Overarching Theme: Prompt initiation of IV corticosteroids was suggested if patients do not respond to oral corticosteroids

ALI Management Strategies Considered*
Keep current oral corticosteroid dose
Increase current oral corticosteroid dose
IV corticosteroids
IVIG
Sirolimus
Combination of immunosuppressants
Other immunosuppressant

*Not intended to provide guidance regarding the use of combination treatment strategies

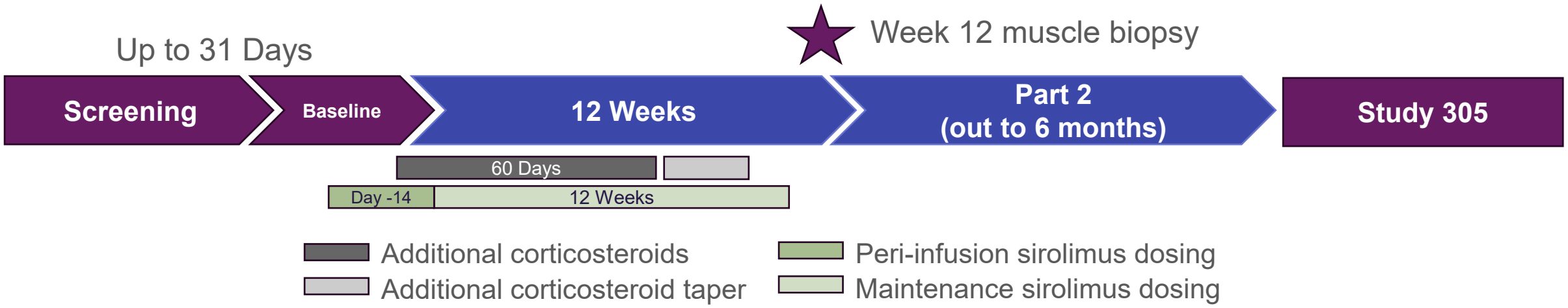
- Some advisors suggested **escalation to IV corticosteroids** if patients do not respond to oral corticosteroids
- Advisors supported **earlier initiation** of IV corticosteroid at **lower hepatic thresholds**
- Potential sirolimus AEs[1] were discussed

[a]Not FDA approved for combination use with delandistrogene moxeparvovec
AE, adverse event; ALI, acute liver injury; IV, intravenous; IVIG, intravenous immunoglobulin
1. US Food and Drug Administration. RAPAMUNE (sirolimus) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021083s059,021110s076lbl.pdf (Accessed March 2025).

Future steps: Overview of proposed ENDEAVOR cohort 8 in non-ambulatory patients[1]

Pending FDA review and approval

Overarching Theme: Need for real-world and clinical trial data; most favored the study of prophylactic immunosuppression in high-risk subgroups due to limited mechanistic data and potential for overtreatment



- **ENDEAVOR (NCT04626674)** is a two-part, open-label, multi-cohort Phase 1b study assessing the transduction, expression, and safety of delandistrogene moxeparvovec in patients with DMD[2]
- **Objective:** Investigate the effectiveness of additional prophylactic immunosuppression in non-ambulatory patients receiving delandistrogene moxeparvovec
- Duration of sirolimus treatment:
  - 14 days prior to delandistrogene moxeparvovec administration & at least 12 weeks post-infusion

Protocol will include antibiotic prophylaxis to mitigate against the potential of increased risk of infection (pneumocystis jirovecii pneumoni), pending FDA approval of ENDEAVOR cohort 8.

1. Sarepta Therapeutics. Data on File. 2. ClinicalTrials.gov. NCT04626674. https://clinicaltrials.gov/study/NCT04626674 (Accessed September 2025).

Other discussion points

Potential Compounding Mechanistic Explanations of ALI

- Advisors debated whether ALI and ALF exist on a spectrum; most suggested that a secondary insult may differentiate fatal cases
- Advisors proposed the role of T cell-mediated liver injury as the leading hypothesis for ALI; complement-mediated injury was not implicated
- Advisors noted value of analyzing demographics, hepatic variables, trends, and liver condition compared to entire treatment population to uncover potential mechanistic explanations
- Advisors noted value of investigating $CD8^+$ T cell responses to AAV capsid proteins using tools (e.g., ELISpot and bile acid transporter staining)

AAV, adeno-associated virus; ALF, acute liver failure; ALI, acute liver injury; CD8, cluster of differentiation; ELISpot, enzyme-linked immunospot assay

Conclusions

Advisors endorsed modifying hepatic biomarker thresholds in ALI to facilitate timely intervention

Advisors recommended considering enhancing baseline liver characterization (e.g., lipid panels, transient elastography, and ultrasound) to better understand risk factors of developing ALI

For ALI prevention, these was broad recommendation for adding prophylactic sirolimus 1-2 weeks prior to delandistrogene moxeparvovec infusion as a second agent to the current corticosteroid regimen as opposed to increasing corticosteroid doses

For ALI management, prompt initiation of IV corticosteroids was suggested if patients do not respond to oral corticosteroids

There is need for real-world data and clinical trials; Cohort 8 of ENDEAVOR aims to investigate the effectiveness of additional prophylactic immunosuppression in non-ambulatory patients receiving delandistrogene moxeparvovec

ALI, acute liver injury.

Expert committee members

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Jawad Ahmad, MD	Transplant Hepatology
Diana Bharucha-Goebel, MD	Neuromuscular
Carsten Bönnemann, MD	Neuromuscular
John Brandsema, MD	Neuromuscular
Barry J. Byrne, MD, PhD	Immunology, Cardiology
Catherine Chapin, MD, MS	Transplant Hepatology, Gastroenterology
Tamir Diamond, MD	Transplant Hepatology, Gastroenterology
Susan Matesanz, MD	Neuromuscular

Name	Specialty
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Crystal Proud, MD	Neuromuscular
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Benjamin Samelson-Jones, MD, PhD	Hematology, Oncology
Perry Shieh, MD, PhD	Neuromuscular
Jonathan Soslow, MD	Cardiology
Aravindhan Veerapandiyan, MD	Neuromuscular
Benjamin Wilkins, MD, PhD	Pathology

Expert Committee Sponsor Attendees: Damon Asher, Stefanie Mason, Marianne Gerber

Acknowledgements and disclosures

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Disclosures

- PS reports being a consultant for Novartis, Biogen, Roche, Pfizer, Sarepta, argenx, Alexion, UCB, Catalyst, Grifols, and CSL Behring, and is receiving grants/research support from Novartis, Biogen, Solid, Pfizer, Sarepta Therapeutics, Avidity, Dyne, UCB, Abcuro, Arcellx, Astellas
- CP participates on an advisory board and is a consultant for Biogen, Sarepta Therapeutics, Inc., AveXis/Novartis Gene Therapies, Genentech/Roche, and Scholar Rock; serves as a speaker for Biogen; and is a Principal Investigator of studies sponsored by AveXis/Novartis Gene Therapies, AMO, Astellas, Biogen, CSL Behring, FibroGen, PTC Therapeutics, Pfizer, Sarepta Therapeutics, Inc., and Scholar Rock
- TD has no relevant disclosures
- CC has been a consultant for Sarepta Therapeutics.
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- AS has no relevant disclosures
- CB* has no relevant disclosures
- JS has no relevant disclosures
- BJB* has no relevant disclosures
- AV has a consultancy/advisory role with AMO Pharma, AveXis, Biogen, Edgewise Therapeutics, FibroGen, Novartis, Pfizer, PTC Therapeutics, Sarepta Therapeutics, Inc., UCB Pharma, Catalyst, and Scholar Rock; has received research funding from AMO Pharma, Capricor Therapeutics, Edgewise Therapeutics, FibroGen, Muscular Dystrophy Association, Novartis, Parent Project Muscular Dystrophy, Pfizer, RegenxBio, and Sarepta Therapeutics, Inc.; and has other relationship(s) with MedLink Neurology for editorial services
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- BS-J* has no relevant disclosures
- BW has no relevant disclosures
- MG is an employee of F. Hoffmann-La Roche Ltd and may have stock options
- S.Mason and DA are employees of Sarepta Therapeutics and may have stock options
- CM reports grants from Capricor Therapeutics, Catabasis, Edgewise Therapeutics, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc.; and has a consultancy/advisory role with Biomarin, Capricor Therapeutics, Catalyst, Edgewise Therapeutics, Italfarmaco, PTC Therapeutics, F. Hoffmann-La Roche Ltd, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc. He has received honoraria from PTC Therapeutics and Sarepta Therapeutics, Inc

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