Supplement 1: Literature Review

- Search strings for ALI included the following: ti,ab("Acute liver injury") and ("Duchenne muscular dystrophy"); "ti,ab("Acute liver injury") and ("gene ther*"); ti,ab("Duchenne muscular dystrophy") and (transamin*); ti,ab(“Duchenne muscular dystrophy”) and (“drug induced liver injury“ or “drug-induced liver injury”)
- Search strings for myocarditis included these terms: ti,ab(Troponin) and (cardiomyopath* or myocarditis) and ("Duchenne muscular dystrophy") and (pediatr* or child* or adolescen* or teen* or infant* or newborn* or neonat*); ti,ab (“Cardiac troponin”) and ("Duchenne muscular dystrophy"); and ti,ab(Troponin) and (cardiomyopathy* or myocarditis) and ("gene therap*")
- Search strings for IMM contained these terms: ti,ab(“immune mediated myopathy”) or (“immune mediated inflammatory myopathy”) or (“immune-mediated inflammatory myopathy”) or (“inflammatory myopathy”) or (“idiopathic inflammatory myopathy”) or (“immune mediated myasthenia”) or (“immune-mediated myasthenia”) or (“autoimmune myositis”) or (“immune mediated necrotizing myopathy”) or (“immune-mediated necrotizing myopathy”) not (non-human or nonhuman or animal* or veterinary* or mice or mouse OR rat OR rats OR canine* or dog or dogs or pig or pigs or rabbit* or horse* or cow or cows* or monkey* or chicken*)

Acute liver injury literature

- To prevent delays in diagnosis, as well as unnecessary invasive testing, it was suggested to maintain a high index of suspicion for extrahepatic sources of alanine transaminase (ALT) and aspartate transaminase (AST) [1]
- In alignment with prescribing guidelines, prophylactic prednisolone should be used, and providers should consider increasing dosages and/or a longer treatment duration [2]
- It was observed that persons with DMD had deviations in the indices of their immune status; of note, the T helper cell level was below normal in nearly half of examined patients [3]
- A few case studies offer guidance for detecting and managing liver injury following gene therapy, but overall, there is a scarcity of data available to clinicians for treatment considerations [2, 4, 5]
    - Suggested laboratory studies include AST/ALT, gamma-glutamyl transferase (GGT), total and direct bilirubin, and prothrombin time (PT) and international normalized ratio (INR) [4]
    - A liver ultrasound and physical exams should be performed [4]

- Consider admitting the patient to the hospital for intravenous (IV) corticosteroids 10 mg/kg/day if lab values continue to rise [4]

Myocarditis literature

- A key finding was that only corticosteroids have been demonstrated to reduce cardiac mortality and slow progressive muscular decline [6]
- Recommendations were made by the Parent Project Muscular Dystrophy Expert Panel for cardiac disease in DMD to address the monitoring and treatment of troponin I elevation [7]
- Laboratory studies described in the literature used for patient evaluation and management included testing for troponin I and T, creatine kinase (CK), creatine kinase-myocardial band (CK-MB), N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), lactate levels, alkaline phosphatase (ALP), and transaminases [6-17]
- Imaging and diagnostics that were suggested to evaluate myocarditis included electrocardiogram (ECG), echocardiogram (echo), computed tomography (CT), late gadolinium enhancement on cardiac magnetic resonance (LGE-CMR), and coronary angiography [6, 7, 11-20].
- Additional treatments for consideration included use of supportive care, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and prednisone, with prednisone being the most commonly suggested medication for preventative and maintenance therapy [6, 11, 12, 15, 16, 18, 19]

Immune-mediated myositis literature

- The Myositis Association provides guidelines for diagnostic tests that detect electrical abnormalities in nerves and muscles that can indicate the presence of an inflammatory disease [21]
- A few case studies offer guidance for differential diagnosis and treatment of IMM, noting that the involvement of an interdisciplinary team is vital [22]
- According to the literature, testing for AST/ALT, gamma-glutamyl transpeptidase (GGT), CK, BNP, total bilirubin, activated partial thromboplastin time (aPTT), and antinuclear antibodies (ANA) could be considered [23, 24]
- Manual muscle testing, muscle CT, muscle MRI, ECG, chest x-ray, abdominal ultrasound, and muscle biopsy were also suggested [21, 23]
- Additional medications and treatments that could be considered included oral prednisone, IV pulse steroids, intravenous immunoglobulin (IVIg), azathioprine, methotrexate, cyclophosphamide, ursodeoxycholic acid, and plasmapheresis [23, 25]

Supplement 2: Questionnaires and Results

QUESTIONNAIRE 1

1. How far in advance of the infusion would you order baseline labs and do a physical exam to reliably establish a patient's health status and readiness for gene therapy *(insurance is not an issue)*
    a. Is 1 month prior to infusion acceptable?
    b. Is 1 week prior to infusion acceptable?
    c. Is 1 day prior to infusion acceptable?
    d. Other: _____

2. What labs would you collect at baseline? AST, ALT, T bilirubin, GGT, Troponin-I, CBC with diff, PT, INR, aPTT, other?

3. If the following post-infusion protocol was proposed, is there anything you would like to change or add?
    - Monitor liver function before infusion, and weekly for the first 12 weeks. Continue monitoring until results return to baseline.
    - Monitor Troponin-I before infusion, and weekly for the first 4 weeks.
    - Monitor platelet count before infusion, and weekly for the first 2 weeks.
    - Initiate a corticosteroid regimen according to the following table for a minimum of 60 days:
    - Corticosteroid dose modifications recommended for patients with acute liver injury when indicated, see following table:

Peri-infusion corticosteroid dosing	Modified peri-infusion corticosteroid dose (prednisone equivalent)	Recommended maximum total daily dose	Recommended corticosteroid regimen taper duration
Baseline + 1 mg/kg/day	Increase to 2 mg/kg/day (and continue baseline dose)	120 mg/day	2 weeks if tapering from added corticosteroids back to baseline dose
Baseline + 1 mg/kg/day taken on days without high-dose corticosteroid treatment	Increase to 2 mg/kg/day taken on days without high-dose corticosteroid treatment (and continue baseline dose)	120 mg/day	2 weeks if tapering from added corticosteroids back to baseline dose
1.5 mg/kg/day	Increase from 1.5 mg/kg/day to 2.5 mg/kg/day	120 mg/day	4 weeks if tapering from added corticosteroids back to no corticosteroids

[a] GGT >= 150 U/L and/or other clinically significant liver function abnormalities following infusion. For elevations that do not respond to these oral corticosteroid increases, or for serious or severe elevations in hepatic biochemistries (including GGT, bilirubin, ALT relative to baseline), IV bolus corticosteroids may be considered.

- In person follow-up frequency:
    - Examine patient in person every 2-4 days the first 2 weeks
    - then examine patient every week for 2 weeks
    - then examine patient every month for 2 months
    - After 3 months post infusion resume frequency of routine follow-up visits
    - Follow-up schedule modifications recommended for patients with adverse events when indicated

- What does the physical exam include? Would anything else be included for evaluation?

4. Would you start all patients on H2-blocker or PPI coinciding with the infusion? When would they start and how long would patients remain on this treatment?

5. Would you start all patients on an anti-emetic coinciding with the infusion? When would patients start and how long would patients remain on this treatment?

Part 1: Acute Liver Injury / Elevated AST/ALT

Case Study #1

JM is a 4 yo male with a history of DMD (deletion of exons 56-60), who is ambulant. He weighs 17 kg. He has been on a corticosteroid daily. His assay was antibody negative, <1:400. He was determined to be a candidate for gene therapy. His steroid dose was increased to 1 mg/kg/day the day prior to his infusion. He was examined the morning of his infusion and had no signs of concurrent infection. His nurse placed two peripheral IVs and obtained baseline labs. He was uneventfully infused.

Baseline Lab Values

Test	Results	Reference Ranges
CK	19479	65-250 U/L
Troponin I HS	0.041	0.000 – 0.058 ug/L
AST	342 U/L	0-41 U/L
ALT	846 U/L	5-30 U/L
T bili	<0.2 mg/dL	0.2-0.9 mg/dL
GGT	12 U/L	0-65 U/L
INR	0.9	0.87-1.18
Platelets	192 x10^3u/L	175-420 x10^3u/L
PT	10.6	8.4-10.7 sec
APTT	25	24.3-30.4 sec
CH50	40 U/mL	38.7-89.9 U/mL

1-week post-infusion follow up

Clinical findings and/or caregiver observations:

JM is being seen in person 1 week after his infusion. He and his parents report nausea with a decreased appetite the first 3 days which resolved after initiating an H2 blocker and anti-emetic. No other concerns noted. He has been taking his corticosteroids daily as prescribed. His parents feel his activity level has increased. His physical exam remains at baseline. Labs were collected and results are below.

1-week Post Lab Values

Test	Results	Reference Ranges

CK	12048	65-250 U/L
Troponin I HS	0.042	0.000 – 0.058 ug/L
AST	755 U/L	0-41 U/L
ALT	1792 U/L	5-30 U/L
T bilirubin	<0.2 mg/dL	0.2-0.9 mg/dL
GGT	28 U/L	0-65 U/L
INR	1.01	0.87-1.18
PT	10.3	8.4-10.7 sec
APTT	24.9 sec	24.3-30.4 sec
Platelets	321 x10^3u/L	175-420 x10^3u/L

1. Do the above changes in lab results, clinical findings and/or caregiver observations indicate the need to deviate from your protocol in any way?

2. At what increase of AST/ALT do you get concerned about acute liver injury (ALI)? How does the total bilirubin result influence your assessment? At what point do you decide to monitor closely (increase monitoring) versus treat?
    a. 2x the baseline result
    b. 3x the baseline result
    c. >1000 U/L

3. Based on this information, please indicate if or how you might further manage the patient using the following:

    - Laboratory studies:
    - Imaging studies:
    - Medications and treatments:
    - Consults:
    - Nothing

6-week post-infusion follow up

Clinical findings and/or caregiver observations:
JM has returned home. He had labs drawn locally for his 6-weeks post-infusion timepoint. Results are shown below:

6-weeks Post Lab Values

Test	**Results**	**Reference Ranges**
CK	20067 U/L	65-250 U/L
AST	1355 U/L	0-41 U/L
ALT	2115 U/L	5-30 U/L
T bili	0.9 mg/dL	0.2-0.9 mg/dL
GGT	250 U/L	0-65 U/L

INR	1.01	0.87-1.18
PT	10.3 sec	8.4-10.7 sec
APTT	26.2 sec	24.3-30.4 sec

Clinical findings and/or caregiver observations:
JM was seen by his local provider. The local neurologist reports his exam is at baseline. No signs of hepatomegaly, right upper quadrant tenderness, or rebound tenderness. No decrease in urine output reported. Stool color is not pale, and consistency has been normal. He appears well hydrated. His parents report he has been taking his corticosteroid therapy as prescribed.

1. Are there any concerns with these results?
   a. If so, based on the above findings, would you examine the patient in person, have his local provider examine him, or send him to an emergency room for evaluation? What should be included in the examination?

2. Based on this information, please indicate if or how you might further manage the patient using the following:

- Laboratory studies:
- Imaging studies:
- Medications and treatments:
- Consults
- Nothing

3. If you repeated labs and his GGT remains elevated and the total bilirubin level increases outside normal range, please indicated if or how would you further manage the patient using the following:

- Laboratory studies:
- Imaging studies:
- Medications and treatments:
- Consults
- Nothing

Part 2: Acute Myocarditis / Elevated Troponin

<u>Case Study #2</u>
CW is a 7-year-old male with a history of DMD (deletion of exons 48-58), who is ambulant. He has no evidence of cardiac disease by echocardiogram or electrocardiogram. He does not use ventilatory support. His resting heart rate is 116 bpm. He weighs 31 kg. He takes a corticosteroid daily. His assay was antibody negative, <1:400. He was determined to be a candidate for gene therapy. His steroid dose was increased to baseline + 1mg/kg/day and he was prescribed H2 blocker the day prior to his infusion. Two IVs were placed, and his baseline labs were drawn. He was uneventfully

infused. He experienced some nausea and vomiting later that evening and was prescribed an anti-emetic.

Baseline Lab Values

Test	Results	Reference Ranges
CK	20389	65-250 U/L
Troponin I HS	0.042	0.000 – 0.058 ug/L
AST	342 U/L	0-41 U/L
ALT	846 U/L	5-30 U/L
T bili	<0.2 mg/dL	0.2-0.9 mg/dL
GGT	12 U/L	0-65 U/L
INR	0.9	0.87-1.18
PT	10.6	8.4-10.7 sec
Platelets	368 x10^3u/L	175-420 x10^3u/L
APTT	26	24.3-30.4 sec

1-week post-infusion follow up.

Clinical findings and/or caregiver observations:
CW returns in person for his 1 week follow up visit. He and his parents report continued nausea, vomiting and a decreased appetite. He has been taking his corticosteroid dose as prescribed. His physical exam remains at baseline.

1-week Post Lab Values

Test	Results	Reference Ranges
CK	12016	65-250 U/L
Troponin I HS	0.741	0.000 – 0.058 ug/L
AST	364	0-41 U/L
ALT	379	5-30 U/L
T bili	0.2	0.2-0.9 mg/dL
GGT	16	0-65 U/L
INR	0.89	0.87-1.18
Platelets	171 x10^3u/L	175-420 x10^3u/L
PT	9.2	8.4-10.7 sec
APTT	24.6	24.3-30.4 sec

1. Are there any thoughts or concerns with these results (week 1)?
   a. What changes in lab results, clinical findings and/or caregiver observations might indicate the need to initiate therapy for treatment of acute myocarditis / elevated troponin?

2. Based on this information, please indicate if or how you might further manage the patient using the following:

- Laboratory studies:

- Imaging studies:
- Medications and treatments:
- Consults
- Nothing

3. Labs will be repeated the following week. If at week 2 ***CW***'s platelet count continued to drop, please indicate if or how would you further manage the patient using the following:

- Laboratory studies:
- Imaging studies:
- Medications and treatments:
- Consults
- Nothing

4-week post-infusion follow up

Clinical findings and/or caregiver observations:
CW reports he is doing well.

4-week Post Lab Values

Test	Results	Reference Ranges
CK	8151	65-250 U/L
Troponin I HS	0.121	0.000 – 0.058 ug/L
AST	249	0-41 U/L
ALT	208	5-30 U/L
T bili	<0.2	0.2-0.9 mg/dL
GGT	64	0-65 U/L
INR	0.99	0.87-1.18
Platelets	198 x10^3u/L	175-420 x10^3u/L
PT	9.1	8.4-10.7 sec
APTT	25	24.3-30.4 sec

1. Are there any concerns with these results?
   a. If so, based on the above findings, would you examine the patient in person, have his local provider examine him, or send him to an emergency room for evaluation? What should be included in the examination?

2. Based on this information, please indicate if or how you might further manage the patient using the following:

- Laboratory studies:
- Imaging studies:
- Medications and treatments:

- Consults
- Nothing

Part 3: Drug-Induced Immune-Mediated Myositis

Case Study #3

AJ is a 6 yo male with a history of DMD (deletion of exons 17-26), who is ambulant. He weighs 24.6 kg. He is on daily corticosteroid. His assay was antibody negative, <1:400. He has no recent acute illnesses. He was determined to be a candidate for gene therapy. Two IVs were placed, and his baseline labs were drawn. His steroid dose was increased the day prior to his infusion. He was uneventfully infused.

Baseline Lab Values

Test	Results	Reference Ranges
CK	23890	65-250 U/L
Troponin-I HS	0.046	0.000 – 0.058 ug/L
AST	482	0-41 U/L
ALT	436	5-30 U/L
T bili	<0.2	0.2-0.9 mg/dL
GGT	9	0-65 U/L
INR	0.89	0.87-1.18
PT	9.2	8.4-10.7 sec
Platelets	265 x 10^3/uL	175-420 x10^3u/L
APTT	23	24.3-30.4 sec

4-week post-infusion follow up

Clinical findings and/or caregiver observations:

AJ's parents report complaints of bilateral muscle weakness in his arms that has been progressive the last few days. He is having more trouble walking and complains of calf tenderness. He describes a tingling sensation in his throat with mild difficulty swallowing.

4-week Post Lab Values

Test	Results	Reference Ranges
CK	13403	65-250 U/L
Troponin I HS	0.043	0.000 – 0.058 ug/L
AST	678	0-41 U/L
ALT	752	5-30 U/L
T bili	0.3	0.2-0.9 mg/dL
GGT	28	0-65 U/L
INR	1.14	0.87-1.18
Platelets	175 x 10^3/uL	175-420 x10^3u/L
PT	9	8.4-10.7 sec
APTT	20.8	24.3-30.4 sec

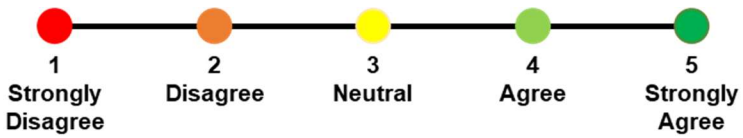
1. What changes in lab results, clinical findings and/or caregiver observations might indicate the need to initiate therapy for treatment of drug-induced immune-mediated myositis?
    a. Based on the above findings, would you examine the patient in person, have his local provider examine him, or send him to the emergency room?

2. Based on this information, please indicate if or how you might further manage the patient using the following:

    - Laboratory studies:
    - Imaging studies:
    - Medications and treatments:
    - Consults
    - Nothing

Questionnaire 2

Please consider each of the following statements and rate your agreement with question statements using a 5-point Likert scale from strongly agree to strongly disagree.



Part 1.0: Procedures and protocol

Q1. Please rate your agreement with the following statements describing how far in advance of delandistrogene moxeparvovec infusion you would schedule a visit to reliably establish a patient's health status and readiness for gene therapy.

1-2-3-4-5	Assess the patient 1 month prior to the procedure to determine patient readiness and health status for gene transfer therapy
1-2-3-4-5	Assess the patient 1 week prior to the procedure to determine patient readiness and health status for gene transfer therapy
1-2-3-4-5	Perform a physical exam 1 day prior to the procedure to determine patient readiness and health status for gene transfer therapy
1-2-3-4-5	Perform a physical exam on the morning of the procedure to determine patient readiness and health status for gene transfer therapy

Additional comments

Q2. Please rate your agreement with the following statements describing how far in advance of delandistrogene moxeparvovec infusion would you collect labs to reliably establish a patient's baseline levels.

1-2-3-4-5	Collect labs 1 month prior to the procedure
1-2-3-4-5	Labs should be done 1 month ahead, and repeated 1-2 weeks prior to infusion
1-2-3-4-5	Collect labs 1 week before the procedure
1-2-3-4-5	Labs should be done 1 week ahead, and repeated 1-2 days prior to infusion
1-2-3-4-5	Collect labs the morning of infusion therapy

Additional comments

Q3. Please rate your agreement that the following commercially available tests should be included in the panel to monitor liver function, troponin elevation, and/or immune mediated myositis

Note: Select 5 if you recommend this test to be included in the baseline panel and select 1 if you do not recommend this test to be included

General labs	
1-2-3-4-5	Complement (C3, C4, CH50)
1-2-3-4-5	CBC with diff, complete blood count with differential measures (includes platelets, RBC, WBC, Hg, Hct, MCV)
1-2-3-4-5	CMP, Comprehensive metabolic panel (AST, ALT, T bilirubin, ALP, albumin, alkaline phosphatase, eGFR, BUN/creatinine ratio)
1-2-3-4-5	Serum IgG
Liver Function	
1-2-3-4-5	AFP, alpha fetoprotein
1-2-3-4-5	aPTT, activated partial thromboplastin time
1-2-3-4-5	GGT, gamma-glutamyl transferase
1-2-3-4-5	PT/INR, prothrombin time and international normalized ratio
1-2-3-4-5	Liver ultrasound
1-2-3-4-5	Myoglobin
1-2-3-4-5	Direct bilirubin
Cardiac	
1-2-3-4-5	BNP, Brain natriuretic peptide
1-2-3-4-5	CK, Creatine kinase
1-2-3-4-5	CRP, C-reactive protein
1-2-3-4-5	Troponin I
1-2-3-4-5	Echo, Echocardiogram and/or EKG, Electrocardiogram
1-2-3-4-5	ESR, Erythrocyte sedimentation rate
Infection	
1-2-3-4-5	CMV, Cytomegalovirus
1-2-3-4-5	Hepatitis (A, B, C)
1-2-3-4-5	HIV, Human immunodeficiency virus
1-2-3-4-5	EBV, Epstein-Barr virus
1-2-3-4-5	TB, Tuberculosis
Renal Function	
1-2-3-4-5	Cystatin C
1-2-3-4-5	Urinalysis
Other:	

Q4. Please rate your agreement with the following approaches for preventative measures and pharmacological interventions to address gastrointestinal symptoms that may arise from gene transfer therapy

1-2-3-4-5	I provide an H2-blocker prophylactically when steroids are initiated
1-2-3-4-5	I provide a PPI prophylactically when steroids are initiated
1-2-3-4-5	I provide an H2-blocker with symptoms of reflux/heartburn
1-2-3-4-5	I provide a PPI only with symptoms of reflux/heartburn

Q5. Please rate your agreement with the following approaches for managing post-infusion nausea and vomiting

1-2-3-4-5	I provide an anti-emetic starting at infusion prophylactically
1-2-3-4-5	I provide a prescription for an anti-emetic to be used as indicated by symptoms

Part 1.1: Procedures and protocol – exploratory questions not included on Questionnaire-1

Q6. Please rate your agreement with the following recommendations for the length of time needed to monitor patients on the day of infusion following gene transfer therapy

1-2-3-4-5	Patient should be monitored for 6-8 hours post infusion
1-2-3-4-5	Patient should be monitored for 4-6 hours post infusion
1-2-3-4-5	Patient should be monitored for 3-4 hours post infusion
1-2-3-4-5	Patient should be monitored for 2-3 hours post infusion
1-2-3-4-5	Patient should be monitored for 1-2 hours post infusion
1-2-3-4-5	Less than an hour of monitoring is needed following infusion

Additional comments

Q7. Please rate your agreement with the following statements describing communication methods that patients/caregivers can use to contact the gene therapy team once they are discharged from the hospital if they have concerns that arise following gene transfer therapy.

1-2-3-4-5	Give patients a phone number where they can reach a gene therapy team member directly with instructions to call if they have concerns or experience side effects
1-2-3-4-5	I give patients the phone number for a 24/7 call line where they can report concerns and get help if they experience side effects
1-2-3-4-5	Patients directly contact the gene therapy team in the clinic during daytime hours for urgent needs; patients use EMR messaging/email for non-urgent needs; patients use the clinic after-hours service number where they can connect with a physician on-call to be transferred to team

Additional comments

Part 2: Acute Liver Injury (ALI)

Q8. After gene transfer therapy with delandistrogene moxeparvovec, acute liver injury is suspected. Please rate your agreement with the following statements describing recommendations for patient care.

Monitoring	
1-2-3-4-5	I request a telehealth visit, or phone call with the parent/caregiver
1-2-3-4-5	I ask that the patient is seen for a physical exam
1-2-3-4-5	The patient should be admitted to the hospital
Laboratory Studies	
1-2-3-4-5	I continue to follow the protocol without deviation for another week
1-2-3-4-5	I would repeat baseline labs sooner than the protocol specifies (within 1 week)
Additional Testing	
1-2-3-4-5	None needed
1-2-3-4-5	The patient should have a liver ultrasound
Medications and Treatments	
1-2-3-4-5	I do not change the level of steroids yet
1-2-3-4-5	I increase the oral steroid dose to 2mg/kg/day to a max of 120mg/kg/day
Consults	
1-2-3-4-5	A consult with a specialist is needed
1-2-3-4-5	

How does your response change if your patient is symptomatic

Additional general comments:

Q9. After gene transfer therapy with delandistrogene moxeparvovec, acute liver injury is diagnosed. Please rate your agreement with the following statements describing recommendations for patient care.

Monitoring	
1-2-3-4-5	I request a telehealth visit, or phone call with the parent/caregiver
1-2-3-4-5	I ask that the patient is seen for a physical exam
1-2-3-4-5	The patient should be admitted to the hospital

Laboratory Studies	
1-2-3-4-5	I would repeat labs immediately
1-2-3-4-5	I would repeat labs within a week
	I would like additional commercially available tests of liver function to include:
1-2-3-4-5	Rh 74 Antibody test
1-2-3-4-5	Viral testing (Hepatitis panel, HIV, EBV, CMV)
Additional Testing	
1-2-3-4-5	None needed
1-2-3-4-5	The patient should have a liver ultrasound
Medications and Treatments	
1-2-3-4-5	I do not change the level of steroids yet
1-2-3-4-5	I increase the oral steroid dose to 2mg/kg/day to a max of 120mg/kg/day
1-2-3-4-5	I recommend the patient begin a 3-day course of IV methylprednisolone
Consults	
1-2-3-4-5	A consult with a specialist is needed
Additional comments:	

Q10. After gene transfer therapy with delandistrogene moxeparvovec, acute liver injury is diagnosed and not responding to initial interventions. Please rate your agreement with the following statements describing recommendations for patient care.

Laboratory Studies	
	I would like additional commercially available tests of liver function to include:
1-2-3-4-5	Indirect bilirubin
1-2-3-4-5	Thyroid Stimulating Hormone (TSH)
1-2-3-4-5	triiodothyronine (T3) and thyroxine (T4)
1-2-3-4-5	Viral testing (Hepatitis panel, HIV, EBV, CMV)
Additional Testing	
1-2-3-4-5	None needed
1-2-3-4-5	The patient should have a liver ultrasound
Medications and Treatments	
1-2-3-4-5	I recommend the patient begin a 3-day course of IV methylprednisolone
Consults	
1-2-3-4-5	A consult with a specialist is needed
Additional comments:	

Part 3: Acute Myocarditis / Elevated Troponin

Q11. After gene transfer therapy with delandistrogene moxeparvovec, there are cardiac concerns because troponin I is elevated. Please rate your agreement with the following statements describing recommendations for patient care, noting that the patient is <u>asymptomatic</u>.

1-2-3-4-5	I request a telehealth visit, or phone call with the parent/caregiver
1-2-3-4-5	I ask that the patient is seen for a physical exam
1-2-3-4-5	The patient should be admitted to the hospital
Laboratory Studies	
1-2-3-4-5	I continue to follow the protocol without deviation for another week
1-2-3-4-5	Repeat labs sooner than the protocol calls for (1-week later)
1-2-3-4-5	Request an additional test for complement (C3, C4, CH50)
Additional Testing	
1-2-3-4-5	The patient should have an Echo/EKG
Medication and treatment	
1-2-3-4-5	I do not change the level of steroids, yet
1-2-3-4-5	I increase the oral steroid dose to 2mg/kg/day to a max of 120mg/kg/day
Consults	
1-2-3-4-5	A consult with a specialist is needed
Additional comments:	

Q12. After gene transfer therapy with delandistrogene moxeparvovec, elevated troponin is suspected. Please rate your agreement with the following statements describing recommendations for patient care, noting that the patient is <u>symptomatic</u>

1-2-3-4-5	I request a telehealth visit, or phone call with the parent/caregiver
1-2-3-4-5	I ask that the patient is seen for a physical exam
1-2-3-4-5	The patient should be admitted to the hospital
Laboratory Studies	
1-2-3-4-5	I continue to follow the protocol without deviation for another week
1-2-3-4-5	Repeat labs sooner than the protocol calls for (1-week later)
	I want additional commercially available tests such as
1-2-3-4-5	Complement (C3, C4, CH50)
1-2-3-4-5	CKMB

1-2-3-4-5	CK
1-2-3-4-5	CRP, C-reactive protein
1-2-3-4-5	Urinalysis
1-2-3-4-5	Cystatin C
Additional testing	
1-2-3-4-5	The patient should have an echo/EKG
1-2-3-4-5	cMRI
Medication Changes	
1-2-3-4-5	I do not change the level of steroids
1-2-3-4-5	I increase the oral steroid dose to 2mg/kg/day to a max of 120mg/kg/day
1-2-3-4-5	I recommend the patient begin a 3-day course of IV methylprednisolone
1-2-3-4-5	Consider IVIG
1-2-3-4-5	Consider immune-modulating pharmacotherapy
Consults	
1-2-3-4-5	A consult with a specialist is needed
Additional comments:	

Q13. After gene transfer therapy with delandistrogene moxeparvovec, myocarditis is diagnosed and not responding to initial interventions. Please rate your agreement with the following statements describing recommendations for patient care.

1-2-3-4-5	I ask that the patient is seen for a physical exam
1-2-3-4-5	The patient should be admitted to the hospital
Laboratory Studies	
	I ask for additional commercially available tests to include
1-2-3-4-5	Complement (C3, C4, CH50)
1-2-3-4-5	CRP, C-reactive protein
1-2-3-4-5	CBC with differential (includes platelets, RBC, WBC, Hg, Hct, MCV)
1-2-3-4-5	Cystatin C
1-2-3-4-5	Urinalysis
Additional Testing	
1-2-3-4-5	The patient should have an echo/EKG
1-2-3-4-5	cMRI
Medications and treatments	

1-2-3-4-5	I do not change the level of steroids
1-2-3-4-5	I increase the oral steroid dose to 2mg/kg/day to a max of 120mg/kg/day
1-2-3-4-5	I recommend the patient begin a 3-day course of IV methylprednisolone
1-2-3-4-5	Initiate immune-modulating pharmacotherapy
1-2-3-4-5	I would consider treating the patient with IVIG
Consults	
1-2-3-4-5	A consult with a specialist
Additional comments:	

Part 4: Drug-Induced Immune-Mediated Myositis

Q14. A healthcare provider has administered delandistrogene moxeparvovec to a patient and is following the prescribing information to monitor patient health following infusion. The parent/caregiver reports that the patient is exhibiting physical signs of IMM (muscle pain, muscle tenderness, muscle weakness) that are progressive over days. Please rate your agreement with the following approaches for monitoring and treating a potential case of IMM in response to this initial report of clinical signs

1-2-3-4-5	I request a telehealth visit, or phone call with the parent/caregiver
1-2-3-4-5	I ask that the patient is seen for a physical exam
1-2-3-4-5	The patient should be admitted to the hospital
Laboratory Studies	
1-2-3-4-5	Continue to follow protocol without deviation for another week
1-2-3-4-5	Repeat labs sooner than the protocol calls for (1-week later)
	I ask for additional commercially available tests to include
1-2-3-4-5	aldolase
1-2-3-4-5	Myositis diagnostic panel (Jo-1, PL-7,PL-12,EJ Ab, OJ Ab, SRP Ab, Mi-2 Alpa Ab, Mi-2 Beta Ab, MDA5, Ab, TIF1 Gamma Ab, NXP-2 Ab)
1-2-3-4-5	Rh 74 Antibody test
1-2-3-4-5	ANA
1-2-3-4-5	Complement (C3, C4, CH50)
1-2-3-4-5	CPK, Creatine phosphokinase
1-2-3-4-5	CRP, C-reactive protein
1-2-3-4-5	Cystatin C
1-2-3-4-5	D-dimer test

1-2-3-4-5	ESR, Erythrocyte sedimentation rate
1-2-3-4-5	Myoglobin
1-2-3-4-5	Serum IgG
1-2-3-4-5	Thyroid Stimulating Hormone (TSH)
1-2-3-4-5	triiodothyronine (T3) and thyroxine (T4)
1-2-3-4-5	Urinalysis and urine output
Additional Testing	
1-2-3-4-5	The patient should have an echo/EKG
1-2-3-4-5	The patient should have a liver ultrasound
1-2-3-4-5	MRI (skeletal/muscle)
Diagnostics	
1-2-3-4-5	The patient should have an EMG/nerve conduction study
1-2-3-4-5	The patient should have a swallow study
1-2-3-4-5	The patient should have a neuromuscular strength assessment
1-2-3-4-5	I would collect a muscle biopsy
1-2-3-4-5	I would collect a nerve biopsy
Medications and treatments	
1-2-3-4-5	I do not change the level of steroids
1-2-3-4-5	I increase the oral steroid dose to 2mg/kg/day to a max of 120mg/kg/day
1-2-3-4-5	I recommend the patient begin a 3-day course of IV methylprednisolone
1-2-3-4-5	Patient should receive plasmapheresis
1-2-3-4-5	Patient should be placed on IVIG
1-2-3-4-5	Consider other immune-modulating pharmacotherapy
Consults	
1-2-3-4-5	A consult with a specialist

Do your recommendations change if the patient is having difficulty chewing/swallowing?
Additional comments:

Delphi Panel Poll Results

Statement*	Panelists in Agreement (%)
General Assessment and Management of the Patient	
Physical Exam	
Assess the patient 1 month prior to the procedure to determine patient readiness and health status for gene transfer therapy	66.7
Assess the patient 1 week prior to the procedure to determine patient readiness and health status for gene transfer therapy	50.0
Perform a physical exam 1 day prior to the procedure to determine patient readiness and health status for gene transfer therapy	33.3
Perform a physical exam on the morning of the procedure to determine patient readiness and health status for gene transfer therapy	66.7
To provide the greatest level of safety for the general patient population, I recommend a physical exam at the initial visit when I determine if the patient is a candidate for gene therapy (approx. 1 month prior) and then I examine the patient again within 48 hours of the procedure to make sure the patient is ready for treatment.	83.3
Baseline Lab Collection	
Collect baseline labs 1 month prior to the procedure	41.7
Baseline labs should be done 1 month ahead, and repeated 1-2 weeks prior to infusion	16.7
Collect baseline labs 1 week before the procedure	33.3
Baseline labs should be done 1 week ahead, and repeated 1-2 days prior to infusion	33.3
Collect baseline labs the morning of infusion therapy	41.7
To provide the greatest level of safety for the general patient population, I recommend collecting baseline labs two times prior to gene therapy: the initial sampling should take place at the evaluation appointment (approx. 1 month prior) and the second sampling should be collected within 1 day of the procedure.	75.0
The following commercially available tests should be included in the baseline panel to monitor liver function, troponin I elevation, and/or IMM:	
Complement (C3, C4, CH50)	66.7
CBC with diff, complete blood count with differential measures (includes platelets, RBC, WBC, Hg, Hct, MCV)	82.0
CMP, Comprehensive metabolic panel (AST, ALT, total bilirubin, ALP, albumin, alkaline phosphatase, eGFR, BUN/creatinine ratio)	83.3
Serum IgG	50.0

AFP, alpha fetoprotein	8.3
aPTT, activated partial thromboplastin time	82.0
GGT, gamma-glutamyl transferase	100.0
PT/INR, prothrombin time and international normalized ratio	100.0
Liver ultrasound	16.7
Myoglobin	33.3
Direct bilirubin	83.3
BNP, brain natriuretic peptide	16.7
CK, creatine kinase	91.7
CRP, C-reactive protein	16.7
Troponin I	83.3
Echo, echocardiogram and/or EKG, electrocardiogram	66.7
ESR, erythrocyte sedimentation rate	8.3
CMV, cytomegalovirus	50.0
Hepatitis (A, B, C)	66.7
HIV, human immunodeficiency virus	50.0
EBV, Epstein-Barr virus	50.0
TB, tuberculosis	8.3
Cystatin C	75.0
Urinalysis	58.3
Treatment for Gastritis	
I provide an H2-blocker prophylactically when steroids are initiated	33.3
I provide a PPI prophylactically when steroids are initiated	25.0
I provide an H2-blocker with symptoms of reflux/heartburn	58.3
I provide a PPI only with symptoms of reflux/heartburn	41.7
To provide the greatest level of safety for the general patient population, I recommend that an H2 blocker is safest for treatment of gastritis.	100.0
To provide the greatest level of safety for the general patient population, I recommend waiting until GI symptoms arise before treating a patient.	58.3
Treatment for Vomiting	
For managing post-infusion vomiting, I provide an anti-emetic starting at infusion prophylactically	25.0
For managing post-infusion vomiting, I provide an anti-emetic to be used as indicated by symptoms	66.7
My greatest concern about patient emesis in the event that the anti-emetic is ineffective is potential dehydration.	90.9
My greatest concern about patient emesis in the event that the anti-emetic is ineffective is the inability to tolerate oral steroids.	100.0
Patient Monitoring	

Patient should be monitored for 6-8 hours post infusion	8.3
Patient should be monitored for 4-6 hours post infusion	25.0
Patient should be monitored for 3-4 hours post infusion	33.3
Patient should be monitored for 2-3 hours post infusion	33.3
Patient should be monitored for 1-2 hours post infusion	16.7
Less than an hour of monitoring is needed following infusion	16.7
To provide the greatest level of safety for the general patient population, I recommend that the patient should be monitored for 2-4 hours post infusion.	75.0
I give patients a phone number where they can reach a team member directly with instructions to call if they have concerns or experience side effects	58.3
I give patients the phone number for a 24/7 call line where they can report concerns and get help if they experience side effects	83.3
I give my patients the clinic after-hours service number where they can connect with a physician on-call to report concerns and get help if they experience side effects	66.7
A direct line of communication between the patient and gene therapy team should be available for updates on the patient	25.0
An outside team can be utilized to provide on-call coverage for triaging the patient; the gene therapy team can be contacted if warranted	0.0
Acute Liver Injury (ALI)	
After gene transfer therapy, acute liver injury is suspected. Please rate your agreement with the following statements describing recommendations for patient care:	
Monitoring	
I request a telehealth visit or phone call with the parent/caregiver	66.7
I ask that the patient is seen for a physical exam	25.0
The patient should be admitted to the hospital	0.0
Laboratory Studies	
I continue to follow the protocol without deviation for another week	25.0
I would repeat baseline labs sooner than the protocol specifies (within 1 week)	75.0
Additional Testing	
The patient should have a liver ultrasound	0.0
Medications and Treatments	
I do not change the level of steroids yet	91.7
I increase the oral steroid dose to 2 mg/kg/day with a max of 120 mg/kg/day	0.0
Consults	
A consult with a specialist is needed	16.7

After gene transfer therapy with delandistrogene moxeparvovec, acute liver injury is diagnosed. Please rate your agreement with the following statements describing recommendations for patient care:	
Monitoring	
I request a telehealth visit or phone call with the parent/caregiver	33.3
I ask that the patient is seen for a physical exam	83.3
The patient should be admitted to the hospital	16.7
Laboratory Studies	
I would repeat labs immediately	50.0
I would repeat labs within a week	50.0
I would like additional commercially available tests including:	
Direct bilirubin	91.7
Viral testing (hepatitis panel, HIV, EBV, CMV)	33.3
Additional Testing	
The patient should have a liver ultrasound	25.0
Medications and Treatments	
I do not change the level of steroids yet	8.3
I increase the oral steroid dose to 2 mg/kg/day with a max of 120 mg/kg/day	83.3
I recommend the patient begin a 3-day course of IV methylprednisolone	33.3
Consult	
A consult with a specialist is needed	33.3
To provide the greatest level of safety for the general patient population when ALI is diagnosed after gene therapy, if labs that monitor liver enzymes continue to trend in the wrong direction, I recommend repeating lab collection within 1 week, sooner than the next timepoint.	100.0
To provide the greatest level of safety for the general patient population, if labs that monitor liver enzymes continue to indicate ALI (trend in the wrong direction), I request the following additional testing:	
The patient should have viral testing (hepatitis panel, HIV, EBV, CMV)	25.0
The patient should not have viral testing (hepatitis panel, HIV, EBV, CMV)	75.0
After gene transfer therapy, acute liver injury is diagnosed and not responding to initial interventions. Please rate your agreement with the following recommendations for patient care.	
Laboratory Studies	
I would like additional commercially available tests of liver function to include:	
Direct bilirubin	91.7

Thyroid Stimulating Hormone (TSH)	33.3
Triiodothyronine (T3) and thyroxine (T4)	33.3
Viral testing (hepatitis panel, HIV, EBV, CMV)	66.7
Additional Testing	
The patient should have a liver ultrasound	83.3
Medications and Treatments	
I recommend the patient begin a 3-day course of IV methylprednisolone	91.7
Consults	
A consult with a specialist is needed	83.3
To provide the greatest level of safety for the general patient population after delandistrogene moxeparvovec administration, I recommend the following testing:	
Thyroid Stimulation Hormone (TSH)	0.0
Triiodothyronine (T3) and thyroxine (T4)	0.0
Myocarditis	
After gene transfer therapy with delandistrogene moxeparvovec, elevated troponin is suspected. Please rate your agreement with the following statements describing recommendations for patient care, noting that the patient is **asymptomatic**:	
Monitoring	
I request a telehealth visit or phone call with the parent/caregiver	50.0
I ask that the patient is seen for a physical exam	50.0
The patient should be admitted to the hospital	0.0
Laboratory Studies	
I continue to follow the protocol without deviation for another week	25.0
I would repeat baseline labs sooner than the protocol specifies (within 1 week)	75.0
Request an additional test for complement (C3, C4, CH50)	33.3
Additional Testing	
The patient should have an Echo/EKG	58.3
Medications and Treatment	
I do not change the level of steroids, yet	66.7
I increase the oral steroid dose to 2 mg/kg/day to a max of 120 mg/kg/day	0.0
Consults	
A consult with a specialist is needed	25.0
I recommend monitoring the patient with elevated troponin that is <2.5x ULN or if the baseline value of the patient is abnormal, then the elevated troponin is <2.5x baseline:	
I request a telehealth visit or phone call with the parent/caregiver	8.3
I ask that the patient is seen for a physical exam	0.0

I request a telehealth visit or phone call with the parent/caregiver AND ask that the patient is seen for a physical exam	0.0
I request a telehealth visit or phone call with the parent/caregiver and MAY ask to see the patient for a physical exam depending on the conversation	83.3
To provide the greatest level of safety for the general patient population after delandistrogene moxeparvovec administration, I do not request an additional test for complement (C3, C4, CH50) for the patient with initial troponin elevation.	100.0
After gene transfer therapy with delandistrogene moxeparvovec, there are cardiac concerns because troponin I is elevated. Please rate your agreement with the following statements describing recommendations for patient care, noting that the patient is **symptomatic**:	
I request a telehealth visit, or phone call with the parent/caregiver	33.3
I ask that the patient is seen for a physical exam	75.0
The patient should be admitted to the hospital	75.0
Laboratory Studies	
I continue to follow the protocol without deviation for another week	0.0
I would repeat baseline labs sooner than the protocol specifies (within 1 week)	91.7
I would like additional commercially available tests for elevated troponin to include:	
Complement (C3, C4, CH50)	91.7
CKMB	75.0
CK	83.3
CRP, C-reactive protein	75.0
Urinalysis	66.7
Cystatin C	91.7
Additional Testing	
Echo/EKG	91.7
cMRI	50.0
Medications and Treatments	
I do not change the level of steroids	0.0
I increase the oral steroid dose to 2mg/kg/day to a max of 120mg/kg/day	25.0
I recommend the patient begin a 3-day course of IV methylprednisolone	75.0
Consider IVIG	25.0
Consider immune-modulating pharmacotherapy	8.3
Consults	
A consult with a specialist is needed	91.7

To provide the greatest level of safety for the general patient population after delandistrogene moxeparvovec administration, I recommend the following imaging for patients with elevated troponin:	
The patient should have a cMRI	91.7
The patient should not have a cMRI	8.3
For the patient who has elevated troponin and symptoms, if elevated troponin persists after initial treatment with increased steroids, we recommend considering escalating treatment by (multiple selections allowed):	
Adding IVIG	100.0
Adding non-steroidal immunosuppressant pharmacotherapy	66.7
High dose steroids	0.0
After gene transfer therapy with delandistrogene moxeparvovec, myocarditis is diagnosed and not responding to initial interventions. Please rate your agreement with the following statements describing recommendations for patient care, noting that the patient is **asymptomatic**.	
Monitoring	
I ask that the patient is seen for a physical exam	58.3
The patient should be admitted to the hospital	66.7
I would like additional commercially available tests of liver function to include:	
Complement (C3, C4, CH50)	58.3
CRP, C-reactive protein	66.7
CBC with differential (includes platelets, RBC, WBC, Hg, Hct, MCV)	91.7
Cystatin C	58.3
Urinalysis	58.3
Additional Testing	
Echo/EKG	83.3
cMRI	50.0
Medications and Treatments	
I do not change the level of steroids yet	8.3
I increase the oral steroid dose to 2mg/kg/day with a max of 120mg/kg/day	41.7
I recommend the patient begin a 3-day course of IV methylprednisolone	58.3
I recommend immune-modulating pharmacotherapy	33.3
I recommend treating the patient with IVIG	41.7
Consults	
A consult with a specialist is needed	75.0
To provide the greatest level of safety for the general patient population after delandistrogene moxeparvovec administration, I request the following additional testing for patients with myocarditis:	

The patient should have a cMRI	91.7
The patient should not have a cMRI	8.3
To provide the greatest level of safety for the general patient population after delandistrogene moxeparvovec administration, after initial treatment with steroids, I recommend considering the following medications/treatments for patients with myocarditis:	
I recommend IVIG	100.0
I recommend immune-modulating pharmacotherapy	33.3
Immune-Mediated Myositis (IMM)	
A healthcare provider has administered delandistrogene moxeparvovec to a patient and is following the prescribing information to monitor patient health following infusion. The parent/caregiver reports that the patient is exhibiting physical signs of IMM (muscle pain, muscle tenderness, muscle weakness) that are progressive over days. Please rate your agreement with the following approaches for monitoring and treating a potential case of IMM in response to this initial report of clinical signs:	
Monitoring	
I request a telehealth visit or phone call with the parent/caregiver	25.0
I ask that the patient is seen for a physical exam	66.7
The patient should be admitted to the hospital	66.7
Laboratory Studies	
I continue to follow the protocol without deviation for another week	0.0
I would repeat baseline labs sooner than the protocol specifies (within 1 week)	91.7
I ask for additional commercially available tests to include:	
Myositis diagnostic panel (Jo-1, PL-7,PL-12,EJ Ab, OJ Ab, SRP Ab, Mi-2 Alpa Ab, Mi-2 Beta Ab, MDA5, Ab, TIF1 Gamma Ab, NXP-2 Ab)	41.7
ALP, Alkaline phosphatase	41.7
Cystatin C	50.0
D-dimer test	33.3
Serum IgG	25.0
Thyroid Stimulating Hormone (TSH)	33.3
Triiodothyronine (T3) and thyroxine (T4)	33.3
ANA	58.3
Complement (C3, C4, CH50)	58.3
CPK, Creatine phosphokinase	91.7
CRP, C-reactive protein	75.0
Aldolase	58.3
ESR, Erythrocyte sedimentation rate	66.7
Myoglobin	58.3
Urinalysis and urine output	83.3

To provide the greatest level of safety for the general patient population after delandistrogene moxeparvovec administration, I recommend the following tests to evaluate, diagnose, or guide the treatment of IMM:	
Myositis diagnostic panel	16.7
ALP, Alkaline phosphatase	25.0
Cystatin C	100.0
D-dimer test	8.3
Serum IgG	33.3
TSH, Thyroid stimulating hormone	16.7
Triiodothyronine (T3) and thyroxine (T4)	8.3
I ask for additional tests and diagnostic studies such as:	
The patient should have an echo/EKG	50.0
The patient should have a liver ultrasound	16.7
MRI (skeletal/muscle)	33.3
The patient should have an EMG/nerve conduction study	41.7
The patient should have a swallow study	66.7
The patient should have a neuromuscular strength assessment	91.7
I would collect a muscle biopsy	25.0
I would collect a nerve biopsy	0.0
To provide the greatest level of safety for the general patient population after delandistrogene moxeparvovec administration, I recommend the following tests to evaluate, diagnose, or guide the treatment of IMM:	
Echocardiogram	100.0
Electrocardiogram	83.3
MRI (skeletal/muscle)	8.3
EMG/nerve conduction study	25.0
Collect muscle biopsy	8.3
Medications and Treatments	
I do not change the level of steroids	0.0
I increase the oral steroid dose to 2mg/kg/day to a max of 120mg/kg/day	58.3
I recommend the patient begin a 3-day course of IV methylprednisolone	58.3
Patient should receive plasmapheresis	25.0
Patient should be placed on IVIG	25.0
Consider other immune-modulating pharmacotherapy	33.3
Consults	
A consult with a specialist is needed	75.0
I recommend the following approach to treat suspected IMM: Start with increasing steroids and if that doesn't work, consider adding the following:	
Plasmapheresis	100.0

IVIG	100.0
Targeted immunosuppressive therapy	100.0
To provide the greatest level of safety for the general patient population after delandistrogene moxeparvovec administration, I recommend the following medication strategy to treat confirmed IMM:	
First, increase steroid therapy. If the response is inadequate, I recommend escalating treatment by considering plasmapheresis, IVIG, and/or immunosuppressant therapy until response is achieved	100.0
First, increase steroid therapy. If the response is inadequate, I recommend escalating treatment by continuing to increase steroid dose until response is achieved	0.0
First increase steroids and then add or transition to targeted immunosuppressant therapy	0.0

*Italicized statements are those that were voted upon during the in-person meeting.

Supplement 3: Clinical Trial Experience With Select Treatment-Related Adverse Events

1. Clinical trial case of vomiting

On the day of the infusion of delandistrogene moxeparvovec, a patient experienced non-serious grade 3 vomiting approximately seven hours after the infusion in the evening. He had nausea and vomiting three times overnight and subsequently the next morning. He was given ondansetron (Zofran) in the evening after vomiting started, and in the morning, the subject's cheeks were erythematous (an ecchymosis or petechiae was noted). He was not able to keep oral prednisolone down. On Day 2 post-infusion, his examination was benign, and his abdomen was soft and nondistended with normal bowel sounds. Grade 2 nausea along with decreased appetite was noted on Day 3, but no vomiting was reported. On Day 4, although no nausea or vomiting was reported, the patient began having diarrhea in the evening. On Day 5, the subject took ondansetron and vomited twice. He was taken to the emergency room and admitted to the hospital in the evening due to persistent vomiting, his unresponsiveness to ondansetron, his inability to keep pulse steroids down, and the necessity of IV fluids to avoid dehydration. On admission, he complained of abdominal pain, and kidney, ureter, and bladder imaging showed some dilated bowel loops (mild). Treatment medications that were given included methylprednisolone 1.0 mg/kg. The patient vomited twice more after admission at midnight and again the next day and had one episode of diarrhea. No fever, eye discharge, rhinorrhea, cough, or chest pain was reported. He was given ondansetron and diphenhydramine (Benadryl) for vomiting, IV methylprednisolone (in place of oral administration), and IV fluids to avoid dehydration. Severe vomiting recovered on Day 6 and nausea on Day 19. By discharge on Day 7,

the subject had made steady progress to his home, was given a soft solid with thin liquid diet and was able to keep down his home oral steroids (prednisolone and deflazacort). He was discharged with ondansetron, famotidine (Pepcid), and vitamin D in addition to his home steroids and allergy medications.

2. Clinical trial case of acute liver injury

In this case of acute liver injury observed during the clinical trial program, the patient's medical history included allergy to tree nuts, atopic dermatitis, asthma, and focal seizures (the first 2 episodes occurred on Study Day -1). The patient's mother reported he had abdominal pain and nausea following the infusion, with daily vomiting beginning first thing in the morning. On Day 41, the patient experienced increased vomiting. The following day, he had a focal seizure and was brought to the emergency room. A physical examination revealed mild jaundice (as well as under the tongue), no rash, scleral icterus, breath sounds that were clear to auscultation, and a soft and nontender abdomen, and the liver was felt below the costal margin. No unusual bleeding or bruising was noted. Initial laboratory results revealed an ALT of 2203 U/L (9.1× baseline), an AST of 1569 U/L (7.1× baseline), a GGT of 151 U/L (2.5× ULN), and a total bilirubin of 5.3 mg/dL (5.3× ULN). The patient was treated with phenobarbital for the seizure and was hospitalized for acute cholestatic hepatitis. As reported, "these were thought to be secondary to T cell activation in response to the vector and therefore the recommendation was to treat with intravenous steroids. The subject was not considered to be in liver failure due to the normal INR and no evidence of encephalopathy." On Day 43, an abdominal ultrasound revealed a prominent but not enlarged lymph node in the porta hepatis with periportal edema, mildly elevated hepatic

artery velocity, and gallbladder wall thickening/edema. The findings were noted to be non-specific but could be seen in the setting of liver infection. On Day 45, the patient was discharged with additional medications including daily prednisone, ursodiol, and omeprazole, at which time he was medically stable. His laboratory testing showed an ALT of 1824 U/L, an AST of 896 U/L, a total bilirubin of 4.4 mg/dL, and a GGT of 133 U/L. On Day 54, the patient was considered to have recovered from vomiting, decreased appetite, and jaundice. On this date, the patient had a pediatric hepatology consultation, and his physical exam revealed Grade 2+ erythematous macular rash on his palms and soles with no oral lesions and no jaundice. The physician noted that the subject was likely developing hand, foot, and mouth disease and provided treatment advice. All other work-up for other etiologies was negative except for parvovirus IgM. Laboratory studies revealed improving liver enzymes and bilirubin. The physician reported that there were features suggestive of parvovirus-associated hepatitis and that the patient's immunosuppressed status made it likely; however, it was difficult to completely rule out drug-induced hepatitis. His treatment included increased steroids administered both orally and intravenously. He recovered on Day 85.

3. Clinical trial case of myocarditis

In this case of myocarditis, an 11-year-old boy was initially admitted two days post-infusion for vomiting. A severe elevation in troponin I was noted incidentally Day 3 post-infusion when he was intended to be discharged from this hospitalization. No cardiac symptoms or signs accompanied this laboratory finding, and the initial echocardiogram was unchanged from baseline. His global function was preserved with normal biventricular size and function on

echocardiogram and cMRI. According to the cardiologist, cMRI findings were consistent with myocarditis superimposed on DMD cardiomyopathy. At around one month post-event, cMRI showed normal function and partial resolution of myocarditis changes. Echocardiogram at four months post-event showed normal systolic function. The patient was on lisinopril at baseline and then started spironolactone (Aldactone) Day 10 post-infusion and carvedilol Day 93 for cardiac remodeling. He recovered with sequelae following a modification in cardiac-modifying therapy.

Based on clinical trial experience, it is recommended that troponin I be monitored before infusion, as well as weekly for the first month, with continued monitoring if clinically indicated. The clinical relevance of elevated troponin in these patients, however, is unknown.

4. Clinical trial case of immune-mediated myositis

In the clinical trial program, a life-threatening case of IMM with symptoms of severe muscle weakness, including dysphagia, dyspnea, and hypophonia, was observed approximately one month after infusion of delandistrogene moxeparvovec in a patient with a deletion mutation involving exons 3-43 in the *DMD* gene. This immune reaction was believed to be caused by a T cell-based immune response due to a lack of self-tolerance to a specific region (hinge 1) encoded by the transgene corresponding to exons 1-17 of the *DMD* gene and the absence of native dystrophin corresponding to the transgene protein. This 9-year-old ambulant male complained of bilateral extremity and central weakness with trouble swallowing Day 31 post-infusion. On Day 33 post-infusion, he was seen at the local emergency department for evaluation and noted to be slightly hypophonic but otherwise well and was sent back home. He was prompted to be seen

sooner than his routine follow-up appointment at a telehealth visit on Day 34 and presented with difficulty swallowing, nasal speech with difficulty articulating “g” sounds, and difficulty in getting up from the couch and lifting his arms up past 45 degrees, all which he was able to do the previous week. After consulting with the sponsor, it was determined that he be sent to the emergency department for urgent evaluation and management. On examination, it was noted he had significant facial weakness, oropharyngeal swelling, hypophonia, and tachypnea on room air with an oxygen saturation of 96%. He was unable to walk without assistance, and his strength was not antigravity at the shoulder or the hips. MRI revealed normal neuroaxis, abnormal muscle noted to be edematous throughout, and oropharyngeal swelling. A swallow study showed severe oropharyngeal dysphagia characterized by oral and pharyngeal weakness and poor endurance. His weakness acutely progressed, and he became non-ambulant. He was supported on BiPAP and with a nasogastric tube. A muscle biopsy revealed suggestion of T cell-mediated rejection against the transgenic dystrophin protein, and he was treated with six rounds of plasmapheresis and started on tacrolimus. His strength slowly improved, and he started walking independently on Day 67 post-infusion. He remains on tacrolimus and has recovered with sequelae.

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