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U.S. FOOD & DRUG ADMINISTRATION

Cellular, Tissue, and Gene Therapies Advisory Committee

BLA 125842
Deramiocel (CAP-1002)

Proposed Indication: Treatment of Cardiomyopathy in Duchenne Muscular Dystrophy (DMD)

Applicant: Capricor, Inc.

Center for Biologics Evaluation and Research | FDA

July 29, 2026

Clinical Overview

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Deramiocel (CAP-1002)

- Allogeneic cardiosphere-derived cells derived from cadaver donor hearts
- Proposed mechanism of action: anti-fibrotic, anti-inflammatory, immunomodulatory, and pro-angiogenic activities mediated through secretion of exosomes and growth factors
- Dosage: 150 million cells every 3 months, administered by IV infusion

Duchenne Muscular Dystrophy (DMD)

- Functional deficiency of dystrophin protein in skeletal and cardiac muscles
- Progressive muscle damage leading to weakness
  - Prognostic factors have been identified but further research is needed
- Symptom onset in early childhood; loss of ambulation in adolescence; progresses to respiratory failure and cardiomyopathy
- Cardiac complications are the leading cause of death

DMD Skeletal Muscle Weakness

- Characterized by a predictable, stage-dependent progression of skeletal muscle weakness
- Ambulatory:
  - Weakness first affects the hip and thigh muscles, leading to delayed motor milestones
  - Difficulty running or climbing stairs, frequent falls, and compensatory maneuvers
- Non-ambulatory:
  - Upper limb weakness becomes more prominent and functionally limiting
  - A proximal to distal pattern of involvement, where shoulder and elbow function decline before wrist and hand function
- Trunk, respiratory, and cardiac muscle weakness lead to reduced independence, postural instability, scoliosis, and eventual respiratory and cardiac failure

DMD Skeletal Muscle Function Assessment: Performance of the Upper Limb (PUL)

- Established DMD-specific clinical outcome measure
- Clinician-reported outcome
- Evaluates upper limb functional ability at shoulder, elbow, and wrist/fingers
  - Entry Item
  - Total score ranges from 0 to 42 points; higher scores indicate better function
  - Minimum 1-point change from baseline reflects clinically meaningful change in function (worsening or improvement)

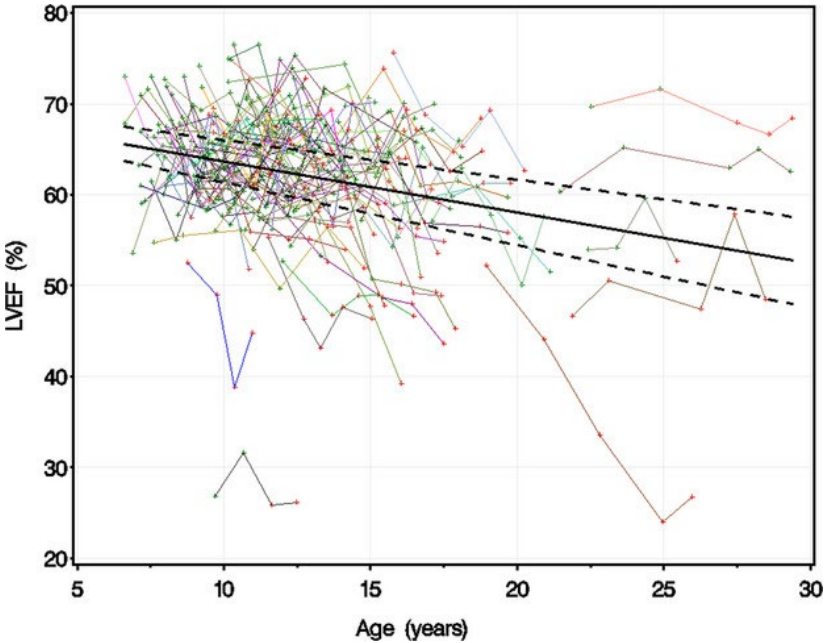
Cardiac Imaging in DMD

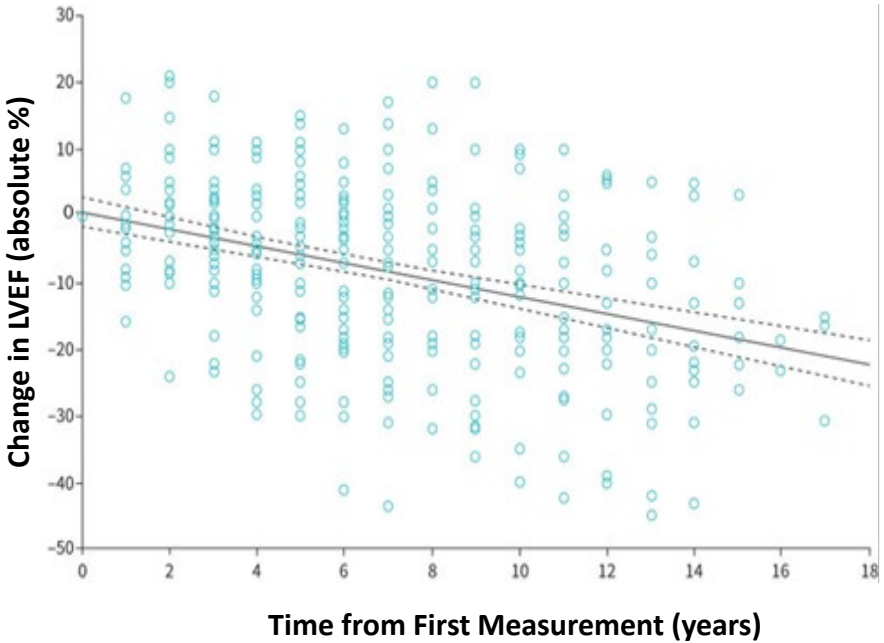
- Cardiac imaging is used clinically to track the progression of cardiomyopathy
- Left ventricular ejection fraction (LVEF): measure of systolic function
- LV end diastolic volume (LVEDV): measure of dilation
- LV end systolic volume (LVESV): measure of dilation
- Late gadolinium enhancement (LGE): measure of myocardial fibrosis (scarring)

Cardiac Imaging in DMD: LVEF

- Imaging marker of systolic function
  - Calculated from LV volumes: (LVEDV-LVESV)/LVEDV
  - Hemodynamic measurement influenced by heart rate, hydration, medications, illness, and other factors
- LVEF declines slowly starting in adolescence in DMD (average 15 years)
  - Mean 1.6% decline/year; adjusted for age, corticosteroid use, ACEi use, b-blocker use (James 2020)
  - LVEF rate of decline is highly variable and influenced by age, ambulatory status, positive pressure ventilation, current/past corticosteroids, duration of corticosteroid therapy, cardiac medications
- There is variability in imaging measurements
  - Repeating the same test with different MRI readers or on different days can lead to different measurement results
  - LVEF may vary by 2-3 percentage points (Danilouchkine 2005, Moody 2015, Backhaus 2021)

Variable LVEF Decline in DMD





Sources: Tandon 2015; Modified from Lechner 2023

Outcome Measures in DMD Cardiomyopathy

- Clinical outcomes (e.g., cardiac symptoms, exercise capacity) not feasible given muscle weakness/physical activity limitations
- Progression of DMD cardiomyopathy is gradual, detecting treatment effects on mortality would require prolonged follow-up
- Imaging biomarkers assessing cardiac function and structure have prognostic value

BLA 125842 Key Regulatory History

Date	Milestone and Background Information
December 31, 2024	• Original BLA submission seeking traditional approval of deramiocel for the treatment of cardiomyopathy in patients with DMD. • BLA was based on results from randomized, double-blind, placebo-controlled Phase 2 study **HOPE-2** in which enrollment was terminated early, and interim results of open-label extension study **HOPE-2-OLE.**
July 9, 2025	• HOPE-2 and HOPE-2-OLE did not provide evidence of effectiveness. • **Complete Response Letter** issued to Applicant.
August 13, 2025	• Type A meeting to discuss Complete Response Letter.
December 29, 2025	• BLA resubmission, which was deemed incomplete.
February 20, 2026	• **BLA resubmission seeking traditional approval of deramiocel for the treatment of cardiomyopathy in DMD.** • **BLA resubmission is based on results from one clinical study: multicenter, randomized, double-blind, placebo-controlled, two cohort, Phase 3 study (HOPE-3).**

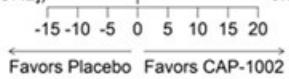
Study HOPE-2 (Original BLA Submission)

- Multicenter, randomized, double-blind, placebo-controlled Phase 2 study
- Males with DMD; mean age 14 years; skeletal muscle weakness; ambulatory and non-ambulatory
- Designed to enroll 84 patients, but enrollment terminated early at 6 months for administrative reasons.
  - 20 patients enrolled (8 deramiocel, 12 placebo)
  - 16 patients completed study (7 deramiocel, 9 placebo)
- After data unblinding, Applicant modified the statistical analysis plan and transformed efficacy data from the original scale to percentile rank, without adequate scientific justification

Study HOPE-2 Results

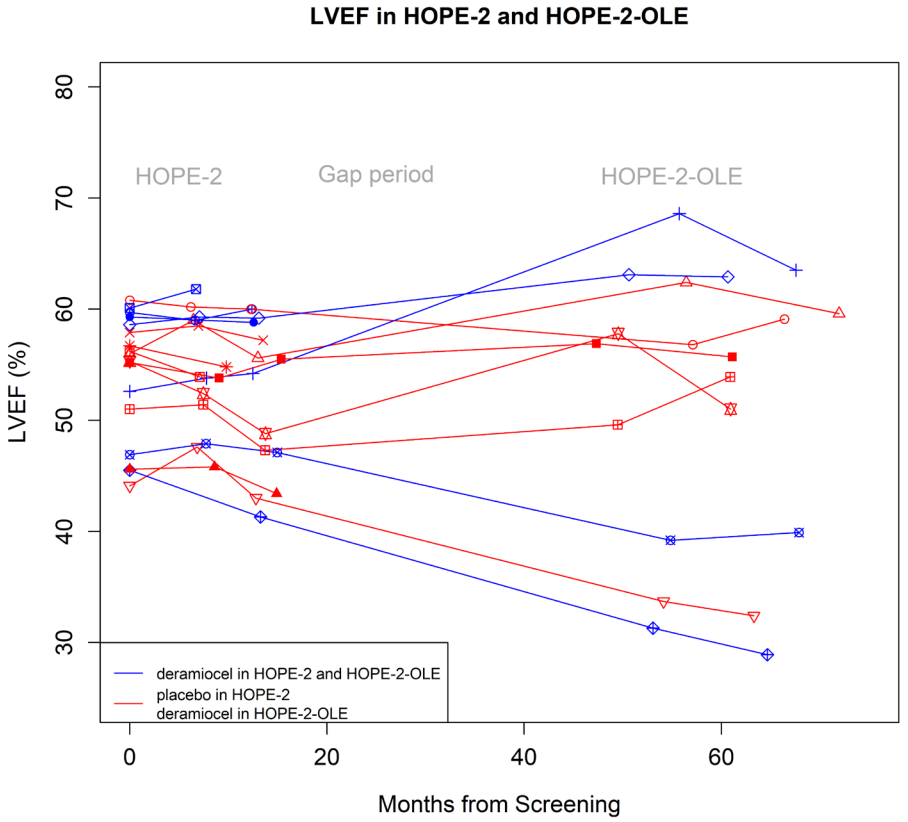
- Small study was not powered to detect treatment effect on primary efficacy endpoint (PUL 1.2 elbow domain) or cardiac imaging parameters
- Based on the analysis model prespecified before data unblinding, HOPE-2 did not show statistically significant treatment effect of deramiocel compared to placebo on the primary efficacy endpoint or the secondary efficacy endpoints
- No overall consistency in treatment effect was observed across the exploratory cardiac endpoints

Outcome	Least square mean (95% CI)	p-value
LV Ejection Fraction	3.2 (0.7 to 5.6)	0.0197
LV ES Volume	7.7 (2.3 to 13.1)	0.0105
LV ED Volume	3.0 (-1.9 to 7.8)	0.2088
LV ES Volume, Indexed	7.4 (0.7 to 14.1)	0.0353
LV ED Volume, Indexed	9.2 (-1.6 to 20.0)	0.0840
Systolic Wall Thickening Anterior LV	-0.3 (-3.3 to 2.7)	0.8321
Systolic Wall Thickening Lateral LV	2.5 (-5.0 to 10.0)	0.4752
Systolic Wall Thickening Inferior LV	2.4 (-3.4 to 8.1)	0.3622
Systolic Wall Thickening Septal LV	-0.3 (-5.5 to 4.9)	0.8895
ES Wall Thickness Average, Anterior	0.9 (-0.4 to 2.2)	0.1658
ES Wall Thickness Average, Lateral	0.6 (-0.9 to 2.2)	0.3745
ES Wall Thickness Average, Inferior	1.2 (-0.3 to 2.7)	0.1086
ES Wall Thickness Average, Septal	0.2 (-1.0 to 1.4)	0.7244
ED Wall Thickness Average, Anterior	0.7 (-0.1 to 1.6)	0.0917
ED Wall Thickness Average, Lateral	0.5 (-1.2 to 2.1)	0.5390
ED Wall Thickness Average, Inferior	0.4 (-0.7 to 1.6)	0.4020
ED Wall Thickness Average, Septal	0.1 (-1.1 to 1.3)	0.8502
Circumferential Strain, Anterior	0.1 (-2.6 to 2.8)	0.9159
Circumferential Strain, Lateral	2.5 (-4.1 to 9.0)	0.4168
Circumferential Strain, Inferior	2.8 (-0.8 to 6.4)	0.1035
Circumferential Strain, Septal	1.6 (-4.1 to 7.4)	0.4393
Global Circumferential Strain	0.0 (-1.2 to 1.2)	0.9896
LV Stroke Volume	1.8 (-0.8 to 4.3)	0.1356
LV (Myocardium) Mass	-0.8 (-9.3 to 7.7)	0.8322
LV Mass Index	-1.5 (-8.2 to 5.2)	0.5970
Regional Wall Motions (Dyssynchrony [CURE])	0.0 (-0.1 to 0.1)	0.6890



Study HOPE-2-OLE (Original BLA Submission)

- Open-label, uncontrolled extension study of Study HOPE-2, designed to assess long-term safety
- Re-treatment (after ~1 year gap) of 13 male DMD patients who had previously completed Study HOPE-2
- All patients were non-ambulatory at study entry; mean age 16 years
- External/historical cohort of patients (variably treated with SoC therapies) used for comparative analyses using propensity-score matching
- Inadequate matching led to inconclusive analyses



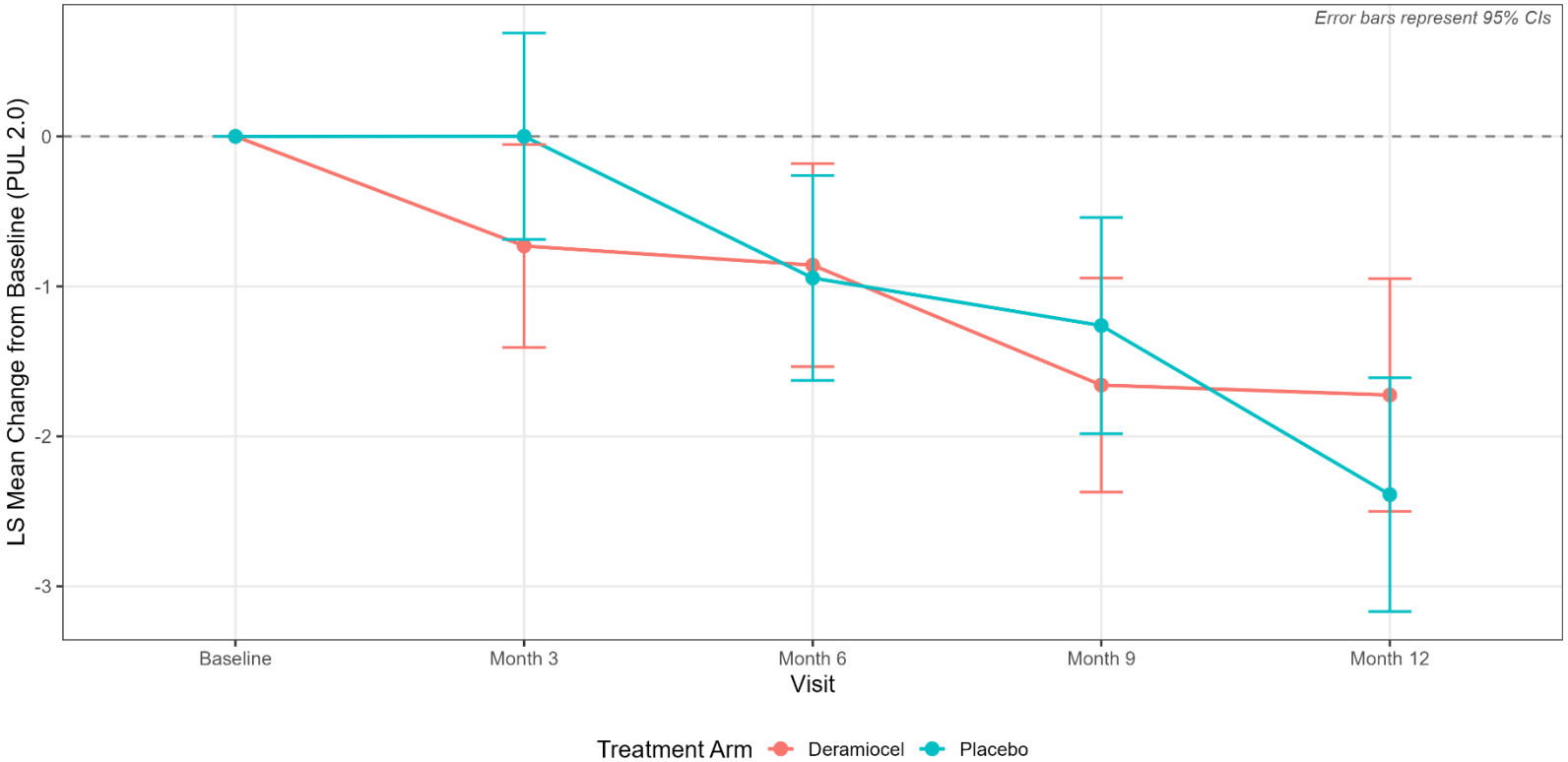
Study HOPE-3

Study Element	Description
Study design	• Randomized, double-blind, placebo-controlled, multicenter, Phase 3 study • Subsequent open-label phases: open-label extension (OLE) and long-term open-label extension (LT-OLE)
Cohorts	• 2 cohorts (based on manufacturing facilities: Los Angeles and San Diego)
Eligibility criteria	• Male subjects at least 10 years of age with genetically confirmed DMD • PUL 2.0 entry item score 2-6 and total PUL 2.0 score ≤ 40 • No eligibility requirement for a diagnosis of cardiomyopathy or reduced LVEF
Treatment	• Deramiocel or placebo (excipients) IV every 3 months for 12 months
Study size	• 106 patients randomized (54 deramiocel, 52 placebo)
Baseline characteristics	• Mean age 15 years (SD: 3.04, range: 10-22 years) • 84.9% non-ambulatory • Mean LVEF: 57.3% (SD: 7.21, range: 36.5-74.0)

Primary Efficacy Endpoint Results: PUL 2.0

Parameter	Pre-Specified SAP 1.1 (FDA Analysis) N=104	Post-Study, Modified SAP 3.0 (Applicant's Post-Hoc Analysis) N=105
Methods finalized	• Before double-blind period ended	• After double-blind period ended (and further modified in Clinical Study Report)
Primary endpoint	• Mean **change** from baseline to Month 12 in PUL 2.0 total score	• Mean **percent change** from baseline to Month 12 in PUL 2.0 total score
Mean difference	• 0.66 (p=0.24)	• 4.55% (p=0.029)

Mean Change from Baseline in PUL 2.0 (SAP 1.1)

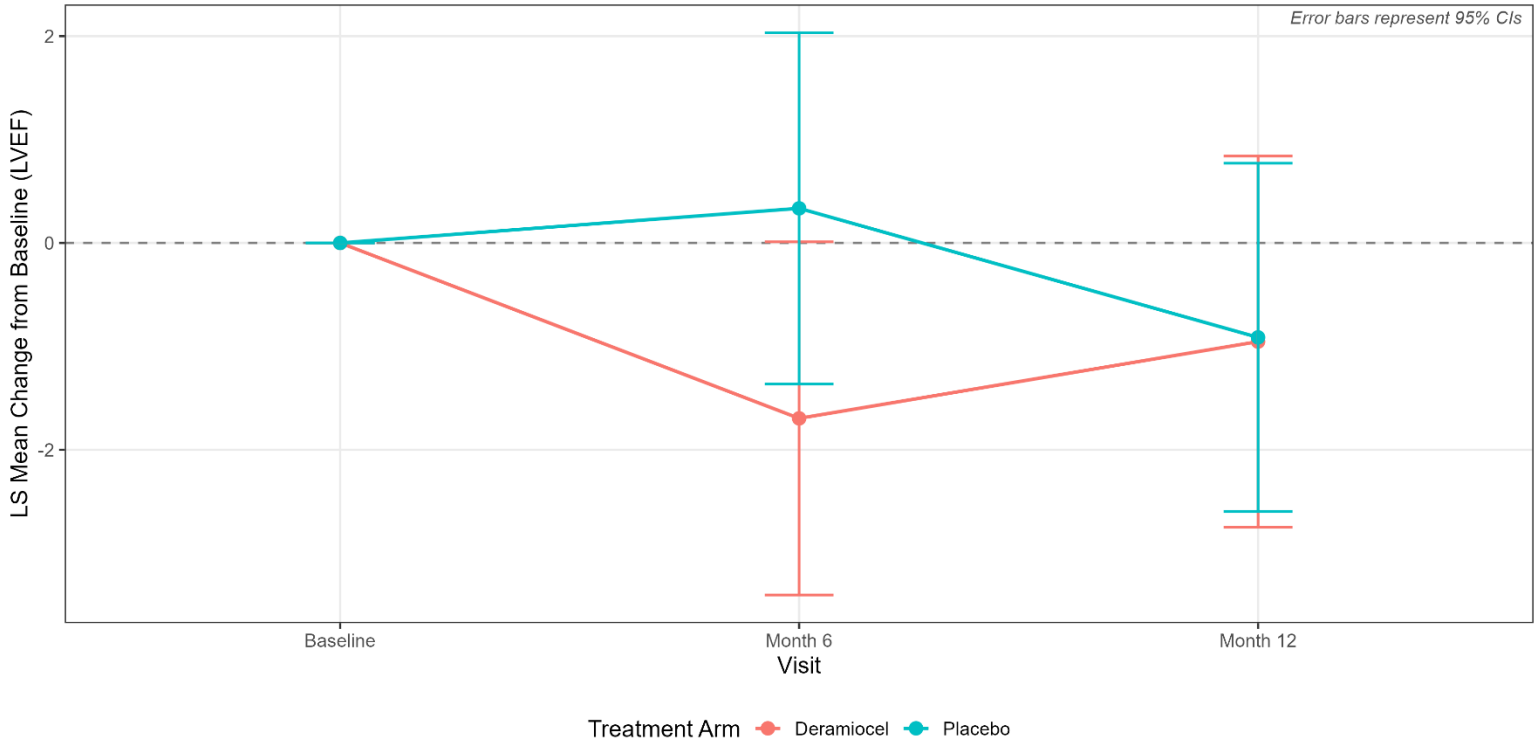


Key Secondary Efficacy Endpoint Results: Left Ventricular Ejection Fraction

Parameter	Pre-Specified SAP 1.1 (FDA Analysis) N=89	Post-Study, Modified SAP 3.0 (Applicant's Post-Hoc Analysis) N=83
Methods finalized	• Before double-blind period ended	• After double-blind period ended (and further modified in Clinical Study Report)
Key secondary endpoint	• Mean **change** from baseline to Month 12	• Mean **ranked change** from baseline to Month 12
Clinical interpretation	• Raw change from baseline is clinically interpretable • Established metric of LV function used in cardiac imaging and in clinical practice	• No units • Lacks clinical interpretation • Not used in cardiac imaging or clinical practice in any cardiac disease
Mean difference	• -0.04% (p=0.97)	• No clinical meaning of ranks (p=0.041)

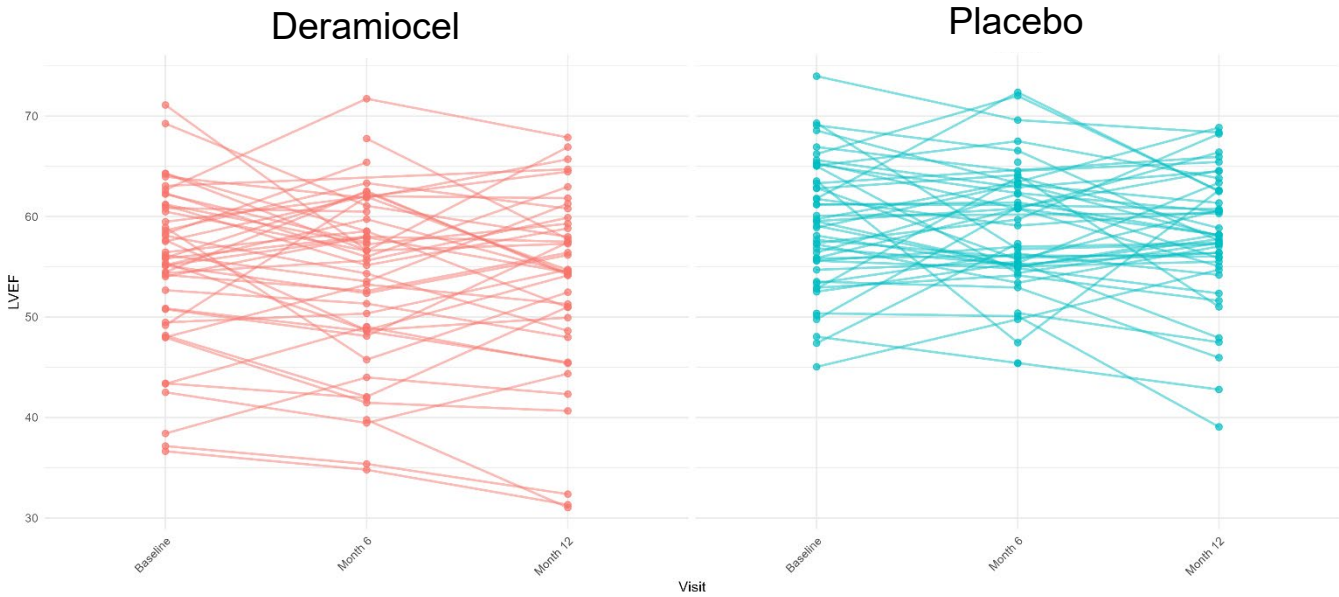
- Note: Applicant's analysis excludes 6 additional patients without Month 12 data (5 deramiocel, 1 placebo). 3 of the 5 patients in the deramiocel group had decreases in LVEF at Month 6 (5-15%), and the patient in the placebo group had a 10% increase in LVEF at Month 6.

Mean Change from baseline in LVEF (SAP v1.1)



Patient Trajectories of LVEF

- Mean LVEF at baseline was lower in the deramiocel group compared to placebo (55.3% vs. 59.3%)
- There is variability in LVEF among patients, without clear evidence of a treatment effect



LVEF and LV Volumes

Endpoint	Visit	Deramiocel (Mean, SD)	Placebo (Mean, SD)	Sample Size Treated (N=54) / Control (N=52)	
LVEF (%)	Baseline	55.3 (7.7)	59.3 (6.1)	45	46
	Month 6	54.1 (7.9)	59.1 (5.9)	43	43
	Month 12	**54.2 (8.5)**	**58.3 (6.4)**	39	44
LV end-diastolic volume index (mL/m^2)	Baseline	72.9 (18.3)	66.7 (15.7)	44	46
	Month 6	72.9 (17.3)	64.6 (15.7)	42	43
	Month 12	**74.6 (16.9)**	**64.6 (15.6)**	38	44
LV end-systolic volume index (mL/m^2)	Baseline	33.0 (13.3)	27.6 (8.9)	44	46
	Month 6	33.8 (12.3)	26.9 (9.4)	42	43
	Month 12	**34.4 (12.8)**	**27.4 (9.9)**	38	44

- The deramiocel group had a lower LVEF at baseline
- LV dilatation, as measured by LVEDVi and LVESVi, increased over time in the deramiocel group
- LVEDVi decreased over time in the placebo group, LVESVi was relatively stable

LVEF and LV Volumes (Cardiomyopathy Subgroup)

Endpoint	Visit	Deramiocel (Mean, SD)	Placebo (Mean, SD)	Sample Size Treated (N=54)/Control (N=52)	
LVEF (%)	Baseline	53.2 (7.1)	58.6 (6.3)	35	33
	Month 6	53.3 (8.6)	58.9 (6.3)	34	30
	Month 12	**53.0 (8.7)**	**57.4 (6.7)**	32	31
LV end-diastolic volume index (mL/m^2)	Baseline	76.0 (18.8)	63.5 (15.6)	34	33
	Month 6	75.3 (17.7)	63.4 (15.9)	33	30
	Month 12	**75.9 (18.0)**	**63.8 (16.6)**	31	31
LV end-systolic volume index (mL/m^2)	Baseline	35.8 (13.6)	26.8 (9.3)	34	33
	Month 6	35.5 (12.9)	26.6 (9.7)	33	30
	Month 12	**35.8 (13.5)**	**27.8 (11.0)**	31	31

- The cardiomyopathy subgroup includes patients with a medical history of cardiomyopathy or cardiac involvement on imaging
- No clear evidence of a treatment effect on LVEF or LV volumes in this subgroup

LVEF and LV Volumes (Non-Cardiomyopathy Subgroup)

Endpoint	Visit	Deramiocel (Mean, SD)	Placebo (Mean, SD)	Sample Size Treated (N=54) /Control (N=52)	
LVEF (%)	Baseline	62.9 (4.7)	61.1 (5.4)	10	13
	Month 6	56.9 (3.8)	59.6 (5.1)	9	13
	Month 12	**59.4 (5.7)**	**60.5 (5.2)**	7	13
LV end-diastolic volume index (mL/m^2)	Baseline	62.5 (12.2)	74.9 (13.3)	10	13
	Month 6	64.1 (13.5)	67.3 (15.7)	9	13
	Month 12	**68.8 (9.2)**	**66.6 (13.3)**	7	13
LV end-systolic volume index (mL/m^2)	Baseline	23.4 (6.6)	29.6 (7.9)	10	13
	Month 6	27.8 (7.6)	27.7 (8.9)	9	13
	Month 12	**28.0 (6.1)**	**26.5 (6.9)**	7	13

- This subgroup includes patients who do not meet the criteria for cardiomyopathy subgroup
- The patients who received deramiocel showed a decrease in LVEF and increased LV dilatation over time

LVEF, LV Volumes, and LGE
Cohort B Patients With Month 12 LGE Data

Endpoint	Visit	Deramiocel (Mean, SD)	Placebo (Mean, SD)	Sample Size Treated (N=54) /Control (N=52)	
LVEF (%)	Baseline	51.8 (9.6)	59.3 (6.4)	8	13
	Month 6	51.4 (10.8)	59.2 (6.0)	9	12
	Month 12	52.0 (9.5)	57.2 (6.6)	9	12
LV end-diastolic volume index (mL/m^2)	Baseline	85.1 (29.7)	62.6 (15.9)	8	13
	Month 6	78.2 (25.2)	62.2 (16.9)	9	12
	Month 12	77.8 (24.8)	62.8 (17.6)	9	12
LV end-systolic volume index (mL/m^2)	Baseline	43.1 (23.6)	25.8 (8.6)	8	13
	Month 6	39.2 (19.7)	25.8 (9.7)	9	12
	Month 12	39.0 (20.6)	27.3 (10.0)	9	12
LGE (% LV mass)	Baseline	11.8 (17.4)	2.1 (2.7)	9	13
	Month 12	10.4 (14.9)	4.8 (4.7)	9	12

- Results are challenging to interpret due to missing data for over 50% of patients

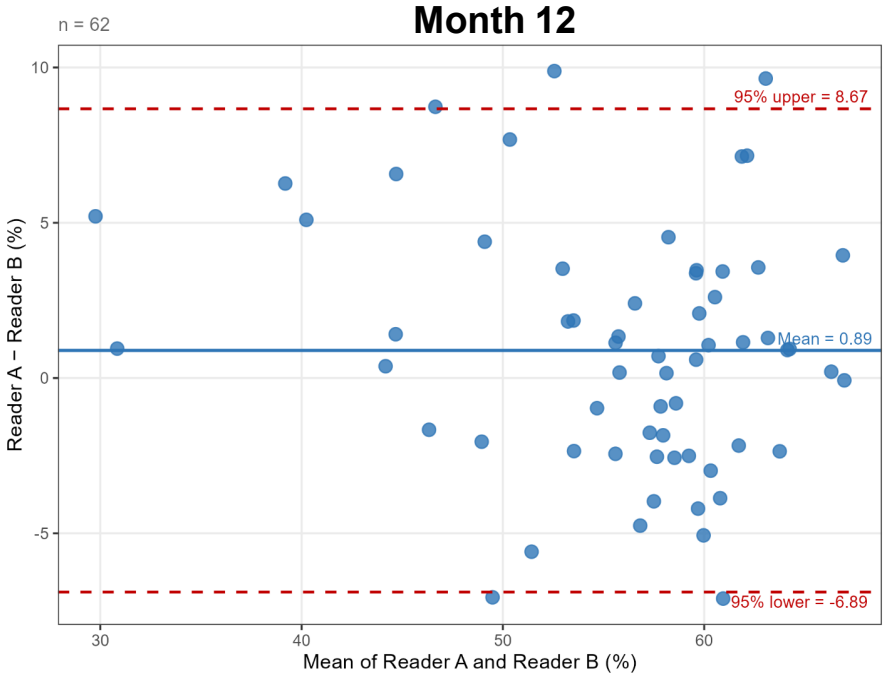
Cardiac MRI Adjudication

- Imaging Charter specified a 2+1 consensus review: each cMRI read by 2 independent reviewers, with an adjudicator reviewer for cases that meet pre-defined criteria for disagreement

- The Applicant modified the pre-specified plan, and instead used cMRI reads from only a single reviewer (Reviewer A)
  - Applicant's justification is that Reviewer B only provided reads for 62 of 83 subjects due to an issue with the imaging platform
  - Based on the Imaging Charter, the 2+1 review paradigm would still have applied to the reads where both Reviewer A and Reviewer B data were available

- Changes to cMRI adjudication process limits the reliability of the data

Cardiac MRI Inter-Rater Variability



Parameter	Reader A vs Reader B Screening	Reader A vs Reader B Month 12
LVEF (%)		
n	62	62
Mean Difference	**2.99**	**3.2**
Standard Deviation	2.57	2.48
Median	2.56	2.47
Minimum	0.02	0.07
Maximum	12.67	9.88
Coverage Probability	0.85	0.77

Source: Adapted from Imaging Variability Analysis Report, version 1.0 (02 April 2026)
Coverage probability is the proportion of cases with absolute difference ≤5%.

Study HOPE-3: Safety Overview

- Treatment-emergent adverse events related to deramiocel or administration procedure
- >5% more frequent in deramiocel group compared to placebo group

Event	Deramiocel (N=53) n (%), e	Placebo (N=52) n (%), e	Overall (N=105) n (%), e
Headache	32 (60.4), 91	2 (3.8), 2	34 (32.4), 93
Pyrexia	13 (24.5), 22	0 (0), 0	13 (12.4), 22
Cough	7 (13.2), 12	1 (1.9), 1	8 (7.6), 13
Nausea	7 (13.2), 12	2 (3.8), 2	9 (8.6), 14
Dizziness	6 (11.3), 6	0 (0), 0	6 (5.7), 6
Tachycardia	6 (11.3), 9	3 (5.8), 3	9 (8.6), 12
Throat irritation	6 (11.3), 8	0 (0), 0	6 (5.7), 8
Infusion related reaction	5 (9.4), 12	1 (1.9), 1	6 (5.7), 13
Pain	5 (9.4), 8	0 (0), 0	5 (4.8), 8
Chest pain	3 (5.7), 3	0 (0), 0	3 (2.9), 3
Malaise	3 (5.7), 5	0 (0), 0	3 (2.9), 5
Palpitations	3 (5.7), 3	0 (0), 0	3 (2.9), 3

Safety population includes patients who began an infusion of deramiocel or placebo

Study HOPE-3: Hypersensitivity Reactions

System Organ Class/ Preferred Term	Deramiocel (N=53) n (%), e	Placebo (N=52) n (%), e	Overall (N=105) n (%), e
Hypersensitivity Reactions	22 (41.5), 55	8 (15.4), 18	30 (28.6), 73
Cardiac disorders			
Tachycardia	6 (11.3), 9	3 (5.8), 3	9 (8.6), 12
General disorders and administration site conditions			
Pyrexia	13 (24.5), 22	0	13 (12.4), 22
Immune system disorders	1 (1.9), 2	1 (1.9), 1	2 (1.9), 3
Anaphylactic reaction	0	1 (1.9), 1	1 (1.0), 1
Hypersensitivity	1 (1.9), 2	0	1 (1.0), 2
Investigations	3 (5.7), 5	1 (1.9), 4	4 (3.8), 9
Heart rate increased	3 (5.7), 5	1 (1.9), 4	4 (3.8), 9
Respiratory, thoracic and mediastinal disorders	7 (13.2), 11	1 (1.9), 2	8 (7.6), 13
Throat irritation	6 (11.3), 8	0	6 (5.7), 8
Tachypnea	1 (1.9), 2	1 (1.9), 2	2 (1.9), 4
Throat tightness	1 (1.9), 1	0	1 (1.0), 1
Skin and subcutaneous tissue disorders	2 (3.8), 5	1 (1.9), 1	3 (2.9), 6
Rash	2 (3.8), 5	1 (1.9), 1	3 (2.9), 6
Vascular disorders	1 (1.9), 1	2 (3.8), 7	3 (2.9), 8
Flushing	1 (1.9), 1	2 (3.8), 7	3 (2.9), 8

Source: HOPE-3 Clinical Study Report, Table 32

Hypersensitivity Reactions Leading to Drug Discontinuation/Non-Entry Into OLE

Study	Treatment Group	Event
HOPE-OLE	Deramiocel	During infusion of second dose, patient developed lightheadedness, nausea, and flushing. Treated with IM epinephrine. On arrival to the ED, patient was hypotensive (SBP 70s) and tachycardic. Admitted to the PICU.
HOPE-2	Deramiocel	During infusion of second dose, patient developed difficulty breathing and throat tightness which did not respond to treatment with IM epinephrine, steroids, and diphenhydramine. Patient became cyanotic (MAP 66) and tachycardic with wheezing. Transferred to the ED and admitted to the PICU.
HOPE-2	Deramiocel	During infusion of third dose, patient developed dizziness. This was followed by throat tightness, wheezing, tachycardia, BP 90s/60s. Patient received IV diphenhydramine and was hospitalized for further monitoring.
HOPE-3	Placebo	During infusion of the first dose, patient developed chest tightening, itching, swollen lips, slurred speech, drooling and cough. Treated with IM epinephrine and diphenhydramine. Patient was discharged home, and experienced vomiting overnight.

Note: placebo consisted of same cell preservation solution as for deramiocel, but without cells (contains DMSO and other excipients)

Source: Adapted from ISS Table 23, Briefing Document Table 21, safety narratives

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Statistical Overview

Tingting Zhou, PhD

Division of Biostatistics
Office of Biostatistics and Pharmacovigilance
CBER | FDA

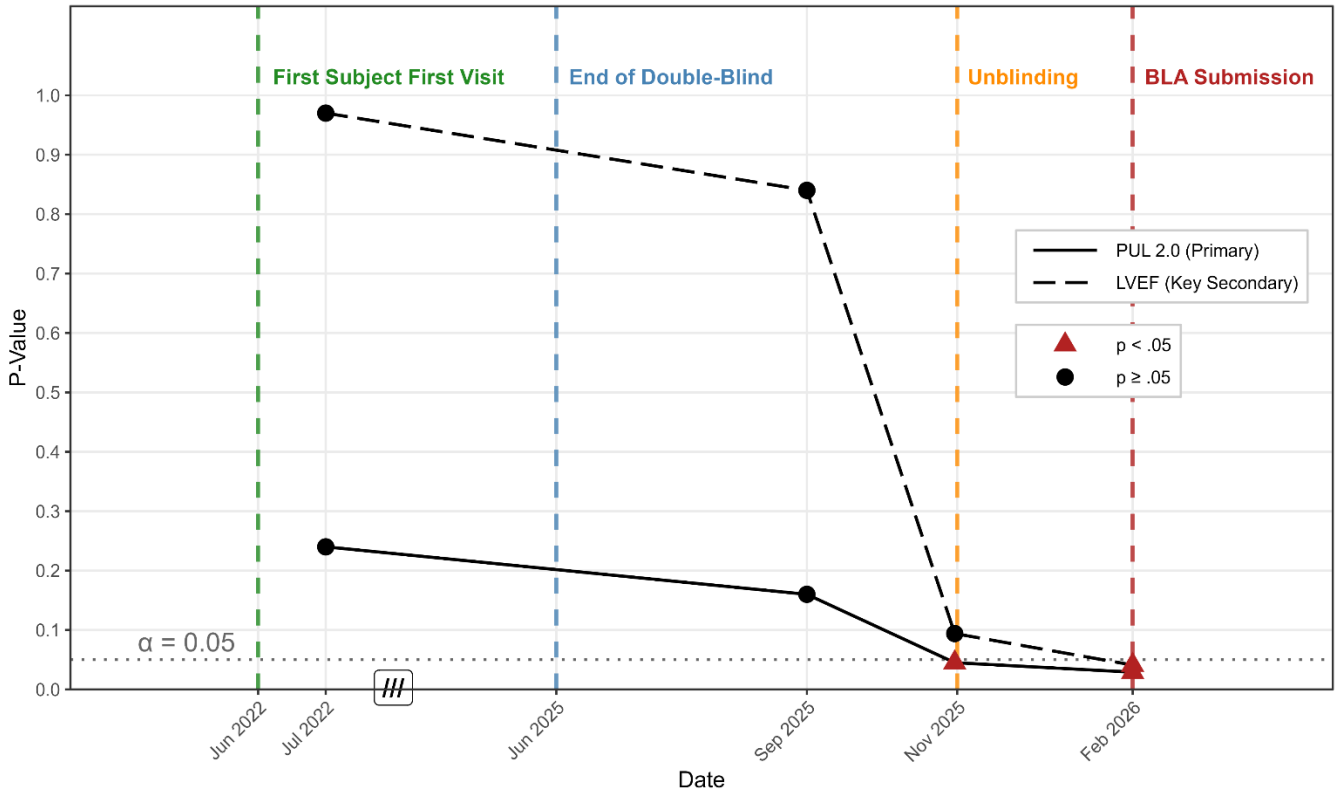
Key Statistical Concerns: Two Overarching Issues

1. Late Statistical Analysis Plan (SAP) Changes Lack Adequate Scientific Justification
   - Substantial modifications to endpoints and analysis methods were made after complete data collection, without documented protocol amendments or sound scientific rationales
   - Applicant's final analyses included further post-hoc changes beyond the final SAP that lack justification and violate the key principle of pre-specification

2. Study Conclusions Lack Robustness
   - The apparent treatment effect is highly sensitive to analytical choices and to missing data handling for two placebo subjects

Together, these concerns raise questions regarding whether there is substantial evidence of effectiveness for deramiocel.

SAP Changes Had Substantial Impact on Study Results



Study HOPE-3: Key FDA Conclusions

- Deramiocel did not show a statistically significant effect on the pre-specified primary efficacy endpoint, change from baseline to month 12 in PUL 2.0

- Deramiocel did not show a statistically significant effect on the pre-specified key secondary endpoint, change from baseline to month 12 in LVEF

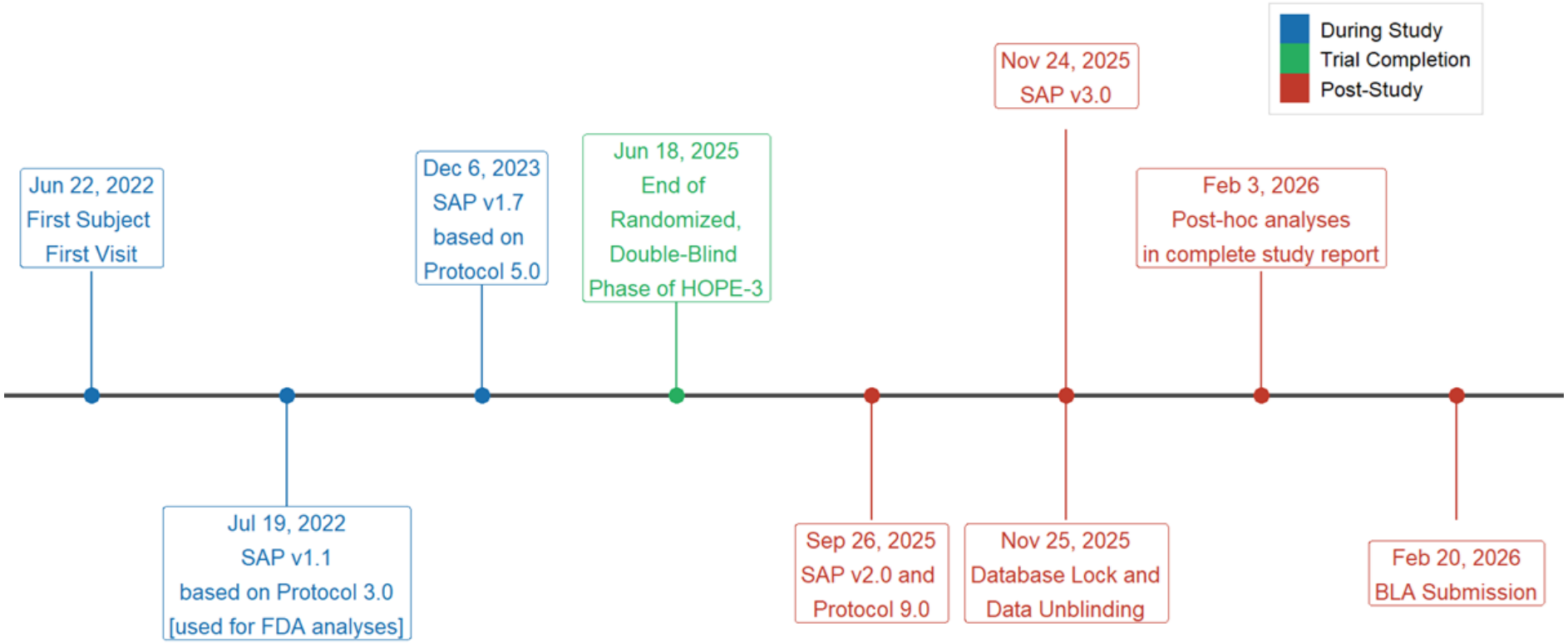
- Applicant's analyses have major limitations and show lack of robustness:
  - Unjustified approach to handling missing data (placebo subjects) fundamentally changes the results
  - Major SAP changes after study completion lack a scientific basis and limit interpretability of analyses
  - Further *post-hoc* changes beyond the final SAP version (in CSR) also lack justification and violate the key principle of pre-specification

Theme 1: Late SAP Changes Lack Scientific Justification

ICH E9: Pre-Specification Is Foundational

- Determination of endpoints and methods to analyze data must be made during trial design, so that the study is able to detect and confirm a treatment effect without increasing the chance of false positive findings
- Per ICH E9: "…all important details of [a trial's] design.. the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins."
- Any subsequent changes to statistical methods must have strong scientific justification and "should be documented in a protocol amendment" (ICH E9)
- Changes made in the final SAP and applicant's final analyses (post-hoc) were not documented in any protocol amendment

Overview of Study HOPE 3 Timeline



Potential for Partial Unblinding

- Blinding is not an all or nothing concept
  - Before full unblinding, there can be a variety of reasons for partial information leakage
- In HOPE-3, hypersensitivity reactions were markedly asymmetric: 41.5% (deramiocel) vs 15.4% (placebo); a distinct treatment-emergent adverse event profile for deramiocel group
- Available open-label extension treatment data could further provide opportunities to infer treatment assignment
- Post-collection changes, even under nominal blinding, introduce additional analytical flexibility that may inflate the risk of a false-positive result
- Per ICH E9: “The extent to which…the primary analysis is planned a priori will contribute to the degree of confidence in the final results and conclusions of the trial.”

Statistical Analysis Methods: Primary Efficacy and Secondary Efficacy Endpoints Under SAP 1.1

- FDA analysis based on SAP 1.1:
  - Mixed Model Repeated Measures (MMRM) with change from baseline as outcome variable
- Covariates: treatment, site, visit, treatment-by-visit interaction, baseline score, baseline score by visit interaction, and cohort*
  - Unstructured covariance structure to model within-patient errors
- All available data included, no imputation was proposed

* Because the study consisted of two cohorts randomized separately, FDA's analysis included cohort as a covariate for statistical rigor.

Applicant's *Post-Hoc* Analysis for Primary Efficacy Endpoint (PUL 2.0)

- Applicant's *post-hoc* analyses based on modified SAP v3.0:
  - MMRM with percent change from baseline as outcome variable
- Covariates: treatment, cohort, site, visit, treatment-by-visit interaction, baseline score, slow progressor indicator
  - Heterogeneous first-order autoregressive (ARH[1]) to model within-patient errors
  - Slow progressor indicator should not have been included based on specified criteria in SAP v3.0*
- Intercurrent event strategy:
  - Subjects withdrawn due to death/AE imputed with worst observed value
  - Observed data after prohibited medication use excluded

* SAP v3.0 states: If a categorical variable had fewer than 2 subjects per treatment arm, it would be omitted from the model. There was only one slow progressor in the deramiocel group

FDA's Evaluation of PUL 2.0 Endpoint Change

- Applicant's rationale: disease heterogeneity justifies switching to percent change from change
  - FDA's view: Disease heterogeneity was known at the time of trial planning. Baseline heterogeneity was addressed through randomization stratification by PUL entry item score and inclusion of baseline PUL total score as a covariate
  - The study was powered based on change from baseline, not percent change from baseline
- Applicant's rationale: blinded data showed variance assumption violation
  - FDA's view: Diagnostic checks did not show evidence of variance assumption violation. Normality is less well-supported under Applicant's final analysis model.
- Per ICH E9, the decision to transform a variable is best made during trial planning and should be influenced by the "preference for a scale that facilitates clinical interpretation"

Applicant's *Post-Hoc* Analysis for Key Secondary Efficacy Endpoint (LVEF)

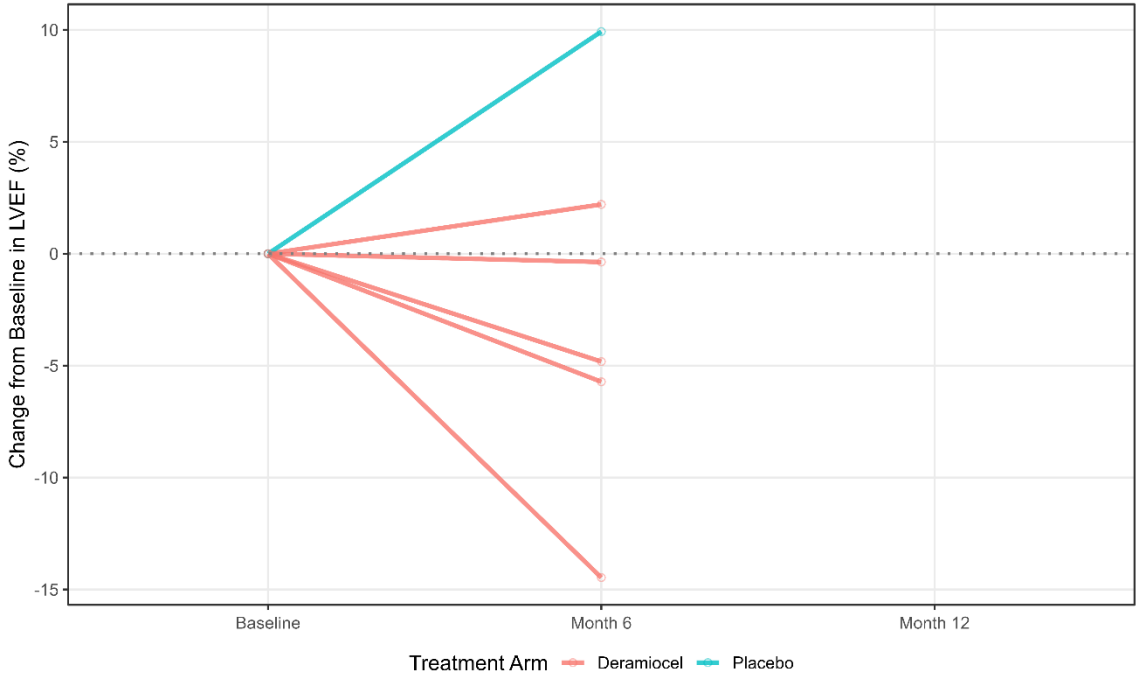
- Applicant's *post-hoc* analyses based on modified SAP v3.0:
  - Analysis of Covariance (ANCOVA) with ranked change from baseline as outcome variable
- Covariates: treatment, cohort, slow progressor indicator, indicator for screening LVEF greater than or equal to 45%, ranked baseline LVEF, age at baseline, and interaction term between ranked baseline LVEF and age at baseline
  - The interaction term was not specified in SAP v3.0
- Intercurrent event strategy:
  - Subjects withdrawn due to death/AE imputed with worst observed value
  - Observed data after prohibited medication use excluded

FDA's Evaluation of LVEF Endpoint Change (1)

- Applicant's rationale: Specific LVEF modeling need identified one day before formal unblinding, outliers and normality violation, informed by HOPE-2 study (N=17, completed March 2020)
  - FDA's view: These facts were known at the time of the HOPE-3 design, not one day before formal unblinding
  - Important model covariates should be identified during trial planning
  - No evidence of violation of normality assumption
- Per ICH E9, the decision to transform a variable is best made during trial planning and should be influenced by the "preference for a scale that facilitates clinical interpretation"

FDA's Evaluation of LVEF Endpoint Change (2)

- The Applicant's analysis excluded all Month 6 data and excluded subjects without both baseline and Month 12 data observed, meaning 23 randomized subjects (22%) were entirely excluded
  - Violates the intent-to-treat principle, potentially introducing substantial bias
  - Six subjects (5 treated and 1 placebo) with baseline and Month 6 data excluded, pictured below:



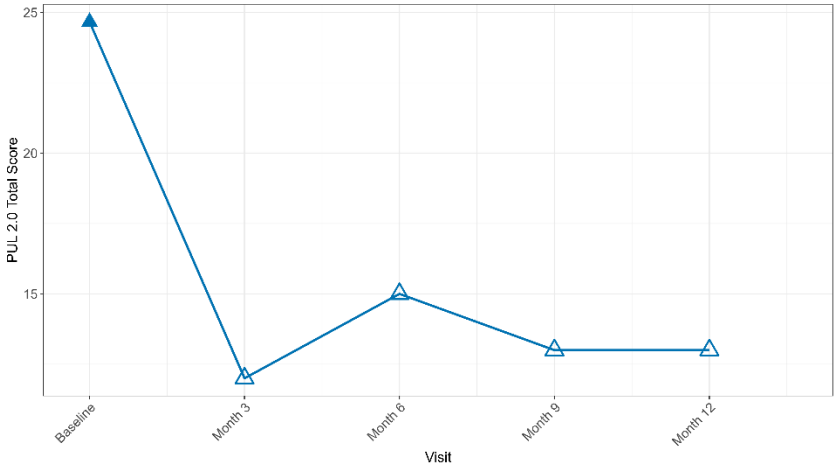
FDA's Evaluation of LVEF Endpoint Change (3)

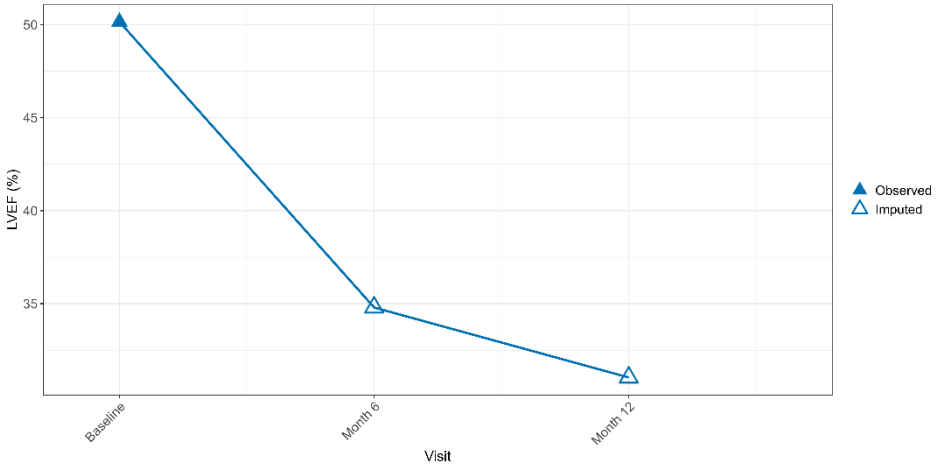
- The revised analysis adjusts for categorical LVEF ≥ 45%, instead of continuous LVEF score
  - Dichotomizing a variable loses information

- The revised analysis does not account for study design features
  - Not adjusting for randomization factors could exacerbate imbalance in an already biased sample
  - Including randomization factors in Applicant's *post-hoc* model removes statistical significance

FDA's Evaluation of the Intercurrent Event Strategy (1)

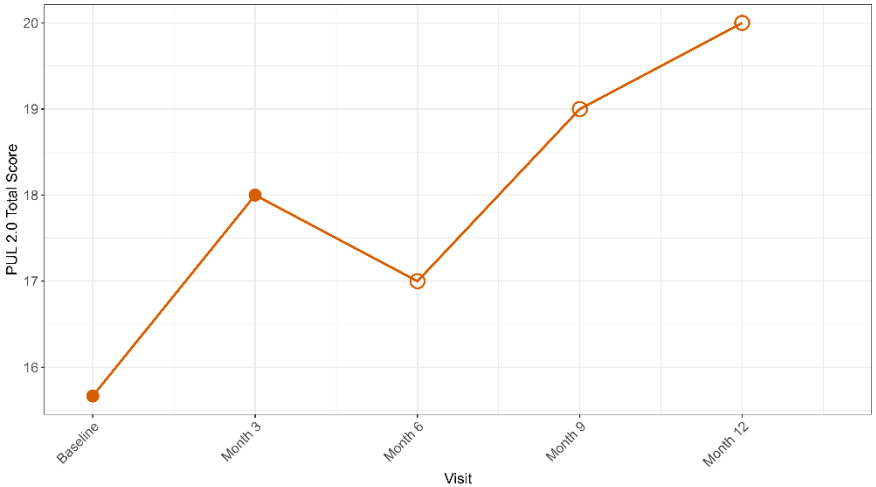
- The Applicant assigned the worst observed score to a placebo subject who discontinued due to an AE
  - A clinically plausible assumption would be that the subject would continue a placebo-like trajectory, not suddenly experience the worst observed decline
  - Two deramiocel subjects who withdrew consent had multiple AEs prior to withdrawal (intermittent palpitation and nausea, respectively) but treated as having average outcomes

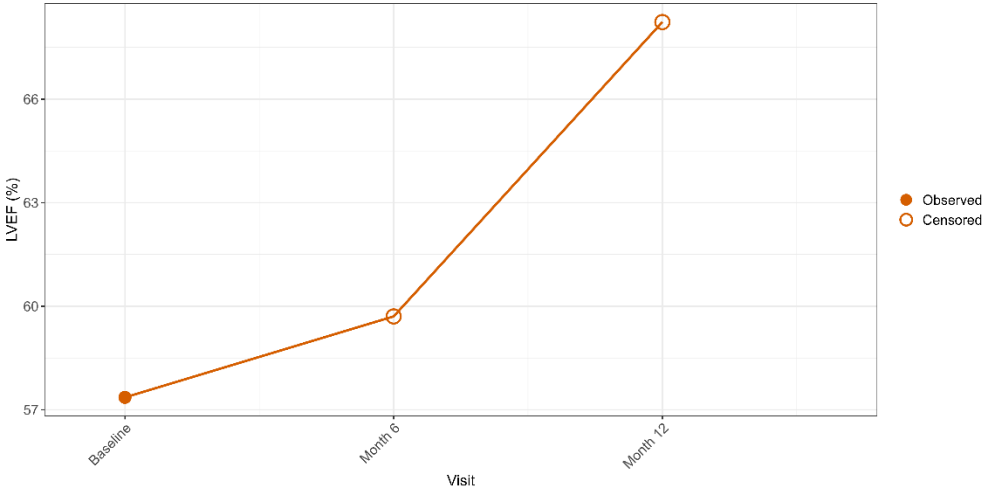




FDA's Evaluation of the Intercurrent Event Strategy (2)

- The Applicant proposed exclusion of data after prohibited medication use for one placebo subject
  - This strategy was introduced in SAP 3.0





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Theme 2: Study Conclusions Lack Robustness

The apparent treatment effect is highly sensitive to missing data handling and analytical choices

HOPE-3: Primary Endpoint (ΔPUL 2.0 Total Score): Across SAPs: Without Data Imputation

	FDA Analysis (SAP 1.1)*	SAP 1.7 Without Data Imputation**	SAP 2.0 Without Data Imputation	SAP 3.0 Without Data Imputation
Document Date	**July 19, 2022**	December 6, 2023	September 26, 2025	November 24, 2025
Endpoint	**Mean change**	Mean Change	Mean percent change	Mean percent change
Sample Size	**Treated: 53 Placebo: 51**	Treated: 53 Placebo: 51	Treated: 53 Placebo: 51	Treated: 53 Placebo: 51
Mean Difference	**0.66**	0.61	2.38%	2.53%
p-value	**0.24**	0.64	0.26	0.21

* FDA analysis included cohort as covariate in analysis model.

** Applicant's results differ because their analysis was based on a subgroup of "non-slow progressors"; cohort included as covariate for statistical rigor

- Last patient last visit was on June 18, 2025
- Unblinding occurred on November 25, 2025

HOPE-3: Primary Endpoint (ΔPUL 2.0 Total Score): Across SAPs: With Data Imputation

	SAP 1.1 With Data Imputation*	SAP 1.7 With Data Imputation**	SAP 2.0 With Data Imputation	SAP 3.0 With Data Imputation	SAP 3.0 Modified in CSR
Document date	July 19, 2022	December 6, 2023	September 26, 2025	November 24, 2025	February 3, 2026
Endpoint	Mean change	Mean Change	Mean percent change	Mean percent change	Mean percent change
Sample size	Treated: 53 Placebo: 52	Treated: 53 Placebo: 52	Treated: 53 Placebo: 52	Treated: 53 Placebo: 52	Treated: 53 Control: 52
Mean difference	0.92	0.59	3.74%	4.16%	4.55%
p-value	0.11	0.66	0.08	0.045	0.029

* FDA analysis included cohort as covariate in analysis model.

** Applicant's results differ because their analysis was based on a subgroup of "non-slow progressors"; cohort included as covariate for statistical rigor

- Last patient last visit was on June 18, 2025
- Unblinding occurred on November 25, 2025

HOPE-3: Primary Endpoint (ΔPUL 2.0 Total Score): Lack of Robustness

	SAP 3.0 Without Data Imputation	SAP 3.0 With Data Imputation
Document date	November 24, 2025	November 24, 2025
Endpoint	Mean percent change	Mean percent change
Sample size	Treated: 53 Placebo: 51	Treated: 53 Placebo: 52
Mean difference	2.53%	4.16%
p-value	0.21	0.045

- Last patient last visit was on June 18, 2025
- Unblinding occurred on November 25, 2025

- The apparent treatment effect is unstable and unreliable
- The study conclusion is highly sensitive to the handling of only two placebo subjects and to different analytic approaches

HOPE-3: Key Secondary Endpoint (ΔLVEF): Across SAPs: Without Data Imputation

	FDA Analysis (SAP 1.1)*	SAP 1.7* Without Data Imputation	SAP 2.0 Without Data Imputation	SAP 3.0 Without Data Imputation
Document date	**July 19, 2022**	December 6, 2023	September 26, 2025	November 24, 2025
Endpoint	**Mean change**	Mean change	Mean change	Mean ranked change
Sample size	**Treated: 44 Placebo: 45**	Treated: 44 Placebo: 45	Treated: 44 Placebo: 45	Treated: 39 Placebo: 44
Mean difference	**-0.04%**	0.38%	-0.37%	6.88
Nominal p-value	**0.97**	0.77	0.77	0.22

* FDA analysis included cohort as covariate in analysis model.

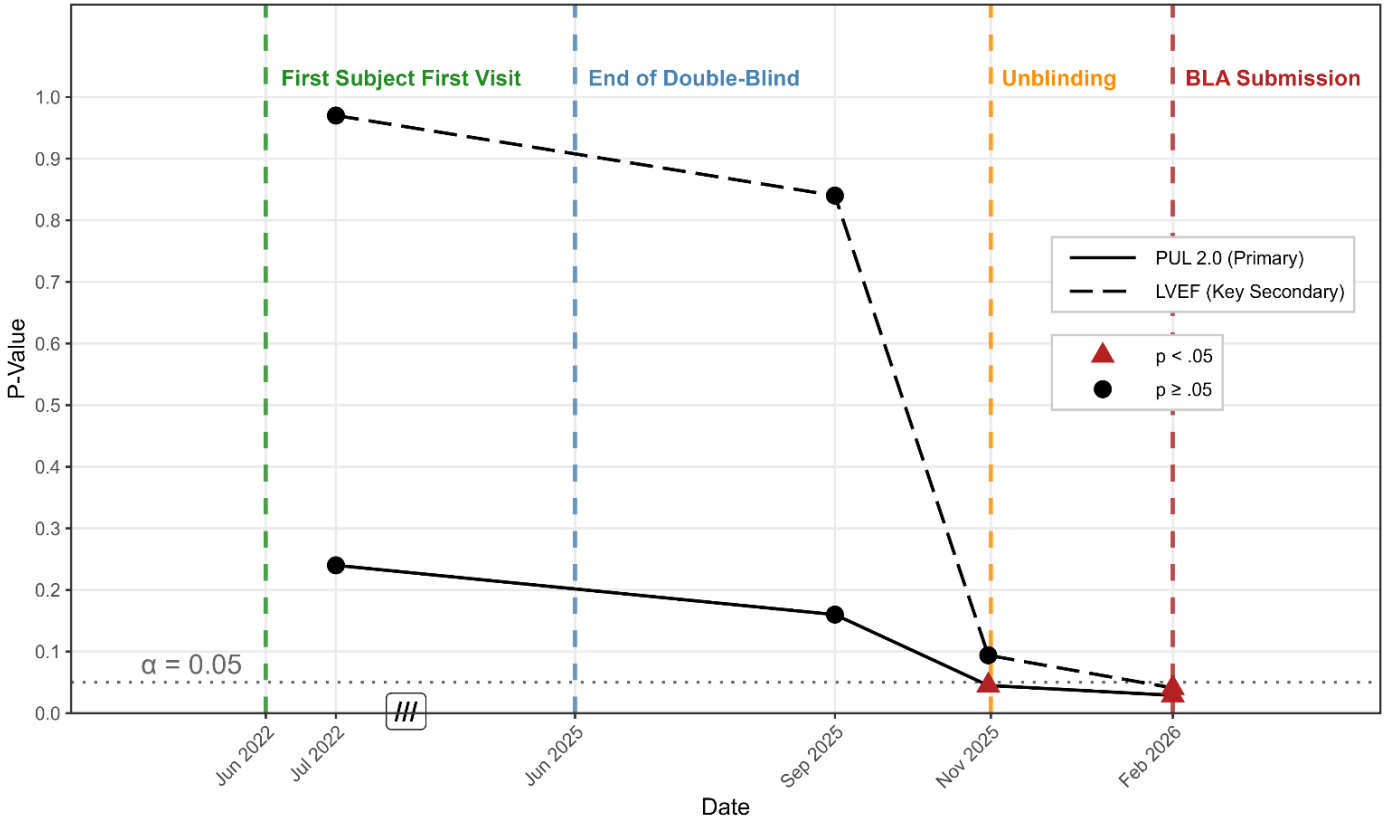
- Last patient last visit was on June 18, 2025
- Unblinding occurred on November 25, 2025

HOPE-3: Key Secondary Endpoint (ΔLVEF): Across SAPs: With Data Imputation

	SAP 1.1 With Data Imputation*	SAP 1.7* With Data Imputation	SAP 2.0 With Data Imputation	SAP 3.0 With Data Imputation	SAP 3.0 Modified in CSR
Document date	July 19, 2022	December 6, 2023	September 26, 2025	November 24, 2025	February 3, 2026
Endpoint	Mean change	Mean change	Mean change	Mean ranked change	Mean ranked change
Sample size	Treated: 44 Placebo: 45	Treated: 44 Placebo: 45	Treated: 44 Placebo: 45	Treated: 39 Placebo: 44	Treated: 39 Placebo: 44
Mean difference	1.08%	1.55%	0.74%	9.51	11.65
Nominal p-value	0.42	0.24	0.57	0.09	0.041

* FDA analysis included cohort as covariate in analysis model.
- Last patient last visit was on June 18, 2025
- Unblinding occurred on November 25, 2025

SAP Changes Have Substantial Impact on Study Conclusions



HOPE-3 Summary and Concerns

- The cumulative statistical evidence does not support a treatment effect of deramiocel for either PUL 2.0 or LVEF
- Substantial late-stage changes to the endpoints and SAP that improve p-values do not have persuasive scientific justifications
- The Applicant's *post-hoc* analyses do not provide substantial evidence of effectiveness
  - High risk of false positive findings
  - Lack of control for multiple testing
- The study conclusions are highly sensitivity to handling of missing data for a small number of subjects and to other analytical choices
- The interpretability of a clinical trial depends on adherence to prospectively specified analytical methods

Supporting Context: HOPE-2 and HOPE-2-OLE

Prior studies exhibit the same pattern of *post-hoc* analytical modification

Study HOPE-2: Key FDA Conclusions

- Study HOPE-2 did not show a statistically significant difference in primary endpoint of skeletal muscle function (mid-level PUL 1.2) or on any key secondary efficacy endpoints
- In *post-hoc* analyses, the Applicant transformed the data from the original scale to percentile ranks citing normality violation
  - Percentile rank has no clinical interpretation, unstable in a small sample
  - Other more interpretable data transformation or non-parametric approaches available
  - No normality assumption violation based on pre-specified analysis model with unstructured covariance structure

Study HOPE-2-OLE Key Conclusions

- Exploratory and *post-hoc* analyses in an open-label long term study of a selected sample of subjects who consented to additional follow up cannot provide substantial evidence of effectiveness
  - Uncontrolled Type I error rate for *post-hoc* analyses
  - Potential selection bias in OLE participants and in subset (10 of 20; 50%) included in external LVEF comparison
  - High degree of disease heterogeneity
  - Inadequate control of potential confounders

- Per FDA guidance on use of external controls: Protocol and SAP should be finalized before data collection, not after data collection

Summary and Conclusions

Prateek Shukla, MD

Division of Clinical Evaluation General Medicine
Office of Therapeutic Products
CBER | FDA

DMD Affects Individuals and Families

- Serious and rare neuromuscular disease affecting boys from early childhood
- Symptoms are debilitating and incompletely managed by currently available therapies
- Current FDA-approved products for treatment of DMD have unknown effects on cardiac progression or cardiac disease
- No FDA-approved therapy targets cardiomyopathy in DMD
- FDA recognizes the urgency for safe and effective therapies addressing the cardiac disease in DMD

Deramiocel Studies HOPE-2 & HOPE-3

Study	HOPE-2 (phase 2, randomized) (n=20; stopped early)	HOPE-3 (phase 3, randomized) (n=106)
Primary Endpoint	**Change in PUL 1.2 Elbow Domain (mid-level)** 2.98 points (p = 0.13) [95% CI: -0.95 – 6.91] **NOT MET**	**Change in PUL 2.0 Total Score** 0.66 points (p = 0.24) **NOT MET**
Secondary Endpoint	**Regional Systolic LV Wall Thickening** All 4 regions: p = 0.36–0.89 **NO EFFECT**	**Change in LVEF (Cardiac MRI)** −0.04% (p = 0.97) **NO EFFECT**
Key Points	• Pre-specified primary and secondary endpoints not met • 23 of 26 exploratory cardiac endpoints favored placebo or showed no effect • Limited enrollment	• Pre-specified primary and secondary endpoints not met • *Post-hoc* analyses (SAP changes) are difficult to interpret
Summary	**Studies HOPE-2 and HOPE-3 failed to demonstrate a treatment effect of deramiocel compared to placebo on the pre-specified primary or key secondary endpoint.**	

Conclusions

- Phase 2, randomized Study HOPE-2 did not demonstrate clinical benefit on skeletal muscle or cardiac function
- Phase 3, randomized Study HOPE-3 did not demonstrate clinical benefit on skeletal muscle or cardiac function
- Study HOPE-3 together with Study HOPE-2 do not provide substantial evidence of effectiveness of deramiocel
- The benefit-risk assessment for deramiocel is unfavorable in the absence of evidence of clinical benefit

CTGTAC Discussion Topic 1

Discuss whether the results of Study HOPE-3 on the pre-specified secondary endpoint of change from baseline to month 12 in left ventricular ejection fraction (LVEF) support a conclusion that deramiocel is effective in slowing the rate of decline in cardiac function in patients with DMD.

CTGTAC Discussion Topic 2

Discuss whether the results of Study HOPE-3 on the pre-specified primary and secondary endpoints assessing upper limb function and cardiac imaging parameters support a conclusion that deramiocel is effective in the treatment of patients with DMD.

CTGTAC Voting Question

Does the available evidence provide substantial evidence of effectiveness of deramiocel for the treatment of cardiomyopathy in patients with DMD?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Back-Up Slides

HOPE 2: Statistical Analysis Methods

- Primary, key secondary and exploratory cardiac endpoints:
  - Mixed model repeated measures (MMRM) with the change from baseline to Month 12 as the outcome variable, and visit, treatment, baseline measurement, site and stratification of entry item score of the PUL 1.2 at screening as the main effects and the interaction between treatment and visit.

HOPE 2: Lack of Efficacy on the Primary and All Key Secondary Efficacy Endpoints (1/2)

LSM Change From Baseline to Months 3, 6, 9, and 12 in the Mid-Level (Elbow) Dimension of PUL 1.2 (N=19, not ITT)

Visit	LSM (SE) Difference	95% CI Difference	Nominal p-Value
Month 3	1.82 (1.46)	-1.47, 5.11	0.24
Month 6	2.15 (1.49)	-1.15, 5.46	0.18
Month 9	2.26 (2.08)	-2.25, 6.78	0.30
Month 12	2.98 (1.82)	-0.95, 6.91	0.13

One placebo subject with baseline mid-level dimension PUL 1.2 score of 34 was excluded from the analysis due to missing post baseline assessments.

HOPE 2: Lack of Efficacy on the Primary and All Key Secondary Efficacy Endpoints (2/2)

LSM Change From Baseline to Months 6 and 12 in the Four Regional Systolic Left Ventricular Wall Thickening Endpoints (N=17, not ITT)

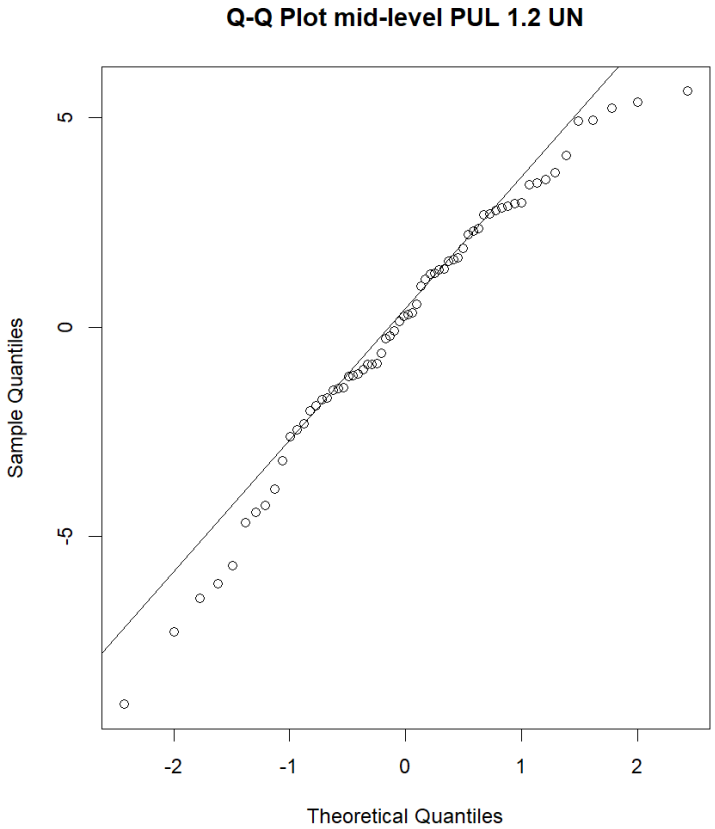
Endpoint	Visit	LSM (SE) Difference	95% CI Difference	Nominal p-Value
Systolic wall thickening anterior LV	Month 6	1.33 (2.35)	-3.85, 6.52	0.58
Systolic wall thickening anterior LV	Month 12	-0.28 (1.29)	-3.30, 2.73	0.83
Systolic wall thickening inferior LV	Month 6	-3.08 (4.53)	-12.96, 6.80	0.51
Systolic wall thickening inferior LV	Month 12	2.35 (2.41)	-3.38, 8.08	0.36
Systolic wall thickening lateral LV	Month 6	1.84 (2.05)	-3.00, 6.68	0.40
Systolic wall thickening lateral LV	Month 12	2.50 (3.37)	-5.01, 10.01	0.48
Systolic wall thickening septal LV	Month 6	-3.51 (5.03)	-14.50, 7.48	0.50
Systolic wall thickening septal LV	Month 12	-0.32 (2.20)	-5.52, 4.89	0.89

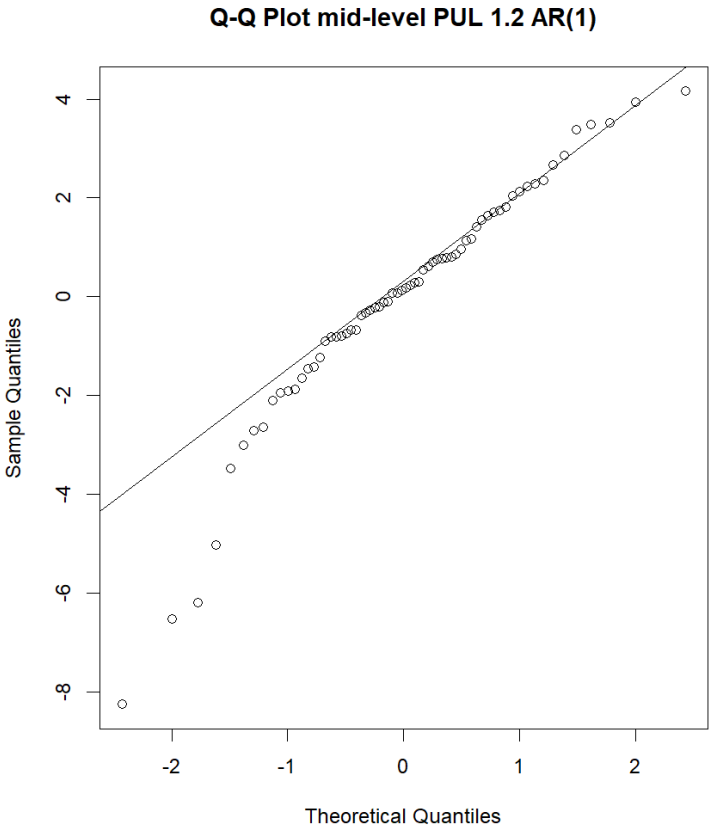
HOPE-2 Justification for Data Transformation

- The applicant's rationale for mid-level PUL 1.2
  - Shapiro-Wilk test for normality on the residuals from MMRM with AR(1) model yielded a p-value of 0.0019 (p-value of 0.003 for treated arm only)
  - FDA's view: the same Shapiro-Wilk test on the residuals from the prespecified MMRM with UN model yielded a p-value of 0.133

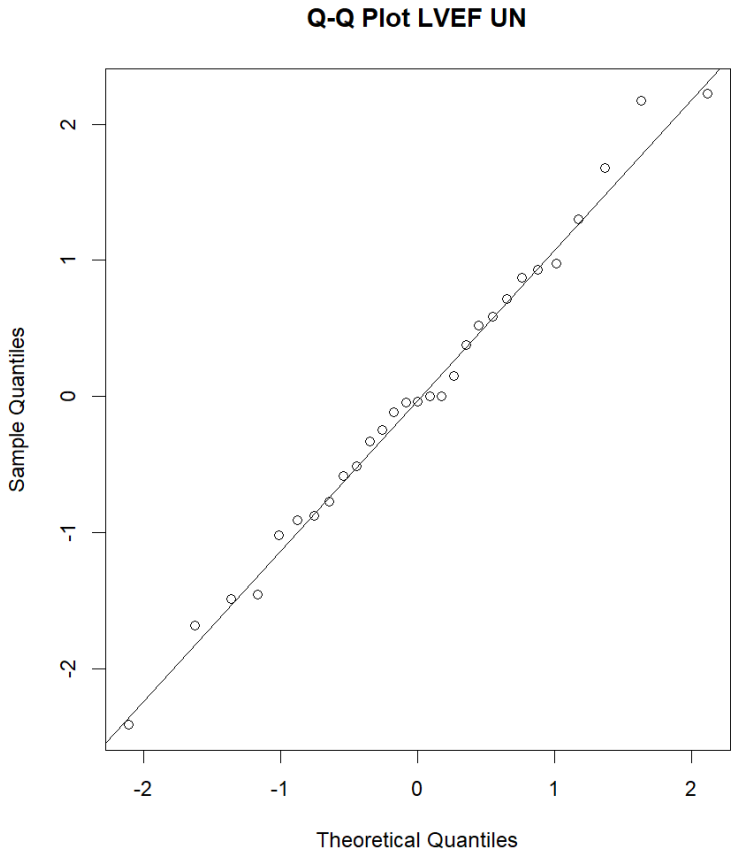
- For LVEF, the Shapiro-Wilk test on the residuals had a p-value of 0.98 using MMRM with UN variance structure, and a p-value of 0.99 using MMRM with AR(1) variance structure.

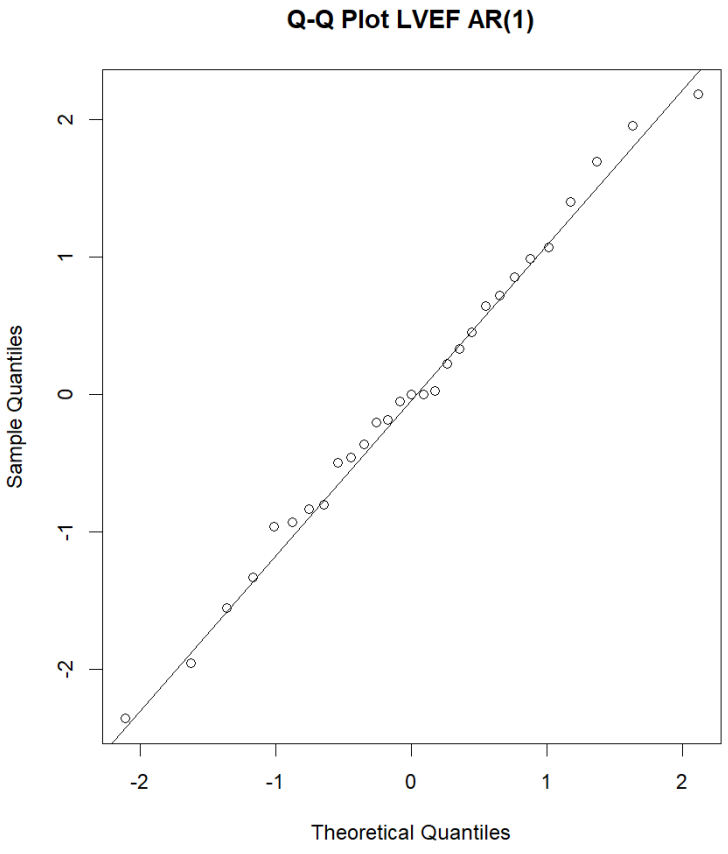
HOPE-2: Diagnostic Checks mid-level PUL 1.2





HOPE-2: Diagnostic Checks for LVEF





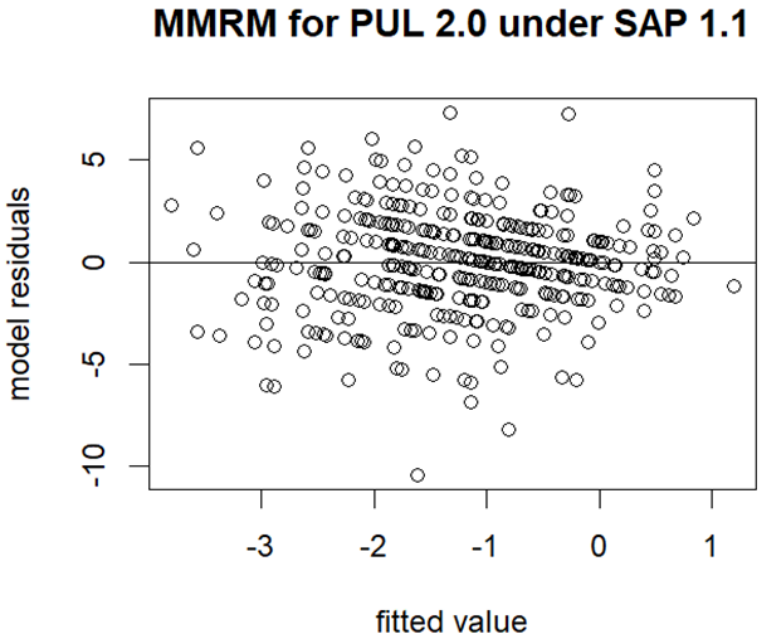
Study HOPE 3: Key SAP Differences

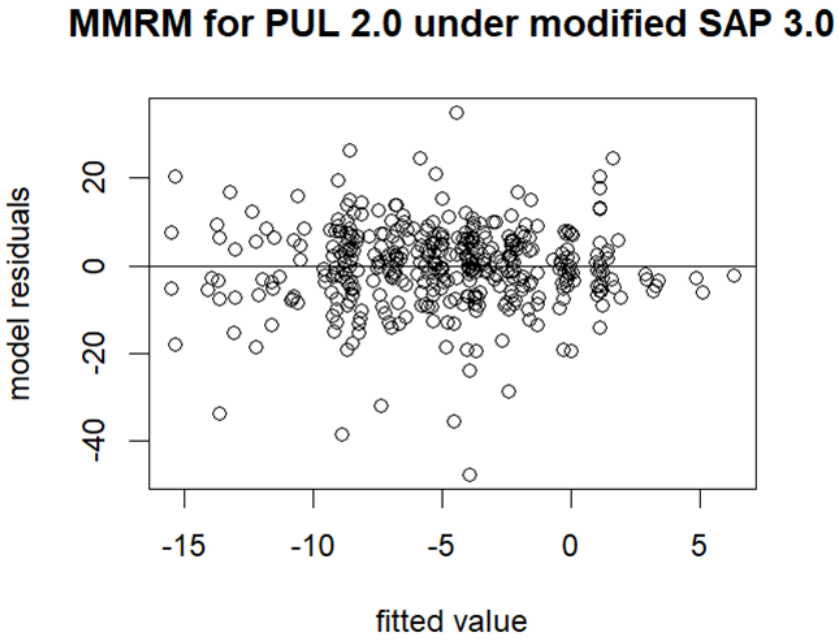
SAP | Protocol	Date	Key Changes | Milestones
SAP 1.1 *Protocol 3.0*	July 19, 2022	• All available data included • No data imputation • First subject, first visit: June 22, 2022
SAP 1.6 *Protocol 5.0*	August 21, 2023	• Used new covariate of “slow progressor”*
SAP 1.7 *Protocol 5.0*	December 6, 2023 **Futility assessment: December 7, 2023**	• Used new “worst observed” imputation for subjects withdrawn due to AE • Modified futility threshold from -1.67 to -1.75 • DSMB study futility discussion: futility not met (≥-1.74); determination made by Applicant; interim results not provided/reviewed by DSMB
SAP 2.0 *Protocol 9.0*	September 26, 2025	• Changed primary endpoint to **percent change** from baseline in PUL 2.0 total score
SAP 3.0 *Modified Protocol 9.0*	November 24, 2025 **HOPE-3 data unblinded: November 25, 2025**	• Changed key secondary endpoint to **ranked change** from baseline in LVEF • Introduced removal of observed data after prohibited medication use • Revised slow progressor definition
Clinical Study Report (CSR)	February 3, 2026	• Post-hoc analyses with analysis models further modified • “Slow progressor” definition further revised

* Defined as entry score 6 or genetic makeup with Exon 44 skipping amenable and deletions of Exons 3 through 7

FDA's Evaluation of PUL 2.0 Change (1)

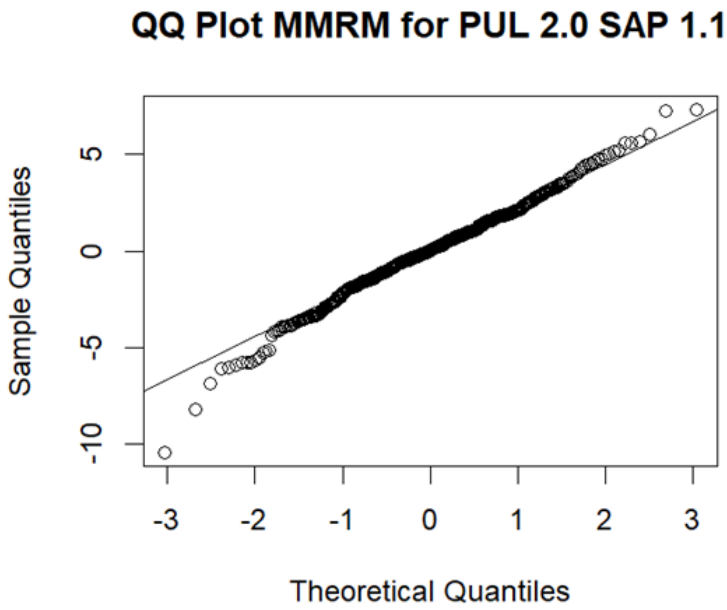
- Applicant cited variance assumption violation; however, diagnostic check on the model residuals did not show violation.

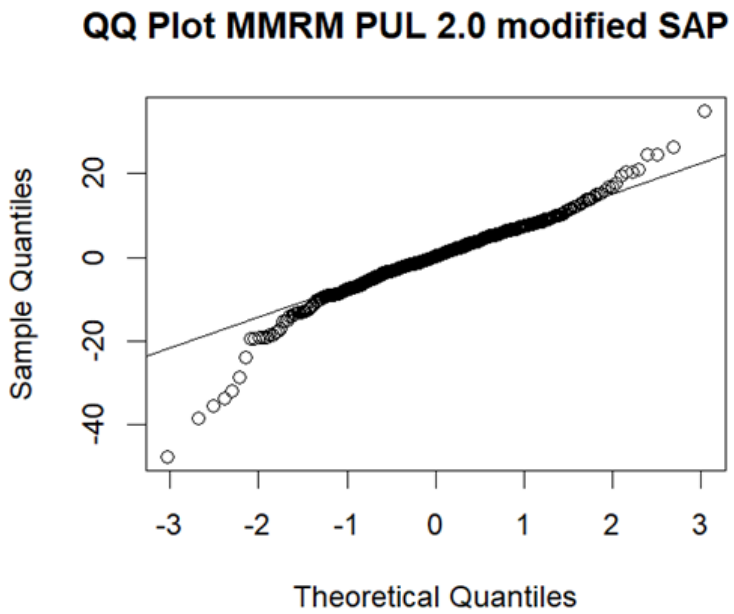




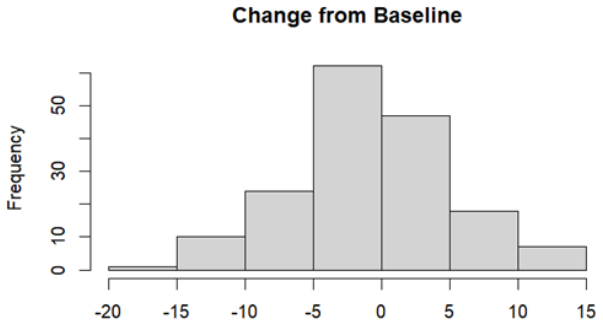
FDA's Evaluation of PUL 2.0 Change (2)

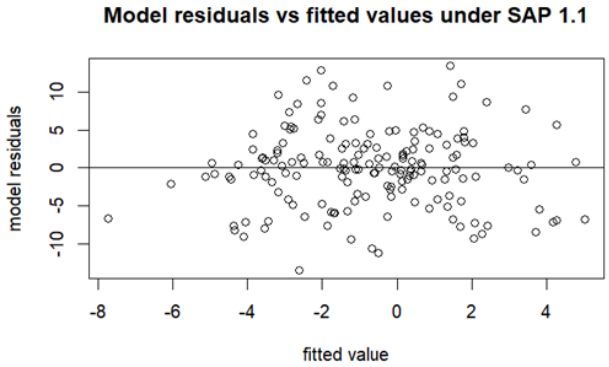
- Normality assumption is less well supported under Applicant's final model

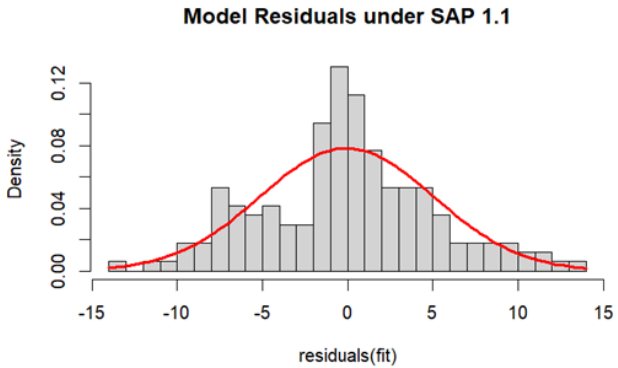


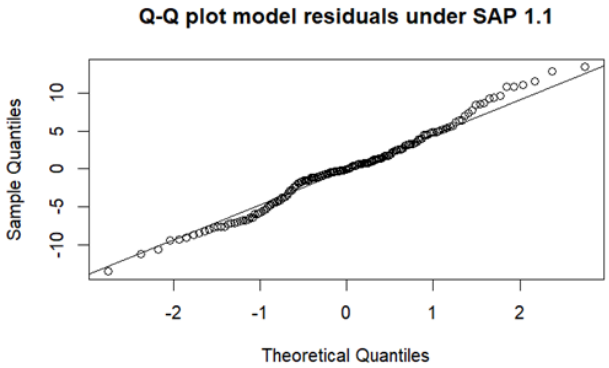


Diagnostic Checks for LVEF under SAP 1.1









FDA's Primary and Key Secondary Efficacy Analyses Under SAP 1.7

- FDA analysis based on SAP 1.7:
  - Mixed Model Repeated Measures (MMRM) with change from baseline as outcome variable
  - **Primary analysis based on ITT population**

- Covariates: treatment, investigative site, visit, treatment-by-visit interaction, slow progressor and its interactions with visit and treatment, baseline score, baseline score by visit interaction, and cohort
  - Unstructured covariance structure to model within-patient errors

- Intercurrent event strategy:
  - Subjects withdrawn due to death/AE imputed with worst observed value

Applicant's Primary Efficacy Analysis Under SAP 1.7

- Applicant analysis based on SAP 1.7:
  - Mixed Model Repeated Measures (MMRM) with change from baseline as outcome variable
  - **Primary analysis based on subgroup of non-slow progressors**

- Covariates: treatment, investigative site, visit, treatment-by-visit interaction, slow progressor and its interactions with visit and treatment, baseline score, baseline score by visit interaction, and cohort
  - Unstructured covariance structure to model within-patient errors

- Intercurrent event strategy:
  - Subjects withdrawn due to death/AE imputed with worst observed value
  - **Observed data after prohibited medication use excluded (introduced in SAP 3.0)**

Applicant's Key Secondary Efficacy Analysis Under SAP 1.7

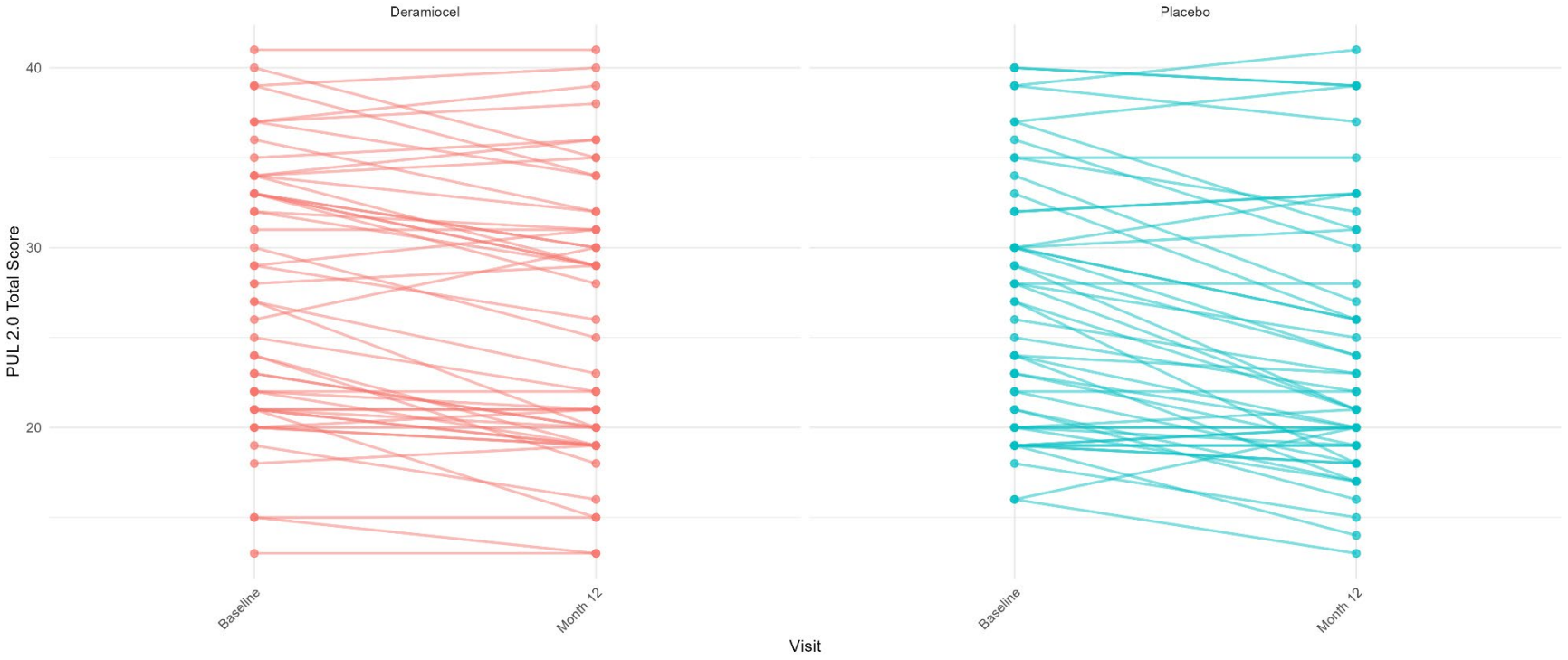
- Applicant analysis based on SAP 1.7:
  - Mixed Model Repeated Measures (MMRM) with change from baseline as outcome variable
  - **Primary analysis based on subgroup of non-slow progressors**

- Covariates: treatment, investigative site, visit, treatment-by-visit interaction, slow progressor and its interactions with visit and treatment, baseline score, baseline score by visit interaction, cohort, and **age-by-baseline interaction (not specified in SAP 1.7)**
  - Unstructured covariance structure to model within-patient errors

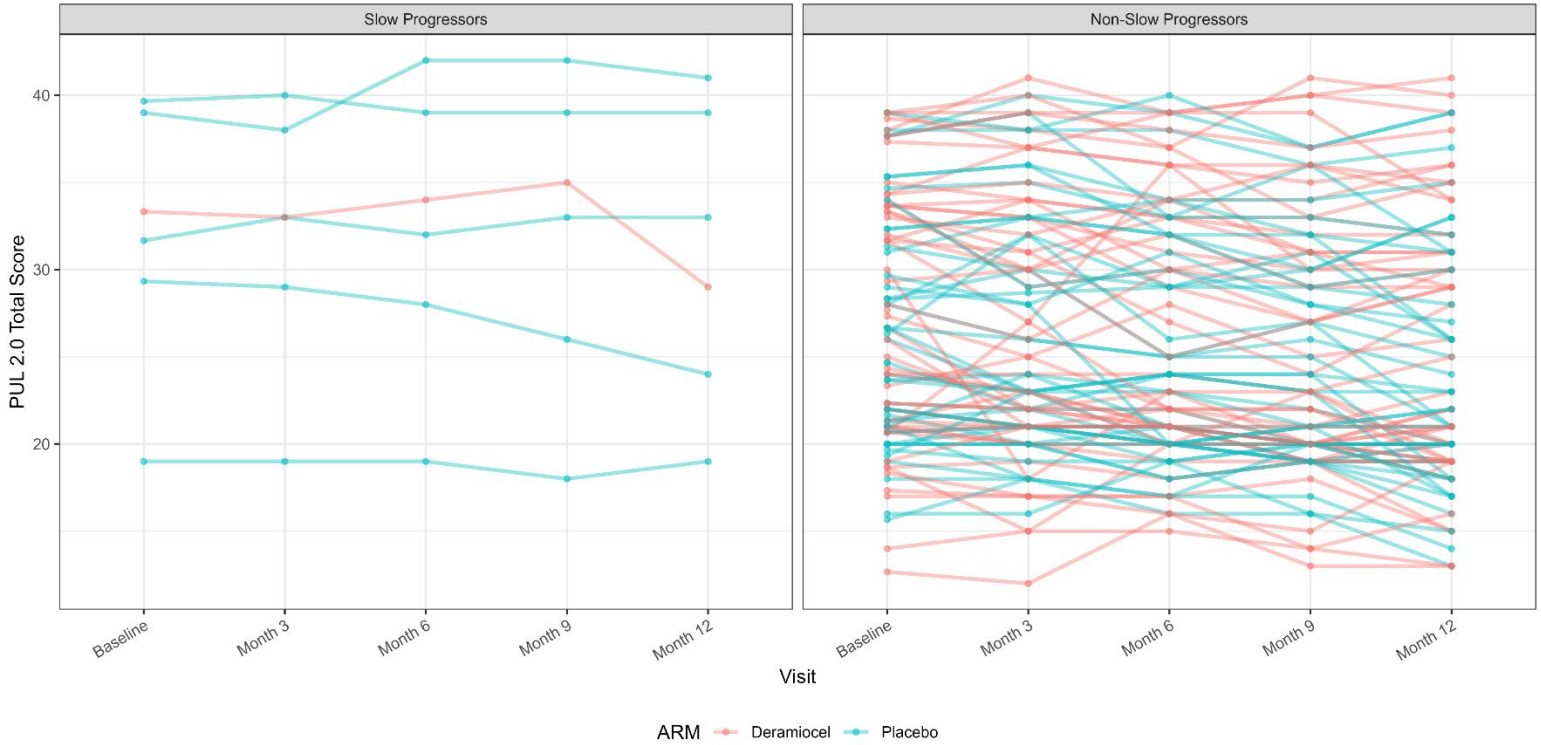
- Intercurrent event strategy:
  - Subjects withdrawn due to death/AE imputed with worst observed value
  - **Observed data after prohibited medication use excluded (introduced in SAP 3.0)**

Primary Endpoint

Patient Trajectories of PUL 2.0 Total Score



Patient Trajectories of PUL 2.0 Total Score



Slow Progressor Definition

SAP Version	Document Date	Definition
SAP 1.6-2.0	August 21, 2023 – September 26, 2025	Those having an entry score of 6 or genetic makeup with Exon 44 skipping amenable and deletions of Exons 3 through 7
SAP 3.0	November 24, 2025	Those who meet any of the four following criteria: • Any subject with a PUL entry-item score of 6 in at least 2 of the 3 screening/baseline visits • Exon 44 skipping amenable • Exon 3 through 7 deletions • Genetic mutations that are also known to be potentially associated with Becker's Muscular Dystrophy and/or a mild dystrophy phenotype (for example Exon 51-55 duplication)
SAP 3.0 Modified	February 3, 2026	Additional requirement of a PUL entry-item score of 6 at both screening visits

Primary Endpoint Analysis Model (PUL 2.0)

SAP version	SAP 1.1 July 19, 2022	SAP 2.0 Sept. 26, 2025	SAP 3.0 Nov 24, 2025 (FDA Analysis)	Modified SAP 3.0 in CSR Post Hoc
Endpoint	Mean change from baseline	Mean percent change from baseline	Mean percent change from baseline	Mean percent change from baseline
Mixed Model Repeated Measures (MMRM) covariates	Treatment, investigative site, visit, treatment-by-visit interaction, baseline score baseline score by visit interaction	Treatment, investigative site, visit, treatment-by-visit interaction baseline score cohort slow progressor indicator (removed based on criteria), slower progressor interaction with visit and treatment (removed based on criteria) If cell sizes fall below 2 subjects per treatment arm, categorical variables, omitted from the model	Treatment, investigative site, visit, treatment-by-visit interaction baseline score cohort slow progressor indicator (redefined, should be removed by criteria) If cell sizes fall below 2 subjects per treatment arm, categorical variables, omitted from the model	Treatment, investigative site, visit, treatment-by-visit interaction baseline score cohort slow progressor indicator (redefined, added in the model) If cell sizes fall below 2 subjects per treatment arm, categorical variables, omitted from the model
Baseline PUL 2.0	Collected at day 1	Collected at day 1	Average of screenings and day 1	Average of screenings and day 1
Site pooling	Sites < 2 per treatment arm at Month 12 pooled	Sites < 2 subjects in each treatment group pooled	Smaller sites pooled until pooled sites have at least 10 subjects each	Smaller sites pooled until pooled sites have at least 10 subjects each
Covariance structure	Unstructured	Autoregressive with heterogeneous variance (ARH[1])	ARH[1]	ARH[1]

HOPE-3: Primary Endpoint (ΔPUL 2.0 Total Score): Post-Study SAP Changes & Results

SAP version	FDA Analysis (SAP 1.1)*	SAP 1.7[a]	SAP 2.0	SAP 3.0	SAP 3.0 (Modified in CSR)
Document date	**July 19, 2022**	Dec. 6, 2023	Sept. 26, 2025	Nov. 24, 2025	Feb. 3, 2026
Endpoint	**Change**	Change	Percent Change	Percent Change	Percent Change
Sample size	**Treated: 53 Placebo: 51**	Treated: 53 Placebo: 52	Treated: 53 Placebo: 52	Treated: 53 Placebo: 52	Treated: 53 Control: 52
Mean difference	**0.66**	0.55	3.06%	4.16%	4.55%
p-value	**0.24**	0.69	0.16	0.045	0.029

* FDA analysis included cohort as covariate in analysis model.

[a] Applicant's results differ because their analysis is based on a subgroup of non-slow progressors; Applicant censored data from one placebo subject which does not align with SAP 1.7; futility criteria were changed

- DSMB data review for futility determination was on Dec 7, 2023 (one day after SAP 1.7)
- Last patient last visit was on June 18, 2025
- Unblinding occurred on November 25, 2025

HOPE-3: Primary Endpoint (ΔPUL 2.0 Total Score): SAP Changes & Results

Analysis	FDA Analysis (SAP 1.7)	Applicant (Subgroup) Analysis (SAP 1.7)*	FDA Analysis (SAP 2.0)	Applicant (Subgroup) Analysis (SAP 2.0)**	FDA Analysis (SAP 3.0)	Applicant Analysis (SAP 3.0)
Document date	Dec. 6, 2023	Dec. 6, 2023	Sept. 26, 2025	Sept. 26, 2025	Nov. 24, 2025	Nov. 24, 2025
Endpoint	Change	Change	Percent Change	Percent Change	Percent Change	Percent Change
Sample size* **	Treated: 53 Placebo: 52	Treated: 52 Placebo: 47	Treated: 53 Placebo: 52	Treated: 52 Placebo: 47	Treated: 53 Placebo: 52	Treated: 53 Placebo: 52
Mean difference	0.55	1.12	3.06%	4.85%	4.16%	4.55%
p-value	0.69	0.052	0.16	0.022	0.045	0.029

* Applicant's results differ because their analysis is based on a subgroup of non-slow progressors; Applicant censored data from one placebo subject which does not align with SAP 1.7; futility criteria were changed

** Applicant's results differ because their analysis was based on a subgroup of non-slow progressors; Applicant included slow progressor term and its interactions with visit and treatment, which should have been removed; Applicant censored one placebo subject not aligned with SAP 2.0

*** Applicant's primary analysis was conducted in the non-slow progressor subgroup; however, the model was fit on the full ITT population.

- DSMB data review for futility determination was on Dec 7, 2023 (one day after SAP 1.7)
- Last patient last visit was June 18, 2025
- Unblinding occurred on November 25, 2025

Key Secondary Endpoint

Key Secondary Endpoint Analysis Model (LVEF)

SAP version	SAP 1.1 July 19, 2022	SAP 2.0 Sept. 26, 2025	SAP 3.0 Nov 24, 2025 (FDA Analysis)	Modified SAP 3.0 in CSR Post Hoc
Endpoint	Mean change from baseline	Mean change from baseline	Mean ranked change from baseline	Mean ranked change from baseline
Analysis model with covariates	MMRM Treatment, investigative site, visit, treatment-by-visit interaction, baseline score baseline score by visit interaction	MMRM Treatment, investigative site, visit, treatment-by-visit interaction baseline score cohort slow progressor indicator (removed based on criteria), slower progressor interaction with visit and treatment (removed based on criteria) If cell sizes fall below 2 subjects per treatment arm, categorical variables, omitted from the model	ANOVA Treatment, cohort, slow progressor indicator, an indicator for screening LVEF greater than or equal to 45%, baseline LVEF, and age at baseline	ANOVA Treatment, cohort, slow progressor indicator, an indicator for screening LVEF greater than or equal to 45%, baseline LVEF, age at baseline, interaction between baseline LVEF and age at baseline
Baseline LVEF	Collected at day 1	Collected at day 1	Collected at day 1	Collected at day 1
Site pooling	Sites < 2 per treatment arm at Month 12 pooled	Sites < 2 subjects in each treatment group pooled	Smaller sites pooled until pooled sites have at least 10 subjects each	Smaller sites pooled until pooled sites have at least 10 subjects each
Covariance structure	Unstructured	Autoregressive with heterogeneous variance (ARH[1])	NA	NA

HOPE-3: Key Secondary Endpoint (ΔLVEF): Post-Hoc SAP Changes & Results

Version	FDA Analysis (SAP 1.1)*	SAP 1.7[a]	SAP 2.0[b]	SAP 3.0	SAP 3.0 (Modified in CSR)
Document date	**July 19, 2022**	Dec. 6, 2023	Sept. 26, 2025	Nov. 24, 2025	Feb. 3, 2026
Endpoint	**Change**	Change	Change	Ranked Change	Ranked Change
Sample size	**Treated: 44 Placebo: 45**	Treated: 44 Placebo: 46	Treated: 44 Placebo: 46	Treated: 39 Placebo: 44	Treated: 39 Placebo: 44
Mean difference	**-0.04%**	1.06%	0.27%	9.51	11.65
Nominal p-value	**0.97**	0.44	0.84	0.094	0.041

*FDA analysis included cohort as covariate in analysis model

a Applicant included additional age-by-baseline interaction term; censored placebo subject not aligned with SAP 1.7

b Applicant included additional age-by-baseline interaction term, slow progressor term, and its interactions with visit and treatment; censored placebo subject not aligned with SAP 2.0

- Last patient last visit was June 18, 2025
- Unblinding occurred on November 25, 2025

HOPE-3: Key Secondary Endpoint (ΔLVEF): SAP Changes & Results

Analysis	FDA Analysis (SAP 1.7)	Applicant (Subgroup) Analysis (SAP 1.7)*	FDA Analysis (SAP 2.0)	Applicant (Subgroup) Analysis (SAP 2.0)**	FDA Analysis (SAP 3.0)	Applicant Analysis (SAP 3.0)
Document date	Dec. 6, 2023	Dec. 6, 2023	Sept. 26, 2025	Sept. 26, 2025	Nov. 24, 2025	Nov. 24, 2025
Endpoint	Change	Change	Change	Change	Ranked Change	Ranked Change
Sample size* **	Treated: 44 Placebo: 46	Treated: 44 Placebo: 41	Treated: 44 Placebo: 46	Treated: 44 Placebo: 41	Treated: 39 Placebo: 44	Treated: 39 Placebo: 44
Mean difference	1.06%	1.72%	0.27%	1.34%	9.51	11.65
Nominal p-value	0.44	0.203	0.84	0.311	0.094	0.041

* Applicant's results differ because their analysis is based on a subgroup of non-slow progressors; Applicant censored data from one placebo subject which does not align with SAP 1.7; Applicant included additional age-by-baseline interaction term; censored placebo subject not aligned with SAP 1.7

** Applicant's results differ because their analysis was based on a subgroup of non-slow progressors; Applicant included age-by-baseline interaction term, slow progressor term and its interactions with visit and treatment, which should have been removed; Applicant censored one placebo subject not aligned with SAP 2.0

*** Applicant's primary analysis was conducted in the non-slow progressor subgroup; however, the model was fit on the full ITT population.

- Last patient last visit was June 18, 2025
- Unblinding occurred on November 25, 2025

Secondary Endpoints

PUL 2.0 Components

Change from Baseline to Month 12 (score)	Deramiocel	Placebo	Treatment Difference
Distal (hands/fingers)	53	51	0.19 (95% CI: -0.18, 0.56)
Mid-level (elbow)	53	51	0.69 (95% CI: 0.007, 1.36)
High (shoulder)	53	51	-0.05 (95% CI: -0.58, 0.48)

Mean Change From Baseline in Mid-Level Domain of PUL 2.0 at Month 12

SAP Version	SAP 1.1* Without Data Imputation	SAP 1.1* With Data Imputation	SAP 2.0 Without Data Imputation	SAP 2.0 With Data Imputation	SAP 3.0 Without Data Imputation	SAP 3.0 With Data Imputation	SAP 3.0 Modified in CSR
Document date	**July 19, 2022**	**July 19, 2022**	Sept. 26, 2025	Sept. 26, 2025	Nov. 24, 2025	Nov. 24, 2025	Feb. 3, 2026
Endpoint	Change	Change	Percent Change	Percent Change	Percent Change	Percent Change	Percent Change
Sample size	Treated: 53 Placebo: 51	Treated: 53 Placebo: 52	Treated: 53 Placebo: 51	Treated: 53 Placebo: 52	Treated: 53 Placebo: 51	Treated: 53 Placebo: 52	Treated: 53 Placebo: 52
Mean difference	0.69	0.89	6.21%	7.98%	5.36%	7.80%	8.12%
Nominal p-value	0.048	0.018	0.044	0.014	0.063	0.011	0.008

*FDA analysis included cohort as covariate in analysis model. Without the cohort covariate, the mean difference is 0.69 (p-value: 0.046)
Note: Mid-level domain was not an endpoint until SAP 2.0

Change in the Number of Segments of Myocardial Scarring as Observed by Late Gadolinium Enhancement (LGE) at Month 12 (Cohort B)

SAP Version	SAP 2.0 Without Data Imputation	SAP 2.0 With Data Imputation	SAP 3.0 Without Data Imputation	SAP 3.0 With Data Imputation	SAP 3.0 Modified in CSR Without Data Imputation	SAP 3.0 Modified in CSR
Document date	Sept. 26, 2025	Sept. 26, 2025	Nov. 24, 2025	Nov. 24, 2025	Feb. 3, 2026	Feb. 3, 2026
Endpoint	Change from Baseline	Change from Baseline	Change from Baseline	Change from Baseline	Change from Baseline	Change from Baseline
Sample size	Treated: 9 Placebo: 12	Treated: 9 Placebo: 13	Treated: 8* Placebo: 12	Treated: 8* Placebo: 13	Treated: 8* Placebo: 12	Treated: 8* Placebo: 13
Mean difference	-2.46	-4.1	-1.94	-3.02	-1.85	-3.01
Nominal p-value	0.084	0.012	0.038	0.017	0.0503	0.022

* One treated subject without baseline LVEF data was excluded from analysis

Change in the Percentage of Myocardial Scarring as Observed by Late Gadolinium Enhancement (LGE) at Month 12 (Cohort B)

SAP Version	SAP 2.0 Without Data Imputation	SAP 2.0 With Data Imputation	SAP 3.0 Without Data Imputation	SAP 3.0 With Data Imputation	SAP 3.0 Modified in CSR Without Data Imputation	SAP 3.0 Modified in CSR
Document date	Sept. 26, 2025	Sept. 26, 2025	Nov. 24, 2025	Nov. 24, 2025	Feb. 3, 2026	Feb. 3, 2026
Endpoint	Change from Baseline	Change from Baseline	Ranked Change from Baseline	Ranked Change from Baseline	Ranked Change from Baseline	Ranked Change from Baseline
Sample size	Treated: 9 Placebo: 12	Treated: 9 Placebo: 13	Treated: 8* Placebo: 12	Treated: 8* Placebo: 13	Treated: 8* Placebo: 12	Treated: 8* Placebo: 13
Mean difference	-8.51	-17.3	-3.87	-4.82	-3.41	-4.6[a]
Nominal p-value	0.0009	0.0047	0.20	0.092	0.223	0.094[a]

* One treated subject without baseline LVEF data was excluded from analysis

[a] Applicant reports mean difference of -4.829 with p-value of 0.1049

ΔLVEF (Cardiomyopathy Subgroup)

SAP Version	SAP 1.1* Without Data Imputation	SAP 1.1* With Data Imputation	SAP 2.0 Without Data Imputation	SAP 2.0 With Data Imputation	SAP 3.0 Without Data Imputation	SAP 3.0 With Data Imputation	SAP 3.0 Modified in CSR Without Data Imputation	SAP 3.0 Modified in CSR
Document date	**July 19, 2022**	**July 19, 2022**	Sept. 26, 2025	Sept. 26, 2025	Nov. 24, 2025	Nov. 24, 2025	Feb. 3, 2026	Feb. 3, 2026
Endpoint	Change from Baseline	Change from Baseline	Change from Baseline	Change from Baseline	Ranked Change from Baseline	Ranked Change from Baseline	Ranked Change from Baseline	Ranked Change from Baseline
Sample size	Treated: 35 Placebo: 32	Treated: 35 Placebo: 33	Treated: 35 Placebo: 32	Treated: 35 Placebo: 33	Treated: 32 Placebo: 31	Treated: 32 Placebo: 32	Treated: 32 Placebo: 31	Treated: 32 Placebo: 32
Mean difference	0.85	1.90	0.64	1.68	9.24 ranks	10.9 ranks	10.6 ranks	12.4 ranks
Nominal p-value	0.59	0.27	0.68	0.32	0.073	0.035	0.037	0.017

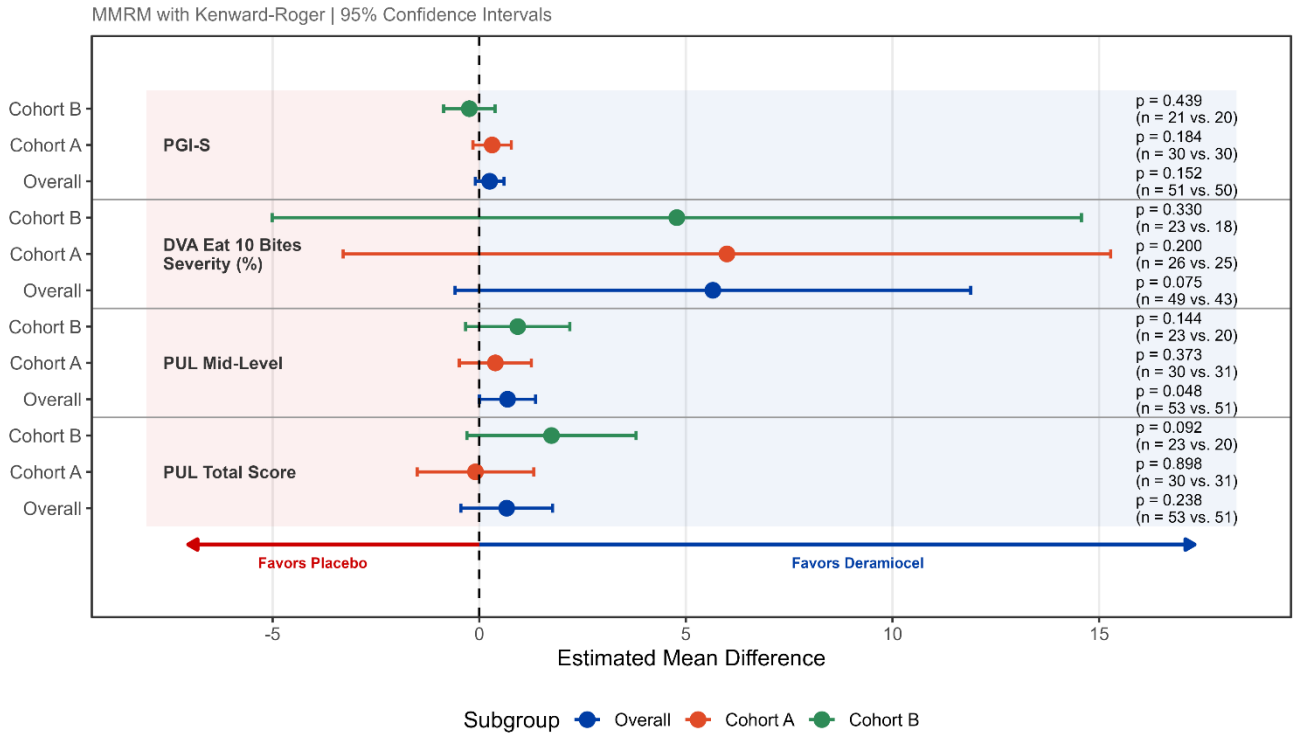
*FDA analysis included cohort as covariate in analysis model. Without the cohort covariate, the mean difference is 0.77 (p-value: 0.62)

Other Secondary Efficacy Endpoints (SAP 1.1)

Endpoint Change from Baseline to Month 12	No. of Treated	No. of Controls	Treatment Difference
Mid+distal PUL 2.0	53	51	0.74 (95% CI: -0.10, 1.59)
Mid-level PUL 2.0	53	51	0.69 (95% CI: 0.007, 1.36)
Duchenne Video Assessment (DVA) Eat 10 Bites Severity Percentage	49	43	-5.65 (95% CI: -11.89, 0.59)
CKMB (absolute)	49	40	-2.61 (95%: -22.27, 17.04)
Patient Global Impression of Severity (PGI-S)	51	50	-0.25 (-0.60, 0.09)

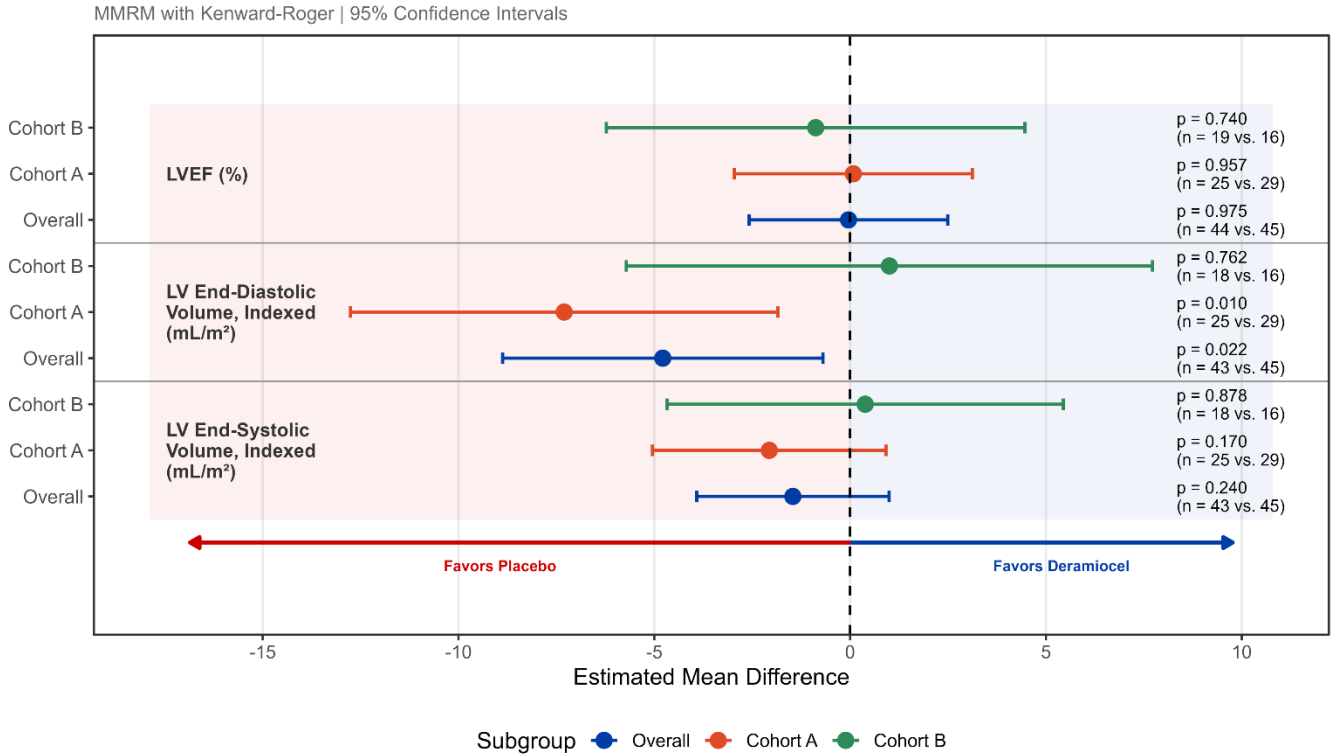
Based on SAP 1.1. FDA analysis included cohort as covariate in analysis model.

Forest Plot: PUL, DVA, and PGI-S



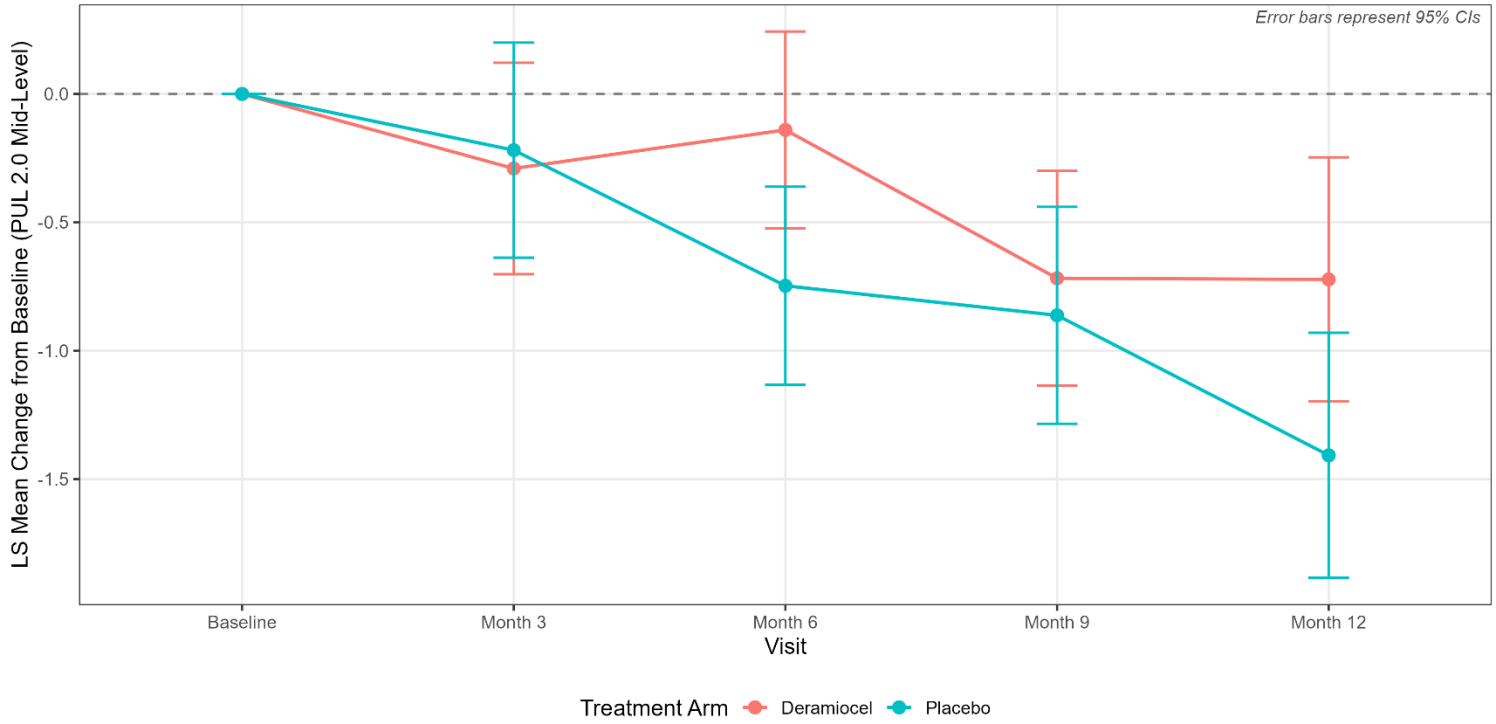
P-values are nominal and have not been adjusted for multiplicity.

Forest Plot: Cardiac Endpoints

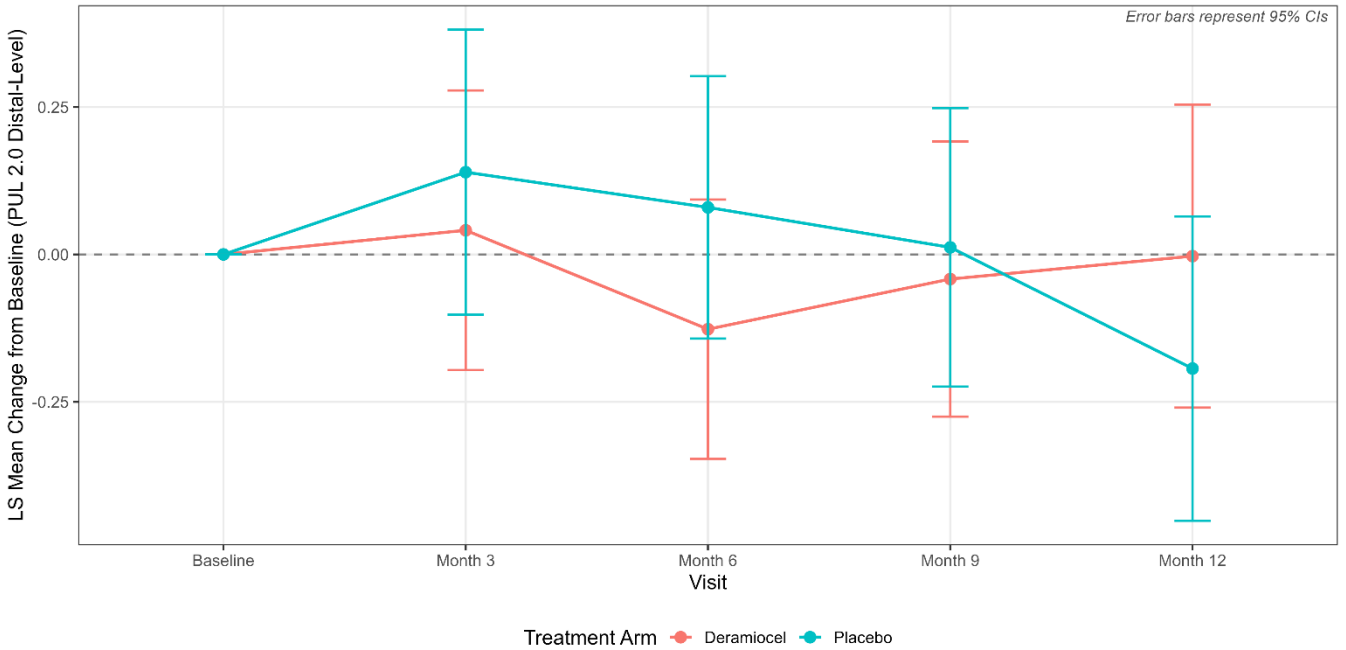


P-values are nominal and have not been adjusted for multiplicity.

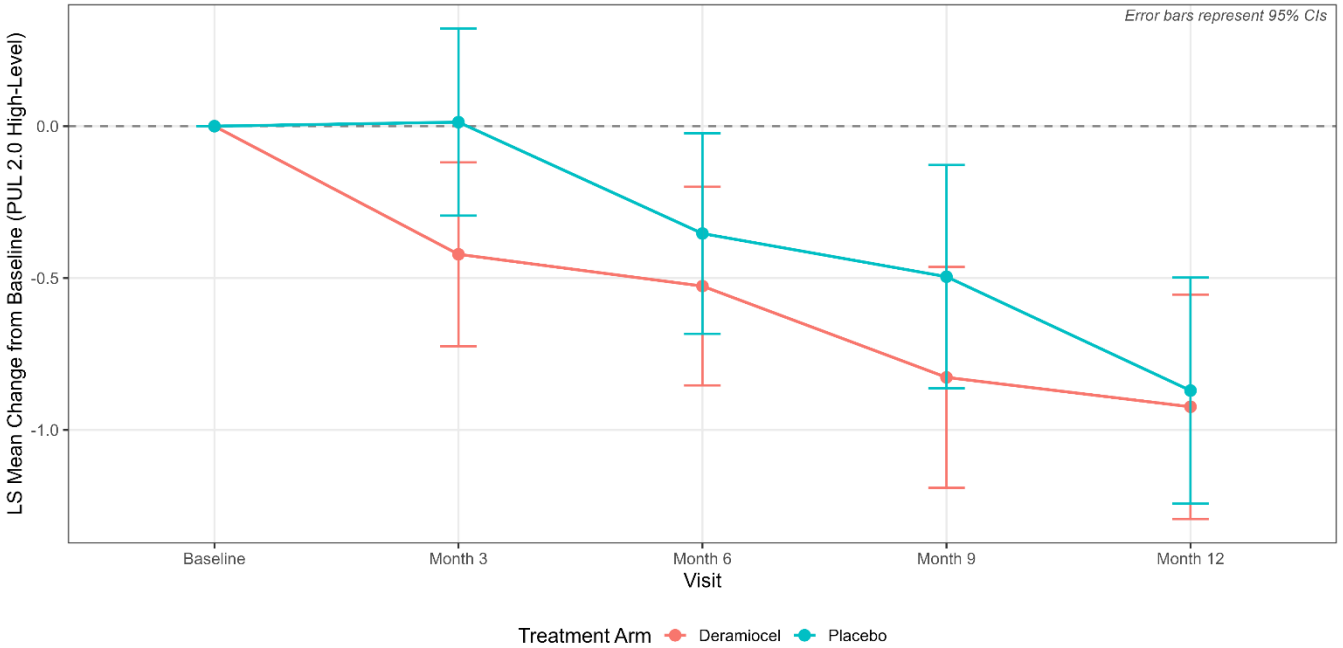
PUL 2.0 Mid-Level (SAP 1.1)



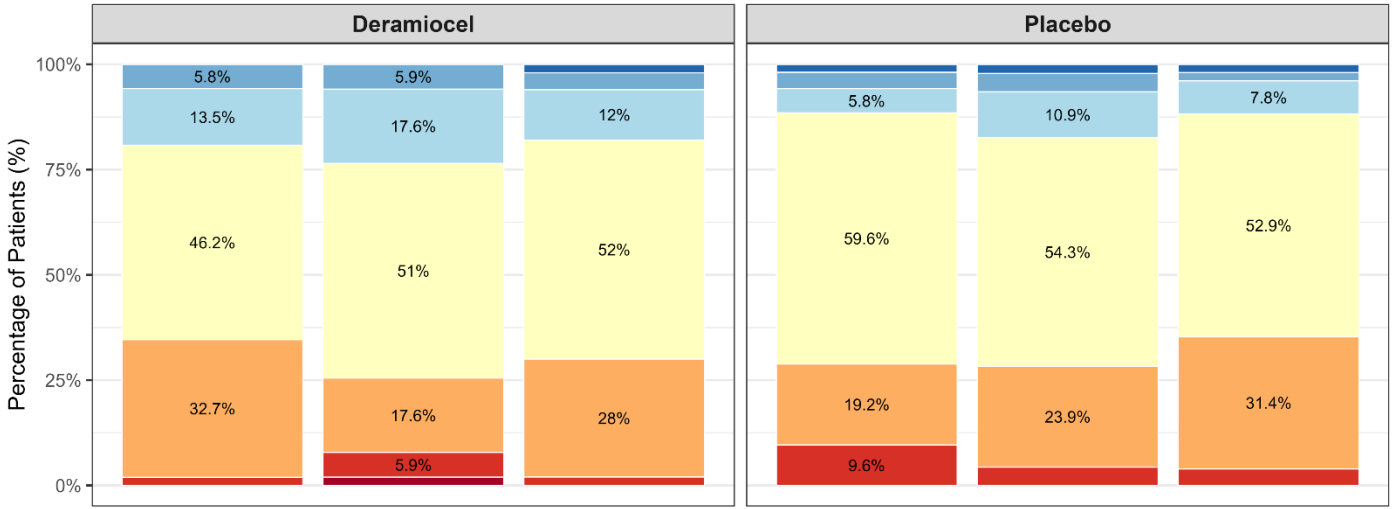
PUL 2.0 Distal-Level (SAP 1.1 Analysis Model)



PUL 2.0 High-Level (SAP 1.1 Analysis Model)



PGI-S Distribution



	Baseline	Month 6	Month 12	Baseline	Month 6	Month 12
PGI-S Completed	52	51	50	52	46	51
PGI-S Not Completed	2	3	4	0	6	1
Total	**54**	**54**	**54**	**52**	**52**	**52**

PGI-S Category None | Very Mild | Mild | Moderate | Moderately Severe | Severe | Extremely Severe

Percentages shown for categories ≥ 5%.

Subgroup Analyses

Subgroup Analyses for PUL 2.0 Based on SAP 1.1

Subgroup	Sample Size Treated (N=54)/Control (N=52)		Mean Difference Deramiocel-Placebo
Cohort A (N=61)	30	31	-0.09 (-1.50, 1.32)
Cohort B (N=45)	23	20	1.75 (-0.30, 3.79)
Ambulatory (N=16)	8	8	-0.43 (-3.98, 3.11)
Non-ambulatory (N=90)	45	43	0.77 (-0.40, 1.94)
Slow progressors (N=6)	1	5	-
Non-slow progressors (N=100)	52	46	0.92 (-0.21, 2.05)
PUL 2.0 Entry Score: 2, 3 (N=54)	26	27	-0.17 (-1.48, 1.15)
PUL 2.0 Entry Score: 4, 5, 6 (N=52)	27	24	0.73 (-1.22, 2.67)

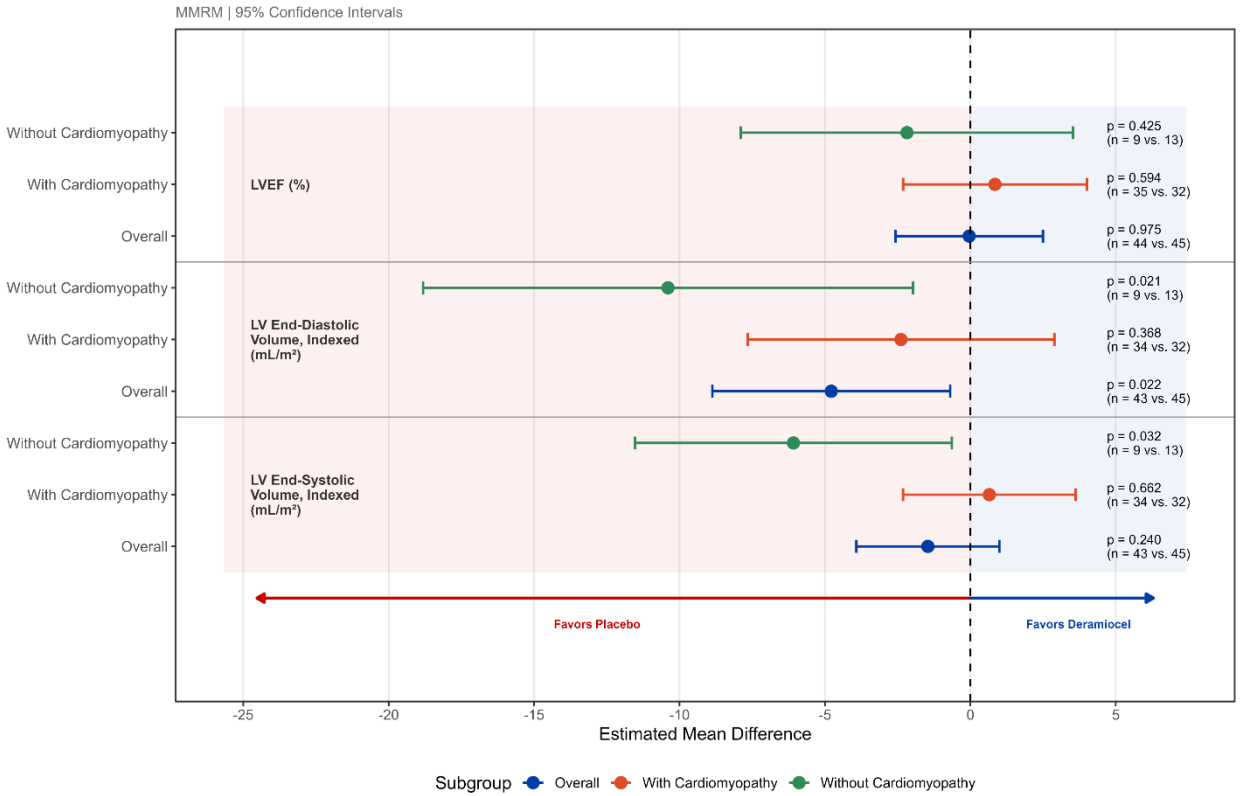
- Model did not converge

Subgroup Analyses for LVEF Based on SAP 1.1

Subgroup	Sample Size Treated (N=54)/Control (N=52)		Mean Difference Deramiocel-Placebo
Cohort A (N=61)	25	29	0.08 (-2.96, 3.12)
Cohort B (N=45)	19	16	-0.88 (-6.22, 4.47)
Ambulatory (N=16)	6	7	2.84 (-2.37, 8.05)
Non-ambulatory (N=90)	38	38	-0.29 (-3.03, 2.46)
Slow progressors (N=6)	0	4	-
Non-slow progressors (N=100)	44	41	0.60 (-1.83, 3.04)
Cardiomyopathy (N=79)	35	32	0.85 (-2.31, 4.01)
No cardiomyopathy (N=27)	9	13	-2.18 (-7.89, 3.53)

- Model did not converge

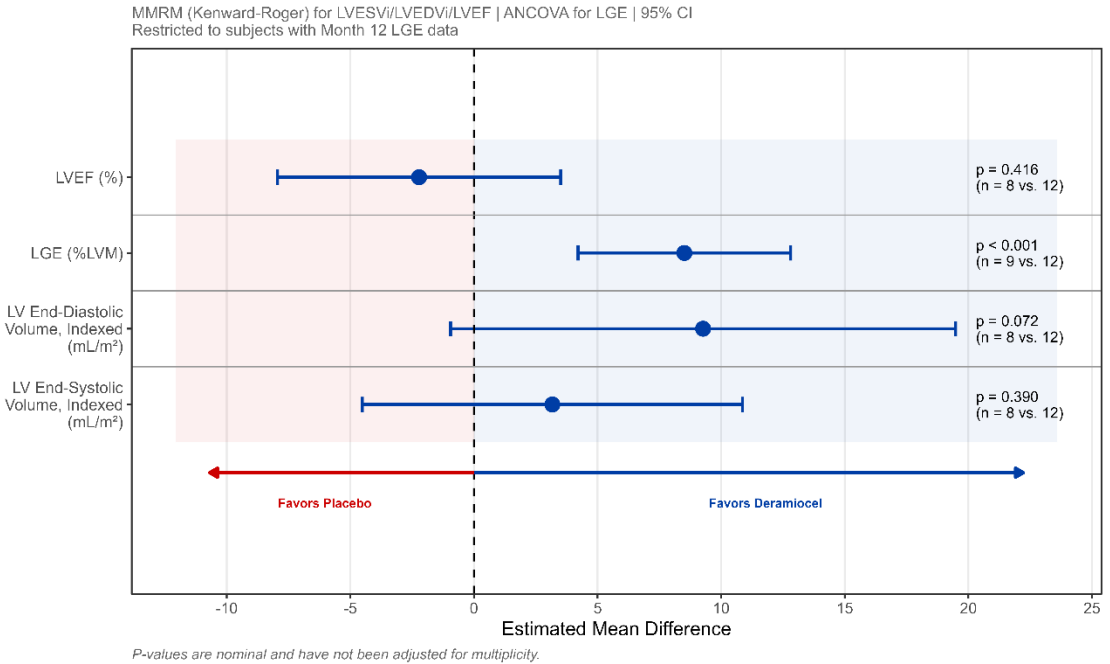
Change From Baseline to Month 12 LVEF/LVEDVi/LVESVi (SAP 1.1)



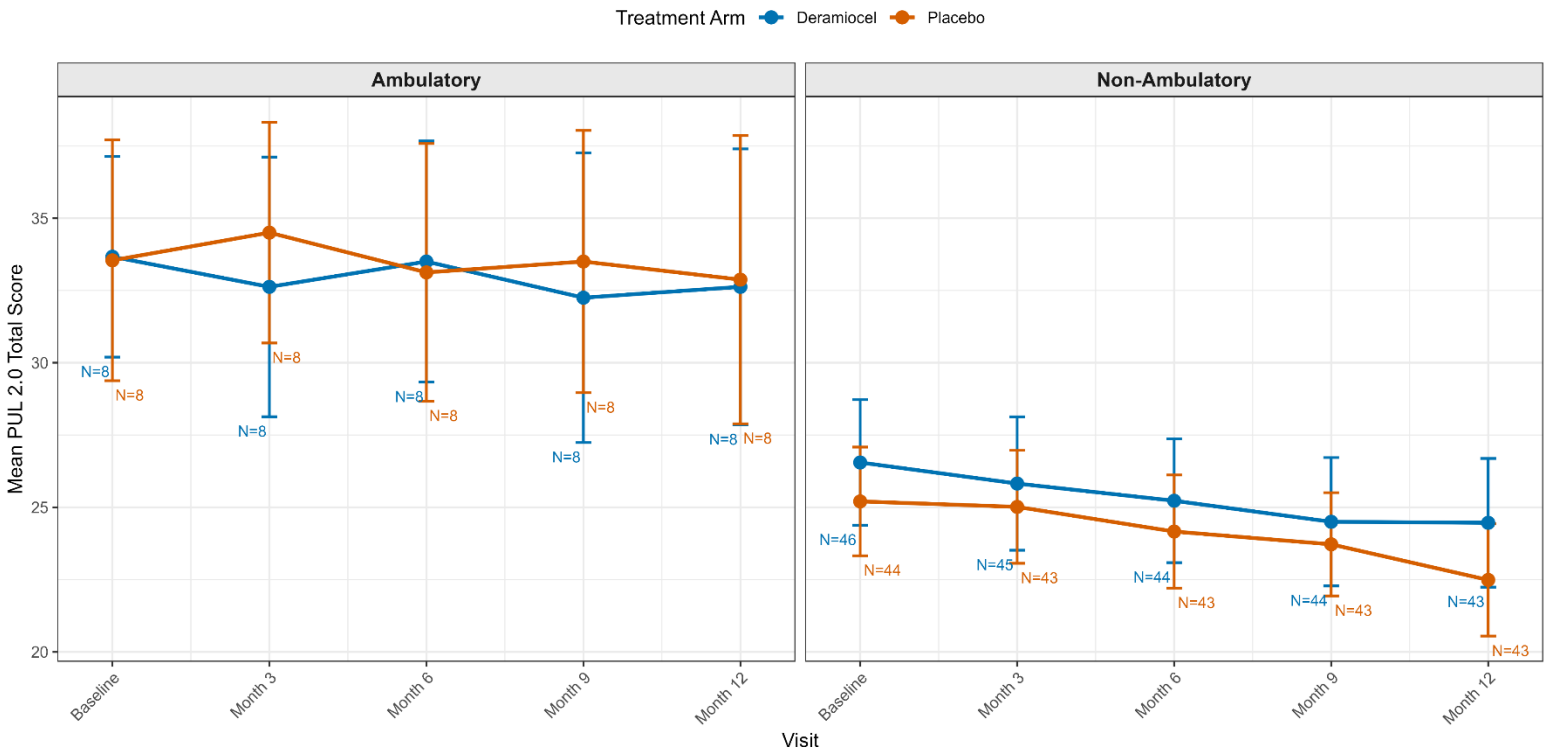
P-values are nominal and have not been adjusted for multiplicity.

Change From Baseline to Month 12 LVEF/LVEDVi/LVESVi/LGE Cohort B Patients With Month 12 LGE Data (SAP 1.1)

- Baseline and Month 12 LGE measurements were missing for over 50% of patients in HOPE-3
- p-values are nominal and have not been adjusted for multiplicity



PUL 2.0 Total Score by Ambulatory Status



HOPE-3 Concomitant Medications

Corticosteroid	Placebo (N=52)	Deramiocel (N=53)	Overall (N=105)
Any corticosteroid	51 (98.1%)*	53 (100%)	104 (99.0%)
Deflazacort	43 (82.7%)	39 (73.6%)	82 (78.1%)
Prednisone	7 (13.5%)	14 (26.4%)	21 (20.0%)
Prednisolone	1 (1.9%)	0	1 (0.9%)

*One placebo patient (27-0002) was initially recorded as not receiving corticosteroids due to a data entry omission; source record review confirmed ongoing deflazacort use on a weekend dosing regimen.

Givinostat and Vamorolone: Prohibited during DB, allowed in OLE with sponsor approval

Original BLA Submission: Efficacy Conclusions (1/2)

- Study design
  - Enrollment was terminated early, and the HOPE-2 and HOPE-2-OLE studies were not powered to detect a treatment effect.
  - There is variability between the deramiocel and placebo arms of HOPE-2 with regards to baseline cardiac history and concomitant cardiac therapies.
  - There are limitations of a non-randomized, single-arm, open-label extension study such as HOPE-2-OLE. Other issues include the gap period after HOPE-2 without a true baseline MRI, and post-hoc comparison to multiple external comparators.
- Totality of evidence
  - The clinical data submitted demonstrate inter- and intra-subject variability, without clear evidence of a beneficial treatment effect.
  - There is a lack of cohesiveness among the nonclinical studies, biomarker data from the clinical studies, and anatomic and functional data from cardiac imaging.

Original BLA Submission: Efficacy Conclusions (2/2)

- The final version of the SAP and all post hoc addenda were submitted after the first unblinded interim analysis was performed.
- Only the primary efficacy endpoint was formally tested – there was no multiplicity adjustment strategy proposed for overall Type I error control.
- The percentile rank data transformation performed by the Applicant is not justified and unreliable in a small sample, and the clinical interpretation is challenging.
- Violation of the intent-to-treat principle can introduce bias.
- A treatment policy strategy was used to handle intercurrent events of using concomitant cardiac and DMD treatments (not standardized).
- Exploratory and post-hoc analyses of exploratory endpoints cannot provide substantial evidence of effectiveness.
  - High risk of obtaining false positive results
  - Lack of control for multiple hypothesis testing
  - Pre-specification is the cornerstone of reliable regulatory evidence

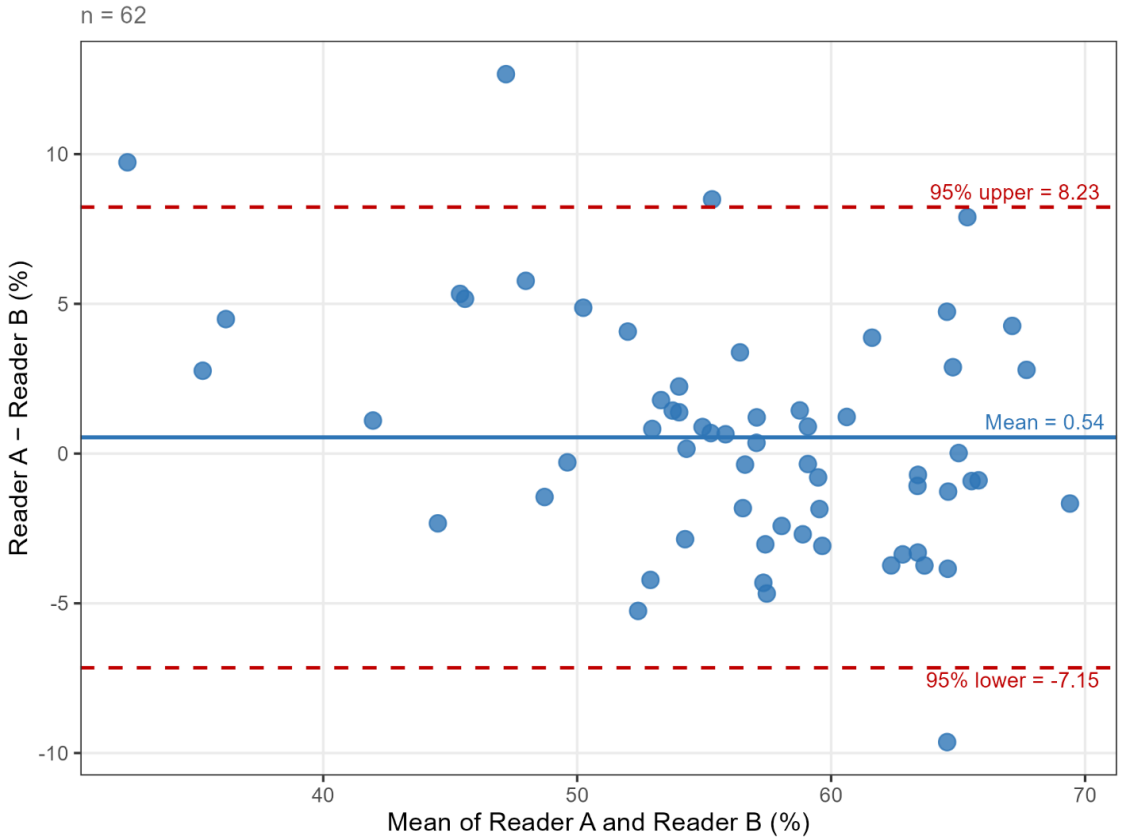
Study HOPE-3 Serious Adverse Events (SAEs)

- 5 SAEs in 5 patients who received placebo
  - One related to placebo: Grade 4 life-threatening anaphylaxis during the first infusion (patient discontinued participation in study)
  - Note: placebo consisted of same cell preservation solution as for deramiocel, but without cells (contains DMSO and other excipients)
- 1 SAE in 1 patient who received deramiocel
  - Related to deramiocel: Grade 2 infusion-related reaction at time of the second infusion

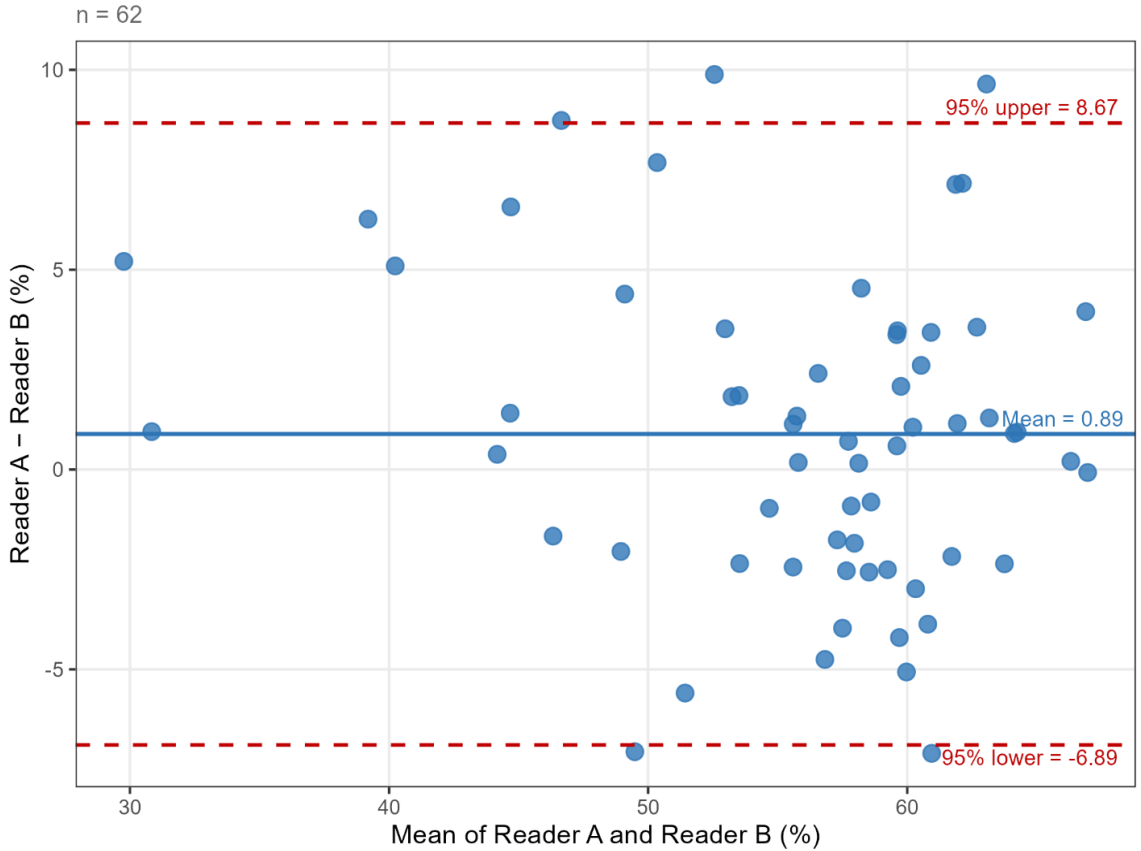
Hypersensitivity Reactions

- 5 SAEs due to hypersensitivity reactions
- HOPE-OLE: 1 event of hypersensitivity reactions in 1 subject which was SAE
- HOPE-2: 6 events of hypersensitivity reactions in 3 subjects
  - One case of anaphylaxis, prompted protocol change with pre-medication (high-dose steroids and H1/H2 blockers)
  - Only 1 case of hypersensitivity reaction occurred after premedication implementation
- HOPE-2-OLE: 12 events of hypersensitivity reactions in 7 subjects
- HOPE-3 (ongoing, blinded): Incidence not reported, reactions occurred in 29 subjects
  - One case of anaphylaxis
  - One infusion-related reaction

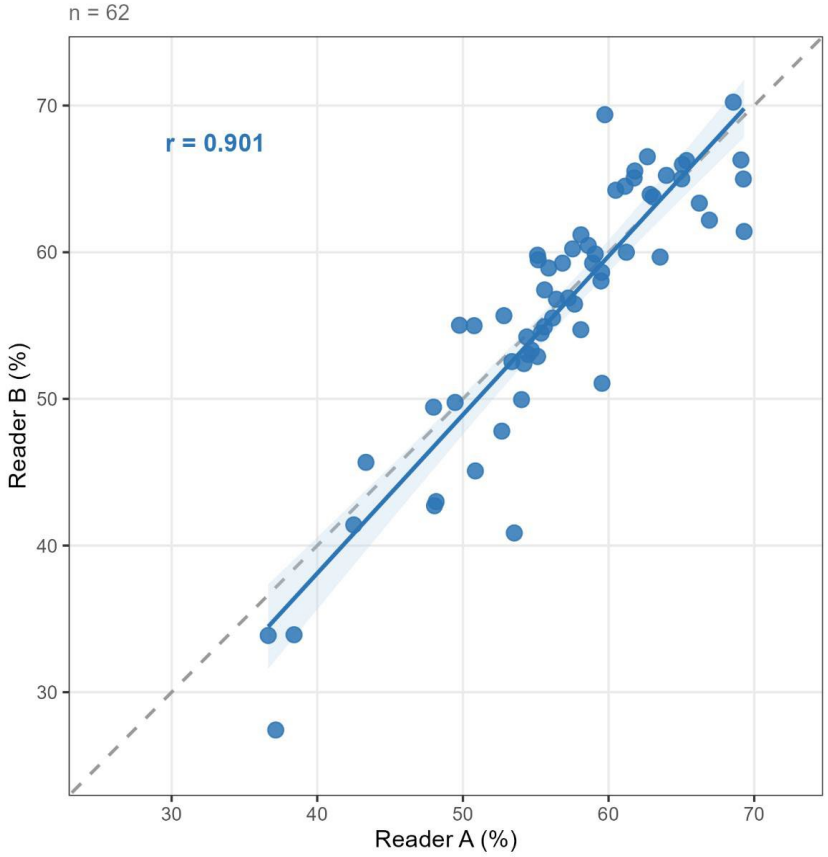
Pairwise Reading Comparison of LVEF (%) at Screening



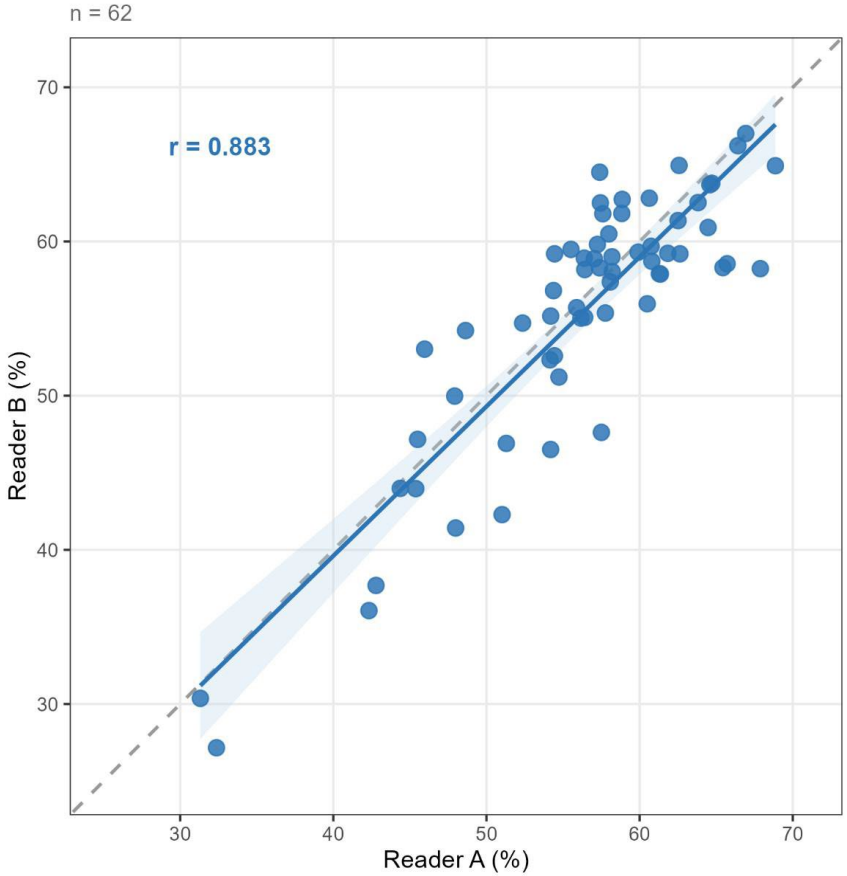
Pairwise Reading Comparison of LVEF (%) at Month 12



Pairwise Reading Comparison of LVEF (%) at Screening



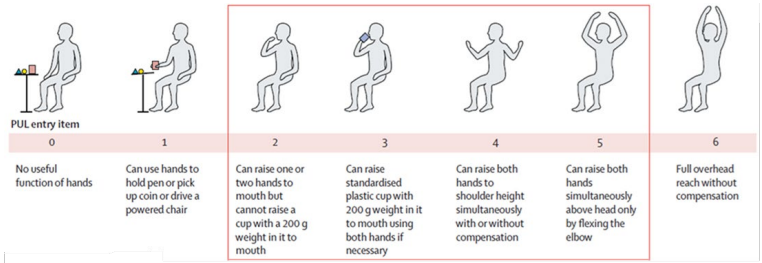
Pairwise Reading Comparison of LVEF (%) at Month 12

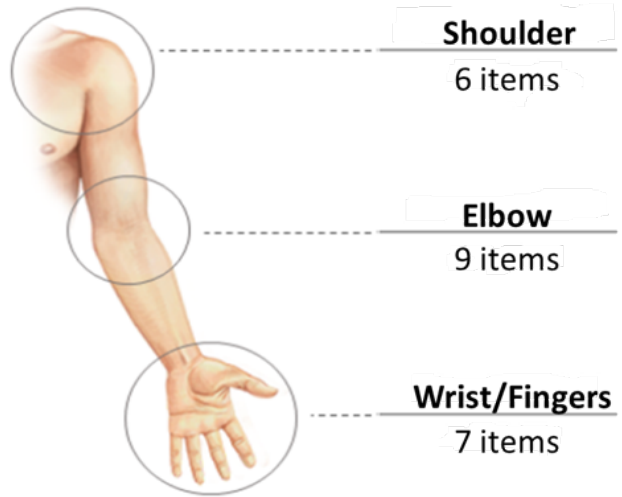


Absolute Difference in Imaging Scores Between Reader A and Reader B

Parameter / Statistic	Reader A vs Reader B Screening	Reader A vs Reader B Month 12
LVEF (%)	-	-
n	62	62
Mean	2.99	3.2
Standard deviation	2.57	2.48
Median	2.56	2.47
Minimum	0.02	0.07
Maximum	12.67	9.88
Coverage probability	0.85	0.77

Performance of Upper Limb (PUL 2.0) Assessment





Images: Modified from Applicant; McDonald et al (2022) Lancet 399:1049–1058

- Validated, clinician-reported evaluation of upper limb motor function
- Skeletal muscle weakness in DMD typically progresses from proximal to distal
  - Entry Item is evaluated first, to determine the subject's starting functional level
- PUL 2.0 consists of 22 items total, separately assessing ability to carry out practical tasks using the shoulder, elbow, and hand
  - Overall score range 0 to 42 points; higher is better
  - 20 items are scored as 0 - unable to perform, 1 - perform with compensation, or 2 - perform normally
  - 2 items are scored only as 0 or 1
- **Each 1-point change is considered clinically significant**

HOPE-2: Eligibility Criteria for PUL

Target population

PUL entry item	0	1	2	3	4	5	6
	No useful function of hands	Can use hands to hold pen or pick up coin or drive a powered chair	Can raise one or two hands to mouth but cannot raise a cup with a 200 g weight in it to mouth	Can raise standardised plastic cup with 200 g weight in it to mouth using both hands if necessary	Can raise both hands to shoulder height simultaneously with or without compensation	Can raise both hands simultaneously above head only by flexing the elbow	Full overhead reach without compensation
Brooke Upper Extremity Scale	6	5	4	3		2	1

Source: McDonald 2022

Performance of Upper Limb 2.0 – Mid-Level Domain

Key Features

- Mid-level domain evaluates elbow flexion/extension and proximal forearm function: 9 items, max score 17
- Items scored 0 (unable), 1 (impaired/compensated), or 2 (unimpaired); administered in the preferred arm
- Mid-level domain declines at a measurable, steady rate over 12 months — more sensitive than shoulder or distal for trial detection
- Natural history: ~1.3-pt decline/24 months in mid-level domain

Pros and Cons

- Pros
  - Clinician-administered — controlled, standardized conditions
  - Sensitive to clinically meaningful change in 12-month window
  - Directly maps to independence-critical ADLs (feeding, grooming, wheelchair use)
- Cons
  - Does not assess endurance or fatigue during sustained tasks
  - Scoring heterogeneity at extreme baselines (entry item 2 vs. 6)

Duchenne Video Assessment (DVA) – Eat 10 Bites

Key Features

- Observer-rated, video-based assessment; caregivers record patient at home using a secure mobile app
- Evaluates hand-to-mouth function during a standardized eating task (10 spoonfuls/bites)
- Scores severity of compensatory movement, fatigue, and task efficiency — not just task completion
- Higher score is worse

Pros and Cons

- Pros
  - Patient- and caregiver-centered; directly relevant to independence
  - Reflects typical (real-world) performance rather than optimal clinic performance
  - Sensitive to incremental, fatigue-related decline missed by PUL 2.0
- Cons
  - MCID not formally established for the Eat 10 Bites sub-task
  - Video quality and home environment variability may introduce noise
  - Scoring depends on availability and training of certified raters

Patient Global Impression of Severity (PGI-S)

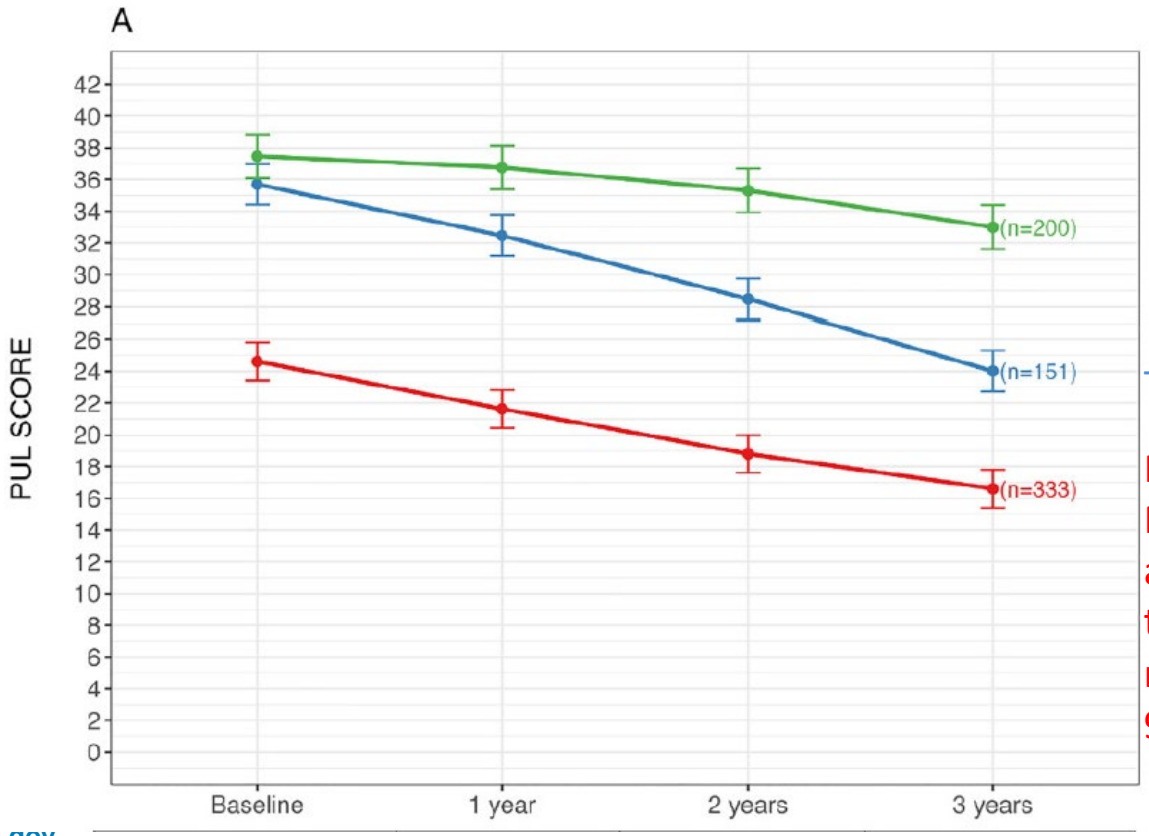
Key Features

- Single-item patient-reported outcome (PRO): patient rates overall severity of their DMD condition
- Ordinal 7-point Likert scale: 1 = Normal (not at all ill) to 7 = Among the most extremely ill
- Assesses the patient's own global perception of disease burden at a given timepoint

Pros and Cons

- Pros
  - Direct patient voice: reflects lived experience of disease severity
  - Integrates holistic burden not captured by motor/cardiac measures alone
- Cons
  - Highly subjective; susceptible to mood, expectations, and recall bias
  - Single item — limited granularity compared to multi-domain PRO instruments
  - In pediatric DMD: child vs. caregiver response may differ; cognitive impairment affects validity
  - Response shift bias: patients may normalize or adapt to worsening over time

Natural History of Upper Limb Function



Ambulatory

Transitioning

Non-ambulatory
N=116 pts with 333 assessments, baseline mean total score 24.35, 3-year reduction -8.09,
95% CI: -8.66, -7.51)

Coratti et al. 2025

Prognostic factors in DMD Cardiomyopathy

- Observational study in 78 patients with DMD who underwent cMRI (Soslow et al., 2023)
  - Median age 12.5 years (range 7.4-27.5 years), majority non-ambulatory
  - Median LVEF 57%, 32 patients (41%) had LVEF < 55%, 62% were on ACEi, 9% on ARB
- cMRI measures showed association with all-cause mortality
  - LVEF, LV volume measurements (LVEDVi and LVESVi), LGE (FWHM), circumferential strain
  - A 3% decrease in LVEF over 2 years was associated with mortality (HR 1.32, CI 1.12-1.55)

Limitations:

- Follow-up cMRI not available for all patients
  - 15 patients (19%) with only 1 cMRI study
- Single center
  - Generalizability to other centers, different cMRI protocols not studied
- Relatively small number of events: 15 deaths (19%)
- Analyses do not account for confounders
- Observational
  - Whether interventions leading to improved imaging parameters will also improve clinical outcomes is unknown

BLA Key Milestones

Milestone	Date	Comments
First subject-first visit	June 22, 2022	-
SAP 1.1-1.8	July 19, 2022 - June 11, 2024	Primary: PUL 2.0 - mean change from baseline Secondary: LVEF - mean change from baseline
pre-BLA meeting	August 2, 2024	-
original BLA submission	December 31, 2024	Studies HOPE-2, HOPE-2-OLE
Last subject-last visit	June 18, 2025	-
Complete Response Letter	July 9, 2025	Lack of substantial evidence of effectiveness
Type A meeting	August 13, 2025	Proposal to change HOPE-3 primary endpoint to LVEF
SAP 2.0	September 26, 2025	Primary endpoint (PUL 2.0) changed to mean % change from baseline LVEF- mean change from baseline (made key secondary endpoint)
SAP 3.0	November 24, 2025	Key secondary endpoint (LVEF) changed to mean ranked change from baseline
Data unblinding	November 25, 2025	-
BLA resubmission	December 29, 2025	Study HOPE-3
Incomplete Response Letter	January 13, 2026	-
BLA resubmission	February 20, 2026	Study HOPE-3

Regulatory History of BLA Resubmission

Date	Milestone and Background Information
December 31, 2024	BLA submission
July 9, 2025	**Complete Response Letter** sent to Applicant
August 13, 2025	Type A meeting to discuss Complete Response Letter
December 29, 2025	BLA resubmission
January 13, 2026	Incomplete Response Letter sent to Applicant. Submission deemed incomplete due to missing documents (complete CSR for HOPE-3, narrative summaries of SAEs, and all versions of the clinical protocol and SAP).
February 6, 2026	Informal teleconference to discuss Incomplete Response Letter
February 20, 2026	**BLA resubmission**
March 4, 2026	**IR**: Applicant discussed precautions taken to minimize risk of unblinding HOPE-3. Applicant committed to providing additional data from HOPE-3.
March 25, 2026	**IR**: Applicant provided the Blinding and Unblinding Plans for HOPE-3. Applicant provided additional information regarding assessments of cardiac MRI quality, inter-reader variability, and the adjudication process.
April 3, 2026	**IR**: Applicant provided documentation related to the DSMB for HOPE-3, including DSMB charter and meeting minutes.
April 14, 2026	**IR**: Applicant provided information about changes to the SAP and maintenance of blinding during HOPE-3.
May 1, 2026	**IR**: Applicant provided information about the following items: unblinding procedures and documentation, criteria for slow progressors, clinical correlations with donor-specific antibody levels, code used for efficacy analyses, and the changes to the prespecified analysis models.
May 14, 2026	**IR**: Applicant provided information describing how their analyses of efficacy were performed. Long-term clinical data were requested.
June 4, 2026	**IR**: Additional narrative summaries and safety information were requested.

Nonclinical Pharmacology

- **Proposed mechanism of action (MOA):**
  - Composite effect including anti-fibrotic, anti-inflammatory, immunomodulatory, and pro-angiogenic effects mediated through the secretion of exosomes and growth factors[1].

- **In Vivo Nonclinical data:**
  - A single IV administration of murine cardiosphere-derived cells (CDCs) to female mdx mice[2] (a mouse model of DMD) increased mean LVEF by ~20±10%, qualitatively reduced cardiac fibrosis, increased myofiber number and increased ex vivo soleus muscle specific force by ~5% 3-weeks following administration. A non-statistically significant trend towards increase in the distance traveled on a treadmill was also observed.
  - A second IV administration at 3-weeks produced no significant additional improvement in skeletal muscle function at the 6-week assessment. Cardiac endpoints were not assessed.

- **Model and Study Limitations:**
  - Mdx mice develop cardiac pathology, including decreased left ventricular ejection fraction, but do not recapitulate the progressive decline in skeletal muscle function in DMD. Therefore, the relevance of the animal data to support clinical benefit is difficult to interpret.
  - This 6-week pilot study was not adequately designed to demonstrate functional changes overtime or to assess the biological activity of repeated doses on cardiac or skeletal muscle function.
  - The study used a murine surrogate CDC product, not deramiocel. Comparability assessment was not performed.
  - The report for the study did not discuss randomization of animals, masking of assessments, and study deviations.

- **Conclusion:**
  - While these nonclinical findings provide preliminary support for the biological activity of CDCs in DMD cardiomyopathy, the data do not provide support for the MOA of deramiocel. Key limitations, including lack of mechanistic evidence and use of the surrogate product, do not support the use of these data as confirmatory evidence of effectiveness for deramiocel in DMD cardiomyopathy.

[1]Angiopoietin-2, bFGF, HGF, IGF-1, SDF-1, VEGF [2]C57BL/10ScSn-Dmd^{mdx}/J (mdx) mice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