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DERAMIOCEL

SPONSOR BRIEFING DOCUMENT

CELLULAR, TISSUE, AND GENE THERAPY ADVISORY COMMITTEE

MEETING DATE: 29 JULY 2026

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ACE	angiotensin-converting enzyme
ANCOVA	analysis of covariance
ARBs	angiotensin II receptor blockers
BLA	Biologics License Application
BMI	body mass index
BNP	brain natriuretic peptide
CDC	cardiosphere-derived cell
CI	Confidence interval
CM	conditioned media
CMR	cardiac magnetic resonance
cMRI	cardiac magnetic resonance imaging
COL1A	collagen type 1 alpha 1 chain
COL3A	collagen type 3 alpha 1 chain
DMD	Duchenne muscular dystrophy
DMDCM	DMD-associated cardiomyopathy
DSMB	data safety monitoring board
DVA	Duchenne Video Assessment
ECC	external comparator for cardiac parameters
ECP	external comparator for the PUL
EDV	end diastolic volumes
EDVI	end diastolic volumes-indexed
EF	ejection fraction
ESV	end systolic volumes
ESVI	end systolic volumes-indexed
ET	early termination
FDA	Food and Drug Administration
GDMT	guideline directed medical therapy
GST	Global Statistical Test
HCT/P	Human Cells, Tissues, and Cellular and Tissue-Based Products
HR	hazard ratio
IC	Intracoronary
ICC	intraclass correlation coefficient
IP	investigational product
ITT	intent to treat
IV	Intravenous
LGE	late gadolinium enhancement
LS	least squares

LVEF	left ventricular ejection fraction
LVEDVI	left ventricular end-diastolic volume index
LVESV	left ventricular end-systolic volume
LVESVI	left ventricular end-systolic volume index
MMRM	mixed model with repeated measures
OR	odds ratio
PDUFA	Prescription Drug User Fee Act
PGI-S	Patient Global Impression of Severity
PPMD	Parent Project Muscular Dystrophy
PUL	performance of upper limb
RMAT	Regenerative Medicine Advanced Therapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SGLT-2	Sodium-Glucose Cotransporter-2
TEAE	treatment-emergent adverse event
US	United States

1 EXECUTIVE SUMMARY

1.1 Introduction

This briefing document summarizes the evidence supporting approval of deramiocel for the treatment of Duchenne muscular dystrophy (DMD). The evidence is primarily based on the Phase 3 HOPE-3 study and is supported by findings from the HOPE-2 study and its long-term open-label extension (HOPE-2 OLE).

Deramiocel has shown consistent and long-term benefits in both skeletal muscle function, particularly the performance of the upper limb, as well as cardiac function with a favorable safety profile. Evidence from the HOPE clinical program, one of the largest clinical development programs conducted in DMD to date, supports a positive benefit-risk profile for deramiocel.

Clinical studies in rare, heterogeneous diseases such as DMD are inherently challenging because of small patient populations and individual outliers which can influence interpretation of data. Despite these challenges, deramiocel has demonstrated consistent results across multiple complementary analytical approaches and across multiple studies, including two randomized placebo-controlled trials, HOPE-3 and HOPE-2. Although several therapies are approved for DMD, none are approved for the treatment or prevention of DMD-associated cardiomyopathy (DMDCM), the leading cause of death in DMD, and no therapy has a regulatory indication based on preservation of upper-limb function, particularly in non-ambulatory patients. Consequently, there remains a substantial unmet medical need for therapies that address both skeletal muscle disease and cardiac function across the course of DMD.

HOPE-3 is the largest randomized, placebo-controlled trial to evaluate a therapy targeting both skeletal and cardiac muscle in DMD and one of the few pivotal trials specifically designed for the non-ambulatory DMD population, and the only one to report positive primary results. HOPE-3 met its prespecified primary endpoint and key secondary endpoint. HOPE-2 also demonstrated significant skeletal and cardiac muscle benefit, and HOPE-2 OLE continues to demonstrate the long-term (up to 3 years) clinically meaningful benefit in patients with DMD.

Throughout the clinical development program, Capricor has remained responsive to Food and Drug Administration (FDA) feedback while adapting to emerging scientific evidence, the evolving understanding of DMD, and the needs of patients. To that end, based on the tenor of information requests received during the BLA review, Capricor understands that the FDA may have questions regarding the final statistical analysis plan (SAP). Accordingly, in the interest of transparency, Capricor has provided analyses using earlier versions of FDA-submitted SAPs, in addition to the final version. Importantly, the estimated treatment effect is consistent across all models and indicates clinically meaningful benefits for patients with DMD, particularly those who are non-ambulatory patients or have DMDCM.

Overall, HOPE-3 provides substantial evidence of deramiocel's ability to improve the lives of patients with DMD, with HOPE-2 and its long-term extension study HOPE-2-OLE offering supportive and consistent evidence of efficacy and longer-term safety. Across these studies, deramiocel showed a consistent benefit on the two outcomes central to the proposed indication, upper-limb function (Performance of the Upper Limb, PUL 2.0) and cardiac function (left ventricular ejection fraction [LVEF]); see Section 5.2 for endpoint selection details. Table 1 summarizes the treatment effect on each endpoint in the pivotal, placebo-controlled HOPE-3 trial, the earlier randomized HOPE-2 trial, and the long-term open-label HOPE-2-OLE study, in which the direction and magnitude of benefit are reproduced across independent populations, metrics, and follow-up durations.

Table 1: Deramiocel Treatment Effects on Upper-Limb Function (PUL 2.0) and Left Ventricular Ejection Fraction Across the HOPE Clinical Program

	HOPE-3[c] (N=106)	HOPE-2[a] (N=20)	HOPE-2-OLE[b] (N=13)
PUL 2.0 Total Score Analysis model and timepoint	MMRM percent change; mo 12	Percentile-ranked change; mo 12	Modeled vs external comparator; mo 36
Treatment effect (95% CI)[e]	4.55 (0.47 to 8.63)	28.8 (1.5 to 56.1)	3.73 (0.66 to 6.81)
P value	0.03	0.04	0.02
LVEF Analysis model and timepoint	Ranked ANCOVA; mo 12[d]	Percentile-ranked change; mo 12	Modeled vs external comparator; mo 24
Treatment effect (95% CI)[e]	11.65 (0.47 to 22.82)	45.7 (19.1 to 72.2)	6.40 (1.82 to 10.97)
P value	0.04	0.002	0.008

ANCOVA, analysis of covariance; CI, confidence interval; ITT, intention-to-treat; LVEF, left ventricular ejection fraction; mo, month; MMRM, mixed-effects model for repeated measures; PUL, Performance of the Upper Limb.
[a] HOPE-2: randomized, double-blind, placebo-controlled; analysis cohort, deramiocel n=8 and placebo n=12; ITT. The prespecified primary endpoint was the mid-level (elbow) dimension of PUL 1.2 (between-group difference, 36.2 [7.9 to 64.5]; P = .01); the PUL 2.0 total score shown is a concordant re-analysis.
[b] HOPE-2-OLE: open-label extension without an internal control; effects are modeled between-group differences versus a propensity-matched external comparator (cardiac comparator n=16; upper-limb comparator n=13).
[c] HOPE-3: randomized, double-blind, placebo-controlled; ITT, deramiocel n=54 and placebo n=52; LVEF-evaluable population n=83.
[d] Ranked ANCOVA including treatment, cohort, slow-progressor indicator, an indicator for screening LVEF ≥45%, baseline LVEF, age, and the age-by-baseline-LVEF interaction; the change score and baseline are ranked separately.
[e] Effect is the between-group difference (deramiocel minus comparator); a positive value favors deramiocel. The effect scale differs by study (rank units, percentage points, or percent change) and is not directly comparable across columns.
P values are 2-sided; HOPE-2-OLE comparisons are exploratory and nominal.

1.2 Deramiocel Description

Deramiocel is a cellular therapy consisting of human allogeneic cardiosphere-derived cells (CDCs). Deramiocel is administered as an intravenous (IV) infusion containing 1.5 x 10^8 (150 million) CDCs per dose every three months.

Preclinical studies demonstrate that CDCs in deramiocel exert anti-fibrotic and immunomodulatory therapeutic effects predominantly through paracrine signaling via secreted exosomes and growth factors, rather than direct engraftment, which in turn aids in muscle survival and attenuation of fibrosis. The clinical data reported here are consistent with these preclinical observations and show evidence of deramiocel's impact on skeletal and cardiac function and directly demonstrate the inhibition of cardiac fibrosis as measured by cardiac magnetic resonance imaging (cMRI) using late gadolinium enhancement (LGE). Cardiac segmental scarring in DMD is present in 15% of boys <10 years of age and prevalence increases progressively with age. It is an irreversible progressive process and a predictor of cardiac functional decline and mortality. This disease-modifying activity distinguishes deramiocel from existing therapies that primarily address dystrophin replacement without clear evidence of impact on muscle fibrosis and functional decline. See Section 3 for an overview of deramiocel and the mechanism of action.

1.3 Target Indication

The indication proposed for deramiocel in the BLA (December 2024) is for the treatment of cardiomyopathy in DMD, an indication pursued at FDA's suggestion during the pre-BLA meeting and a cardiology-focused follow-up (both in August 2024), based on HOPE-2 and its follow-on long-term OLE study, HOPE-2-OLE.

The addition of the HOPE-3 Phase 3 study in the BLA resubmission, which included both skeletal muscle and cardiac functional assessments, provides a comprehensive characterization of treatment effects that supports an indication encompassing both skeletal muscle and cardiac function. This is consistent with the post-action Type A meeting, at which FDA stated that it "remains committed in collaborating with the Applicant and will exercise further regulatory flexibility by reviewing the data from the HOPE-3 study to assess its primary endpoint as PUL and see the contribution of LVEF in the overall disease progression of the enrolled subjects." Discussions with FDA regarding labeling have not yet occurred.

1.4 Regulatory History

The clinical development program for deramiocel was designed in collaboration with the FDA to establish safety and efficacy in patients with DMD, with engagement since 2015. Following a Complete Response Letter (CRL) for BLA 125842 in July 2025 and subsequent alignment at a Type A post-action meeting (August 2025), Capricor submitted a complete BLA resubmission in February 2026 incorporating safety and efficacy data from the Phase 3 study HOPE-3; FDA classified it as a complete, Class 2 response with a PDUFA goal date of August 22, 2026. See Section 4 for additional discussions on regulatory milestones.

The HOPE-3 protocol (Versions 5-9, see Section 4.1.1 for details) and SAP evolved over the course of the study as its regulatory purpose shifted, progressing from a pivotal Phase 3 trial using clinical drug supply, through the addition of commercial supply (cohort B) and

support for ex-US authorization, to addressing the CRL and ultimately supporting the BLA resubmission. Key regulatory highlights supporting this evolution are summarized in Table 2. The major protocol amendments and milestone SAP versions, including the two versions reviewed by the FDA without further feedback (v1.7 and v2.0) and the final version (v3.0), along with the regulatory context and associated changes for each, are detailed in Section 4.1.1. Based on the information requests received during the BLA review, Capricor understands that the FDA may have questions regarding the final SAP (v3.0); accordingly, Capricor has provided analyses using earlier SAP versions, in addition to the final version.

Table 2: Key Regulatory and Study Conduct Milestones

Date	Document/Milestone	Description
08JUN2023	SAP 1.5	First SAP version submitted to FDA for feedback as part of Type B meeting briefing package to add an additional cohort (Cohort B) to assess efficacy of product from proposed commercial facility.
21AUG2023	Protocol Amendment 5 And SAP 1.6	Protocol amended to include Cohort B, as agreed at Type B meeting. Added LGE assessments for Cohort B. SAP 1.6 submitted in response to FDA feedback on SAP 1.5.
06DEC2023	SAP 1.7	Submitted to FDA in response to FDA feedback on SAP 1.6. No additional feedback received.
02AUG2024	Pre-BLA FDA meeting	FDA recommended Capricor file BLA with cardiac-focused indication based on review of data from HOPE-2, HOPE-2-OLE, and propensity-matched natural history data. Agreement reached to combine Cohorts A and B into a single analysis group and use for OUS study expansion (Protocol Amendment 6, submitted 03Dec2024).
09JUL2025	Complete Response Letter	Capricor received a CRL requesting additional data to support the cardiomyopathy indication.
25JUL2025	Protocol Amendment 8 (never implemented or submitted to IRB)	In response to the CRL, reverted plans to USA-only enrollment and changed the primary efficacy endpoint from PUL to LVEF by cMRI, reflecting the shift in focus toward cardiomyopathy.
13AUG2025	Type A FDA meeting	Capricor held a Type A meeting to address the CRL.
12SEPT2025	Type A FDA meeting minutes	FDA requested that the primary endpoint be maintained to be Total PUL 2.0 and change from baseline in LVEF designated as a key secondary endpoint. Specifically, FDA commented that change from baseline in LVEF could potentially be considered a key secondary and continued to acknowledge the clinical significance of skeletal muscle function, as assessed by PUL and as presented by the Applicant in the historical disease progression of DMD. Furthermore, FDA stated that it remains committed in collaborating with the Applicant and will exercise further regulatory flexibility by reviewing the data from the HOPE-3 study to assess its primary endpoint as PUL and see the contribution of LVEF in the overall disease progression of the enrolled subjects.
26SEPT2025	Protocol Amendment 9.0	Submitted to IND with cross reference to BLA, to revert the primary efficacy endpoint to the original endpoint of Total PUL

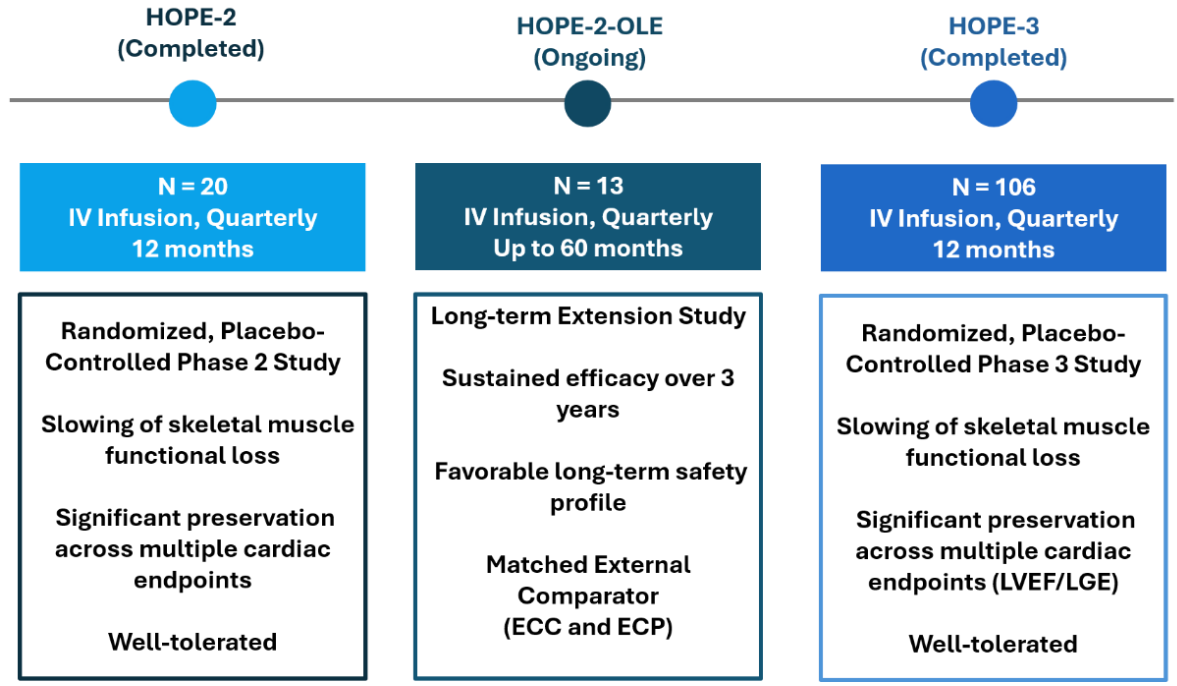
Date	Document/Milestone	Description
	and SAP 2.0	2.0 per FDA request at Type A Meeting, and analytic approach changed from absolute change to percent change from baseline based on recent publications supporting this as a more sensitive and clinically meaningful measure of function. LVEF was updated to a key secondary endpoint (see Appendix 10.2).
24NOV2025	SAP 3.0	Specified analysis for the key secondary endpoint LVEF utilizing an ANCOVA on ranks model using Month 12 change from baseline values to protect against the influence of outlying observations in a small cardiac-evaluable sample, given the anticipated non-normal, with few influential outliers seen in prior LVEF data and clinical knowledge.
25NOV2025	Database lock	HOPE-3 Phase 3 Clinical Study milestone
25NOV2025	Unblinding	HOPE-3 Phase 3 Clinical Study milestone

1.5 Clinical Development Program

Primary evidence for the safety and efficacy of deramiocel for the treatment of cardiomyopathy and skeletal muscle pathology in patients with DMD is based on the results of HOPE-3 and is supported by the HOPE-2 and HOPE-2-OLE clinical studies (Table 1, Figure 1). HOPE-3 is the first Phase 3 trial of systemic non-autologous cell therapy in a genetic disease, and the first Phase 3 registration trial in late-ambulant and non-ambulant patients with DMD. This pivotal trial confirms the findings of the HOPE-2 trial; both studies demonstrated preservation of cardiac and upper limb function relative to placebo. HOPE-2-OLE demonstrates the consistency and continuity of benefit over time. See Section 5 for additional discussion on the clinical development program.

Upper limb function measured by PUL was selected as the primary efficacy endpoint across all three clinical studies based on its validation as a clinically meaningful measure of disease progression in non-ambulant DMD populations and in alignment with FDA guidance. Cardiac function was assessed by cMRI across all three studies, with LVEF as the key secondary endpoint in HOPE-3 based on its established clinical relevance. See Section 5.2 for a detailed summary endpoint selection.

Figure 1: Clinical Efficacy and Safety Studies of Deramiocel in DMD



ECC: external comparator for cardiac parameters ; ECP: external comparator PUL

1.6 Efficacy Summary: HOPE-3

HOPE-3 was a multicenter, randomized, double-blinded, placebo-controlled Phase 3 study of 106 patients with DMD who were either late-ambulatory (defined as having a 10-meter walk/run time of 10 seconds or greater, and thus predicted to lose significant upper limb function and ambulation within 2 years) or non-ambulatory with preserved hand-to-mouth function. All patients were treated with stable doses of corticosteroids and the majority received standard-of-care heart failure medications. At 12 months of follow up, all prespecified, type 1 error controlled primary and secondary endpoints were statistically significant, confirming prior clinical evidence that deramiocel slows progression of both skeletal myopathy (PUL 2.0) and cardiomyopathy (LVEF including LGE, a measure of fibrofatty replacement of cardiac tissue). Deramiocel was safe and well tolerated. This is the first Phase 3 trial in advanced DMD to meet its primary efficacy endpoint.

Significant findings:

- For PUL 2.0, LS-mean percent change at 12 months favored deramiocel by 4.55% for Total, the primary endpoint (95% confidence interval [CI]: 0.47, 8.63; p=0.029), and 8.12% for Mid-level, a pre-specified secondary endpoint (95% CI: 2.12, 14.11; p=0.008). This corresponds to an average of 1.2-point difference in Total and 1.0-point difference in Mid-level.
- For LVEF, the pre-specified key secondary endpoint, least squares (LS)-mean ranked change from baseline favored deramiocel by 11.65 (95% CI: 0.47, 22.82; p=0.041). The absolute mean change in LVEF showed a treatment benefit of

2.4-percentage points. The subgroup analysis of patients with cardiomyopathy also favored deramiocel by 12.36 (95% CI: 2.34, 22.38; p=0.0165).

- For LGE, a measure of cardiac scarring, the LS-mean change from baseline in number of affected segments favored deramiocel by -3.01 (95% CI: -5.50, -0.51; p=0.022).
- The Global Statistical Test (GST) favored deramiocel with an LS-mean difference of 0.28 (z-score) (95% CI: 0.05, 0.52; p=0.017).

1.7 Clinical Meaningfulness

The therapeutic effects of deramiocel are not subtle. The 1.2-point difference seen in the Total PUL 2.0 score at 12 months, in the context of a highly heterogeneous disease in which PUL score may continuously decline over 1-2 decades, indicates a clinically relevant delay in disease progression. The 54% slowing of mean skeletal muscle disease progression, relative to placebo, represents >1 year of progression saved for every 2 years of natural progression in the absence of deramiocel. In addition, since the mid-level PUL has the most predictable and linear decline over 12 months, it was employed as a pre-specified type 1 error controlled secondary endpoint in HOPE-3 and the primary endpoint for the HOPE-2 trial. Changes in the mid-level PUL are particularly relevant, as they are highly associated with quality-of-life indicators such as the ability to eat independently.

DMD leads to progressive and irreversible loss of upper limb function in all cases that begins to be measurable prior to loss of ambulation and is a major determinant of quality of life for non-ambulatory patients and caregivers. Surveys conducted by Parent Project Muscular Dystrophy (PPMD) confirm hand to mouth function and independent feeding to be one of the most important determinants of quality of life for both patients and caregivers and relative stabilization or slowing of disease progression has been determined by these stakeholders to be a key determinant of an efficacious therapeutic in terms of meaningful benefit (Peay et al. 2016). The HOPE-3 Phase 3 results for deramiocel should be read through that lens.

Clinical meaningfulness of the total PUL results can be appreciated by focusing specifically on the treatment effect for the mid-level domain of the PUL 2.0. This domain captures elbow and forearm function, the movements that let a person bring a hand to the mouth, lift and handle objects, and hold the arm steady. In a disease where decline is inevitable, holding on to function is critical. In fact, patients report that their first thought of the day, is “no worse today”. While the full PUL 2.0 is a reasonable tool to assess upper limb function over the entire course of upper limb disease progression in a broad population of patients with DMD, the mid-level domain is where preserved function is most detectable in a 12-month study and directly meaningful to patients in terms of activities of daily living. Even a one-point change in a total PUL score or a PUL domain such as the mid-level PUL 2.0 has been deemed to be a meaningful change to patients (Gillman et al. 2025).

In order to provide contextual interpretation of the clinic-based assessment of the PUL, Capricor employed the DVA (Duchenne Video Assessment) which is a home-based video assessment of quality of movement and compensations to maintain activities of daily living that was developed by the DMD community (caregivers, patients and physiotherapists). It has been validated as an endpoint to measure meaningful disease progression in DMD. Of the entire panel of DVA tests, the Eat-10 Bites assessment, an independent video-based measure of how a patient can bring their hand to their mouth to self-feed 10 times assessed in a blinded manner, was prespecified as a secondary endpoint, which was a clinically meaningful measure of self-feeding and the DVA scorecard most related to functions assessed by the mid-level PUL 2.0.

Of great importance, in the HOPE-3 clinical trial, both the mid-level PUL and the DVA Eat 10 bites measure move in concert with regard to assessment of a deramiocel treatment effect. Among placebo patients, the progressive loss of hand-to-mouth function was accompanied by loss of ability and/or greater compensations to bring the hand to mouth to effectively feed 10 times, with mean eating ability declining by roughly 10 points in placebo patients compared to a decline of 3 points in the deramiocel-treated group. Because these are two independent instruments, a clinician-administered motor scale and a centrally read video assessment of an activity of daily living (self-feeding) developed as a meaningful measure by the DMD community, their agreement demonstrates that both endpoints capture a similar meaningful underlying loss of hand to mouth function, providing construct and face validity and clinically meaningful contextualization to the mid-level PUL results.

The focus on hand-to-mouth function is not arbitrary; patients who are non-ambulatory most often identify this item as the one that matters most. Its importance reaches well beyond the one movement scored, because bringing the hand to the face and head is a gateway to ordinary daily life: eating and drinking, brushing teeth, shaving, putting glasses back on when they slip, scratching an itch, raising a hand to block something coming toward the face. A person who can bring the hand to mouth-and-head level can also bring the head down to meet the hand, and that reciprocal range opens the door to washing and drying the hair and to pulling a shirt off and putting it back on. Maintaining hand-to-mouth function preserves independence, a key benchmark of quality of life.

There are no approved DMD-specific therapies for cardiomyopathy. Cardiomyopathy is the leading cause of death in DMD, and progressive decline in left ventricular function, accompanied by accumulating myocardial fibrosis, defines its course. Duchenne-associated cardiomyopathy is a silent killer. The heart muscle is damaged in a slow and asymptomatic fashion and the myocardium is slowly replaced by fibrofatty scar, a combination of fibrosis and fat. However, the skeletal muscle weakness that defines DMD means that the heart is essentially unloaded. Thus, the early symptoms that typically accompany cardiac injury and subsequent dysfunction can't be felt or assessed due to muscle weakness. The signs that the heart is being irreversibly injured are only visible by advanced cardiac imaging such as cardiac MRI. As a result, the early stages of heart failure go unnoticed. The first symptoms occur in the latest stages of disease, where the

heart has become so damaged that even at rest and with little muscle movement, heart failure has become unmanageable. Because the dystrophin-deficient heart deteriorates in a gradual and often clinically silent manner, preservation of ejection fraction and attenuation of fibrotic progression represent clinically meaningful objectives, particularly in a population for which no therapy is approved for the cardiomyopathy

Current recommendations suggest the use of generic guideline directed medical therapy (GDMT), based on clinical trials of adult patients with ischemic and non-ischemic heart failure and reduced LVEF. However, the population, pathogenesis, and disease course of such patients are all unlike those of DMD cardiomyopathy. In DMD, irreversible fibrosis and fibrofatty replacement of the myocardium (Sunthankar et al. 2023; Breaux et al. 2024) mirrors the histologic progression of the skeletal myopathy (Forbes et al. 2020). Such histologic changes in the heart underlie deteriorating cardiac function (Starnes et al. 2024b).

Due to the limitations of symptom assessment in non-ambulatory patients, cardiac imaging has become the primary mode of assessing cardiomyopathy in DMD. Such imaging is now performed routinely for prognostic and monitoring purposes (Tandon et al 2015; Wittlieb et al. 2020), with cardiac magnetic resonance imaging (cMRI) preferred over echocardiography in advanced DMD due to improved precision and technical ease. The association between a decline in systolic function and all-cause mortality provides additional context to the present results. For every 3% decline in LVEF, risk of death increases by 32% (hazard ratio [HR]: 1.32) (Soslow et al. 2023). Thus, there is good reason to believe that the 1-year treatment difference of 2.4% in LVEF with deramiocel is clinically meaningful. Of note, the subset of patients with pre-existing cardiomyopathy showed greater benefit, consistent with the finding that LVEF decline begins after scar burden begins to accumulate (Tandon et al. 2015). Thus, treatment with deramiocel shows long term efficacy in preserving cardiac function and the HOPE-3 study demonstrates significantly less LGE (scar) in treated patients versus patients on placebo. This is likely to have long term consequences for preservation of life in boys and young men with DMD.

The challenges of managing heart failure in DMD and the consistent relationship of scar burden and cardiac dysfunction to mortality have led to a shift in the clinical paradigm. The priority has shifted from neurohormonal blockade when heart failure develops to early, prophylactic therapy aimed at slowing scar progression and preserving heart function. Early initiation of disease-modifying therapy has become the priority. Yet even with current therapy, cardiac injury persists and dysfunction follows. The HOPE-3 study demonstrates deramiocel can disrupt this process of scar progression and decline in cardiac function.

An ejection fraction of 45% represents a critical threshold in DMD cardiomyopathy, as below 45% the decline is rapid, while above 45% relatively little morbidity or mortality occurs as a result of heart dysfunction (Soslow et al. 2023). Current GDMT does not prevent fibrosis or decreased ejection fraction but merely delays progression. Treatment with deramiocel shows long term efficacy in preserving cardiac function and the HOPE-3 study demonstrates significantly less LGE (scar) in treated hearts compared to placebo

hearts. This is likely to have long term consequences for preservation of life in boys and young men with DMD.

Taken together, the data from HOPE-3, HOPE-2, and HOPE-2-OLE (natural history) all point to the same findings; deramiocel produces stabilization of upper limb function that represents a clinically meaningful benefit that is predictive of long-term improvements in quality of life, and unlike any other therapy approved for DMD, deramiocel treatment results in stabilization of cardiac function with greater relative improvement in LVEF in those patients with DMD and diagnosed cardiomyopathy. This improvement in left ventricular function is supported by a reduction in fibrosis by cMRI LGE in those treated with deramiocel. In the evolving landscape of understanding the pathophysiology of DMD cardiomyopathy, deramiocel results in significant improvement in cardiomyopathy which could lead to a positive impact on the leading cause of mortality in DMD and improved survival (Soslow et al. 2023).

1.8 Benefit-Risk Summary

Deramiocel addresses a critical unmet need in DMD, where no approved therapy exists for DMD cardiomyopathy, the leading cause of death, or for preserving upper limb function in non-ambulatory patients.

Across the clinical development program, including the pivotal HOPE-3 study, deramiocel demonstrates a favorable and consistent safety profile in 265 patients receiving more than 1,000 intravenous doses. Unlike corticosteroids and gene therapies, which are associated with clinically significant hepatic, renal, immune, and cardiac toxicities, deramiocel has been associated with few serious treatment-related adverse events (AEs) and no evidence of cumulative or organ-specific toxicity with repeated dosing. Ongoing pharmacovigilance will continue to monitor its long-term safety and benefit-risk profile in the broader patient population.

Deramiocel demonstrated clinically meaningful and statistically significant efficacy in both skeletal and cardiac muscle. In HOPE-3, treatment significantly slowed upper limb functional decline, resulting in a 1.2-point improvement in PUL 2.0 total score versus placebo, representing approximately a 54% reduction in disease progression over 12 months. This degree of functional preservation is expected to translate into prolonged independence and improved quality of life in a disease characterized by irreversible functional loss.

In addition, deramiocel significantly slowed progression of DMD cardiomyopathy, preserving LVEF and stabilizing myocardial scar progression, as assessed by LGE, with the greatest benefit observed in patients with pre-existing cardiomyopathy. These findings support the potential of deramiocel to delay progression of cardiomyopathy and eventual heart failure, the leading cause of morbidity and mortality in DMD.

Overall, the clinical benefits of deramiocel, including stabilization of cardiac and upper-limb function and slowing of disease progression, outweigh its manageable treatment-related risks. A detailed discussion of risk/benefit is provided in Section 8. These findings

support a favorable benefit-risk profile and highlight deramiocel's potential to address a significant unmet medical need for safe and effective treatment of cardiomyopathy and functional decline in patients with DMD. Collectively, the available evidence demonstrates the potential of deramiocel to safely and meaningfully modify the course of both cardiac and skeletal muscle disease in patients with DMD, particularly those who are non-ambulatory.

2 DUCHENNE MUSCULAR DYSTROPHY BACKGROUND

Summary

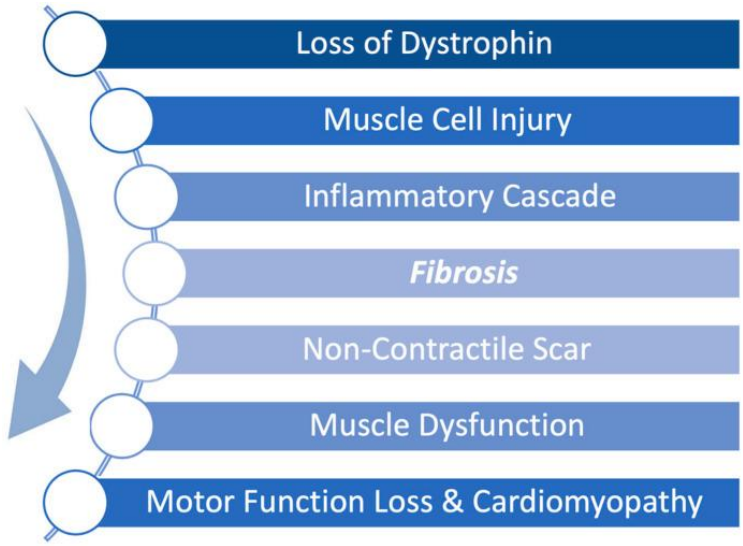
- DMD is a progressive, multisystem neuromuscular disorder characterized by irreversible degeneration of skeletal and cardiac muscle, ultimately leading to loss of ambulation, upper-limb dysfunction, cardiomyopathy, and premature mortality.
- Progressive fibrosis and fibrofatty replacement drive skeletal muscle weakness and myocardial dysfunction, leading to cardiomyopathy in most individuals with DMD and representing the leading cause of mortality.
- There are no currently approved therapies for DMDCM and no therapy carries a regulatory indication for preservation or improvement of upper-limb function. Most therapies are geared towards younger ambulant patients.

2.1 Duchenne Muscular Dystrophy (DMD)

DMD is a severe, progressive, X-linked, multisystem, neuromuscular disorder caused by mutations in the DMD gene that result in absence or near-absence of functional dystrophin protein in muscle tissue characterized by irreversible degeneration of skeletal and cardiac muscle, ultimately leading to loss of ambulation, upper-limb dysfunction, cardiomyopathy, and premature mortality (D'Ambrosio & Mendell 2023). Dystrophin is required for maintenance of sarcolemmal integrity and intracellular signaling in both skeletal and cardiac muscle. Its deficiency leads to repeated contraction-induced myofiber injury, chronic inflammation, and ongoing tissue remodeling (Duan et al. 2021). Over time, fibrosis and fibrofatty replacement contribute to worsening skeletal muscle weakness and myocardial dysfunction, which leads to the development of cardiomyopathy in most individuals with DMD (Figure 2). Cardiomyopathy is the leading cause of mortality in patients with DMD (Soslow et al. 2023).

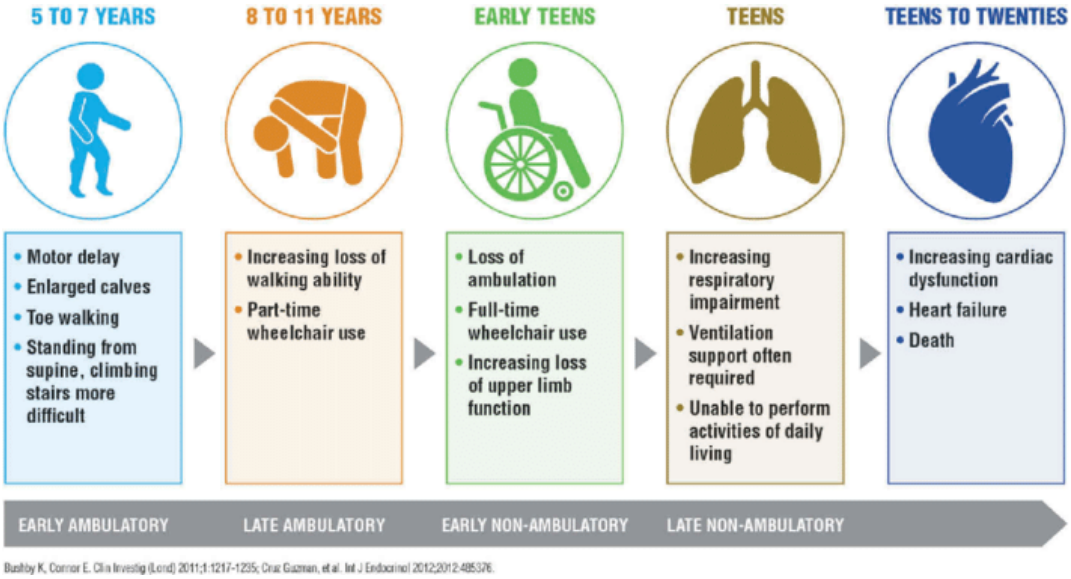
Clinically, DMD presents in early childhood with skeletal muscle weakness that typically follows a proximal-to-distal pattern. Disease progression is associated with loss of ambulation, decline in upper limb function, and increasing dependence in activities of daily living (Figure 3). Loss of ambulation commonly occurs during the second decade of life and is followed by continued deterioration in upper limb, truncal, and respiratory muscle strength. As respiratory muscle weakness advances, ventilatory support is frequently required. Improvements in respiratory management have extended survival; as a result, cardiac complications account for an increasing proportion of disease-related morbidity and mortality over time.

Figure 2: Pathogenesis of DMD



Cardiac involvement in DMD is characterized by myocardial injury and fibrosis leading to cardiomyopathy and left ventricular systolic dysfunction. DMDCM typically emerges during adolescence or early adulthood and worsens over time (Law et al. 2020). Early cardiac disease may be clinically silent, in part because reduced physical activity lowers cardiac workload and may delay symptom recognition (Tandon et al. 2015). Structural myocardial abnormalities and fibrotic changes can often be detected prior to overt functional decline using contemporary cardiac imaging techniques, supporting the importance of routine cardiac surveillance and timely clinical management. Despite guideline-directed background cardiac therapy and advances in supportive care, deterioration of cardiac function remains common in DMD.

Figure 3: DMD Disease Progression



2.2 Existing Therapies for DMD and Unmet Medical Need

Several therapies are approved for the treatment of DMD, but none are specifically indicated for the treatment or prevention of DMDCM, and none carries a regulatory indication for preservation or improvement of upper-limb function, particularly in non-ambulatory patients. Substantial unmet medical need therefore persists across stages of disease progression.

The currently approved therapies for DMD are summarized in Table 3. Most are indicated for younger, ambulatory patients and the majority target the underlying dystrophinopathy (gene therapies, exon-skipping agents). Only glucocorticoids and givinostat address the secondary consequences of inflammation and fibrosis. Givinostat is an anti-fibrotic without immunomodulatory activity or cardiac benefit. None of the approved therapies are indicated for the later stage, non-ambulatory patients, and many did not meet their primary efficacy endpoints yet remain on the market as a result of accelerated approval. Several of the dystrophinopathy targeting therapies received accelerated approval based on measurement of dystrophin/micro-dystrophin protein as a surrogate endpoint and required confirmatory trials; as of June 2026, the confirmatory trials that have reported did not meet their clinical primary endpoints, yet these therapies remain on the market. Capricor has conducted more clinical trials in this population than any other sponsor, with consistent results and demonstrated long-term safety.

Cardiomyopathy is a major driver of morbidity and mortality in DMD, yet no approved therapy has demonstrated disease-modifying effects on DMD-associated cardiomyopathy or carries a cardiac indication. Management is largely extrapolated from adult heart failure GDMT, including angiotensin-converting enzyme (ACE) inhibitors/ angiotensin II receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists, and Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors (Heidenreich et al. 2022); however, these recommendations are supported by limited DMD-specific evidence and have not been shown to have durable benefit or modify the underlying myocardial fibrosis characteristic of DMD (Duboc et al. 2005; Raman et al. 2015).

Upper-limb function is a parallel area of unmet need. As DMD progresses and patients lose ambulation, preservation of upper-limb function becomes a primary determinant of independence. Although validated measures such as the PUL scale are increasingly recognized as clinically meaningful, no currently approved therapy has been approved based on upper-limb functional endpoints, and none is approved specifically for non-ambulatory patients based on functional benefit.

Thus, current therapies remain limited in addressing later-stage disease, including upper-limb functional decline and progressive cardiomyopathy, underscoring the need for disease-modifying treatments capable of providing clinically meaningful benefit across the full spectrum of DMD. Deramiocel offers a unique and necessary component of the multiagent approach likely required for long-term DMD management and may be complementary to approved or investigational dystrophinopathy modifying therapies.

Table 3: Deramiocel and FDA-Approved Therapies for DMD

Generic name (brand)[1]	Approval year	Labeled indication[2]	n treated at approved dose (pivotal)[3]	Age range, yrs (active)	% ambulatory (active)[2]	Exposed patients at approval	Primary endpoint	Primary endpoint p-value	Approval pathway[4]
Deramiocel	Review Pending (PDUFA 2026)	Patients with DMD and DMD cardiomyopathy	53	10-22 yrs median 14	15%	265	Change in PUL2.0 score at 12 months Key Secondary: LVEF	p=0.029	**Traditional**
Givinostat (Duvyzat)[5]	2024	DMD in patients 6 years of age and older	118 (81 in primary analysis)	6–17 (mean 9.8)	100%	222	Change in four-stair-climb time, baseline to Month 18	p=0.037	**Traditional**
Delandistrogene moxeparvovec (Elevidys)	2023/ 2024	2023: Ambulatory pediatric patients 4–5 yrs DMD with a confirmed mutation: 2024 - ambulatory ≥4 yrs	20 /63	4–7	100%	85/156	Micro-dystrophin protein expression at Week 12 ; co-primary NSAA at Week 48 not met EMBARK: change in NSAA total score, baseline to Week 52	p<0.0001 (surrogate) NSAA p=0.37 (2023), p=0.2441 (2024)	**2023: Accelerated** **2024: Traditional**
Vamorolone (Agamree)	2023	DMD in patients 2 years of age and older	30	4–6 (mean 5.4)	100%	164	Change in TTSTAND velocity, baseline to Week 24 (6 mg/kg)	p=0.002	**Traditional**
Casimersen (Amondys 45)	2021	DMD with a confirmed DMD-gene mutation amenable to exon 45 skipping	57 (27 evaluable)	7–13 (median 9)	100%	76	Change in dystrophin, baseline to Week 48	p<0.001 Δ from baseline; p=0.004 vs placebo	**Accelerated** (ESSENCE confirmation negative)
Viltolarsen (Viltepso)	2020	DMD with a confirmed DMD-gene mutation amenable to exon 53 skipping	8	4–9 (median 7)	100%	32	Change in dystrophin, baseline to Week 25	p=0.01	**Accelerated** (RACER53 confirmation negative)
Golodirsen (Vyondys 53	2019	DMD with a confirmed DMD-gene mutation amenable to exon 53 skipping	25	6–13 (median 8)	100%	58	Change in dystrophin, baseline to Week 48	p<0.001	**Accelerated** (ESSENCE confirmation negative)
Deflazacort (Emflaza)	2017	DMD in patients 5 years of age and older	51	5–15	100%	>200	Change in average muscle strength (MRC scale), baseline to Week 12	P=0.017	**Traditional**

Generic name (brand)[1]	Approval year	Labeled indication[2]	n treated at approved dose (pivotal)[3]	Age range, yrs (active)	% ambulatory (active)[2]	Exposed patients at approval	Primary endpoint	Primary endpoint p-value	Approval pathway[4]
Eteplirsen (Exondys 51)	2016	DMD with a confirmed DMD-gene mutation amenable to exon 51 skipping	13 (12 evaluable)	mean 8.9	100%	107	Change in dystrophin, baseline to Week 48	p=0.008	**Accelerated** (MIS51ON confirmation awaited)

[1] DMD-specific approved products, ordered by year of FDA approval. Figures drawn from FDA prescribing information and approval documents (verified June 2026).

[2] All pivotal efficacy/biopsy trials, excluding deramiocel, enrolled ambulatory patients (100% ambulatory at baseline). The eteplirsen label reports only a mean age (8.9 yrs) for the dystrophin-quantitation study.

[3] "n treated at approved dose" is the number of patients who received the drug at the FDA-approved/recommended dose in the pivotal trial; where the dystrophin-biopsy (or primary-analysis) population was smaller, the evaluable number is shown in parentheses.

[4] Accelerated approvals (the four exon-skippers and Elevidys) rest on a dystrophin / micro-dystrophin surrogate and require confirmatory trials. As of June 2026, the confirmatory trials for golodirsen, viltolarsen, and casimersen have reported and none met its clinical primary endpoint; Elevidys' EMBARK missed its primary endpoint but supported 2024 traditional approval for ambulatory patients. Eteplirsen's clinical benefit remains unconfirmed.

[5] Givinostat's primary analysis used a prespecified baseline muscle-fat-fraction subpopulation (n=81 active, 39 placebo) of the 179 randomized patients.

Sources: Exondys 51 (eteplirsen) FDA label, 2016; Eteplirsen PROMOVI confirmatory trial (Muscle & Nerve, 2021); Emflaza (deflazacort) FDA label, 2017; Vyondys 53 (golodirsen) FDA label, 2019; Viltepso (viltolarsen) FDA label, 2020; Viltolarsen RACER53 confirmatory results, 2024; Amondys 45 (casimersen) FDA label, 2021; ESSENCE topline (golodirsen + casimersen, NCT02500381) ; Agamree (vamorolone) FDA label & VISION-DMD (JAMA Neurology 2022); Elevidys (delandistrogene moxeparvovec): FDA approvals 2023 & 2024; Study 102 (Frontiers 2023); EMBARK confirmatory (Nature Medicine 2024); Duvyzat (givinostat) FDA label, 2024

3 DERAMIOCEL OVERVIEW AND MECHANISM OF ACTION

Summary

- Deramiocel, is a cellular therapy consisting of a suspension of human allogeneic CDCs. CDCs are intravenously infused and do not proliferate or engraft following administration.
- CDCs are derived from human donor hearts and are cultivated via a proprietary cell culture process to reproducibly produce the bioactive drug product utilized in clinical trials.
- CDCs have been shown *in vitro* to have anti-fibrotic, anti-inflammatory, and immunomodulatory properties. These effects are mediated by secreted exosomes and growth factors.
- *In vitro* studies generated a comprehensive characterization of CDCs, encompassing cellular phenotype, growth factor secretion, exosome production, immunologic characteristics, and anti-fibrotic activity.
- The activity of CDCs demonstrated *in vitro* is bolstered by *in vivo* pharmacodynamic studies in a variety of animal models.
- CDCs are subject to rigorous chemistry and manufacturing quality controls to ensure identity, potency, and purity.

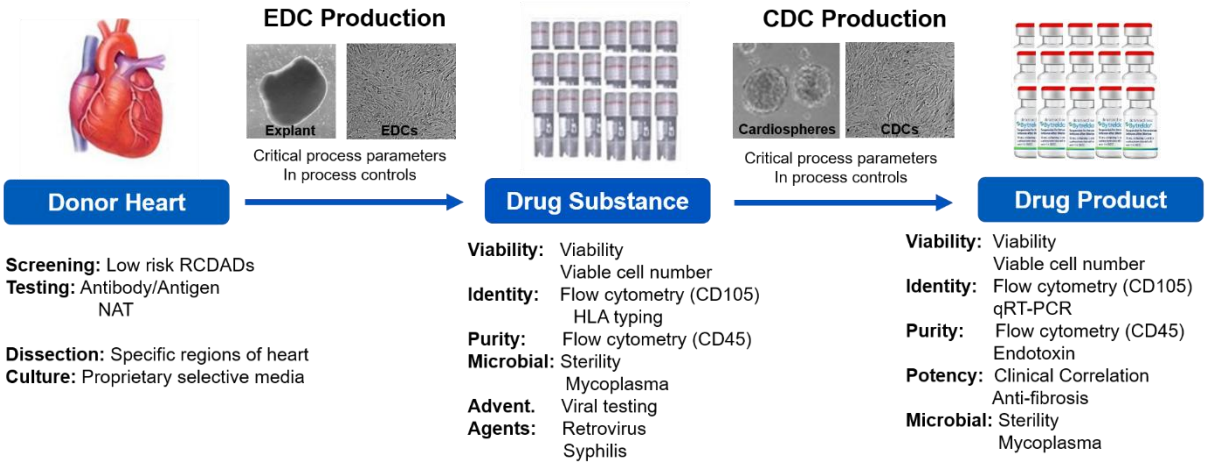
3.1 Deramiocel Description

Deramiocel is a cellular therapy consisting of human allogeneic CDCs. Deramiocel is administered as an IV infusion containing 1.5×10^8 (150 million) CDCs per dose every three months.

CDCs are a rare population of cardiac cells derived from donated human hearts which meet Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) donor eligibility requirements. CDCs are not stem cells and are not genetically manipulated. They have limited expansion potential in vitro and have been shown to senesce after ~10 passages. CDCs do not proliferate or engraft after administration.

CDCs are primary cells which are preferentially expanded using proprietary media in a modular-based manufacturing paradigm (Figure 4). Critical process parameters with defined performance attributes and in-process controls are utilized throughout the manufacturing process. Critical quality attributes of the drug substance and drug product (identity, potency, purity, and safety) are assessed and utilized to release the deramiocel drug product, ensuring that each released lot of deramiocel is suitable for administration to patients and expected to have therapeutic benefit.

Figure 4: Overview of Deramiocel Production



RCDADs: Relevant Communicable Disease Agents and Diseases

3.2 Scientific Background and Mechanism of Action

Deramiocel exerts its anti-fibrotic and immunomodulatory therapeutic effects predominantly through paracrine signaling via secreted exosomes and growth factors, rather than direct engraftment, which in turn aids in muscle survival and regeneration (Gallet et al. 2016; Tseliou et al. 2015; Rogers et al. 2021; Marban 2014; Li et al. 2025). The anti-fibrotic, immunomodulatory and anti-inflammatory mechanism of action of deramiocel is supported by *in vitro* and *in vivo* nonclinical data from Capricor and from more than 55 laboratories worldwide (>300 publications) and by the clinical results of the HOPE program.

Evidence of CDC efficacy and bioactivity in DMD was first demonstrated in several nonclinical mdx mouse studies (Aminzadeh et al. 2018; Rogers et al. 2019), a model which mimics the skeletal, respiratory, and cardiac dysfunction in DMD (Bulfield et al. 1984; Partridge 2013). In these studies, CDCs improved skeletal muscle function, as demonstrated by improved exercise capacity, and improved global cardiac function. In CDC treated mdx mice, ejection fraction (EF) improved within 3 weeks of treatment (Aminzadeh et al. 2018; Rogers et al. 2019). In contrast, vehicle-treated mice continued to decline over the same period. The overall results of the studies showed that the baseline EF was sustained in CDC-treated mice (2 administrations) over a 6-month period. Importantly, a statistically significant reduction in myocardial fibrosis was observed in CDC-treated mdx mice as evidenced by reductions in both histological fibrosis and collagen content in the hearts of mice treated with CDCs (Rogers et al. 2019). This reduction in fibrosis observed *in vivo* in CDC-treated hearts was the seminal demonstration of the anti-fibrotic mechanism of action of CDCs. Similar mechanistic benefits have been observed in myocardial infarction models in mice, rats, and pigs.

Based on nonclinical data, Capricor initiated the first clinical trial in DMD, HOPE-Duchenne, which provided clinical evidence that CDCs have anti-fibrotic activity as

shown by a reduction in cardiac scarring as measured by LGE and overall improvement in both cardiac and skeletal muscle function in patients with DMD. Key findings from the HOPE-Duchenne trial including data demonstrating that the improvement in upper limb function as measured by the PUL was greatest within the first 3 months informed the dosing strategy for later studies. These findings along with data from the open label extension of HOPE-Duchenne informed our current dosing paradigm of 150 million CDCs administered every 3 months by IV infusion.

Exosomes isolated from CDCs have been shown to be necessary and sufficient for the bioactivity of CDCs. In fact, CDC exosomes alone were able to reproduce improvements in cardiac and skeletal myopathy observed with CDCs using mdx mice (Aminzadeh et al. 2018; Ciullo et al. 2022). CDC exosomes have been demonstrated to track to sites of injury and to be rapidly taken up by cardiac and skeletal muscle cells following injury in multiple mouse studies (Ciullo et al. 2022). Importantly, treatment with CDC exosomes reduced myocardial collagen content, reduced myocardial scarring, and improved LVEF to the same levels as CDC treatment alone (Ibrahim et al. 2014; Barile et al. 2014; Gallet et al. 2017; Aminzadeh et al. 2018). In addition, the improvements in LVEF in the mouse model observed after CDC treatment were attenuated when exosome secretion was inhibited (Ibrahim et al. 2014). Similar therapeutic benefits have been observed in large-animal models, including reduced scarring, anti-fibrotic effects, and improved LVEF (Gallet et al. 2017). Mechanistically, this finding suggests that exosomes secreted by CDCs play a critical anti-fibrotic role in stabilizing muscle function through suppression of collagen expression (Rogers et al. 2019).

CDC-exosomes are particularly enriched for RNA species including microRNAs, noncoding RNAs and Y RNAs with demonstrated anti-fibrotic and anti-inflammatory properties (Barile et al. 2014; de Couto et al. 2015; Ibrahim et al. 2025). Specifically, the noncoding RNA TY1, identified by sequencing CDC exosomes, has been shown to attenuate inflammatory signaling and reduce scar size in preclinical models (Ibrahim et al. 2025). The cardioprotective effect of TY1 was mediated by upregulation of Trex1 in macrophages and macrophage-derived exosomes. Thus, secretion of CDC exosomes is critical for mediating the immunomodulatory mechanism of action of CDCs.

Similarly, paracrine signaling via growth factor secretion by CDCs has been implicated in the immunomodulatory and anti-fibrotic mechanism of action of CDCs. CDCs have been shown to secrete large amounts of VEGF, EGF, HGF, IGF1, FGF, IL-6 and CXCL8 (IL-8) (Li et al. 2012; Cheng et al. 2014; Li et al. 2025). In particular, FGF, HGF, EGF, and VEGF are involved in anti-fibrosis via inhibition of myofibroblast activation, attenuation of the inflammatory fibrotic pathway and reduction of hypoxia-driven fibrosis, and have been shown to be anti-fibrotic following injury (Farooq et al. 2021; Fearon et al. 2021; Lai et al. 2018; Murray et al. 2017). The cytokine IL-6 has been shown to be directly involved in the mechanism of action of CDCs by reducing myocardial scarring (Mayfield et al. 2017; Maxeiner et al. 2014). The chemokine CXCL8 (IL-8) is known to be immunomodulatory and has been shown to be associated with improved LVEF following injury (Husebye et al. 2014).

The totality of this data demonstrates the potency of CDCs in deramiocel and the mechanism of action of CDCs observed *in vitro*, *in vivo* in pharmacodynamic studies, and importantly in multiple clinical trials, including the HOPE-3 Phase 3 trial.

3.3 Product Characteristics of Deramiocel

Comprehensive studies of CDCs, encompassing cellular phenotype, growth factor secretion, exosome production, immunologic characteristics, and immunomodulatory and anti-fibrotic activity have been utilized to characterize CDCs in deramiocel.

CDCs are characterized phenotypically by high expression of the surface marker CD105, the regulatory component of the TGF-β complex, and lack of surface expression of CD45. The molecular phenotype of CDCs has also been characterized by high expression of key transcripts including IL-6, CXCL8 (IL-8), and HSPA5, known to play critical roles in cardiac and skeletal muscle immunomodulation, fibrosis, and cardioprotection. Accordingly, these characteristics associated with the mechanism of action are utilized to assess identity of CDCs for release of deramiocel.

Likewise, two confirmatory potency assays are utilized to release each lot of deramiocel Potency of deramiocel is assessed using an *in vitro* cell-based assay using a co-culture system of fibroblasts with conditioned media (CM) collected from CDCs, which is enriched with secreted exosomes and factors. Following co-culture, expression of collagen 1A and 3A (COL1A, COL3A), which represent the major extracellular matrix proteins deposited during fibrotic remodeling and are widely recognized biomarkers of fibroblast activation, is measured by qRT-PCR (Li et al. 2025). Reduction in COL1A and COL3A expression observed by CDCs in deramiocel therefore provides a direct and clinically relevant measure of the anti-fibrotic activity of deramiocel (Li et al. 2025). This assay has been utilized to confirm that CDC exosomes alone can recapitulate the anti-fibrotic activity of CDC CM and that exosome depletion abrogated the anti-fibrotic effects of deramiocel. Additionally, removal of the soluble factors released by deramiocel (including those found at high levels in CM: VEGF, IL-6, CXCL8), results in a loss of anti-fibrotic activity (Li et al. 2025). Likewise, assessment of deramiocel RNA profile by sequencing and analysis of specific transcripts (IL-6, CXCL8) at deramiocel lot release, aligns with the high level detection of soluble factors in CM observed in published literature (Li et al. 2025). These *in vitro* findings demonstrate that CDCs in deramiocel exert quantifiable immunomodulatory and anti-fibrotic activity *in vitro*, mediated through exosomes and soluble factors in a dose-dependent manner.

In addition to the anti-fibrosis potency assay, an independent, confirmatory clinical correlation by RNA sequencing with bioinformatics is utilized to characterize every lot of deramiocel. CDCs have a unique RNA profile with statistically significant differential expression of key transcripts associated with CDCs when compared to non-CDC cells, including cells of cardiac origin and non-cardiac origin. Primary component analysis of ~6500 loci used for differential expression analysis between CDCs and non-CDC cells demonstrates clear clustering of CDCs separately from other cardiac derived cells and

non-CDC cell types. Importantly, the unique CDC profile is then correlated to the profile of CDCs in deramiocel from the HOPE-2 and HOPE-2 OLE studies where clinical benefit was observed. The clinical correlation by RNA sequencing and bioinformatics assay utilizes a highly conservative, stringent P-value of <0.00001. Using this value, ~30 transcripts were identified as distinctive for potent CDCs. This rigorous statistical significance allows for the most accurate distinction between potent and non-potent samples. Notably, many of the ~30 potency related transcripts assessed in the assay are known to play key roles in cardioprotection, immunomodulation and reduction of fibrosis. Thus, each deramiocel lot is confirmed to be CDCs, highly correlated to clinical efficacy, and have anti-fibrotic activity critical for the therapeutic effect of deramiocel.

In summary, the clinically meaningful improvements in cardiac and skeletal function observed in the HOPE-3, HOPE-2, and HOPE-2 OLE clinical studies are directly attributable to the immunomodulatory and anti-fibrotic mechanism of action of CDCs in deramiocel. The signaling and bioactivity of CDCs observed in the *in vitro* characterization, identity, and potency assays aligns with multiple *in vivo* pharmacodynamic studies in the mdx mouse model and large animal models, which demonstrate a decrease in inflammation and fibrosis leading to a reduction in muscle scarring and consequently improved skeletal and cardiac muscle function.

4 REGULATORY MILESTONES

Summary

- The original BLA was developed with direct Agency feedback at a pre-BLA meeting, which supported using HOPE-2 and HOPE-2-OLE as clinical evidence of safety and efficacy.
- Following the CRL issued in July 2025, Capricor elected to move forward and proactively revised HOPE-3 to move LVEF to the primary endpoint (Protocol v8.0) to address the CRL.
- At the Type A meeting, the Agency agreed that HOPE-3 would address the CRL but specified that the PUL should remain the primary endpoint.
- Capricor made the corresponding revisions and submitted Protocol v9.0 and SAP v2.0 to the IND with cross-reference to the BLA on September 26, 2025 (cover letter in Appendix 10.2). No feedback was received.
- Capricor's complete response was submitted to the BLA on February 20, 2026 and accepted as a Class 2 Resubmission with an August 22, 2026 target PDUFA action date.

4.1 Regulatory History

Capricor developed deramiocel for the treatment of DMD in collaboration with the FDA and has been engaged with the agency since 2015. Deramiocel holds Orphan Drug (2015), Rare Pediatric Disease (2017), and Regenerative Medicine Advanced Therapy (RMAT; 2018) designations for the treatment of DMD.

Capricor's regulatory pathway for deramiocel in DMD has involved multiple changes in regulatory review staff and corresponding adjustments to the regulatory pathway. At each stage, Capricor has sought to align its development program with direct feedback from the Agency. The most relevant strategy updates based on this feedback are described in Table 2.

At Capricor's pre-BLA meeting and a subsequent cardiology focused follow-up meeting (both August 2024), FDA recommended that Capricor seek an indication for DMD cardiomyopathy based on HOPE-2 and HOPE-2-OLE, based on the supporting natural history data (real-world evidence) and the unmet need posed by cardiomyopathy in DMD, which had recently been recognized as the leading cause of mortality in DMD. Consistent with this feedback, Capricor submitted BLA 125842 in December 2024, supported by 12-month results from the Phase 2 HOPE-2 study and 36 months of open-label extension data from HOPE-2-OLE, with comparisons to propensity-matched external comparator cohorts.

FDA issued a CRL for BLA 125842 in July 2025, stating that the Agency had completed its review and was unable to grant approval of the BLA in its current form. The CRL

cited one (1) Clinical and Biostatistics deficiency, six (6) CMC deficiencies, and six (6) additional CMC-related comments. All CMC-related items were readily resolved through previously committed studies, additional qualification studies, or hold time modifications.

The Clinical and Biostatistics deficiency recommended an adequate and well-controlled study whose primary objective is evaluation of cardiac outcomes, compared to a randomized, concurrent control group, reflecting the Agency's view that HOPE-2 and HOPE-2-OLE were not adequate and well-controlled. Capricor disagreed with this assessment (refer to Capricor's preliminary response published on its website: www.capricor.com) but elected to move forward and proactively revised HOPE-3 (Protocol v8.0) to move LVEF from a secondary to a primary endpoint to address the CRL and maintain clarity of the indication.

At its Type A post-action meeting in August 2025, the FDA agreed that the HOPE-3 trial would fulfill the CRL's clinical request, with PUL as the primary endpoint and indicated that the Agency would exercise regulatory flexibility in assessing the contribution of LVEF to overall disease progression in the enrolled patients. Consistent with this agreement, Capricor revised the protocol and SAP and submitted Protocol v9.0 and SAP v2.0 to the Investigational New Drug application (with cross-reference to the BLA; see Appendix 10.2) in September 2025. The regulatory purpose of HOPE-3 evolved over the course of its conduct to ultimately support the BLA resubmission. This evolution along with the corresponding protocol and SAP versions is detailed in Section 4.1.1.

In February 2026, Capricor submitted a complete BLA resubmission package incorporating safety and efficacy data from the double-blinded, placebo-controlled phase of the HOPE-3 study. The FDA classified the resubmission as a complete, Class 2 response with a PDUFA goal date of August 22, 2026.

4.1.1 HOPE-3 Protocol and SAP Revision History

The HOPE-3 protocol and SAP evolved over time in response to the study's changing regulatory purpose, emerging literature, and refinements to the planned analyses. Key regulatory and study conduct milestones are summarized in Table 2. The major protocol amendments and the driving factors for each are summarized in Table 4.

Table 4: Milestone Protocol Versions and Associated Regulatory Context

Version & Date	Regulatory Context	Key Changes
Version 1 through 4	Original pivotal Phase 3 trial (clinical drug supply)	HOPE-3 was designed as an adequate and well-controlled pivotal Phase 3 trial intended to support approval with product from the clinical manufacturing facility. Alignment was reached with FDA on endpoints and their clinical meaningfulness.
Version 5 21 Aug 2023	Addition of commercial supply (Cohort B)	Following a Type B meeting (July 2023), the protocol was amended to add Cohort B to evaluate product manufactured at the proposed commercial facility, including late gadolinium enhancement (LGE) assessments for that cohort.
Version 6 15 Nov 2024	Analysis for Cohort A & B combined	Following a Type B meeting (March 2024), FDA agreed to non-clinical comparability assessment between manufacturing sites.
Version 7 28 Feb 2025	Study repositioning for ex-US authorization	Following a Type B pre-BLA meeting (August 2024), FDA supported using HOPE-2 and HOPE-2-OLE for the original BLA, and HOPE-3 was repositioned to support ex-US market authorization.
Version 8 25 Jul 2025	Change made in response to the CRL	Reverted HOPE-3 plans to USA-only enrollment and changed the primary efficacy endpoint from PUL to LVEF by cMRI, reflecting the shift in focus toward cardiomyopathy in response to the CRL.
Version 9 26 Sep 2025	Change made in response to feedback received at Type A Post-Action Meeting and to support the BLA resubmission	Reverted the primary efficacy endpoint to the original endpoint of Total PUL 2.0 per FDA's request during the Type A meeting. In addition, the analytic approach changed from absolute change to percent change from baseline based on recent publications supporting this as a more sensitive and clinically meaningful measure of function. LVEF was updated to a key secondary endpoint. See Appendix 10.2

The HOPE-3 SAP was revised alongside the evolving protocol through documented revisions, all finalized before unblinding. Table 5 summarizes the following key milestone versions: the two versions reviewed by FDA without further feedback (v1.7 and v2.0) and the version in place at unblinding (v3.0). For each, the table provides the regulatory context and the associated changes.

Table 5: Milestone SAP Versions and Associated Regulatory Context

Version & Date	Regulatory Context	Key Changes
1.7 06DEC2023	First FDA-reviewed version to receive no further feedback or requests for modification; resulted from iterative FDA feedback on prior versions (v1.5, v1.6). In place at the time of the futility analysis (07DEC2023 closed DSMB session reviewing the first 30 subjects who had reached the 6-month timepoint).	Specified the cohort structure, futility interim, gatekeeping hierarchy and global statistical tests, site-pooling algorithm, and missing-data and indexing conventions.
2.0 26SEP2025	Revised following the Type A Post Action Meeting (August 2025) and provided to FDA for review (September 2025). See Appendix 10.2 for the letter to FDA summarizing changes.	Primary efficacy endpoint reverted to original endpoint of Total PUL 2.0. Designated LVEF as the key secondary endpoint, refined the primary analysis, added the LVEF sample-size calculation and prespecified sensitivity analyses, and clarified the cardiomyopathy and cardiac-medication definitions.
3.0 24NOV2025	Finalized before database lock and unblinding (25NOV2025); no change to the clinical protocol between v2.0 and v3.0.	Introduced LVEF-specific modeling considerations (see below).

Rationale for Changes Introduced in SAP v3.0:

Prior to SAP v3.0, there was no consideration for unique modeling concerns of LVEF. The default was to use the same method and covariates in the models as the primary analysis of PUL 2.0 Total score. The following are the three main reasons that the changes between the models of PUL 2.0 Total score and LVEF:

Measurement context – PUL is site-administered by a physical therapist, so site is a real source of variability that needs to be in the model. LVEF is centrally read by a blinded reader, so site contributes nothing to the outcome and doesn't belong.

Data structure – PUL has four post-baseline visits, making mixed-effects model for repeated measures (MMRM) with repeated-measures covariance the natural choice and requiring visit and treatment×visit terms.

Pathophysiology – Cardiac and skeletal muscle manifestations of DMD progress largely independently. Age and baseline LVEF level are established prognostic factors for cardiac decline, specifically older patients with lower ejection fraction decline faster, which is why both enter the cardiac model. The LVEF ≥45% threshold captures a clinically meaningful inflection in cardiac risk.* None of those factors drive PUL trajectory the way genetic subtype and functional entry level do, which is why the slow progressor indicator is included in the PUL model instead.

* Left ventricular ejection fraction is an established prognostic marker in DMD cardiomyopathy. In a prospectively enrolled DMD/BMD cohort followed for adverse

cardiac events, LVEF was an independent predictor of outcomes on multivariable analysis (HR 0.94 per unit, 95% CI 0.89-0.97, p=0.001), and a dichotomizing cut-point of 45% carried the highest hazard ratio of any threshold examined for the composite secondary endpoint of heart failure hospitalization and/or ventricular tachycardia (HR 11.50, 95% CI 4.49-29.43, p<0.0001) (Florian et al. 2014). This identifies 45% as the LVEF value most strongly discriminating event risk in this dystrophinopathy cohort, consistent with its use as a threshold for clinically significant systolic dysfunction in DMD.

The prognostic weight of LVEF in DMD specifically has been quantified in contemporary natural history data. In one of the largest prospectively phenotyped DMD cardiac cohorts, each 3 percentage point decrease in LVEF was associated with a 32% increase in all-cause mortality risk (HR 1.32), and LVEF together with indexed left ventricular volumes was among the cardiac measures most strongly associated with mortality (Soslow et al. 2023). A subsequent analysis demonstrated that the rate of change (slope) in LVEF is likewise associated with all-cause mortality, indicating that both absolute function and its trajectory carry prognostic information (Starnes et al. 2024). These findings provide the biological and epidemiological basis for treating preserved versus reduced LVEF as clinically distinct cardiac states.

5 CLINICAL DEVELOPMENT PROGRAM

Summary

- Primary evidence for the safety and efficacy of deramiocel in the treatment of Duchenne cardiomyopathy and skeletal muscle pathology in patients with DMD is based on the results of HOPE-3 and is supported by HOPE-2 and HOPE-2-OLE clinical studies.
- Upper limb function measured by PUL was selected as the primary efficacy endpoint across all three clinical studies based on its validation as a clinically meaningful measure of disease progression in non-ambulant DMD populations and in alignment with FDA guidance.
- Cardiac function was assessed by cMRI across all three studies, with LVEF as the key secondary endpoint in HOPE-3 based on its established clinical relevance.

5.1 Clinical Trial Design

The clinical development program for deramiocel was designed, to establish safety and efficacy in patients with DMD. Multiple clinical trials serve as evidence for the safety and efficacy of deramiocel in the treatment of cardiomyopathy and skeletal function in patients with DMD. HOPE-3 is a Phase 3, 12-month randomized, placebo-controlled clinical study (Section 5.1.3), and is supported by HOPE-2, a Phase 2, 12-month randomized, placebo-controlled study (Section 5.1.1) and HOPE-2-OLE, a long term open-label extension study compared to a propensity matched external comparator for cardiac parameters (ECC) (Section 5.1.2). Each of these studies evaluated the to-be-marketed deramiocel dose of 150 million cells administered by IV infusion every 3 months. These clinical studies were informed by earlier clinical experience in cardiac indications and prior studies utilizing an alternate intracoronary route of administration and dose formulation (see Section 10.1 for a table summarizing the full development program).

5.1.1 HOPE-2 Phase 2 Clinical Trial

HOPE-2 was a multicenter, randomized, double-blind, placebo-controlled Phase 2 trial evaluating IV administration of deramiocel with repeated dosing (once every 3 months up to 4 doses) in male patients (10 years and older) with confirmed DMD and skeletal muscle impairment, assessing safety and exploratory skeletal, cardiac and quality of life outcomes. The study included a blinded 6-month interim futility analysis after the first 20 patients, as this was the first trial of repeated IV administrations at the proposed dose level. Enrollment was subsequently halted after 20 patients due to funding constraints and unanticipated enrollment challenges. The interim analysis, reviewed by

the Data Safety Monitoring Board (DSMB), was encouraging and supported lack of safety concerns and lack of futility.

At interim analysis, unblinding was limited to select sponsor personnel (Capricor) and statistical consultants; all others, including the patient and the site investigators, remained blinded. All 20 of the enrolled patients (8 deramiocel, 12 placebo) continued dosing and study assessments per the protocol to the end of the study (Month 12).

The SAP prespecified a parametric linear MMRM, which relied on an assumption of normality that was not met in the observed data. Maintaining the prespecified parametric model would have violated core model assumptions and led to improper statistical inference, and, therefore, adaptation of the analytical approach was necessary to ensure valid results. A model-adjusted percentile-ranked change from baseline approach was applied due to distributional considerations in the small study population. Results were published and are available for review in The Lancet (McDonald et al. 2022), where peer reviewers concurred with the statistical model used and the evidence of effectiveness for deramiocel.

5.1.2 HOPE-2-OLE Phase 2 Clinical Trial

Patients completing the 12-month HOPE-2 study were eligible to enroll in an OLE, HOPE-2-OLE, designed to allow continued access to deramiocel, to address ethical considerations related to treatment withdrawal in a pediatric population with unmet medical need, and enable collection of extended duration safety, tolerability, and durability data with continued dosing every 3 months until commercial availability. HOPE-2-OLE was initiated following an untreated gap period of approximately 12 months.

In the absence of a concurrent placebo control group in the extended long-term HOPE-2-OLE, two external comparators were selected for cardiac and functional endpoints. These external control data allowed for analyses of the respective treatment benefit of deramiocel in this long-term study. A propensity score matching approach was utilized to establish the external comparator for cardiac parameters (ECC), which were derived from the prospective natural history data provided by Vanderbilt University Medical Center and the DMD Cardiac Care Consortium. Cohort matching was employed to establish the external comparator for the PUL (ECP), which were derived from clinical data at Cincinnati Children's Hospital.

Continued follow-up in the ongoing HOPE-2-OLE study provides evidence of durability, with sustained cardiac and skeletal benefits observed during extended deramiocel treatment, with data reported through Month 36 in the BLA and this briefing document. Patients from the HOPE-2 OLE study are now in their sixth year of treatment.

5.1.3 HOPE-3 Phase 3 Clinical Trial

5.1.3.1 HOPE-3 Trial Design

HOPE-3 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the safety and efficacy of IV infusions of deramiocel (150 million cells) given every 3 months over 12 months (four infusions in total) on neuromuscular function as a primary objective and assessed its therapeutic effect on cardiomyopathy in patients with DMD as a secondary objective (Figure 5). The study was conducted in two sequential cohorts that differed in drug-supply source: Cohort A used investigational product from the initial clinical manufacturing facility in Los Angeles, while Cohort B used supply from the commercial manufacturing site in San Diego and added LGE to the cMRI protocol to assess for fibrosis as an endpoint which serves to establish the presence of cardiac injury as a precursor or in addition to cardiac dysfunction.

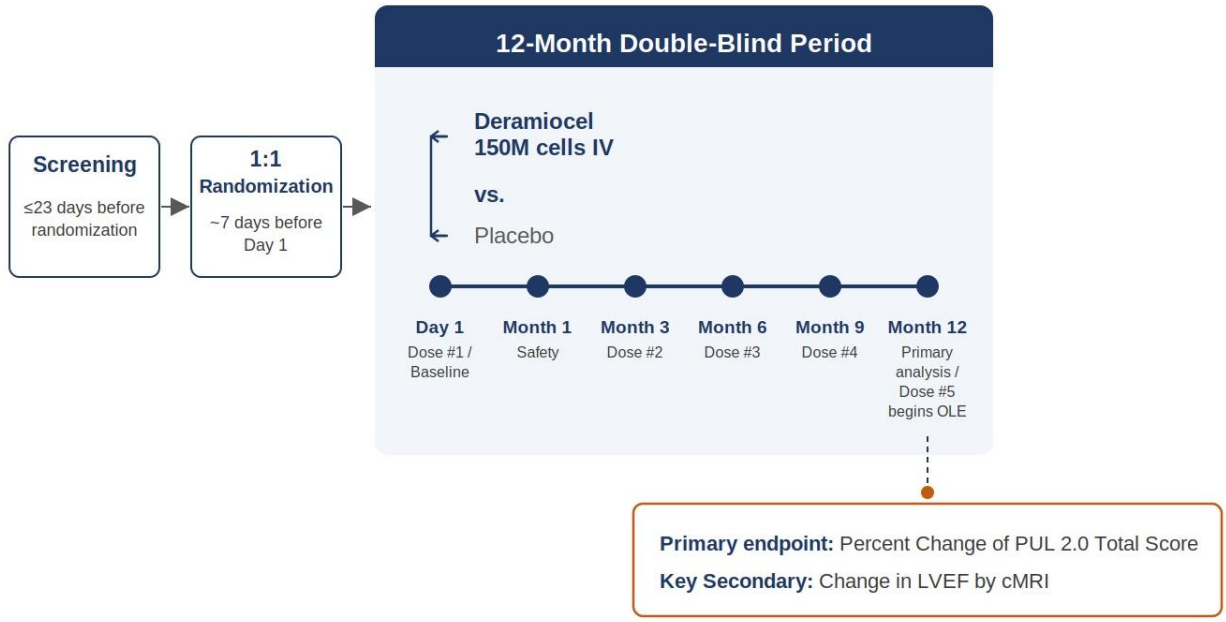
Following completion of the randomized, blinded phase, all patients were eligible to participate in an OLE followed by a long-term OLE (LT-OLE), to provide continued access to deramiocel irrespective of initial treatment assignment, address ethical considerations related to treatment withdrawal in a pediatric population with unmet medical need, and enable collection of additional safety and exploratory efficacy data. The OLE phase consisted of 4 additional infusions of deramiocel, each administered at 3-month intervals over 12 months, after which the LT-OLE phase allowed continued dosing of deramiocel once every 3 months until commercially available, sponsor termination, or patient withdrawal of consent.

HOPE-3 included male patients with a clinical diagnosis of DMD with an LVEF >35% and evidence of skeletal muscle impairment to further characterize treatment effect in a larger population than the preceding HOPE-2 study. Eligible patients were randomized to receive deramiocel or placebo at a 1:1 ratio. Randomization was stratified by entry item score of the PUL 2.0 module. Stratum 1 included patients with PUL 2.0 entry item scores of 2 and 3, and Stratum 2 included patients with PUL 2.0 entry item scores of 4, 5, and 6. Patients underwent baseline safety and efficacy assessments prior to the first infusion of investigational product (IP, deramiocel or placebo).

Prior to each IP infusion, pre-treatment with high dose oral corticosteroid and oral or IV anti-histamine medications are administered to reduce the frequency and severity of hypersensitivity reactions.

See Section 4.1.1 for additional information on the HOPE-3 protocol and SAP version history.

Figure 5: HOPE-3 Study Schema



5.2 Endpoint Selection

Efficacy assessments for the studies included evaluation of upper limb function using PUL (version 1.2 and/or 2.0) and assessment of left ventricular structure and function as measured by cMRI, including LVEF, to characterize treatment effects on cardiac disease progression, the primary cause of mortality in these patients. The placebo-controlled studies (HOPE-3 and HOPE-2) were conducted over a 12-month treatment period to allow for assessment of clinically meaningful change and safety and established in alignment with FDA recommendations as an adequate duration to assess long-term safety and durability of treatment effect (Type B Meeting Nov 2020).

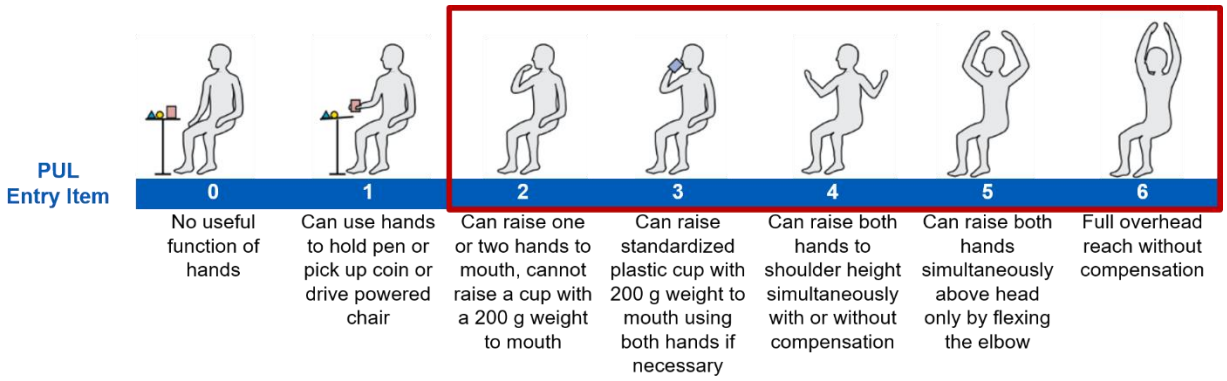
5.2.1 Skeletal Muscle Function Assessed by Performance of Upper Limb (PUL)

Assessment of upper limb function measured by PUL was selected as the primary efficacy endpoint in HOPE-3, HOPE-2, and HOPE-2 OLE, based on its validation as a clinically meaningful measure of disease progression in non-ambulant DMD populations and in alignment with FDA guidance (initial RMAT Meeting Dec 2018; End of Phase 2 Meeting Oct 2019; Type B Meeting Feb 2020; Type B Meeting Nov 2020). PUL 2.0 was the primary endpoint in HOPE-3 with mid-level PUL serving as a type I error controlled secondary endpoint. Both PUL 1.2 and 2.0 were evaluated in HOPE-2, with the mid-level PUL 1.2 serving as the primary endpoint, as PUL 2.0 had not yet been validated at the time of study initiation (Initial RMAT Meeting Dec 2018). Following subsequent validation, PUL 2.0 replaced PUL 1.2 in HOPE-2-OLE to reflect the updated standard for functional assessment.

PUL 2.0 is a physical therapist-assessed scale of upper limb function, which is applicable throughout the disease course, particularly in non-ambulatory patients. It

includes 22 items, with an entry item score from 0 and 6 that determines the starting point based on current upper limb ability (not included in total score) and three subscales: high-level shoulder dimension, mid-level elbow dimension, and distal wrist and hand dimension (shoulder: 6, mid-level: 9, distal: 7 items). Each item is scored on a 3-point scale: 0=unable, 1=compensated, and 2=neurotypical/able to complete fully. Compensation refers to the use of alternative movements or muscle groups (such as momentum, trunk lean, or assistance from the other arm) to complete a task that can no longer be performed through normal movement alone. The maximum possible score is 42 points (Gandolla et al. 2020; Gillman et al. 2025). Figure 6 provides a schematic of the entry-item scale (entry items 0 – 6); the boxed range (entry items 2-6) reflects the functional band enrolled across the HOPE programs (modified from McDonald et al. 2022).

Figure 6: Performance of Upper Limb (PUL 2.0) entry-item scale

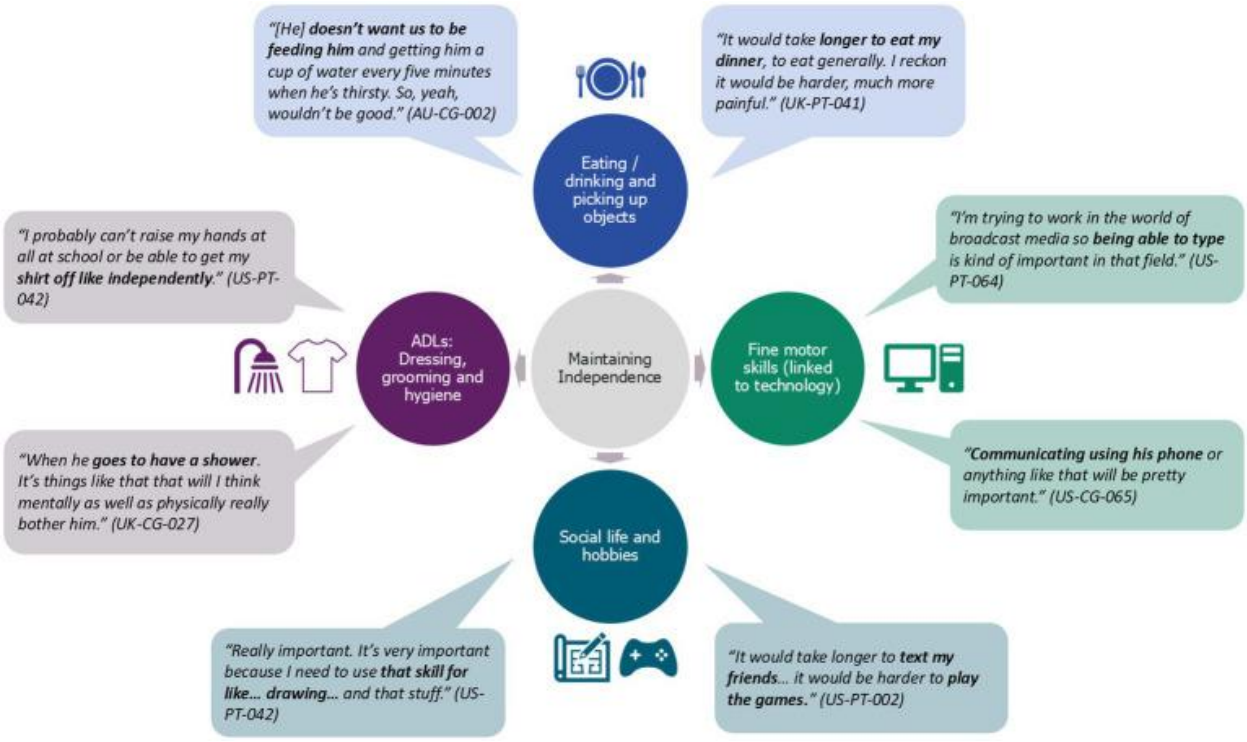


Regulatory guidance stresses the importance of obtaining input from the patient community on defining meaningful change and its impact on daily life (FDA patient focused drug development). Recent studies in DMD to evaluate patient perspectives on meaningful change on the PUL determined that people with DMD consider the maintenance of function or slowing of decline to be a meaningful outcome, especially in a context where decline is inevitable. Additionally, small changes have a large impact on maintenance of patient functional ability in activities of daily living (hygiene), reaching (hug/handshake), eating/drinking and finger function for technology use (communication, powered wheelchairs) (Gillman et al. 2025).

In addition, physical therapists' feedback on meaningful change on the PUL articulated that the less function a person with DMD has remaining, the more that function means. Therefore, the number of points considered meaningful on the PUL depends on the baseline score. A single point has a "huge, positive, significant life changing impact for him" was stated when discussing a patient's ability to eat and drink by oneself and utilize technology. Figure 7 provides quotes from individuals with DMD and caregivers about the impacts associated with maintaining function across different themes measured by PUL 2.0 (Gillman et al. 2025).

Importantly, the FDA stated the following regarding a 1 point change in a Feb 2020 Type B meeting summary, ***"The proposed primary efficacy endpoint (change in full PUL 2.0 score from baseline to Month 12), supported by the planned measures to establish the clinical meaningfulness of a 1-point change, appears suitable from the clinical perspective for a Phase 3 trial intended to provide primary evidence of effectiveness to support a BLA."***

Figure 7: Quotes from individuals with DMD and caregivers about the impacts associated with maintaining function across different themes measured by PUL 2.0 (Gillman 2025)



The tasks associated with the shoulder/upper domain in the PUL 2.0 are typically the first to rapidly deteriorate in those with higher baseline scores (Coratti et al. 2025). The importance of baseline scores was emphasized when interpreting meaningful changes in PUL 2.0 by evaluating percent change from baseline. This analytic approach, while novel for PUL2.0, is widely used in other clinical endpoint analyses for other pathological conditions or diseases and may reflect disease progression more faithfully in heterogeneous neuromuscular disease cohorts. While the minimal clinically important difference for percent change in PUL 2.0 has not been established, the pre-specified choice of percent change in baseline PUL 2.0 as an analysis strategy recognizes the clinical meaningfulness of one-point changes in PUL in patients with more severe upper limb impairment and lower baseline values (Gillman et al. 2025) concomitant with expected large declines in the upper dimension domain over short intervals in patients with higher baseline scores (Coratti et al 2025). Mean percent change allows evaluation

of meaningful treatment effects on the PUL in a wide functional range of patients without over-weighting one domain set of functions over those of another domain depending on the baseline functional status of the patient.

An analysis of changes in the PUL based on points lost from baseline does not account for the variable capacity for point loss based on PUL entry score and functional status. The year before and after loss of ambulation represents the peak of loss of function as reflected in the PUL (Pane et al. 2023). One study found the largest changes in PUL scores in the population transitioning to non-ambulant, followed by the non-ambulant and then ambulant patients (-11,62, -8.09, -4.51 respectively over 36 months) (Coratti et al. 2025). This pattern is reinforced with longitudinal data; in a subgroup of non-ambulant patients, people with PUL entry levels between 6 and 4 declined 8.30 points on the total PUL while people with 3 and 2 entry scores declined 4.25 points, and people with 1 and 0 entry scores declined 1.58 points over 24 months (Pane et al. 2018). Thus, the heterogeneity in PUL scores, the patterns of loss and rates of decline at different stages of disease progression, and the increased meaningfulness of PUL points with decreased function argue for utilizing the percent change from baseline to analyze the PUL rather than point change from baseline.

It is important to note that the mid-level domain is often regarded as especially sensitive to disease progression in non-ambulatory patients, particularly the type of patients enrolled in the HOPE-3 and HOPE-2 trials. At this stage, many patients have low shoulder domain scores while maintaining distal function (higher score). Thus, the mid-level (elbow) domain often changes when patients are experiencing measurable functional decline.

5.2.2 *Duchenne Video Assessment "Eat 10 Bites"*

The DVA was developed by the DMD patient community and physiotherapists and evaluates quality of movements and compensations used to perform functional activities impacted by DMD disease progression. The DVA Eat 10 bites records standardized video assessments in the home environment of during independent eating and measures participant ease of movement through identification of compensatory movement patterns, providing a clinically meaningful activity of daily living. Trained physiotherapists measure important compensations and grade quality of movements in a blinded fashion during a real-world vital functional activity requiring the ability to use the arm with mid-level elbow flexion during independent eating. This additional data supports the clinical meaningfulness of the treatment effect measured by the PUL 2.0 with regard to the potential favorable impact of deramiocel on maintenance of independent feeding.

5.2.3 Cardiac function assessed by LVEF and LGE using cMRI

Global assessments of cardiomyopathy were assessed by cardiac MRI in all three studies: HOPE-3, HOPE-2 and HOPE-2 OLE. All studies incorporated cardiac parameters as secondary endpoints to evaluate effects on cardiomyopathy progression,

as the clinical meaningfulness of cMRI parameters had not yet been fully established at the time of initiation of HOPE-2 and HOPE-3 (Type B Meeting Nov 2020; Type B Meeting Jun 2021). Subsequent literature published in 2023 established the clinical relevance and meaningfulness of cMRI parameters in this population, including LVEF and related ventricular measurements (Soslow et al. 2023). cMRI parameters [including LVEF and LGE] and are now recognized as predictors of disease progression, morbidity, and mortality in DMD cardiomyopathy and are considered among the most appropriate outcome measures for cardiovascular therapeutic trials (Soslow et al. 2023; Starnes et al. 2024a). The HOPE-3 study designated LVEF as the key secondary endpoint, as assessed by change in baseline to Month 12 in LVEF, based on the clinical relevance established in published literature and the outcomes of discussions with the FDA.

Importantly, a prespecified sub-population analysis of DMD patients with documented cardiomyopathy at baseline was performed to assess change in baseline to Month 12 in LVEF in HOPE-3. Cardiomyopathy in DMD patients at baseline was defined as confirmed evidence of cardiomyopathy by medical history, having an LVEF <55%, and/or presence of LGE on baseline cMRI. LGE was utilized in HOPE-3 (measured in Cohort B only) as a Type I error–controlled secondary endpoint to evaluate the presence of myocardial scar or fibrosis and to further characterize the potential effects of deramiocel on the pathogenesis of DMDCM. cMRI enables non-invasive myocardial tissue characterization through LGE imaging and parametric mapping, allowing for the detection of fibrosis and assessment of fibrotic scarring overtime (Silva et al. 2007; Tandon et al. 2015; Soslow et al. 2016). Change in the number of segments of the heart with myocardial scarring by LGE at Month 12 relative to baseline was evaluated to assess changes in cardiac structure associated with cardiomyopathy.

Given the limited utility of clinical symptoms and the recognized limitations of blood biomarkers and echocardiography in DMD, cMRI have been favored by the field as standard clinical assessments. Accordingly, cMRI endpoints were integral to the HOPE-2, HOPE-2-OLE and HOPE-3 study designs.

5.2.4 Global Statistical Test

The Total GST is a patient-level composite outcome designed to integrate multiple dimensions of disease impact into a single, interpretable measure. The Total GST integrated the PUL 2.0 Total Score, LVEF, and the Patient Global Impression of Severity (PGI-S) by standardizing each component's change from baseline against the pooled baseline standard deviation and averaging the standardized values, providing a single measure of treatment effect across functional, cardiac, and patient-reported domains.

6 CLINICAL EFFICACY

Summary

- Primary evidence for the safety and efficacy of deramiocel in the treatment of Duchenne cardiomyopathy and skeletal muscle pathology in patients with DMD is based on the results of HOPE-3 and is supported by the HOPE-2 and HOPE-2-OLE clinical studies.
- HOPE-3 Phase 3 randomized, double-blind, placebo-controlled study outcomes confirm observations from the HOPE-2 Phase 2 randomized, double-blind, placebo-controlled study.
- In HOPE-3, all prespecified, type 1 error controlled primary and secondary endpoints at 12 months follow-up were statistically significant, confirming prior clinical evidence that deramiocel slows progression of both skeletal myopathy (PUL 2.0) and cardiomyopathy (LVEF including LGE, a measure of fibrofatty replacement of cardiac tissue).
- HOPE-2-OLE continues to demonstrate consistent safety and efficacy outcomes as shown in HOPE-3 and HOPE-2 over the 36 months of follow-up reported in the BLA and follow-up is ongoing.

6.1 Introduction

The primary evidence of efficacy of deramiocel is based on the results of HOPE-3 and is supported by HOPE-2 and HOPE-2-OLE.

HOPE-3 study provides randomized, double-blind, placebo-controlled confirmation of the Phase 2 observations that deramiocel slows progression of both upper-limb functional decline and DMD-associated cardiomyopathy. HOPE-3 met all of its multiplicity-controlled primary and secondary endpoints: percent change from baseline in PUL 2.0 Total Score: 4.55 (95% CI: 0.47, 8.63; p=0.029), LVEF by ranked analysis of covariance (ANCOVA): 11.65 (95% CI: 0.47, 22.82; p=0.041), percent change from baseline in PUL 2.0 Mid-level Score: 8.12 (95% CI: 2.12, 14.11; p=0.008), Total GST: 0.28 (95% CI: 0.05, 0.52; p=0.017), and LGE segments: -3.01 (95% CI: -5.50, -0.51; p=0.022).

Results from HOPE-3 demonstrate a clinically meaningful primary effect on upper-limb function together with strong concordant cardiac and structural findings, substantiating the pattern observed in HOPE-2. Continued follow-up in the ongoing HOPE-2-OLE study provides additional evidence of durability of effect, with sustained cardiac and skeletal benefits observed during extended deramiocel treatment, with 3-year follow-up data and comparison to high quality external control groups. A summary of key efficacy

findings across supporting clinical studies for skeletal muscle function and cardiac function are provided in Section 6.4 and Section 6.5, respectively.

6.2 Patients

6.2.1 HOPE-3 Baseline Characteristics, Disposition and Analysis Populations

Figure 8 shows a CONSORT flow diagram for HOPE-3.

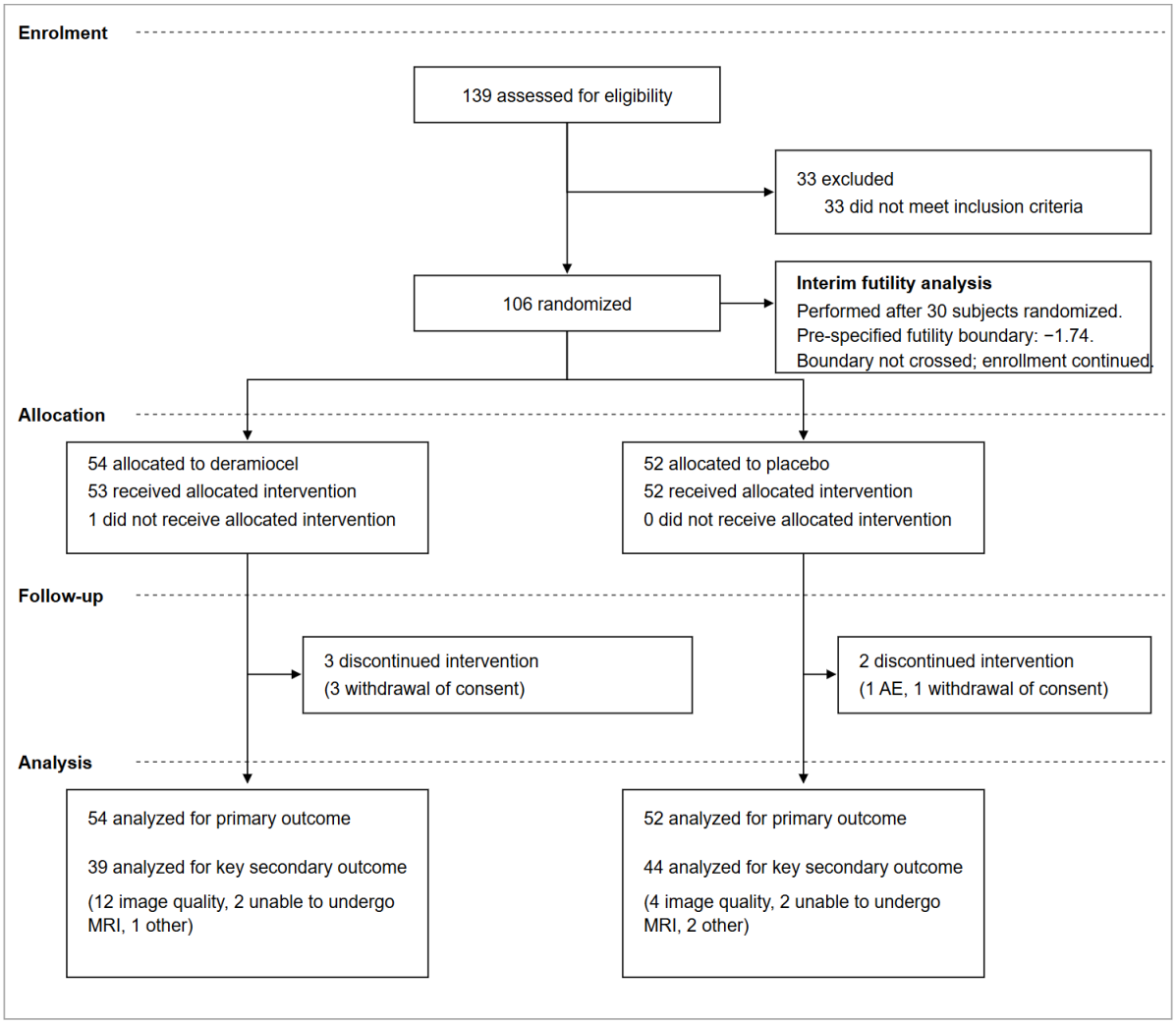
Males at least 10 years of age with genetically confirmed DMD, who had PUL 2.0 entry item score 2-6 and total PUL2.0 score ≤ 40 who were either non-ambulatory or late-ambulatory (with 10-meter walk/run time of >10 seconds), and receiving chronic and stable corticosteroids were eligible for inclusion. LVEF <35%, forced vital capacity % predicted <30%, and severe elbow contractures were exclusionary.

Of 139 participants screened, 106 were randomized and included in the Intent-to-Treat (ITT) population (deramiocel, n=54; placebo, n=52) with 61 participants in Cohort A and 45 in Cohort B.

Five individuals terminated participation early, one with an AE and four withdrew consent. One participant was not dosed following randomization and was excluded from the Safety population.

Those with evaluable cMRI at baseline and 12 months were included in an ITT population for LVEF and other non-LGE endpoints (n=83, 44 on placebo and 39 on deramiocel). Among the 44 participants consented for gadolinium administration, 22 had evaluable paired sets of baseline and 12-month LGE images, with exclusions prior to unblinding due to inadequate cMRI image quality. Baseline demographic characteristics were broadly comparable between groups (Table 6).

Figure 8: CONSORT Diagram - Disposition of Patients



6.2.2 HOPE-3 Patient Baseline Characteristics

Baseline demographic and disease characteristics were generally balanced between treatment arms (Table 6). The mean age was 15.0 years (range, 10–22 years); 76.4% of patients were White. Mean body mass index (BMI) was 27.0 kg/m². Dystrophin gene deletions were the most common mutation type (63.2%). The distribution of corticosteroid use, in terms of the steroid of choice (prednisone, deflazacort) and the regime (daily vs. intermittent) were similar between groups. The proportion of patients receiving exon skipping medication was similar (23.1% placebo; 25.9% deramiocel). The majority of patients were non-ambulatory at baseline (84.9%) and required use of a manual or power wheelchair or scooter. Of note, the baseline demographic characteristics in HOPE-3 were generally consistent with those observed in HOPE-2 and HOPE-2-OLE.

Table 6: HOPE-3 Demographic and Baseline Disease Characteristics, by Treatment Arm (Intent-to-Treat, N = 106)

Characteristic	Placebo (n = 52)	Deramiocel (n = 54)	Overall (N = 106)
Age, years, mean (SD)	14.6 (2.95)	15.4 (3.10)	15.0 (3.04)
Male sex, No. (%)	52 (100)	54 (100)	106 (100)
White race, No. (%)	38 (73.1)	43 (79.6)	81 (76.4)
Not Hispanic or Latino, No. (%)	46 (88.5)	49 (90.7)	95 (89.6)
Body mass index, kg/m^2, mean (SD)	26.9 (6.50)	27.1 (6.99)	27.0 (6.72)
Dystrophin gene deletion, No. (%)	33 (63.5)	34 (63.0)	67 (63.2)
Documented cardiomyopathy, No. (%)	38 (73.1)	41 (75.9)	79 (74.5)
Entry stratum II (PUL item 4 to 6), No. (%)	29 (55.8)	29 (53.7)	58 (54.7)
Slow progressors (prespecified), No. (%)	5 (9.6)	1 (1.9)	6 (5.7)
Baseline PUL 2.0 Total, mean (SD)	26.5 (6.70)	27.6 (7.36)	27.1 (7.03)
Baseline LVEF, %, mean (SD)	59.3 (6.11)	55.4 (7.74)	57.4 (7.21)

Intent-to-treat population (ADSL). Age range 10 to 22 years in both arms; all patients male; non-ambulatory at baseline 84.9% overall. The deramiocel arm entered with a lower mean baseline LVEF and a smaller proportion of prespecified slow progressors. Eligibility required a PUL 2.0 Total Score of 40 or less (observed range 13 to 40).

The HOPE-3 study prospectively collected comprehensive medical history information related to cardiac status and prior/concomitant cardiac medication information at baseline to support the prespecified subgroup and sensitivity analyses to evaluate the efficacy of deramiocel for the treatment of cardiomyopathy in patients with DMD. These data included baseline cardiac status, concomitant cardiac medication, and documented cardiomyopathy (as defined by presence of a clinical diagnosis, LGE on cMRI, and/or a LVEF ≤ 55%). Cardiomyopathy was present at baseline in 79 of 106 patients (74.5%) and was similarly distributed between treatment groups (placebo 73.1%; deramiocel 75.9%) although cMRI data at 12 months was only available in 64 of this subgroup.

6.2.3 Cardiac Evaluable Dataset

Of the 106 randomized patients comprising the ITT population (deramiocel, 54; placebo, 52), the evaluable cardiac dataset comprises 83 patients. Table 7 below displays the reasons for patients not in the cardiac dataset. Fifteen patients had no evaluable baseline cMRI scan and could not contribute a baseline LVEF observation; of the remainder, 8 (8.8%) were missing the Month 12 scan, none due to an AE or death. Images were assessed for image quality (on image file receipt, or if triggered by an image adjudication process) by central readers blinded to treatment, sequence order and treatment allocation or outcome, with the adequacy flag set before database lock and unblinding, so inclusion in the evaluable set is independent of treatment allocation or effect. The sponsor did not receive any data prior to database lock and study unblinding and all images were read by qualified cardiac radiologists in the central core lab.

Table 7: Reasons for not Available for Left Ventricular Ejection Fraction Analysis -- Intent-to-Treat Population (N = 106)

	Placebo (n = 52)	Deramiocel (n = 54)	Total (n = 106)
No Evaluable Baseline Cardiac MRI (n = 15)			
Image quality failure at baseline[a]	3 (5.8)	5 (9.3)	8 (7.5)
Baseline assessment only (Month 12 evaluable)	1 (1.9)	3 (5.6)	4 (3.8)
Baseline and Month 12	2 (3.8)	2 (3.7)	4 (3.8)
Unable to conduct cMRI[b]	2 (3.8)	2 (3.7)	4 (3.8)
Baseline assessment outside protocol-specified window	1 (1.9)	0	1 (0.9)
Never received investigational product[c]	0	1 (1.9)	1 (0.9)
Protocol violation (prohibited medication)	1 (1.9)	0	1 (0.9)
Subtotal	7 (13.5)	8 (14.8)	15 (14.2)
Evaluable Baseline; Missing Month 12 Cardiac MRI (n = 8)			
Image quality failure at Month 12	1 (1.9)	7 (13.0)	8 (7.5)
Missed scheduled assessment (on study or completed study)[d]	--	--	6
Withdrew consent for personal or procedural reasons	--	--	2
Subtotal	1 (1.9)	7 (13.0)	8 (7.5)

a Image quality adjudication was triggered when absolute change in LVEF from baseline to Month 12 exceeded 9%; 16 patients triggered adjudication. Of these, 6 were excluded for inadequate image quality at baseline, Month 12, or both (April 2026 Information Request, Capricor Response 3b); 10 were excluded during initial quality control or Reader A assessment.
b Physical constraints included contractures and anxiety.
c This patient was randomized but never received investigational product and therefore never underwent a protocol-required baseline cardiac MRI assessment.
d Per May 2026 Information Request response: none of the 8 patients were missing Month 12 due to death or adverse event. Treatment-arm allocation for the 6 vs 2 subcategories is not available in submitted tabular output.
Data are expressed as No. (%) unless otherwise indicated. Percentages use the ITT denominator (n = 52 placebo; n = 54 deramiocel; n = 106 overall). Total excluded from LVEF analysis: 23 of 106 (VLVEFFL = N); LVEF-evaluable population: 83 of 106 (VLVEFFL = Y).

Table 8: Baseline Clinical Characteristics and Background Cardiac Therapy, Cardiac-Evaluable Population (N = 83)

Characteristic	Placebo (N = 44)	Deramiocel (N = 39)	Overall (N = 83)
Baseline PUL 2.0 Total, mean (SD)	26.72 (6.25)	27.86 (7.35)	27.25 (6.77)
Baseline PUL 2.0 Total, median	26.50	28.00	26.67
Baseline LVEF, %, mean (SD)	59.62 (5.96)	54.36 (7.60)	57.15 (7.24)
Baseline LVEF, %, median	59.54	55.17	57.53
Baseline LVEF < 45%, No. (%)	0	5 (12.8)	5 (6.0)
Baseline LVEF ≥ 45%, No. (%)	44 (100)	34 (87.2)	78 (94.0)
RAS agents, No. (%)	40 (90.9)	37 (94.9)	77 (92.8)
Beta blockers, No. (%)	17 (38.6)	17 (43.6)	34 (41.0)
Diuretics, No. (%)	29 (65.9)	21 (53.8)	50 (60.2)
No cardiac medication, No. (%)	3 (6.8)	2 (5.1)	5 (6.0)
Non-ambulatory, No. (%)	38 (86.4)	33 (84.6)	71 (85.5)

Cardiac-evaluable population with valid LVEF at baseline and Month 12. RAS = renin-angiotensin system agents. The deramiocel arm entered with a lower mean baseline LVEF (54.36% vs 59.62%) and held all 5 patients below 45%, a structural disadvantage at randomization; background cardiac therapy was balanced or modestly favored placebo (greater diuretic use).

Of note, the distribution of major cardioactive drug classes between patients in the cardiac evaluable group is shown in Table 8 with >90% receiving ACE inhibitors or angiotensin receptor blockers. The use of mineralocorticoid antagonists (eplerenone, spironolactone) was 65.9% in the placebo arm and 53.8% on deramiocel.

6.2.4 Patient Demographics of Supporting Trials

The baseline demographic characteristics of the 20 male patients enrolled in the HOPE-2 study included a mean age of 14.3 years (range, 10–21 years), with 75% White and 90% not of Hispanic or Latino ethnicity, and a mean BMI of 22.6 kg/m². All patients used a manual or power wheelchair or scooter at least part of the time, and 16 had transitioned to full-time use at baseline. Demographic characteristics were generally comparable between the deramiocel and placebo treatment groups.

The HOPE-2-OLE study population consisted of 13 male patients who completed 12 months of follow-up in HOPE-2 and continued into open-label deramiocel treatment. Mean age at HOPE-2-OLE entry was 16.5 years (range, 12–23 years). Patients were primarily White (84.6%), with a mean BMI of 22.83 kg/m². All patients had transitioned to full-time use of a manual or power wheelchair or scooter prior to OLE study entry.

6.3 Methods

A summary of HOPE-3 trial design is provided in Section 5.1.3 and the clinical protocol and SAP history is provided in Section 4.1.1. In addition to prespecified sensitivity analyses we also provide additional sensitivity analyses based on two earlier submitted versions of the SAP (v1.7 and v2.0) for transparency.

6.3.1 Statistical Methods

Family-wise type I error was strongly controlled using a hierarchical gatekeeping procedure. The first family comprised PUL 2.0 Total Score in the combined cohorts and in Cohort B alone, tested together by a Hochberg procedure at the two-sided α level. Only if both hypotheses in this family were rejected did testing proceed, in fixed sequence, to LVEF, mid-level PUL 2.0, the Total GST, and Cohort B late gadolinium enhancement — each at full α, stopping at the first non-rejection. Testing proceeded sequentially while each endpoint met the 0.05 threshold, and endpoints evaluated after the first endpoint not meeting this threshold are reported with nominal p-values.

The Total GST integrated the PUL 2.0 Total Score, LVEF, and the PGI-S by standardizing each component's change from baseline against the pooled baseline standard deviation and averaging the standardized values, providing a single measure of treatment effect across functional, cardiac, and patient-reported domains.

Intercurrent events were handled through a prespecified composite strategy: values missing because of death or an adverse event leading to discontinuation were assigned the worst observed value at the corresponding visit; a treatment-policy strategy was applied to off-treatment data following withdrawal of consent or dosing deviations; and a hypothetical strategy was applied to other discontinuations. Remaining missing data were accommodated under the missing-at-random assumption inherent to the repeated-measures and rank-based analyses. Prespecified sensitivity analyses examined the robustness of the primary and key secondary results, including absolute change in place of percent change, the per-protocol population, a missing-not-at-random copy-increment-from-reference pattern-mixture approach, and, for LVEF, indicator-variable adjustments for baseline cardiac medication use and for initiation of a new class of cardiac medication during the double-blind phase.

The composite strategy assigned the worst observed value at the affected visit rather than the worst possible value, so it is stringent but not maximally conservative. On the primary and key secondary endpoints, it affected a single patient, who was in the placebo arm.

Cardiac magnetic resonance images were assessed for adequacy and analyzed by central readers blinded to treatment assignment or visit. The prespecified central reader provided the complete dataset used for the primary cardiac analyses, and inter-reader agreement (concordance) between readers was evaluated as a supportive measure of measurement reliability.

6.3.1.1 Performance of the Upper-Limb (PUL) Function Endpoint Methods

Assessment of upper limb function measured by PUL 2.0 was selected as the primary efficacy endpoint in HOPE-3 and an exploratory endpoint in HOPE-2, based on its validation as a clinically meaningful measure of disease progression in non-ambulant DMD populations. The PUL aligned with FDA guidance on drug development in DMD

and was assessed throughout the HOPE-2-OLE study (See Section 5.2.1 for details on PUL 2.0).

The primary efficacy endpoint of HOPE-3 was the mean percent change from baseline in PUL 2.0 Total Score at Month 12. This endpoint was analyzed using a mixed model with repeated measures that included the fixed categorical effects of treatment, cohort, pooled investigative site, visit, and treatment-by-visit interaction, together with baseline PUL 2.0 Total Score and an indicator for known slow progressors. Percent change was calculated at the patient level as change from baseline divided by baseline score, multiplied by 100.

The specification of percent change (made in SAP v2.0) rather than absolute change relies on both clinical and statistical rationales.

Clinically, HOPE-3 enrolled patients with baseline PUL 2.0 Total Scores ranging from 13 to 40, spanning a broad range of upper-limb function and disease stage, and patients at such different stages are neither expected nor observed to show the same absolute change over a fixed interval. Emerging clinical studies in DMD have determined that patients and caregivers judge the meaningfulness of a functional change relative to their current ability level (Gillman et al. 2025; Coratti et al. 2025). This approach is also supported by the *FDA Patient-Focused Drug Development Guidance 4: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making, Draft Guidance*, April 2023. Percent change provides a normalized assessment of proportional decline and supports interpretation of the treatment effect across this heterogeneous population.

Statistically, the choice was prespecified on a distributional basis. Inspection of blinded study data showed that the variance of change-from-baseline scores was heterogeneous across baseline scores, indicating a multiplicative error structure in which variance increases with baseline function, a violation of the homoscedasticity assumption of the linear model that reduces statistical power; scaling each patient's change to their own baseline homogenizes that variance. These determinations were made on blinded study data, prior to database lock by personnel without any access to treatment assignment. A Levene test conducted post-hoc confirmed the pattern: absolute change violated variance homogeneity across baseline tertiles at Months 6, 9, and 12 (p=0.009, 0.023, and 0.031), whereas percent change did not at any of the four visits, including those three (p=0.27, 0.54, and 0.26).

The treatment effect is directionally consistent on both absolute and percent scales, and its demonstration does not rest on the choice of metric. The clearest evidence of metric independence is the Cohort B absolute-change difference of 3.26 points (95% CI: 1.44, 5.07; p=0.0007). In the full population, the prespecified percent-change analysis at Month 12 yields a between-group difference of 4.55 percent (95% CI: 0.47, 8.63; p=0.029), the corresponding absolute-change analysis favors deramiocel by a difference of 1.08 (95% CI: 0.00, 2.16; p=0.0503), a result consistent with the loss of power expected under the heteroscedastic error structure that motivated the percent-

change specification. Both metrics are presented across SAP versions in the tables below.

In the HOPE-2 study, both PUL 1.2 and PUL 2.0 were incorporated to assess upper-limb function over 12 months, with a prespecified primary endpoint of change from baseline to the 12-month timepoint in the mid-level dimension in PUL 1.2.

6.3.1.2 Cardiac Endpoint Methods

LVEF was analyzed using a ranked ANCOVA model. Both the dependent variable (change from baseline) and the baseline values were ranked separately prior to analysis. The model included fixed effects for treatment arm, cohort, and slow-progressor status, an indicator variable for screening LVEF ≥ 45%, continuous covariates for baseline LVEF, age at baseline and an age-by-baseline-LVEF interaction.

Through SAP v2.0, no specific analysis method had been designated for LVEF; all secondary endpoints were to follow the primary MMRM approach. In SAP v3.0, finalized prior to unblinding, LVEF was specified to a ranked ANCOVA. This choice was informed by the HOPE-2 study experience, where non-normal distributions at a comparable sample size necessitated a post-hoc rank transformation, a methodologically suboptimal approach that Capricor committed to avoiding prospectively in HOPE-3. The selection of ANCOVA over a rank-based MMRM is grounded in the statistical literature supporting ANCOVA on ranks as the most established nonparametric approach for pre-post designs (Quade 1967; Conover and Iman 1981, 1982; Lawson 1983). In addition, Schuler (Schuler 2022) formally demonstrated that ANCOVA is at least as statistically efficient as MMRM at a single designated timepoint. Additionally, rank transformations embedded in two-factor or repeated-measures models are not generally valid (Akritas 1990, 1991; Blair, Sawilowsky, and Higgins 1987), which a rank-based MMRM would require. Post-hoc analysis confirmed the appropriateness of the approach: Month 12 LVEF change distributions were significantly non-normal in both arms, and parametric MMRM residuals also failed a normality test. The treatment effect is also present without any covariate adjustment (unadjusted Wilcoxon p=0.0525), confirming that the ranked ANCOVA sharpens rather than creates the observed result (prespecified adjusted p=0.0414).

6.3.1.3 Cardiac Endpoint Data Collection and Management

cMRI was used in HOPE-2, HOPE-2-OLE and HOPE-3 to assess changes in cardiac function. In HOPE-2 and HOPE-3, cardiac parameters were evaluated in patients treated with deramiocel or placebo over a 12-month follow-up period, with inclusion of cMRI with LGE in HOPE-3 (cohort B). In HOPE-2-OLE, cMRI was incorporated beginning at Month 24, with the Month 12 HOPE-2 cMRI serving as the baseline for longitudinal assessment, and continued to be evaluated at months 36, 48 and 60 (or Early Termination, if applicable), with data currently available through Month 36.

The HOPE-3 cMRI Imaging Review Charter specifies a 2+1 consensus read paradigm: each timepoint is read independently by a primary reader (Reader A) and a secondary

reader (Reader B), with an adjudicator (Reader C) resolving predefined disagreements. A consensus review is triggered by an absolute LVEF difference of ≥5%, a relative Left Ventricular End-Systolic Volume (LVESV) difference of ≥10%, an absolute LGE difference of ≥2 segments, or when either reader's data are unavailable; absent any trigger, Reader A's read is the final determination. Separately, an image-quality adjudication by Reader C is triggered when Reader A's LVEF changes by an absolute ≥9% between Baseline and Month 12, with Reader C determining whether the Baseline and/or Month 12 images are of adequate quality for analysis. All central reads were performed blinded to patient identity, treatment assignment, time point, and site.

Following the charter, images with both Reader A and B reads available were adjudicated as necessary. However, in this study, an image-transfer configuration issue was identified during adjudication in which Reader B did not receive phase-contrast imaging and therefore provided complete reads for only 62 of the 83 evaluable patients in the LVEF analysis dataset, while Reader A provided results for all 83 patients. Per the Imaging Review Charter, a missing read triggers consensus review, and therefore where Reader B data were missing, the adjudicator assigned Reader A as the only available read.

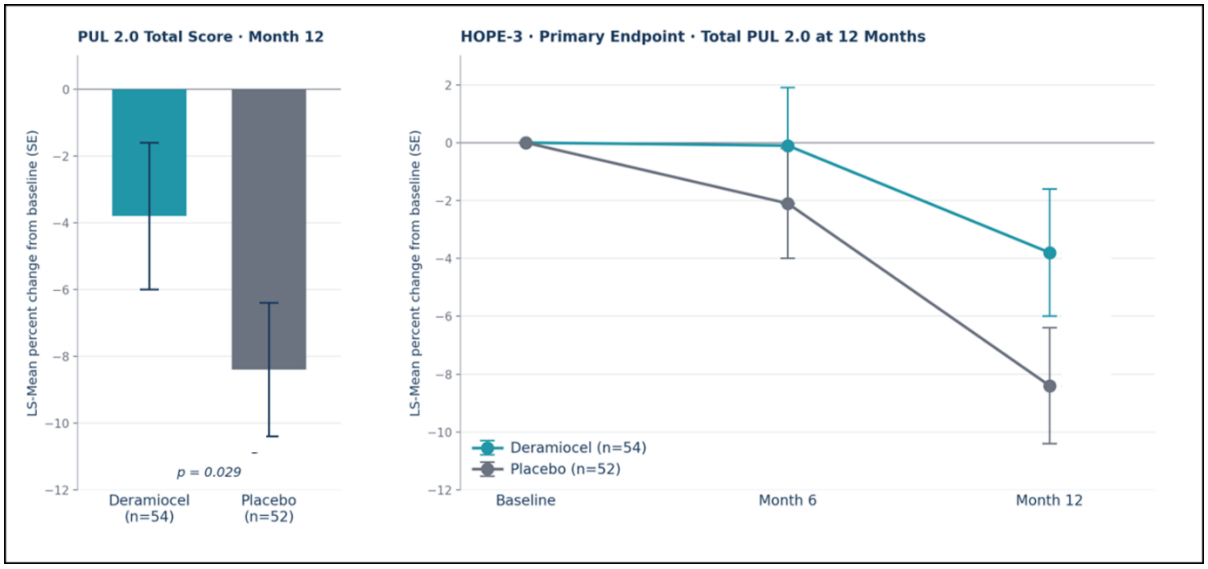
In light of the incomplete Reader B dataset following adjudication, the cMRI expert and adjudicator recommended to the Sponsor that the most methodologically appropriate approach for the cardiac MRI endpoint analyses was to use the complete Reader A dataset, preserving consistent endpoint derivation across subjects and timepoints and avoiding the inconsistency of mixed-reader determinations within a subject. Available Reader B data were retained for supportive inter-reader variability analyses.

Intraclass correlation coefficient (ICC) estimates from the two-way mixed-effects model were excellent for all endpoints. For LVEF, inter-reader ICC (absolute agreement) was near identical at 0.89 (0.80–0.93) at screening and 0.88 (0.77–0.93) at Month 12. For LV-EDV, inter-reader ICCs were 0.98 (0.95– 0.99) at Screening and 0.99 (0.98–0.99) at Month 12. For LV-ESV, inter-reader ICCs were 0.97 (0.95–0.98) at Screening and 0.98 (0.96–0.98) at Month 12.

6.4 Upper-Limb Function Efficacy Results

In HOPE-3, while placebo patients declined as natural history of DMD would suggest; the decline in deramiocel treated patients was significantly slowed (Figure 9). At Month 12, deramiocel demonstrated a 4.55% between-group difference in percent change from baseline (95% CI: 0.47, 8.63; p=0.029), corresponding to an estimated 1.2- point advantage on the PUL 2.0 scale and an approximate 54% reduction in the rate of upper-limb functional decline relative to placebo. A pre-specified sensitivity analysis for the absolute change in total PUL 2.0 over 12-months in treated versus placebo was conducted and yielded 1.08 (95% CI: 0.00, 2.160; p=0.0503) for change in upper limb function, favoring deramiocel.

Figure 9: HOPE-3: LS-mean percent change from baseline in PUL 2.0 Total Score over 12 months



Additionally, in the HOPE-3 study a concordant and larger treatment effect was observed in the mid-level PUL domain, capturing elbow and proximal upper-limb activities critical for self-care tasks. At Month 12, deramiocel demonstrated an 8.12% between-group difference in mid-level PUL 2.0 score (p=0.008), corresponding to an approximate 65% reduction in decline in this domain.

In the empirical cumulative distribution function (CDF) provided in Figure 10, the teal curve sits to the right of the gray curve across most of the range, meaning that *at any given threshold a larger fraction of placebo patients experienced a more negative change*. The separation is most visible in the lower-middle of the distribution; the two curves converge at the favorable upper tail. This rightward shift of the treated distribution is the distributional expression of the smaller mean decline.

Figure 10: Empirical cumulative distribution of the Month 12 percent change in PUL 2.0 by treatment arm (HOPE-3, deramiocel n=51, placebo n=51)

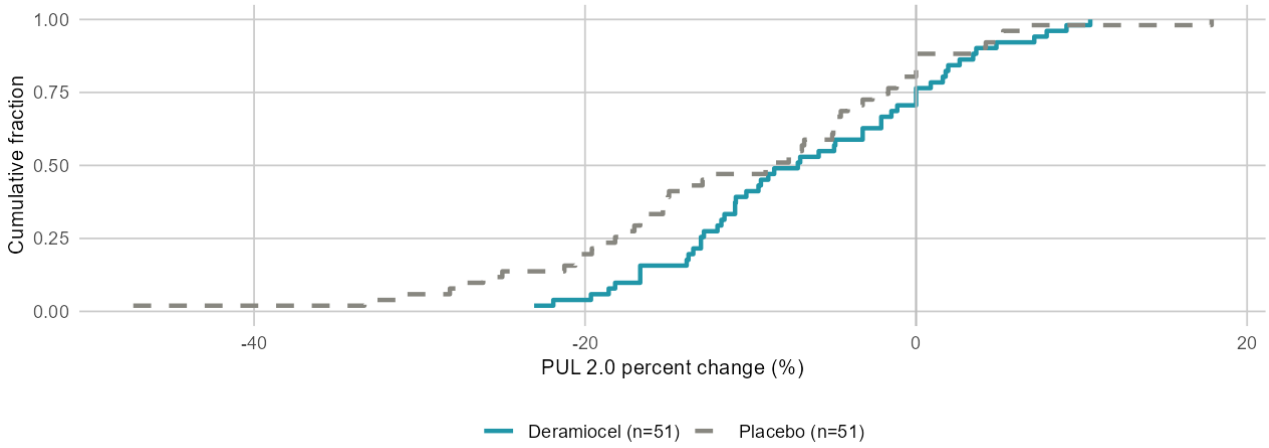


Table 9 presents the Month 12 treatment difference in PUL 2.0 total score, deramiocel minus placebo, estimated under each of the analysis models that has governed this endpoint across the SAP development history. The purpose of the display is to show that the estimated effect on upper-limb function is stable in both magnitude and direction across metrics and across successive model specifications, so that the primary result does not depend on any single analytic choice. Under the prespecified primary analysis in SAP v3.0, the MMRM on percent change yielded a treatment difference of 4.55 percent (95% CI: 0.47 to 8.63, p=0.0290), favoring deramiocel. The prespecified sensitivity analysis on absolute change gave a difference of 1.08 points (95% CI: 0.00 to 2.16, p=0.0503), directionally identical and of the expected magnitude, sitting immediately at the significance threshold.

The consistency of these estimates across earlier, independently specified models is the central observation. The v2.0 model returned effects of essentially the same size as v3.0 on both metrics, 4.85 percent on percent change (p=0.0219) and 1.14 points on absolute change (p=0.0416), and the v1.7 model, which was the last specification derived directly from FDA feedback on v1.6, yielded 1.12 points on absolute change (95% CI: -0.01 to 2.25, p=0.0522). Across five model-and-metric combinations the point estimate for absolute change falls in a narrow band of 1.08 to 1.14 points, and the percent-change estimate in a band of 4.55 to 4.85 percent, with every estimate favoring deramiocel. The p-values for the absolute-change metric cluster at or just above 0.05 (0.0416 to 0.0522) while the percent-change metric is significant under every model, a pattern consistent with percent change being the more sensitive metric for this endpoint rather than with instability in the underlying effect.

Table 9: Performance of the Upper Limb 2.0 Total Score — Month 12 Treatment Difference by SAP Version

MMRM; ITT population (N=54 deramiocel, N=52 placebo); deramiocel minus placebo.

Analysis metric	Estimate, D − P	95% CI	P value
Prespecified primary — CSR / SAP v3.0			
Percent change (PCHG)	4.55	0.47 to 8.63	0.0290
Prespecified sensitivity — SAP v3.0			
Absolute change (CHG)	1.08	0.00 to 2.16	0.0503
Supportive — earlier SAP versions			
PCHG (v2.0)	4.85	0.72 to 8.99	0.0219
CHG (v2.0)	1.14	0.04 to 2.23	0.0416
CHG (v1.7)	1.12	−0.01 to 2.25	0.0522

v1.7 reports change from baseline (CHG): Kenward-Roger denominator df, slow-progressor interaction terms, baseline-by-visit, least-squares means evaluated at slowprgn=0. **This was last SAP version that was based directly on FDA feedback on v1.6.**
v2.0 reports percentage change from baseline (PCHG, primary) and CHG (sensitivity): ARH(1) covariance, slow-progressor interaction terms, least-squares means at slowprgn=0.
v3.0 reports PCHG (prespecified primary) and CHG (sensitivity): ARH(1) covariance, slow-progressor as main effect only, unconditioned; covariance fallback per attempt primary — CSH — CS.
SITEGR1 and SLOWPRGN use the locked ADaM (v3.0) derivations; v1.7 and v2.0 rows differ only in model structure. Locked ADaM 20260129_Final_DB; ANL01FL=Y; APHASE=BLINDED TREATMENT.
Abbreviations: ARH(1), heterogeneous first-order autoregressive covariance; CHG, change from baseline; CI, confidence interval; CS/CSH, compound symmetry/heterogeneous compound symmetry; D − P, deramiocel minus placebo; MMRM, mixed model for repeated measures; PCHG, percentage change from baseline; PUL 2.0, Performance of the Upper Limb module 2.0; SAP, statistical analysis plan.

Table 10 displays the 12-month difference in PUL 2.0 Mid-level score. The prespecified MMRM on percent change displayed 8.12% (95% CI: 2.12, 14.11; p=0.0084) difference, the prespecified sensitivity analysis on absolute change displayed an absolute difference of 0.89 (95% CI: 0.17, 1.61; p=0.0158). SAPs v2.0 and v1.7 yielded very similar results.

Table 10: Mid-level Performance of the Upper Limb 2.0 — Month 12 Treatment Difference by SAP Version

MMRM; ITT population; deramiocel minus placebo (PARAMCD=PULMID).

Analysis metric	Estimate, D − P	95% CI	P value
Prespecified primary — CSR / *SAP v3.0*			
Percent Change (PCHG)	8.12	2.12 to 14.11	0.0084
Prespe*cified sensitivity — SAP v3.0*			
Absolute Change (CHG)	0.89	0.17 to 1.61	0.0158
Supportive — earlier SAP versions			
PCHG (v2.0)	8.76	2.69 to 14.82	0.0050
CHG (v2.0)	0.96	0.23 to 1.69	0.0101
CHG (v1.7)*	0.95	0.21 to 1.69	0.0126

Model structures are identical to those of the PUL 2.0 total score, applied to the mid-level PUL parameter (PARAMCD=PULMID): v1.7 CHG; v2.0 and v3.0 PCHG (primary) and CHG (sensitivity); v3.0 prespecified, ARH(1) covariance with CSH/CS fallback.
SITEGR1 and SLOWPRGN use the locked ADaM (v3.0) derivations; v1.7 and v2.0 rows differ only in model structure. Locked ADaM 20260129_Final_DB; ANL01FL=Y; APHASE=BLINDED TREATMENT.
Abbreviations: ARH(1), heterogeneous first-order autoregressive covariance; CHG, absolute change from baseline; CI, confidence interval; CS/CSH, compound symmetry/heterogeneous compound symmetry; D − P, deramiocel minus placebo; MMRM, mixed model for repeated measures; PCHG, percentage change from baseline; PUL 2.0, Performance of the Upper Limb module 2.0; SAP, statistical analysis plan. ***This was last SAP version that was based directly on FDA feedback on v1.6**

Table 11 summarizes the estimated treatment effects of deramiocel on the PUL 2.0 across the two placebo-controlled studies, HOPE-3 and HOPE-2, at both the total and mid-level dimensions and under both the percent-change and absolute-change metrics. Two consistent patterns are evident. First, every point estimate favors deramiocel across both studies, both PUL 2.0 dimensions, and both metrics, with no reversal of direction in any cell. Second, the magnitude of the effects is closely concordant between the two studies despite their substantial difference in size: the total PUL 2.0 absolute-change effect is 1.1 points in HOPE-3 and 1.8 points in HOPE-2, and the mid-level PUL 2.0 absolute-change effect is essentially identical at 0.9 points in each study. The percent-change effects show the same alignment, with mid-level estimates of 8.1 percent in HOPE-3 and 7.7 percent in HOPE-2. The p-values differ across cells largely in accordance with the available sample sizes, with the smaller HOPE-2 population yielding wider standard errors and correspondingly larger p-values for effects of comparable magnitude. The convergence of independently estimated effects of similar size and direction across two separate trials, and across both the absolute and percent metrics, supports the reproducibility of the deramiocel effect on upper-limb function.

Table 11: Deramiocel PUL 2.0 Treatment Effects: HOPE-3 and HOPE-2

Endpoint	Metric	HOPE-3 (D N=53 vs P N=52)	HOPE-2 (D N=8 vs P N=12)
Total PUL 2.0	PCHG	4.6 (2.1), p=0.03	7.2 (3.8), p=0.07
Total PUL 2.0	CHG	1.1 (0.6), p=0.05	1.8 (0.9), p=0.05[a]
Mid-level PUL 2.0	PCHG	8.1 (3.0), p<0.01	7.7 (4.5), p=0.10
Mid-level PUL 2.0	CHG	0.9 (0.4), p=0.02	0.9 (0.5), p=0.11

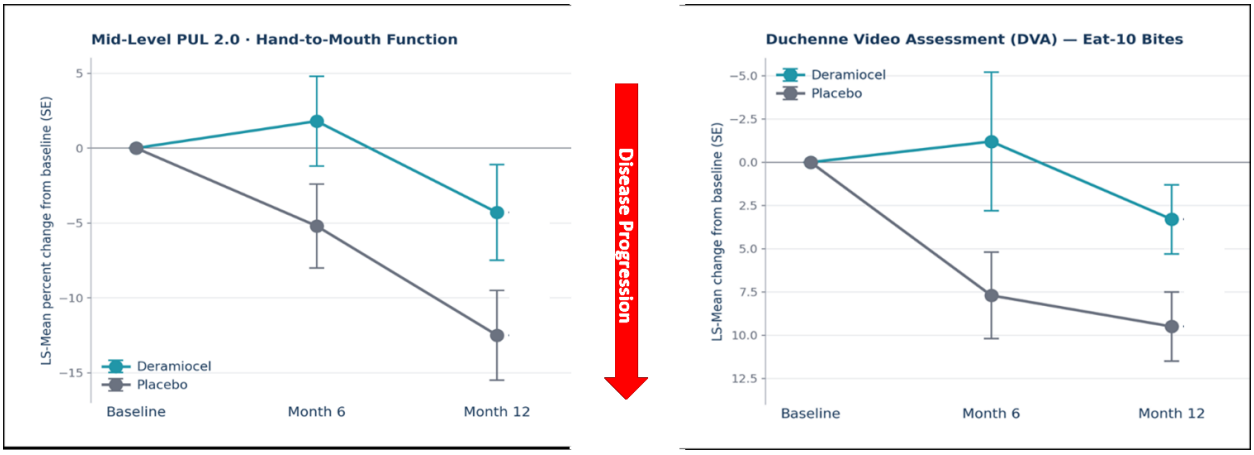
Values are effect (SE); MMRM. CHG = absolute change; PCHG = percent change.
[a] Sensitivity analysis only; CHG is the prespecified primary for HOPE-2, PCHG for HOPE-3.

6.4.1 Totality of Evidence Supporting Skeletal Muscle

6.4.1.1 Mid-level PUL 2.0 and DVA Eat-10-Bites Convergence

Figure 11 presents two independently derived measures of upper-limb function that bear on the same feeding-related activity: the mid-level PUL 2.0 dimension, which captures hand-to-mouth movement, and the DVA Eat-10-bites task, which scores observed feeding performance directly. Although the two instruments differ in construction, one a clinician-administered functional scale and the other a video-based rated assessment, they measure overlapping aspects of the same real-world capability and would be expected to move together if a treatment effect on feeding function were present. Across both measures the pattern is concordant. In each panel the deramiocel and placebo arms separate progressively from a common baseline, with the placebo arm declining steadily through Month 6 and Month 12 while the deramiocel arm shows attenuated decline over the same interval. The convergence of two methodologically distinct instruments on the same directional signal, over the same timeframe and in the same study, provides cross-instrument support for a deramiocel effect on feeding-related upper-limb function.

Figure 11: Mid-level PUL 2.0 and the DVA Eat-10-bites task converge on the same feeding-related function (HOPE-3)



6.4.1.2 Supporting Skeletal Muscle Data in Phase 2 HOPE-2

The direction, magnitude, and consistency of the findings demonstrated in HOPE-3 align with those observed in HOPE-2, reinforcing the reproducibility of deramiocel's effect on upper-limb function over a 12-month follow-up period. HOPE-2 showed a statistically significant difference at Month 12 (p=0.01), corresponding to an approximate 2.6-point advantage when translated back to the original PUL scale. Similar statistically significant findings were observed for combined PUL 1.2 dimensions and PUL 2.0 total score. Across all PUL measures, deramiocel consistently demonstrated a statistically significant advantage over placebo using the percentile-ranked model.

6.4.1.3 Long-Term Stabilization and Durability in HOPE-2-OLE

HOPE-2-OLE patients previously randomized to placebo in HOPE-2 experienced a 3.6-point decline in PUL 2.0 during the placebo-controlled phase and a further 3.7-point decline during the untreated gap period between the completion of HOPE-2 and the start of HOPE-2-OLE (average of 392 days). In contrast, patients previously treated with deramiocel declined by only 1.5 points during the 12-month HOPE-2 treatment phase and by 2.8 points during the gap period. When deramiocel treatment was initiated in HOPE-2-OLE for patients previously on placebo, the magnitude of decline during the first year of treatment (-1.9 points) was consistent with the on-treatment experience observed in HOPE-2.

Across all HOPE-2-OLE patients, year-over-year analyses demonstrated progressive attenuation of decline with continued therapy, with mean decline decreasing from -1.8 points in Year 1 to -1.2 points in Year 2 and -1.1 points in Year 3.

To further contextualize these findings against expected natural history under standard of care (including corticosteroids), an ECP dataset from Cincinnati Children's Hospital was used. In a random effects model incorporating baseline function and age, deramiocel-treated patients demonstrated a modeled 3-year decline of -3.46 points compared with -7.19 points in matched natural history controls, corresponding to a statistically significant treatment difference of 3.73 points (p=0.019) over 3 years.

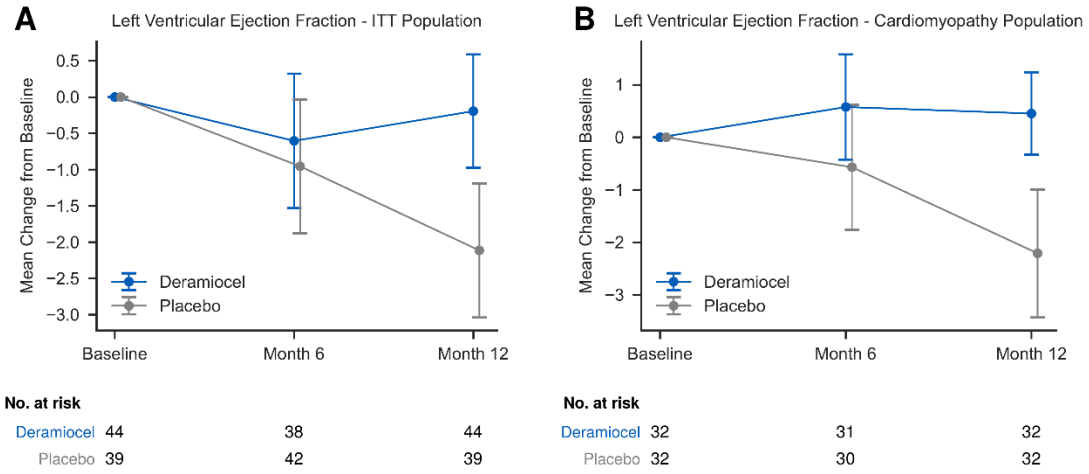
6.5 Cardiac Function and Structure Efficacy Results

6.5.1 Left Ventricular Ejection Fraction

The LVEF analysis in HOPE-3 was the ranked ANCOVA specified in SAP v3.0, fixed before database lock and unblinding. At Month 12, change from baseline in LVEF favored deramiocel by 11.65 ranks (95% CI: 0.47, 22.82; p=0.0414) with covariates of treatment, cohort, slow-progressor indicator, a screening LVEF ≥ 45% indicator, ranked baseline LVEF, age and age by ranked baseline LVEF in the model. In those patients with cardiomyopathy from baseline, the change from baseline in LVEF favored deramiocel by 12.36 ranks (95% CI: 2.34, 22.38; p=0.0165). Confirmatory post hoc proportional odds models were run using the same covariates and the ranked ANCOVA models and show similar pattern of results.

Figure 12 shows the separation of the LVEF means through Month 12 in both the ITT and cardiomyopathy populations.

Figure 12: Change in LVEF through Month 12 in ITT and Cardiomyopathy Population.



The unadjusted Wilcoxon rank-sum test gives p=0.0525. The treatment effect is consistently positive in direction and modest in magnitude, reaching nominal significance only under certain rank-based models.

Of the 106 randomized patients, the evaluable cardiac dataset comprised 83. The directionally positive effect is preserved across the prespecified analysis and a range of imputation approaches, including a missing-not-at-random copy-increment-from-reference approach; significance is not preserved under the most conservative imputations, consistent with a modest effect on a partially observed endpoint.

Table 12: LVEF — Month 12 Treatment Effect by Model and SAP Version

ITT population; deramiocel minus placebo. pp = percentage points; OR = common odds ratio (>1 favors deramiocel).

Model	Estimate (D−P)	95% CI	p-value
CSR: Ranked ANCOVA	11.65 (~2.37 pp)	0.47, 22.82	0.0414
Sensitivity analysis: Proportional odds	OR= 2.45	1.02, 5.87	0.0498
Sensitivity analysis: Wilcoxon rank-sum	—	—	0.0525
Sensitivity analysis: Mean-change MMRM	1.87 pp	−0.65, 4.40	0.1434
Older SAP versions:			
Mean-change MMRM (SAP v2.0)	1.34 pp	−1.28, 3.96	0.3108
Mean-change MMRM (SAP v1.7)	1.72 pp	−0.95, 4.39	0.2030

Mean-change MMRM (SAP v1.7, SAP v2.0) models change from baseline in LVEF (percentage points) with fixed effects for treatment, visit, and treatment-by-visit and a baseline-LVEF covariate, additional age-by-baseline interaction added in; the treatment difference (D − P) is the least-squares mean contrast at Month 12. As in the PUL analyses, the v1.7 and v2.0 rows differ only in model structure (v1.7: Kenward-Roger denominator df, baseline-by-visit; v2.0: ARH(1) covariance).

Ranked ANCOVA (SAP v3.0) ranks the Month 12 outcome across the pooled population and fits ANCOVA on the ranks with treatment and the ranked baseline as covariates; the estimate is the treatment difference on the rank scale, with an approximate percentage-point equivalent in parentheses.

Ranked ANCOVA + age × ranked-baseline and Mean-change MMRM + age × baseline add an age-by-baseline interaction term to the v3.0 ranked ANCOVA and to the mean-change MMRM, respectively.

Unadjusted Wilcoxon rank-sum compares the Month 12 LVEF distributions between treatment groups without covariate adjustment.

Proportional odds + age × baseline fits a cumulative-logit (proportional-odds) model to ordered LVEF response categories with treatment, baseline LVEF, age, and an age-by-baseline interaction; the estimate is the common odds ratio (OR; values above 1 favor deramiocel).

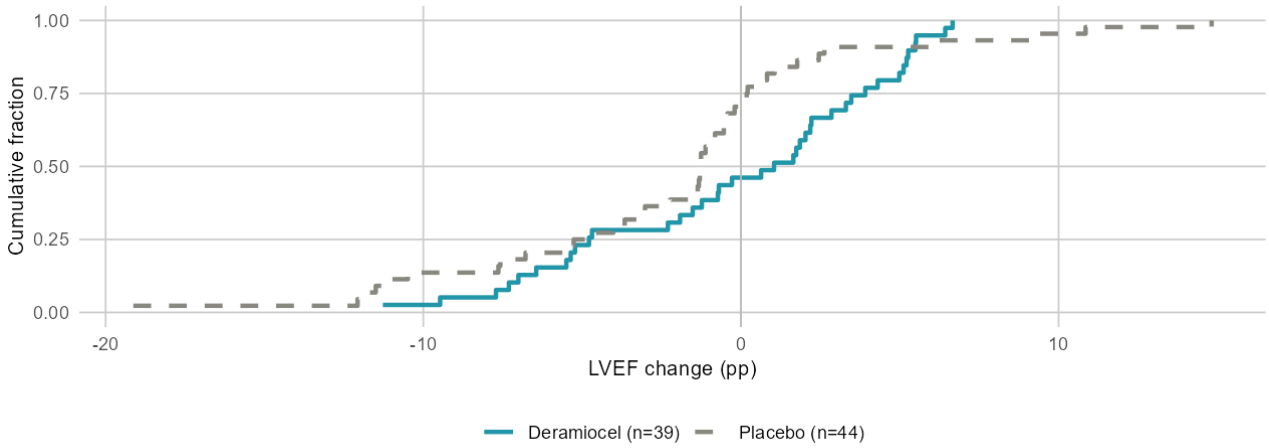
As shown in Table 12, the direction of the LVEF effect does not depend on the class of model used. Estimated at Month 12 with the prespecified covariates, a parametric analysis of covariance on the change scale (1.87 percentage points; p=0.14), the mixed model for repeated measures shown above, the ranked analysis of covariance (p=0.0414), and an ordinal proportional odds model (common odds ratio [OR]: 1.99; 95% CI: 0.83 to 4.77; p=0.0498) all favor deramiocel. The prespecified ranked analysis yields the strongest signal because a rank-based estimator is the more efficient choice for the realized distribution of LVEF change, which is non-normal with a few influential observations. The consistency of direction across otherwise different model families is the relevant robustness property. As a model-independent description of the same comparison, the probability that a deramiocel patient experienced a more favorable Month 12 LVEF change than a placebo patient was 0.62 (concordance statistic), a distribution-free summary that does not depend on any covariate model and is descriptive rather than a hypothesis test.

HOPE-3 included a sensitivity analysis on the secondary endpoint which included cardiac medication use at baseline and, separately, patients who initiated a new class of cardiac medication during the double-blinded, placebo-controlled phase of the study. After adjusting for baseline cardiac medication use, the treatment effect on LVEF remained statistically significant (p=0.0417). The sensitivity analysis accounting for

patients who initiated a new class of cardiac medication during the double-blinded, placebo-controlled phase showed a nominal trend toward significance (p=0.0591). These results support that neither baseline cardiac therapy nor the introduction of new cardiac medications meaningfully impacted the observed treatment effect, reinforcing the reliability and independence of the LVEF findings. The latter analysis conditions on a post-baseline variable, so it is interpreted with the usual caution about post-randomization adjustment and is presented as supportive context rather than a confounder-adjusted causal estimate.

In the empirical CDF, the separation is clearer than for PUL (Figure 13). The teal curve lies distinctly to the right of the gray curve through the middle of the distribution: at a change of 0, roughly three-quarters of placebo patients fall at or below that value versus closer to half of treated patients, indicating that preserved or improved LVEF was more common under Deramiocel. The curves cross at the extreme right tail.

Figure 13: Empirical cumulative distribution function of the Month 12 change in LVEF by treatment arm (HOPE-3, cardiac-evaluable population; deramiocel n=39, placebo n=44)



Key studies in DMD cardiomyopathy suggest that the rate of LVEF decline after definitive cardiomyopathy diagnosis as evidenced for example by a finding of LVEF <55% or following the detection of cardiac scarring by LGE on cMRI (Tandon et al. 2015). As such, it may be anticipated that this population are more likely to decline in LVEF in a clinical study setting over a 12-month period. Within the HOPE-3 study population a subgroup of patients with a definitive diagnosis of cardiomyopathy was identified and analyzed for evidence of a treatment effect as secondary objective.

In the prespecified cardiomyopathy subgroup (n=64), the LVEF treatment effect favors deramiocel across every model class examined and reaches nominal significance in three of the four current-SAP analyses (Table 13). The prespecified ranked ANCOVA (SAP v3.0) yields a rank-scale treatment difference of 12.36 (95% CI: 2.34 to 22.38; p=0.0165), corresponding to approximately 3.3 percentage points. A proportional odds model (OR: 3.24; 95% CI: 1.16 to 9.08; p=0.0252) and unadjusted Wilcoxon rank-sum

test (p=0.0262) are concordant; the mean-change MMRM is directionally consistent (2.88 pp; p=0.0749). The ranked estimator's efficiency advantage for non-normal distributions with influential observations explains both the stronger signal in v3.0 and the non-significance of the older mean-change MMRM specifications from SAP v2.0 (p=0.1981).

Table 13: LVEF in Patients with Cardiomyopathy — Month 12 Treatment Effect by Model and SAP Version

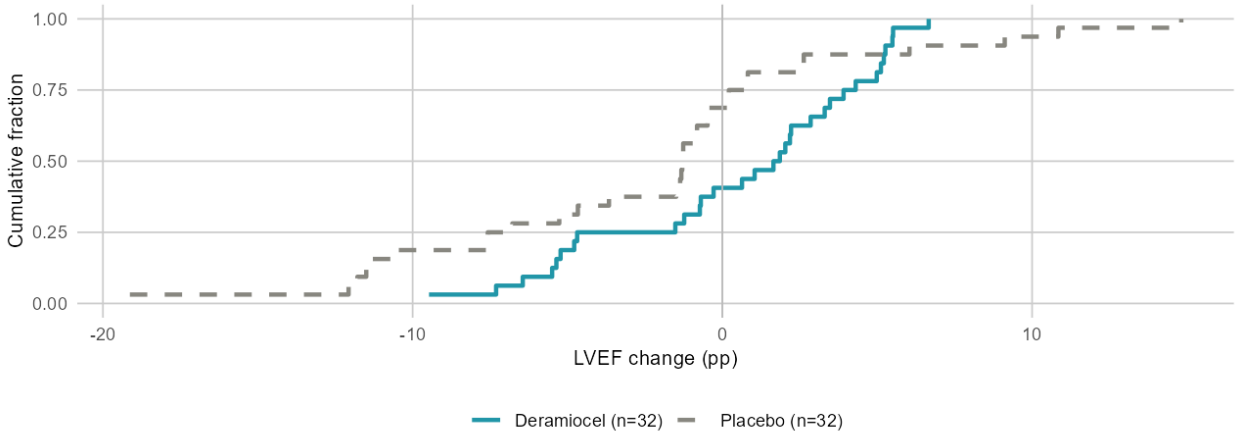
Cardiomyopathy population; deramiocel minus placebo. pp = percentage points; OR = common odds ratio (>1 favors deramiocel).

Model	Estimate (D−P)	95% CI	p-value
CSR: Ranked ANCOVA	12.36 (~3.33 pp)	2.34, 22.38	0.0165
Sensitivity analysis: Proportional odds	OR= 3.24	1.16, 9.08	0.0252
Sensitivity analysis: Mean-change MMRM	2.88 pp	-0.30, 6.05	0.0749
Sensitivity analysis: Wilcoxon rank-sum	—	—	0.0262
Older SAP version w cardiomyopathy subset:			
Mean-change MMRM (SAP v2.0)	2.27 pp	−1.22, 5.77	0.1981

Mean-change MMRM (SAP v2.0) models change from baseline in LVEF (percentage points) with fixed effects for treatment, visit, and treatment-by-visit and a baseline-LVEF covariate, additional age-by-baseline interaction added in; the treatment difference (D − P) is the least-squares mean contrast at Month 12. As in the PUL analyses, v2.0 rows differ only in model structure (v2.0: ARH(1) covariance).
SAP v1.7 was left out as this was not a subgroup identified for analysis in that SAP.
Ranked ANCOVA (SAP v3.0) ranks the Month 12 outcome across the pooled population and fits ANCOVA on the ranks with treatment and the ranked baseline as covariates; the estimate is the treatment difference on the rank scale, with an approximate percentage-point equivalent in parentheses.
Ranked ANCOVA + age × ranked-baseline and Mean-change MMRM + age × baseline add an age-by-baseline interaction term to the v3.0 ranked ANCOVA and to the mean-change MMRM, respectively.
Unadjusted Wilcoxon rank-sum compares the Month 12 LVEF distributions between treatment groups without covariate adjustment.
Proportional odds + age × baseline fits a cumulative-logit (proportional-odds) model to ordered LVEF response categories with treatment, baseline LVEF, age, and an age-by-baseline interaction; the estimate is the common odds ratio (OR; values above 1 favor deramiocel).

The CDF curves for change in LVEF in the cardiomyopathy subgroup, Figure 14, show a clearer separation of LVEF than in Figure 13. Patients on deramiocel experience less decline than placebo.

Figure 14: Empirical cumulative distribution function of the Month 12 change in LVEF by treatment arm (HOPE-3, cardiomyopathy population; deramiocel n=32, placebo n=32)

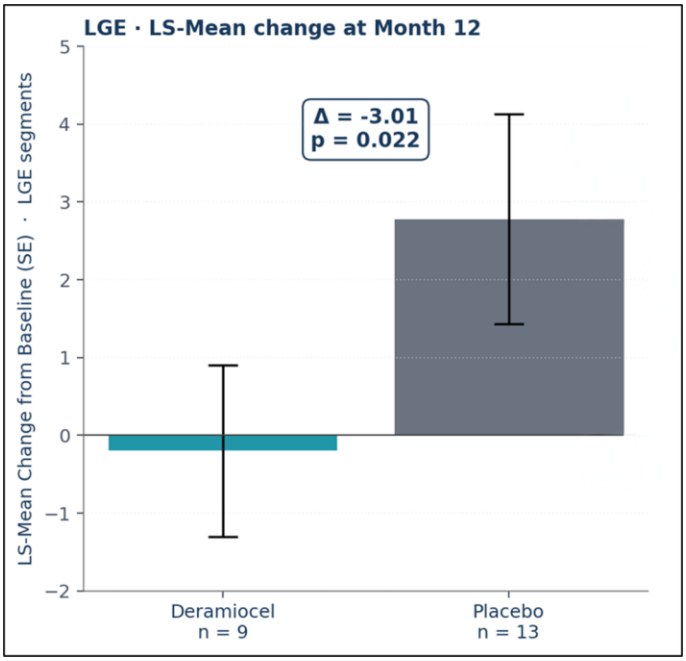


6.5.2 Late Gadolinium Enhancement

DMD associated cardiomyopathy is distinct in its pathophysiology from other forms of cardiac disease and is characterized by a gradual and often clinically silent fibrofatty replacement of myocardium. LGE detected by cMRI serves as a sensitive structural endpoint of myocardial fibrosis and has been strongly correlated with cardiac dysfunction and adverse outcomes in DMD. LGE reflects replacement of viable myocardium with fibrotic tissue, a process that precedes measurable declines in LVEF.

In Cohort B of the HOPE-3 study, changes from baseline to Month 12 in the number of myocardial segments were measured and assessed centrally. Results demonstrate a statistically significant attenuation in the progression of LGE segments in favor of deramiocel (p=0.022; Figure 15). These findings suggest that deramiocel stabilized fibrotic progression, supporting its potential disease-modifying effect on the dystrophin-deficient heart.

Figure 15: Change from baseline at Month 12 in LGE-positive myocardial segments (HOPE-3, Cohort B)



6.5.3 Cardiac Findings in HOPE-3

HOPE-3 measured LVEF by cMRI along with indexed ventricular volumes, left ventricular end-systolic volume index (LVESVI) and left ventricular end-diastolic volume index (LVEDVI). Statistical significance was not achieved for either indexed-volume endpoint. Raw cMRI volumes cannot be interpreted directly across the wide age, height, and weight ranges of the enrolled population, and indexing is used to normalize volumes for these characteristics. The most common indexing method, employed in HOPE-3, uses body surface area, which depends on accurate height and weight measurements that are particularly difficult to obtain in the DMD population. These additional sources of measurement error, together with the greater variability inherent in a larger trial, provide a plausible basis for the non-significant indexed-volume results in HOPE-3.

6.5.4 Supporting Cardiac Data From HOPE-2 and HOPE-2-OLE.

6.5.4.1 Phase 2 HOPE-2

The cardiac findings in HOPE-3 are consistent in direction and magnitude with those of the Phase 2 HOPE-2 study, reinforcing the reproducibility of deramiocel's effect on cardiac function. In HOPE-2, deramiocel-treated patients experienced significantly less deterioration in LVEF than placebo over 12 months (p=0.002), corresponding to an approximate 4.0-percentage-point treatment difference. In addition to LVEF, multiple cardiac measures including LVESV, LVESVI, and LVEDVI favored deramiocel, with 21

of 22 cardiac parameters measured favoring deramiocel and several reaching statistical significance, supporting a consistent cardiac benefit across complementary imaging parameters.

6.5.4.2 Long-term stabilization and durability in HOPE-2-OLE

In HOPE-2-OLE, cardiac MRI was incorporated from Month 24 onward, with the HOPE-2 Month 12 assessment serving as the longitudinal baseline and has continued through Month 36 in the currently available data. With continued deramiocel exposure, cardiac function remained stable, and median LVEF increased at both Month 24 (+1.85 percentage points) and Month 36 (+1.20 percentage points), indicating maintenance of cardiac performance well beyond the randomized period. In comparison with the ECC over two years, modeled LVEF change was -0.03% in deramiocel-treated patients versus -6.42% in the comparator; the difference in slopes favored deramiocel (3.20, 95% CI: 0.91 to 5.49, nominal p=0.0079), corresponding to a modeled treatment difference at Month 24 of 6.40 percentage points (95% CI: 1.82 to 10.97). Among patients with preserved cardiac function at the end of HOPE-2 (baseline LVEF > 45%; deramiocel N=8, comparator N=12), the difference in slopes again favored deramiocel (4.58, 95% CI: 2.22 to 6.94, nominal p=0.0006), corresponding to a modeled treatment difference at Month 24 of 9.16 percentage points (95% CI: 4.44 to 13.88), consistent with greater benefit when treatment is initiated before advanced cardiomyopathy. For indexed volumes, the difference in slopes favored deramiocel for LVESVI (-3.37 mL/m², 95% CI: -6.27 to -0.47, nominal p=0.0244), while LVEDVI numerically favored deramiocel without reaching significance (-2.77 mL/m², 95% CI: -7.08 to 1.53, nominal p=0.1959). A global statistical test incorporating LVEF, LVESVI, and LVEDVI further favored deramiocel over the ECC cohort (0.25, 95% CI: 0.07 to 0.44, nominal p=0.0086). Because these comparisons use an external rather than a randomized control, they are exploratory and the associated p-values are nominal; their role is to characterize durability of effect beyond the controlled phase.

6.5.4.3 Integrated Efficacy Assessment Global Statistical Test

In addition to the assessment of cardiac and skeletal function in the HOPE-3 study, a GST was derived as an integrated efficacy assessment to evaluate the overall impact of deramiocel across multiple clinically relevant dimensions of disease. Given the multisystem nature of DMD, the GST provides a holistic representation of disease status by integrating functional, cardiac, and patient-reported outcomes that reflect how a patient feels, functions, and survives. Specifically, the GST incorporates the PGI-S, reflecting the patient's perception of overall disease severity (feels); the primary endpoint of the trial the PUL 2.0 Total Score, capturing upper-limb functional ability (functions); and the key secondary endpoint of LVEF, representing cardiac performance (survives). Together, these components provide an integrated assessment of disease impact that aligns with the multidimensional clinical burden of DMD. At Month 12, patients in HOPE-3 treated with deramiocel demonstrated a significantly favorable total GST compared with placebo, indicating an overall benefit across the integrated

composite measure (p=0.02; Table 14). Improvement in the Total GST reflects concordant treatment effects across functional, cardiac, and patient-reported domains, rather than an isolated effect in a single endpoint.

Table 14 presents the Month 12 treatment difference for the Total Global Statistical Test, a supportive endpoint that integrates three components, the PUL 2.0 Total score, LVEF, and PGI-S, into a single global statistic analyzed by ANCOVA with terms for treatment and the corresponding baseline covariates. Under the operative SAP v3.0 analysis, the global statistic favored deramiocel by 0.28 (95% CI 0.05 to 0.52, p=0.0168). Because the model specification, comprising the component endpoints, the covariate set, and the baseline handling, is unchanged across SAP v1.7, v2.0, and v3.0, the three versions constitute the same analysis and return identical estimates and intervals.

When interpreted alongside the observed preservation of skeletal muscle function, the favorable Total GST result supports a disease-modifying effect of deramiocel across both cardiac and musculoskeletal systems and underscores its potential to address a critical unmet medical need in patients with DMD. When considered together with the individual efficacy findings for upper-limb function and cardiac outcomes, the GST results reinforce the conclusion that deramiocel exerts a broad, integrated treatment effect consistent with slowing of overall disease progression.

Table 14: Total Global Statistical Test – Month 12 Treatment Difference by SAP Version

SAP version	Estimate (D−P)	95% CI	p-value
Operative plan — CSR / SAP v3.0			
v3.0	0.28	0.05, 0.52	0.0168
Confirmatory — identical model under earlier SAP versions			
v2.0	0.28	0.05, 0.52	0.0168
v1.7*	0.28	0.05, 0.52	0.0168

ANCOVA integrating PUL 2.0 Total, LVEF, and PGI-S; nominal, supportive endpoint.
The Total Global Statistical Test combines three component endpoints — PUL 2.0 Total score, LVEF, and PGI-S — into a single global statistic analyzed by ANCOVA with terms for treatment and the corresponding baseline covariates; the estimate is the treatment difference (D − P) at Month 12.
The model specification — component endpoints, covariate set, and baseline handling — is unchanged across SAP v1.7, v2.0, and v3.0; the three rows therefore report the same analysis and yield identical estimates and intervals.
Component endpoints and baselines use the locked ADaM (v3.0) derivations. *. **This was last SAP version that was based directly on FDA feedback on v1.6**

6.5.5 Robustness Across Subpopulations

For the PUL 2.0 Total score, the effect is robust across all three populations on both metrics. The percent-change estimate rises from 4.55 in the full ITT population (95% CI 0.47 to 8.63, p=0.0290) to 7.51 in the cardiomyopathy subgroup (2.28 to 12.74, p=0.0056) and 12.59 in Cohort B (5.36 to 19.82, p=0.0007), with the lower bound of the interval remaining above zero in every population. The absolute-change estimate

follows the same pattern, from 1.08 in the full ITT population (95% CI 0.00 to 2.16, p=0.0503), with the lower bound at the null, to 3.26 in Cohort B (1.44 to 5.07, p=0.0007) and 2.01 in the cardiomyopathy subgroup (0.64 to 3.37, p=0.0046), where the intervals are wholly positive. The mid-level PUL 2.0 dimension shows the same behavior, with intervals excluding zero in all three populations. Across the PUL endpoints the intervals shift upward and remain positive as the population is enriched, indicating an effect that is consistent in direction and increasing in magnitude rather than dependent on any single population.

The Total GST interval excludes zero in the full ITT and cardiomyopathy populations (0.05 to 0.52; 0.06 to 0.75) but includes it in Cohort B (-0.02 to 0.80). The LVEF ranked ANCOVA ‘s interval excludes zero in the full ITT and cardiomyopathy populations (0.47 to 22.82; 2.34 to 22.38) but includes it in Cohort B (-1.65 to 13.01). LGE-positive segments favored deramiocel with intervals excluding zero across all three populations.

Table 15: Robustness of the Alpha-Controlled Endpoints: Full ITT, Cohort B and Cardiomyopathy

Endpoint (v3.0 prespecified) [mean, 95% CI, p]	Full ITT	Cohort B (N=45)	Cardiomyopathy (N=64)
PUL 2.0 Total, % change	4.55 (0.47, 8.63) p=0.0290	12.59 (5.36, 19.82) p=0.0010	7.51 (2.28, 12.74) p=0.0056
PUL 2.0 Total, absolute change	1.08 (0.00, 2.16) p=0.0503	3.26 (1.44, 5.07); p=0.0007	2.01 (0.64, 3.37); p=0.0046
Mid-level PUL 2.0, absolute change	0.89 (0.17, 1.61) p=0.0158	2.09 (0.63, 3.54); p=0.0059	1.59 (0.61, 2.57); p=0.0020
LVEF, ranked ANCOVA	11.65 (0.47, 22.82) p=0.0414	5.68 (-1.65, 13.01) p=0.1229	12.36 (2.34, 22.38) p=0.0165
Total GST	0.28 (0.05, 0.52) p=0.0168	0.39 (-0.02, 0.80) p=0.0615	0.41 (0.06, 0.75) p=0.0212
LGE positive segments	-3.01 (-5.50, -0.51) p=0.0217	-3.01 (-5.50, -0.51) p=0.0217	-3.13 (-5.74, -0.51) p=0.0228

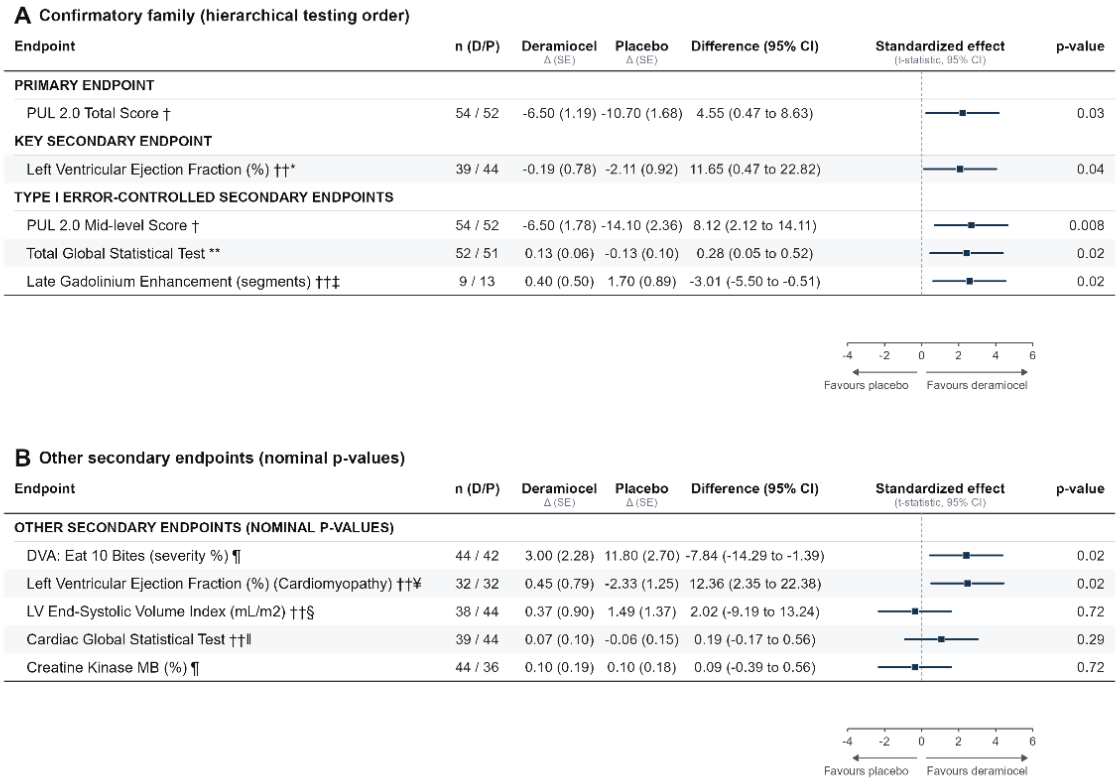
Cohort B single-cohort models drop the constant cohort term.

6.5.6 Other Secondary Endpoints

Across all five prespecified, multiplicity-controlled endpoints in the confirmatory family, the treatment effect favored deramiocel and every 95% CI excluded zero, spanning skeletal-muscle function (PUL 2.0 total and mid-level), cardiac function (LVEF), cardiac structure (LGE), and the global composite (Figure 16). The convergence of benefit across mechanistically distinct domains — rather than an isolated positive endpoint — is the central finding, and it is reinforced by concordant directional effects in the nominal secondary analyses, including the cardiomyopathy-subgroup LVEF and swallowing (DVA) results. Endpoints that did not reach significance straddled the null in both

directions and are presented transparently, underscoring that the confirmatory signal is coherent rather than selective.

Figure 16: Forest Plot of Primary and Secondary endpoints in HOPE-3 as analyzed by CSR models.



6.5.7 Totality of Evidence Supporting Cardiac Function

The cardiac findings across the deramiocel program provide convergent evidence of a treatment benefit on the heart, spanning myocardial structure, ventricular function, and an integrated cardiac assessment, and reproduced across three studies and multiple analysis populations. The evidence is strongest where it is most clinically meaningful. In HOPE-3, late gadolinium enhancement (LGE), a prespecified imaging measure of myocardial fibrosis, favored deramiocel, with the LS-mean change from baseline in the number of affected segments showing less progression of cardiac scarring than placebo (-3.01 segments, 95% CI -5.50 to -0.51, p=0.0217). Because LGE reflects irreversible structural damage to the myocardium rather than a functional index that varies with loading and measurement conditions, a treatment effect on the extent of fibrosis is direct evidence of disease modification at the tissue level.

This structural finding is accompanied by consistent effects on ventricular function. In HOPE-3, LVEF favored deramiocel (ranked ANCOVA, treatment difference 11.65, 95% CI 0.47 to 22.82, p=0.0414), and the effect was more pronounced in the

cardiomyopathy subgroup (p=0.0165). The Total Global Statistical Test, which integrates PUL 2.0 Total, LVEF, and PGI-S into a single measure, also favored deramiocel (0.28, 95% CI 0.05 to 0.52, p=0.0168) and was likewise stronger in the cardiomyopathy subgroup (0.41, 95% CI 0.06 to 0.75, p=0.0212). Across the structural, functional, and composite measures, the direction is uniform and the magnitude increases in the more affected population, a coherence that is not expected under a null cardiac effect.

6.5.7.1 Supporting Cardiac Data in Phase 2 HOPE-2

The HOPE-3 cardiac findings reproduce those observed in the Phase 2 HOPE-2 study. In HOPE-2, deramiocel-treated patients experienced significantly less deterioration in LVEF than placebo over 12 months (p=0.002), corresponding to an approximate 4.0-percentage-point treatment difference. Additional cardiac measures, including indexed end-systolic and end-diastolic volumes, also favored deramiocel, with 21 of 22 cardiac parameters directionally favoring deramiocel and several reaching statistical significance. The reproduction of a directionally uniform cardiac effect in an independent randomized study strengthens the inference that the effect is real.

6.5.7.2 Long-Term Stabilization and Durability in HOPE-2-OLE

In HOPE-2-OLE, cardiac MRI was incorporated from Month 24 onward, with the HOPE-2 Month 12 assessment as the longitudinal baseline, continuing through Month 36 in the currently available data. With continued deramiocel exposure, cardiac function remained stable, and median LVEF increased at both Month 24 (+1.85 percentage points) and Month 36 (+1.20 percentage points), indicating maintenance of cardiac performance well beyond the randomized period. Against the best available natural-history comparators, NIH- and FDA-funded external cardiac cohorts representing the current standard for characterizing untreated cardiac progression in this population, deramiocel-treated patients maintained LVEF over two years (modeled change -0.03%) against a -6.42% decline in the comparator, a treatment difference at Month 24 of 6.40 percentage points (difference of slopes 3.20, 95% CI 0.91 to 5.49, p=0.0079). Among patients with preserved cardiac function at the end of HOPE-2 (baseline LVEF > 45%; deramiocel N=8, comparator N=12), the treatment difference at Month 24 was 9.16 percentage points (difference of slopes 4.58, 95% CI 2.22 to 6.94, p=0.0006), consistent with greater benefit when treatment is initiated before advanced cardiomyopathy. Indexed ventricular volumes showed sustained separation from the comparator, and a global statistical test combining LVEF, LVESVI, and LVEDVI favored deramiocel (0.25, 95% CI 0.07 to 0.44, p=0.0086).

6.6 Clinical Meaningfulness

6.6.1 Clinical Meaningfulness of Deramiocel Treatment Effects on Upper Limb Function

DMD leads to progressive and irreversible loss of upper limb function in all cases that begins to be measurable prior to loss of ambulation and is a major determinant of

quality of life for non-ambulatory patients and caregivers. Surveys conducted by PPMD confirm hand to mouth function and independent feeding to be one of the most important determinants of quality of life for both patients and caregivers and relative stabilization or slowing of disease progression and has been determined by these stakeholders to be a key determinant of an efficacious therapeutic in terms of meaningful benefit (Peay et al. 2016). The HOPE-3 phase 3 results for deramiocel should be read through that lens as the trial utilized a primary efficacy endpoint, the PUL 2.0, that measures upper limb functions that genuinely matter to a patient. The clinical meaningfulness of PUL results are best understood by focusing on 1) interpretation of the primary endpoint in the context of the pre-specified secondary endpoint consisting of the 12-month mid-level PUL domain results (absolute change, percent change from baseline, and percent slowing in the rate of disease progression), 2) the concurrent validation of mid-level PUL provided by the DVA Eat 10 bites, and 3) The proportion of patients able to maintain hand to mouth function without compensations.

Clinical meaningfulness of the total PUL results can be appreciated by focusing specifically on the treatment effect for the mid-level domain of the PUL 2.0. This domain captures elbow and forearm function, the movements that let a person bring a hand to the mouth, lift and handle objects, and hold the arm steady for functional activities. In a disease where decline is inevitable, holding on to function is critical, patients report that their first thought of the day, is “no worse today”. While the full PUL 2.0 is a reasonable tool to assess upper limb function over the entire course of upper limb disease progression in a broad population of patients with DMD, the mid-level domain of the PUL 2.0 is where preserved function is most detectable in a 12-month study and most directly meaningful to patients in terms of activities of daily living. Even a one-point change in a total PUL score or a PUL domain such as the mid-level PUL 2.0 has been deemed to be a meaningful change to patients (Gillman et al. 2025). The therapeutic effects of deramiocel in terms of change in absolute PUL score is not subtle. The 1.2 point difference seen in the Total PUL 2.0 score at 12 months, in the context of a highly heterogeneous disease in which PUL score may continuously decline over 1-2 decades, indicates a clinically relevant delay in disease progression. For the primary endpoint, the between-group LS-mean difference of 4.55% in percent change (standard error [SE] ± 2.06; 95% CI: 0.47, 8.63; p=0.029), reveals meaningful preservation of upper limb function by deramiocel. Importantly, a pre-specified sensitivity analysis for the absolute change in total PUL 2.0 over 12-months also showed a nominally significant treatment effect of deramiocel on the primary endpoint. Furthermore, the 54% slowing of mean skeletal muscle disease progression, relative to placebo, represents >1 year of progression saved for every 2 years of natural progression in the absence of deramiocel.

In addition, since the mid-level PUL has the most predictable and linear decline over 12 months, it was employed as a pre-specified type 1 error controlled secondary endpoint in HOPE-3 and the primary endpoint for the HOPE-2 trial. Changes in the mid-

level PUL are particularly relevant, as they are highly associated with quality-of-life indicators such as the ability to eat independently. The absolute difference on the mid-level PUL 2.0 scale corresponds to 1.2-point advantage with deramiocel treatment, reflecting 65% slowing of disease progression relative to placebo. The mean percent change from baseline to Month 12 in mid-level PUL2.0 score compared with placebo, showed a between-group LS-mean difference of 8.12% (SE ± 3.03; 95% CI: 2.12, 14.11; p=0.008).

Secondly, to provide additional clinical context for the clinic-based assessment of the PUL, the FDA suggested adding additional endpoints to support the meaningfulness of upper limb treatment effects measured by the PUL. To that end, Capricor employed the DVA (Duchenne Video Assessment, DDT COA Tracking Number #000104) which is a home-based video assessment of quality of movement and compensations to maintain function that was developed by DMD caregivers, patients and physiotherapists as a clinically meaningful assessment. It has been validated as an endpoint to measure meaningful disease progression in DMD. Of the entire battery of DVA tests, the Eat-10 Bites assessment – recorded in a home-based environment is an independent video-based measure of how a patient can bring their hand to their mouth to self-feed 10 times. The recordings are submitted to a core lab and then assessed by physiotherapists blinded to treatment allocation. The DVA was prespecified as a secondary endpoint and an additional clinically meaningful measure of self-feeding and directly related to functions assessed by the mid-level PUL 2.0. It is particularly important that in the HOPE3 clinical trial, both the mid-level PUL and the DVA Eat 10 bites measures move in concert with regard to a deramiocel treatment effect on upper limb function. Among placebo patients, the progressive loss of hand-to-mouth function was accompanied by loss of ability and/or greater compensations utilized to bring the hand to mouth to effectively feed 10 times, with mean eating ability declining by roughly 10 points in placebo patients compared to 3 points in the deramiocel group. Because these are two independent instruments, a clinician-administered motor scale and a centrally evaluated video assessment of an important activity of daily living (self feeding) developed as a meaningful measure by the DMD community, their close agreement demonstrates that both endpoints capture the same underlying loss of hand to mouth function, providing construct validity and clinically meaningful contextualization to the mid-level PUL results.

Thirdly, it is important to focus on the ability of deramiocel to preserve normative upper limb hand to mouth function performed without compensation. This result focuses on the preservation of upper limb function without compensation as measured by the PUL 2.0 for an individual patient. Considering only the subgroup of patients who entered HOPE-3 at baseline who were still able to fully bring the hand to the mouth without compensation (a baseline item PUL score of 2): prior to treatment, n=24 of the deramiocel-treated patients (47%) and n=27 of the placebo patients (54%) had full hand to mouth function without compensation. It is instructive to determine the proportion of patients in each treatment group who could continue to perform the hand to mouth task

without compensation after 12 months of treatment. Among deramiocel patients, 23 of 24 (96%) retained full function without compensation; among placebo patients, only 16 of 27 (59%) retained the ability to perform hand to mouth without compensation, a difference nominally significant at a Fisher exact p value of 0.003. This represents preservation of a specific ability in patients with DMD (uncompensated hand to mouth ability) that is clinically meaningful on face value, is directly related to independence in terms of self-feeding, and also determined by non-ambulatory patients and their caregivers to be the function most important to quality of life (Peay et al. 2026). While the impact of a therapeutic on upper limb function in DMD is challenging to demonstrate in a short duration 12-month clinical trial, the totality of the benefit of deramiocel to patients with DMD in terms of relative slowing of disease progression and the preservation of a meaningful degree of function in more functionally intact patients is clear in these clinical investigations. This focus on hand-to-mouth function is not arbitrary, because it is the single item patients who are non-ambulatory and caregivers for such name as the one function that matters most to quality of life. Its importance reaches well beyond the one movement scored, because bringing the hand to the face and head is a gateway to ordinary daily life: eating and drinking, brushing teeth, shaving, putting glasses back on when they slip, scratching an itch, raising a hand to block something coming toward the face. A person who can bring the hand to mouth and hand to the head level can also bring the head down to meet the hand, and that reciprocal range opens the door to washing and drying the hair and to pulling a shirt off and putting it back on. Thus, maintaining hand to mouth function preserves independence, the benchmark of quality of life.

6.6.2 Clinical Meaningfulness of Deramiocel Treatment Effects on Cardiac MRI function (LVEF) and Fibrosis (by LGE)

There are no approved DMD-specific therapies for cardiomyopathy, the leading cause of death in patients with DMD. Cardiomyopathy is the leading cause of death in DMD, and progressive decline in left ventricular function, accompanied by accumulating myocardial fibrosis, defines its course. Because the dystrophin-deficient heart deteriorates in a gradual and often clinically silent manner, preservation of ejection fraction and attenuation of fibrotic progression represent clinically meaningful objectives, particularly in a population for which no therapy is approved for cardiomyopathy.

Current recommendations suggest the use of generic GDMT, based on clinical trials of adult patients with ischemic and non-ischemic heart failure and reduced LVEF. The patient population, pathogenesis and disease course of such patients are all unlike those of DMD cardiomyopathy. In DMD, irreversible fibrosis and fibrofatty replacement of the myocardium (Sunthankar et al. 2023; Breaux et al. 2024) mirrors the histologic progression of the skeletal myopathy (Forbes et al. 2020). Such histologic changes in the heart underlie deteriorating cardiac function (Starnes et al. 2024b). Due to the limitations of symptom assessment in non-ambulatory patients, cardiac imaging has become the primary mode of assessing cardiomyopathy in DMD. Such imaging is now performed routinely for prognostic and monitoring purposes (Tandon et al 2015; Wittlieb

et al. 2020), with cMRI preferred over echocardiography in advanced DMD due to improved precision and technical ease. The association between a decline in systolic function and all-cause mortality provides additional context to the present results. *For every 3% decline in LVEF, risk of death increases by 32% (HR: 1.32)* (Soslow et al. 2023). Thus, there is good reason to believe that the 1-year treatment difference of 2.4% in LVEF with deramiocel is clinically meaningful. Of note, the subset of patients with pre-existing cardiomyopathy showed greater benefit, consistent with the finding that LVEF decline begins after scar burden begins to accumulate (Tandon et al. 2015). Thus, treatment with deramiocel shows long term efficacy in preserving cardiac function and the HOPE3 study demonstrates significantly less LGE (scar) in treated patients versus patients on placebo. This is likely to have long term consequences for preservation of life in boys and young men with DMD.

The HOPE-3 cardiac findings are additionally clinically relevant on two complementary levels. Attenuation of LVEF decline reflects preservation of global pump function, a recognized correlate of heart-failure risk in this disease; its association with survival in DMD is directionally consistent but rests on limited mortality data. The reduction in late-gadolinium-enhancement-positive segments reflects slowing of the fibrotic process that precedes and drives functional decline, addressing the disease at a structural level upstream of overt dysfunction. The concordance of a functional and a structural cardiac signal, observed together with the durability of cardiac stabilization in extended follow-up, supports a clinically meaningful, disease-modifying effect on the dystrophin-deficient heart rather than an isolated change in a single measure.

6.7 Efficacy Conclusions

The cumulative evidence from the DMD (HOPE) clinical development program demonstrates that deramiocel treatment consistently and reproducibly slows the progression of DMD across both skeletal and cardiac muscle pathophysiology, with no other therapy, to date, that shows bioactivity in both domains of disease, one of which is predictive of lifespan attenuation (cardiac).

Across randomized, controlled, long-term studies and extended long-term OLE studies extending to 36 months, deramiocel demonstrated concordant treatment effects on upper limb function, cardiac function, and cardiac structure. These effects were observed in placebo-controlled settings, persisted with continued exposure and bioactivity steadily declined on withdrawal from therapy. These findings were reinforced through formal comparisons with external natural history cohorts, establishing a coherent and durable pattern of benefit across study designs, durations, and endpoints.

HOPE-2 provided the first placebo-controlled evidence that deramiocel favorably influences disease progression in both cardiac and skeletal muscle domains, demonstrating statistically significant attenuation of LVEF decline, improvements in indexed ventricular volumes, and slowing of upper limb functional deterioration over 12 months.

The pivotal HOPE-3 study confirmed the findings observed in HOPE-2 in a larger randomized, placebo-controlled population, meeting its prespecified, multiplicity-controlled primary endpoint of percent change in PUL 2.0 Total Score, LVEF, mid-level PUL, Total GST, and LGE with p-values <0.05. Read as supportive rather than confirmatory, these endpoints are directionally concordant across functional, structural, and patient-reported domains, including the Global Statistical Test integrating how patients feel (PGI-S), function (PUL), and survive (LVEF).

HOPE-2-OLE demonstrated that the effects observed in the 12-month controlled studies strengthen with continued treatment. Over extended follow-up, deramiocel-treated patients exhibited stabilization of cardiac function and progressively slower rates of PUL decline. When these outcomes were compared against matched external natural history datasets for both cardiac MRI parameters and PUL assessments, deramiocel-treated patients showed markedly reduced rates of decline relative to the expected course of disease in DMD. These data provide direct evidence that sustained deramiocel exposure alters the expected natural history trajectory of both cardiomyopathy and upper limb deterioration.

Importantly, the effects observed with deramiocel are not isolated to individual endpoints but reflect a consistent reduction in the rate at which DMD progresses across multiple independent measures of disease burden. These effects were demonstrated across endpoints measured using different methodologies, including functional assessments, imaging-based cardiac measures, and patient-reported outcomes, yet consistently showed the same directional treatment benefit.

The reproducibility of these findings across studies conducted under different designs and durations, together with confirmation against external natural history comparators and in patients receiving contemporary standard of care, makes it unlikely that the observed effects are attributable to background therapy, measurement variability, or study design artifacts. Most importantly, these data demonstrate that the natural course of DMD can be meaningfully altered with sustained treatment with deramiocel. Therefore, it is unlikely that any future clinical trial work in this population of those with DMD would yield data that could further clarify the treatment effect of deramiocel in DMD.

7 CLINICAL SAFETY

Summary

- The HOPE studies offer a substantial exposure base. The integrated safety analysis pools four studies (HOPE-OLE, HOPE-2, HOPE-2-OLE, HOPE-3) through a 13 Feb 2026 cutoff, covering 125 unique deramiocel-treated patients and 266.2 patient-years of exposure, with follow-up reaching 80 months
- AEs were common but mostly mild/moderate. Treatment-emergent AEs (TEAEs) occurred in ~91% of treated patients, but the vast majority were Grade 1–2 and tied to the infusion (headache, cough, pyrexia, tachycardia, nausea). Severe (Grade 3+) and serious events were not more frequent with deramiocel than placebo in the double-blind periods.
- Hypersensitivity is the principal identified risk. Tracked as an AE of special interest (AESI), hypersensitivity/infusion reactions occurred in 38.4% overall (41.0% deramiocel vs 15.6% placebo), driven mainly by transient terms (pyrexia, tachycardia, throat irritation). Severe immune-mediated events (true hypersensitivity, anaphylaxis, excipient allergy) were rare, and reaction rates did not escalate with continued dosing
- Serious events, withdrawals, and death were infrequent and largely unrelated to drug. Serious TEAEs affected 16% overall (fewer on deramiocel than placebo in the controlled period), were heterogeneous, and reflected advancing DMD rather than drug toxicity. Only 4% discontinued for an AE.
- No cumulative was seen toxicity over long-term use. Labs, vital signs, and the overall AE profile stayed stable across prolonged follow-up with no new signals. Transient post-infusion D-dimer elevations were investigated but were non-specific and not associated with clinical thromboembolism.

7.1 Integrated Safety

The safety of deramiocel has been characterized across an integrated database that spans both controlled double-blind exposure and prolonged open-label follow-up in the intended DMD population. This section presents the integrated and long-term safety across the full development program. The studies contributing data to the safety analysis are summarized in Appendix 10.1 support a safety profile that is identifiable, clinically interpretable, and acceptable in the context of a serious and progressive disease.

The integrated analyses extend the controlled HOPE-3 findings across the full development program. Pooled analyses draw on four studies, namely HOPE-OLE,

HOPE-2, HOPE-2-OLE, and HOPE-3. HOPE-OLE and the double-blind phases of HOPE-2 and HOPE-3 are complete, while the HOPE-2-OLE and HOPE-3 extension phases were ongoing at the data cut date and contribute data through that point. The data cut date for the Integrated analysis is 13 February 2026.

To allow direct comparison of deramiocel against placebo in the controlled period while separately characterizing the extent and consistency of longer-term exposure, results are presented for four pooled groups:

- Pooled double-blind placebo group (N=64)
- Pooled double-blind deramiocel group (N=61)
- Pooled open-label and long-term open-label extension (OLE/LT-OLE) deramiocel group (N=119)
- Total Deramiocel population (N=125 unique patients).

7.1.1 Extent of Exposure

Exposure to deramiocel was substantial and supports meaningful assessment of both short-term tolerability and longer-term risk. Across the Total Deramiocel population, patients received a mean of 8.2 doses (median 7.0; maximum 26). Mean exposure duration was 25.6 months (median 21.9) and extended to a maximum of 80.0 months. Dose intensity was consistent at approximately 0.33 doses per month across studies and periods, reflecting adherence to the every-three-months regimen.

The database contributes an estimated 266.2 patient-years of cumulative exposure. This comprises 60.1 patient-years in the pooled double-blind deramiocel population and 206.0 patient-years in the pooled OLE/LT-OLE population. Within the randomized period, exposure was well balanced between arms (mean 11.8 months for deramiocel versus 11.7 months for placebo). The controlled comparison of adverse events is therefore not confounded by differential time at risk.

7.1.2 Overall Adverse Event Profile

The overall AE profile were mild or moderate in severity (Table 16). These were frequent in occurrence but limited in clinical consequence. Across the Total Deramiocel population, 114 of 125 patients (91.2%) experienced at least one TEAE. The clinically informative observation is the distribution of severity beneath that rate. Grade 1 events were the maximum severity in 32.0% of patients and Grade 2 events in 44.0%.

In the randomized comparison, TEAEs occurred in 93.4% of deramiocel-treated and 85.9% of placebo-treated patients. This is a modest difference consistent with the infusion-related nature of the additional events. TEAEs considered related to IP or the administration procedure were reported in 80.3% of deramiocel-treated patients versus 37.5% of placebo patients.

Outcomes of greater clinical consequence remained infrequent relative to the breadth of exposure. Grade 3 or higher TEAEs occurred in 15.2% of the Total Deramiocel population. Within the controlled period, severe events were no more common with deramiocel (4.9%) than with placebo (6.3%). The higher absolute counts of serious and severe events in the OLE/LT-OLE population track with its substantially longer follow-up and greater patient-years at risk, not with an intensification of risk per exposure.

Table 16: Overall Summary of TEAEs (Integrated)

Parameter, n (%)	HOPE-2/HOPE-3 (DB) Placebo N=64	HOPE-2/HOPE-3 (DB) Deramiocel N=61	OLE/LT-OLE Deramiocel N=119	Total Deramiocel N=125*
Any TEAE	**55 (85.9)**	**57 (93.4)**	**107 (89.9)**	**114 (91.2)**
TEAEs related to IP or administration procedure	24 (37.5)	49 (80.3)	84 (70.6)	95 (76.0)
TEAEs related to IP	21 (32.8)	49 (80.3)	81 (68.1)	93 (74.4)
TEAEs related to administration procedure	11 (17.2)	27 (44.3)	39 (32.8)	59 (47.2)
TEAEs by Maximum Severity				
Mild (Grade 1)	24 (37.5)	17 (27.9)	50 (42.0)	40 (32.0)
Moderate (Grade 2)	27 (42.2)	37 (60.7)	41 (34.5)	55 (44.0)
Severe (Grade 3)	3 (4.7)	2 (3.3)	14 (11.8)	16 (12.8)
Life-threatening (Grade 4)	1 (1.6)	1 (1.6)	1 (0.8)	2 (1.6)
Fatal (Grade 5)	0	0	1 (0.8)	1 (0.8)
Outcomes of Clinical Consequence				
Any serious TEAE	5 (7.8)	3 (4.9)	17 (14.3)	20 (16.0)
Serious TEAEs related to IP or admin. Procedure	1 (1.6)	3 (4.9)	3 (2.5)	6 (4.8)
Hypersensitivity reactions (AESI)	10 (15.6)	25 (41.0)	36 (30.3)	48 (38.4)
TEAEs of Grade 3 or higher	4 (6.3)	3 (4.9)	16 (13.4)	19 (15.2)
TEAEs leading to study drug withdrawal	1 (1.6)	3 (4.9)	2 (1.7)	5 (4.0)
TEAEs leading to death	0	0	1 (0.8)	1 (0.8)

* ***The Total Deramiocel population identifies each unique patient treated with Deramiocel. The DB and OLE phase cohorts include overlapping patients.***

7.1.3 Common Treatment-Emergent Adverse Events

Among preferred terms occurring in at least 10% of any treatment group, the most frequent events in the Total Deramiocel population were headache (49.6%), cough (28.8%), pyrexia (22.4%), tachycardia (17.6%), and nausea (17.6%) (Table 17). This pattern is dominated by transient, peri-infusion symptoms rather than by signs of end-organ injury.

Several events were much more common with deramiocel than placebo: headache (57.4% versus 6.3%), pyrexia (23.0% versus 3.1%), cough (21.3% versus 6.3%),

tachycardia (16.4% versus 6.3%), dizziness (14.8% versus 0%), and throat irritation (11.5% versus 0%). Infections and musculoskeletal disorders occurred at similar rates in both arms. These events are tied to the infusion and are mostly self-limited.

Table 17: TEAEs Reported in ≥10% of Patients in Any Treatment Group (Integrated)

Parameter, n (%)	HOPE-2/HOPE-3 (DB) Placebo N=64	HOPE-2/HOPE-3 (DB) Deramiocel N=61	OLE/LT-OLE Deramiocel N=119	Total Deramiocel N=125
Cardiac disorders	5 (7.8)	15 (24.6)	22 (18.5)	31 (24.8)
Tachycardia	4 (6.3)	10 (16.4)	16 (13.4)	22 (17.6)
Gastrointestinal disorders	18 (28.1)	22 (36.1)	37 (31.1)	49 (39.2)
Nausea	8 (12.5)	9 (14.8)	18 (15.1)	22 (17.6)
Vomiting	5 (7.8)	7 (11.5)	12 (10.1)	16 (12.8)
General disorders / admin. site conditions	13 (20.3)	29 (47.5)	51 (42.9)	64 (51.2)
Pyrexia	2 (3.1)	14 (23.0)	21 (17.6)	28 (22.4)
Infections and infestations	28 (43.8)	25 (41.0)	48 (40.3)	63 (50.4)
Nasopharyngitis	11 (17.2)	4 (6.6)	16 (13.4)	19 (15.2)
Upper respiratory tract infection	5 (7.8)	6 (9.8)	13 (10.9)	16 (12.8)
Musculoskeletal / connective tissue disorders	20 (31.3)	19 (31.1)	30 (25.2)	41 (32.8)
Nervous system disorders	8 (12.5)	38 (62.3)	58 (48.7)	68 (54.4)
Headache	4 (6.3)	35 (57.4)	53 (44.5)	62 (49.6)
Dizziness	0	9 (14.8)	2 (1.7)	11 (8.8)
Respiratory, thoracic and mediastinal disorders	**11 (17.2)**	**25 (41.0)**	**54 (45.4)**	**68 (54.4)**
Cough	4 (6.3)	13 (21.3)	26 (21.8)	36 (28.8)
Nasal congestion	2 (3.1)	3 (4.9)	12 (10.1)	15 (12.0)
Throat irritation	0	7 (11.5)	7 (5.9)	13 (10.4)

7.1.4 Adverse Events of Special Interest: Hypersensitivity Reactions

Hypersensitivity associated with intravenous administration is the principal identified risk of deramiocel and was tracked prospectively as an AESI throughout the program. The prespecified grouping comprises eleven preferred terms. These are tachycardia, pyrexia, allergic reaction to excipient, anaphylactic reaction, hypersensitivity, heart rate increased, tachypnoea, throat irritation, throat tightness, rash, and flushing.

Across the Total Deramiocel population, 48 of 125 patients (38.4%) experienced at least one such reaction (Table 18). The controlled comparison confirms a treatment association, with 41.0% on deramiocel versus 15.6% on placebo in the pooled double-blind population. The majority was driven by common, transient reaction terms, namely

pyrexia (17.6%), tachycardia (14.4%), and throat irritation (10.4%). Severe immune-mediated reactions were rare. Hypersensitivity occurred in 2 patients (1.6%), allergic reaction to excipient in 1 (0.8%), and anaphylactic reaction in 1 (0.8%). The grouped AESI rate therefore reflects common, manageable infusion reactions, not a high rate of serious anaphylaxis.

Importantly, the frequency of these reactions did not escalate with continued treatment. The rate in the HOPE-3 OLE/LT-OLE period (28.6%) was lower than in the HOPE-3 double-blind deramiocel period (41.5%). This argues against sensitization or cumulative reactogenicity over prolonged dosing. These events have been mitigated through pretreatment regimens and routine infusion monitoring.

Table 18: Hypersensitivity Reactions (AESI) by Preferred Term (Integrated)

Parameter, n (%)	HOPE-2/HOPE-3 (DB) Placebo N=64	HOPE-2/HOPE-3 (DB) Deramiocel N=61	OLE/LT-OLE Deramiocel N=119	Total Deramiocel N=125
Any hypersensitivity reaction	**10 (15.6)**	**25 (41.0)**	**36 (30.3)**	**48 (38.4)**
Pyrexia	0	14 (23.0)	15 (12.6)	22 (17.6)
Tachycardia	3 (4.7)	7 (11.5)	13 (10.9)	18 (14.4)
Throat irritation	0	7 (11.5)	7 (5.9)	13 (10.4)
Tachypnoea	1 (1.6)	1 (1.6)	8 (6.7)	8 (6.4)
Heart rate increased	1 (1.6)	3 (4.9)	3 (2.5)	6 (4.8)
Rash	2 (3.1)	2 (3.3)	3 (2.5)	5 (4.0)
Flushing	3 (4.7)	1 (1.6)	4 (3.4)	5 (4.0)
Hypersensitivity	0	2 (3.3)	0	2 (1.6)
Throat tightness	0	2 (3.3)	0	2 (1.6)
Allergic reaction to excipient	0	1 (1.6)	0	1 (0.8)
Anaphylactic reaction	1 (1.6)	0	1 (0.8)	1 (0.8)

7.1.5 Serious Adverse Events

Serious TEAEs were uncommon in the controlled setting. While more frequent in the extension population, they were heterogeneous and largely unrelated to study treatment. In the pooled double-blind population, serious AEs (SAEs) were reported less often with deramiocel (4.9%) than with placebo (7.8%) (Table 19). Across the Total Deramiocel population, 20 of 125 patients (16.0%) experienced a serious TEAE. The higher count was concentrated in the OLE/LT-OLE population (14.3%), consistent with its longer surveillance and greater patient-years at risk.

The defining feature of the serious-event profile is its lack of concentration. No single preferred term predominated. The most frequent were pneumonia, scoliosis, femur fracture, infusion-related reaction, and scoliosis surgery. The categories most represented were infections, injuries and procedural complications, and musculoskeletal

events. These are characteristic of the natural history and care of advancing DMD rather than of a drug-specific toxicity. There was no clustering within any single organ system across the program.

Serious events considered related to IP or the administration procedure were rare, occurring in 6 of 125 patients (4.8%). They were driven by the same immune-mediated and infusion-related mechanisms identified as the principal risk. These were allergic reaction to excipient, anaphylactic reaction, hypersensitivity, infusion-related reaction, and a single case of cellulitis. This concordance between the identified risk and the small number of related serious events supports a coherent, well-understood safety characterization.

Table 19: Serious TEAEs by System Organ Class, Patients With ≥1 Event (Integrated)

Parameter, n (%)	HOPE-2/HOPE-3 (DB) Placebo N=64	HOPE-2/HOPE-3 (DB) Deramiocel N=61	OLE/LT-OLE Deramiocel N=119	Total Deramiocel N=125
Any serious TEAE	**5 (7.8)**	**3 (4.9)**	**17 (14.3)**	**20 (16.0)**
Infections and infestations	0	0	6 (5.0)	6 (4.8)
Injury, poisoning and procedural complications	1 (1.6)	1 (1.6)	4 (3.4)	5 (4.0)
Musculoskeletal / connective tissue disorders	1 (1.6)	0	4 (3.4)	4 (3.2)
Immune system disorders	1 (1.6)	2 (3.3)	1 (0.8)	3 (2.4)
Cardiac disorders	0	0	2 (1.7)	2 (1.6)
Metabolism and nutrition disorders	1 (1.6)	0	2 (1.7)	2 (1.6)
Surgical and medical procedures	0	0	2 (1.7)	2 (1.6)
Gastrointestinal disorders	0	0	1 (0.8)	1 (0.8)
Psychiatric disorders	0	0	1 (0.8)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.8)	1 (0.8)

The serious-event experience is shown by study and study period in Table 20, with the contributing preferred terms under each system organ class. This presentation locates each event within its study context and shows that the higher extension-period counts reflect events typical of advancing DMD and its care, distributed across studies rather than concentrated in any single category.

Table 20: Serious TEAEs by System Organ Class and Preferred Term, by Study and Study Period

	HOPE-OLE	HOPE-2		HOPE-2-OLE	HOPE-3 (DB)		HOPE-3 (OLE/LT-OLE)
SOC / Preferred Term, n (%) e*	**Deramiocel N=8**	**Deramiocel N=8**	**Placebo N=12**	**Deramiocel N=13**	**Deramiocel N=53**	**Placebo N=52**	**Deramiocel N=98**
Any Serious TEAEs	**1 (12.5), 1**	**2 (25.0), 2**	**0**	**6 (46.2), 10**	**1 (1.9), 1**	**5 (9.6), 5**	**10 (10.2), 18**
Cardiac Disorders	**0**	**0**	**0**	**2 (15.4), 2**	**0**	**0**	**0**
Cardiac Arrest	0	0	0	1 (7.7), 1	0	0	0
Left Ventricular Dysfunction	0	0	0	1 (7.7), 1	0	0	0
Gastrointestinal Disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1 (1.0), 1**
Haematemesis	0	0	0	0	0	0	1 (1.0), 1
General Disorders and Administration Site Conditions	**0**	**0**	**0**	**0**	**0**	**1 (1.9), 1**	**0**
Chest Pain	0	0	0	0	0	1 (1.9), 1	0
Immune System Disorders	**1 (12.5), 1**	**2 (25.0), 2**	**0**	**0**	**0**	**1 (1.9), 1**	**0**
Allergic reaction to excipient	0	1 (12.5), 1	0	0	0	0	0
Anaphylactic reaction	1 (12.5), 1	0	0	0	0	1 (1.9), 1	0
Hypersensitivity	0	1 (12.5), 1	0	0	0	0	0
Infections and infestations	**0**	**0**	**0**	**3 (23.1), 3**	**0**	**0**	**3 (3.1), 5**
Abdominal Abscess	0	0	0	0	0	0	1 (1.0), 1
Cellulitis	0	0	0	1 (7.7), 1	0	0	0
Gastroenteritis Viral	0	0	0	1 (7.7), 1	0	0	0
Pneumonia	0	0	0	1 (7.7), 1	0	0	2 (2.0), 2
Respiratory Syncytial Virus Infection	0	0	0	0	0	0	1 (1.0), 1
Sepsis	0	0	0	0	0	0	1 (1.0), 1
Injury, Poisoning and Procedural Complications	**0**	**0**	**0**	**1 (7.7), 2**	**1 (1.9), 1**	**1 (1.9), 1**	**3 (3.1), 5**
Fall	0	0	0	1 (7.7), 1	0	0	0
Femur Fracture	0	0	0	0	0	1 (1.9), 1	2 (2.0), 2

	HOPE-OLE		HOPE-2	HOPE-2-OLE	HOPE-3 (DB)		HOPE-3 (OLE/LT-OLE)
Infusion Related Reaction	0	0	0	0	1 (1.9), 1	0	1 (1.0), 1
Injury	0	0	0	1 (7.7), 1	0	0	0
Vascular Injury	0	0	0	0	0	0	1 (1.0), 1
Venous Injury	0	0	0	0	0	0	1 (1.0), 1
Metabolism And Nutrition Disorders	**0**	**0**	**0**	**0**	**0**	**1 (1.9), 1**	**2 (2.0), 2**
Dehydration	0	0	0	0	0	0	1 (1.0), 1
Electrolyte Imbalance	0	0	0	0	0	1 (1.9), 1	1 (1.0), 1
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**0**	**1 (7.7), 1**	**0**	**1 (1.9), 1**	**3 (3.1), 3**
Epiphysiolysis	0	0	0	0	0	0	1 (1.0), 1
Foot Deformity	0	0	0	0	0	1 (1.9), 1	0
Scoliosis	0	0	0	1 (7.7), 1	0	0	2 (2.0), 2
Psychiatric Disorders	**0**	**0**	**0**	**1 (7.7), 1**	**0**	**0**	**0**
Mental Disorder	0	0	0	1 (7.7), 1	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**0**	**1 (7.7), 1**	**0**	**0**	**0**
Acute Respiratory Failure	0	0	0	1 (7.7), 1	0	0	0
Surgical And Medical Procedures	**0**	**0**	**0**	**0**	**0**	**0**	**2 (2.0), 2**
Scoliosis Surgery	0	0	0	0	0	0	2 (2.0), 2

*For each preferred term in each study cohort n=number of individual patients with specified TEAE, (%) = is the percentage of patients with TEAE in the cohort, and e= the number of events of the TEAE.

7.1.6 Deaths

The single death in the integrated safety database occurred in HOPE-2-OLE (1 of 13 deramiocel-treated patients; 7.7%); no deaths occurred in HOPE-OLE, HOPE-2, HOPE-3 double-blind, or HOPE-3 OLE/LT-OLE. The patient died three months after last infusion and was not due to deramiocel or infusion related sequelae. The fatal event was coded as cardiac arrest following a fall, and death was reported only in this single patient.

The patient was a 17-year-old male enrolled in HOPE-2-OLE who received deramiocel every 3 months from Study Day 1, with the last dose on Study Day 1731. On Study Day 1824, he experienced a fatal SAE of cardiac arrest with life-threatening SAEs of trauma and fall.

Per the case narrative, the patient fell from a shower chair and was caught by his parents before striking his head but sustained right knee trauma and a right shin laceration. He subsequently reported back, right knee, and chest pain, then became unresponsive. Emergency medical services found him hypoxic (O_2 sat in the 80s, Glasgow Coma Scale of 3) and transported him under full trauma activation; he was diagnosed with cardiac arrest on arrival at the Emergency Department. Resuscitation was unsuccessful, and he died at 14:00 on Study Day 1824. No autopsy was performed, per the family's wishes.

The Investigator assessed the cardiac arrest as Grade 5, unlikely related to study drug, and unrelated to the administration procedure, citing a reasonable possibility of fat embolism from an undiagnosed fracture and/or hypoxia-associated arrhythmia. The patient had longstanding lower-limb contractures typical of advanced DMD; after the fall, his mother reported his legs had become fully extended, consistent with a sustained fracture. The associated trauma and fall were each assessed as Grade 4 and unlikely related to study drug, with the fall attributed to underlying DMD.

The Sponsor concurred that the events were unlikely related to deramiocel, based on the ~3-month interval since the last dose and clinical circumstances pointing to accidental trauma, possible fat embolism from an undiagnosed fracture, and/or hypoxia-associated arrhythmia.

Overall, the death profile was limited to this single fatal event during extension follow-up. With no deaths in the pooled double-blind population and only 1 fatal event across the total deramiocel-treated population, the data do not suggest a broader pattern of fatal events. Both the Investigator and Sponsor assessed the event as unlikely related to deramiocel and unrelated to the administration procedure, occurring in the setting of accidental trauma with plausible alternative explanations.

7.1.7 Adverse Events Leading to Study Drug Withdrawal

Permanent discontinuation of study drug for an AE was uncommon. It affected 5 of 125 deramiocel-treated patients (4.0%) across the program and only 2 of 119 (1.7%) in the OLE/LT-OLE population (Table 21). The high overall TEAE rate alongside the low

withdrawal rate indicates that most events were tolerable and self-limited, with few necessitating treatment cessation. Withdrawal-associated events (allergic reaction to excipient, hypersensitivity, anaphylactic reaction, cardiac arrest, and pyrexia) are consistent with the identified hypersensitivity risk. The single cardiac arrest reflects the unrelated fatal trauma case described above. This profile is internally consistent and interpretable.

Table 21: TEAEs Leading to Study Drug Withdrawal (Integrated)

Treatment group	**Patients**, n/N (%)	AE(s) leading to withdrawal
HOPE-2/HOPE-3 (DB) Placebo	1/64 (1.6%)	Anaphylactic reaction
HOPE-2/HOPE-3 (DB) Deramiocel	3/61 (4.9%)	Allergic reaction to excipient Hypersensitivity Pyrexia
OLE/LT-OLE Deramiocel	2/119 (1.7%)	Anaphylactic reaction Cardiac arrest
Total Deramiocel	**5/125 (4.0%)**	**Allergic reaction to excipient; Hypersensitivity; Anaphylactic reaction; Cardiac arrest; Pyrexia**

7.1.8 Laboratory Safety

Across studies, hematology and serum chemistry values did not show a consistent pattern of clinically meaningful change with longer-term deramiocel exposure. Mean and median values were generally stable across serial visits, and shifts outside the baseline category were distributed across time rather than progressing. The overall pattern reflected relative stability rather than progressive deterioration.

7.1.8.1 D-Dimer elevations

D-dimer is a fibrin degradation product that is highly sensitive but not specific for venous thromboembolism, since it is also elevated in inflammatory, infectious, and traumatic conditions (Wells et al. 2003). A post-infusion elevation in D-dimer was first observed in a HOPE-3 patient in August 2023, without clinical suspicion of thrombosis. After DSMB review, HOPE-2-OLE Amendment 5 (12 July 2024) added coagulation monitoring before infusion and at 2 and 24 hours, beginning at Month 48.

At Month 48, D-dimer rose several-fold at 2 hours and declined toward pre-dose levels by 24 hours, with transient fibrinogen consumption and elevated CRP but largely unchanged PT, aPTT, and INR.

Elevated D-dimer is non-specific, occurring in pulmonary embolism (Gao et al. 2018; Schutte et al. 2016) but also in inflammatory states without thrombosis (Mori et al. 2023; Feng et al. 2024). Across more than 700 infusions in more than 200 patients over approximately 3 years, only one thrombosis occurred in the reporting period, attributed to prolonged accidental blood pressure cuff inflation on the infusion arm, rather than to deramiocel, with rapid resolution and no sequelae.

Given the low specificity of D-dimer, the transient elevation related to IV infusion and the absence of clinical thromboembolism related to deramiocel, the risk of clinically relevant infusion-related thrombus formation appears low, and monitoring continues.

7.1.9 Long-Term Safety and Absence of Cumulative Toxicity

The longer-term experience provides direct evidence against cumulative toxicity. It includes 119 patients in the pooled OLE/LT-OLE population, with exposure extending to 68.3 months within the extension dataset and 80.0 months overall. Across this prolonged follow-up, the adverse event profile remained qualitatively consistent with that observed in the controlled period. No new safety signal emerged with continued dosing.

This conclusion is supported by objective safety assessments. Longitudinal hematology and serum chemistry summaries in the OLE population showed generally stable mean and median values across serial visits, with shifts outside baseline categories distributed across time rather than progressing. Review of serial vital signs likewise revealed no sustained hemodynamic or respiratory instability. The transient post-infusion D-dimer elevations discussed in Section 7.1.8.1 were not associated with any clinical thromboembolic syndrome and are regarded as an expected laboratory observation rather than an established clinical risk.

7.1.10 Integrated Safety Conclusions

Taken together, the integrated safety database supports a profile that is identifiable, clinically interpretable, and manageable. The principal treatment-associated risk is hypersensitivity and infusion-associated reactions. This risk is recognizable, driven predominantly by transient reactions rather than severe immune-mediated events, and amenable to established mitigation through premedication and infusion monitoring. Serious adverse events, treatment withdrawals, and death all remained infrequent relative to 266.2 patient-years of cumulative exposure. The controlled comparison showed no excess of severe or serious events with deramiocel over placebo.

Long-term follow-up extending to 80.0 months provided no evidence of cumulative toxicity, progressive laboratory deterioration, or physiologic instability. The single reported death was assessed as unlikely related to study treatment in the setting of accidental trauma. On the totality of the evidence, and in the context of the seriousness and progressive course of the underlying disease, the overall safety profile of deramiocel is acceptable in the studied DMD population.

8 BENEFITS AND RISK CONCLUSIONS

Summary

1 *Skeletal muscle benefit*: In pivotal HOPE-3, deramiocel slowed upper-limb decline by ~54% (1.2-point PUL 2.0 difference at 12 months, plus a 1.0-point mid-level/elbow domain effect), roughly a year of function preserved over a 2-year horizon, in a disease where such loss is irreversible and tied to independence and quality of life (eating, hygiene, technology use).

2 *Cardiac benefit*: Deramiocel substantially slowed cardiomyopathy progression (91% across all patients, 119% in those with baseline cardiomyopathy), preserving LVEF (2.4% difference at 12 months) and preventing further myocardial scarring (LGE). These effects are likely to impact mortality.

3 *Risks*: Across 265 patients and >1,000 IV doses, the profile was predictable and manageable with mainly transient, Grade 1–2 infusion-related hypersensitivity reactions that resolved in 24–48 hours, mitigated by premedication and monitoring, with no organ toxicity, no cumulative signal over up to 3 years of quarterly dosing.

4 *Benefit-Risk Assessment*: The meaningful cardiac and skeletal muscle benefits outweigh deramiocel's manageable, infusion-associated risks, supporting a favorable benefit-risk profile for a serious unmet need in DMD.

8.1 Benefits

The totality of clinical evidence demonstrates that treatment with deramiocel is associated with clinically meaningful attenuation of decline in both upper-limb function and cardiac function in patients with DMD. These findings are anchored in the pivotal HOPE-3 study and supported by HOPE-2 and HOPE-2-OLE (>60 months).

In HOPE-3, deramiocel demonstrated a clinically meaningful slowing of skeletal muscle disease progression. The 1.2-point difference seen in Total PUL 2.0 score at 12 months, in the context of a heterogeneous disease in which PUL score may continuously decline over one to two decades corresponds to an approximate 54% slowing of mean skeletal muscle disease progression relative to placebo and represents >1 year of progression saved for every 2 years of natural progression. The 1.0-point treatment effect in the mid-level domain reflects preservation or delay in loss in elbow function. The consistency of the placebo group’s decline in total PUL over one year (-2.72 SD ± 3.18 points) with a large natural history cohort of non-ambulatory patients with DMD (-2.7 annualized, -8.09 over 36 months, with baseline score of 24.3 points), confirms that the study population reflects known DMD upper extremity disease progression (Coratti et al. 2025).

Physical therapists' feedback on meaningful change on the PUL articulated that the less function a person with DMD has remaining, the more that function means. A single point has a "huge, positive, significant life changing impact for him" was reported when discussing a patient's ability to eat and drink by oneself and utilize technology (Gillman et al. 2025). Thus, the 1.2-point difference in Total PUL 2.0 and 1.0-point difference in the mid-level domain are clinically meaningful, in alignment with FDA feedback, and highly associated with quality-of-life indicators such as activities of daily living (hygiene, toileting), reaching (hug/handshake), eating/drinking and finger function for technology use (communication, powered wheelchairs) (Gillman et al. 2025). Likewise, the 12-month treatment effect of deramiocel on the novel DVA Eat 10 bites, which measures a real-world vital activity requiring the ability to use the arm with mid-level elbow flexion, further supports the clinical meaningfulness of the treatment effect measured by the PUL 2.0.

Importantly, treatment effects were also observed on cardiomyopathy progression: 91% slowing of mean cardiac disease progression across all patients, and 119% slowing (i.e., full preservation or slight improvement) in those with cardiomyopathy at baseline. These values confirm the 107% slowing observed with deramiocel in the 12-month HOPE-2 trial, and 99% slowing over three years observed in HOPE-2 OLE, representing a stabilization of cardiomyopathy progression. The 1-year treatment difference of 2.4% in LVEF with deramiocel and the even greater benefit observed in patients with pre-existing cardiomyopathy in HOPE-3 is clinically meaningful. For every 3% decline in LVEF, risk of death increases by 32% (HR: 1.32, Soslow et al. 2023). Although it could only be collected in a relatively small number of patients in HOPE-3 (restricted to Cohort B, and in those with evaluable cMRI scans at baseline and at 12 months) the LGE signal was striking. Deramiocel prevented the development of further myocardial scarring. While this is a structural rather than a functional measurement, myocardial scarring prevalence increases over time from ~15% under the age of 10 years, to ~85% by the age of 18. This process mirrors the fibrofatty replacement of myocardium seen histologically post mortem in DMD. The presence and degree of LGE is associated with accelerating decline in cardiac function (LVEF) and mortality. Stopping its progression is a highly desirable attribute of any cardiac therapy in DMD, and given the irreversibility of segmental scarring in DMD can reasonably be interpreted as a disease modifying activity.

8.2 Risks

Across the clinical development program (265 patients exposed), the safety experience with deramiocel is characterized by predictable, infusion-associated events that are transient, manageable, and non-progressive with repeated dosing. No intrinsic organ toxicity, immune-mediated toxicity, or cumulative safety risk has been identified following single-dose, repeat-dose, or long-term administration.

The principal identified risk is hypersensitivity related to intravenous administration. Recognized early in development, this risk is effectively mitigated through a

standardized pretreatment regimen and routine monitoring procedures prospectively incorporated into later studies, including HOPE-3. In HOPE-3, hypersensitivity reactions were predominantly Grade 1 or 2 in severity, typically occurring during or shortly after infusion and most commonly included tachycardia, throat irritation, pyrexia, flushing, rash, and transient increases in heart rate. Events generally resolved within 24 to 48 hours with standard supportive measures, without sequelae or treatment discontinuation, and showed no escalation in frequency, severity, or pattern of hypersensitivity with repeated dosing across studies. Importantly, no cumulative safety signal emerged with repeated quarterly dosing for up to three years.

Capricor will conduct routine postmarketing pharmacovigilance activities to monitor the safety profile of deramiocel following approval in compliance with applicable regulatory requirements.

8.3 Benefit-Risk Assessment

Deramiocel addresses a critical unmet need in DMD: there is no approved therapy for DMDCM, the leading cause of death, and no therapy that simultaneously addresses skeletal muscle decline particularly in upper limb function.

Deramiocel has demonstrated a favorable and consistent safety profile in 265 patients with >1000 IV doses of deramiocel delivered across the clinical development program, including the pivotal HOPE-3 study, which differs from existing therapies such as corticosteroids and gene therapies, which are associated with serious toxicities affecting the liver, kidneys, immune system, and heart. The incidence of severe adverse reactions has been minimal, with no evidence of cumulative or organ-specific toxicities observed with repeated dosing. An ongoing pharmacovigilance program will continue to monitor the long-term safety of deramiocel and ensure that its benefit-risk remains favorable in the broader patient population.

Regarding the skeletal muscle benefit, deramiocel also demonstrates a clinically meaningful and statistically significant slowing of skeletal muscle disease progression. In HOPE-3, deramiocel significantly reduced the rate of decline in upper limb function resulting in a 1.2-point difference, as measured by the PUL 2.0 total score, corresponding an approximate 54% slowing of disease progression over 12 months. This translates to more than one year of functional preservation over a multi-year treatment horizon in a population in which functional loss is generally irreversible and is highly associated with the preservation of independence and a meaningful improvement in quality-of-life in patients with DMD.

Regarding the cardiac benefit, deramiocel significantly slows the progression of cardiomyopathy in DMD, as evidenced by the stabilization of LVEF and the decreased progression of myocardial scar (assessed by LGE) over one year. In HOPE-3, treatment with deramiocel resulted in a statistically significant and clinically meaningful preservation of LVEF at Month 12 compared with placebo, and even greater benefit observed in patients with pre-existing cardiomyopathy. Cardiac MRI measures of LVEF

and LGE are both strongly predictive of cardiac disease progression and underscore the potential of deramiocel to delay heart failure, the leading cause of morbidity and mortality in DMD for which no approved disease-modifying therapy currently exists.

In conclusion, the overall clinical benefits of deramiocel, including stabilization of cardiac and upper-limb function and slowing of disease progression in DMD, outweigh its manageable treatment-related risks. These findings support a favorable and robust benefit–risk profile and highlight deramiocel's potential to address a significant unmet medical need for safe and effective treatment of cardiomyopathy and functional decline in patients with DMD, particularly the non-ambulatory DMD population. Collectively, the totality evidence indicates that deramiocel is a safe and effective therapy with the potential to meaningfully modify the course of both cardiac and skeletal muscle disease in patients living with DMD.

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10 APPENDICES

10.1 Summary of Clinical Studies with Deramiocel

Study Number/ Status	Study Population	Phase	Study Design	Dosing Regimen	Patient Exposure	FVFP/LPLV
Primary Efficacy and Safety Studies						
HOPE-3 Ongoing	Patients who are 10 years of age or older with genetic-testing confirmed DMD	3	Multicenter, randomized 1:1, double-blinded, placebo-controlled study followed by a OLE phase Cohort A: IP manufacturer Cohort B: commercial manufacturer	4 IV infusions (150 million cells or placebo each), once every 3 months	Deramiocel 53 Placebo 52	22 Jun 2022/--
HOPE-2 Completed	Males (aged 10 years and older) with DMD and evidence of skeletal muscle impairment	2	Randomized 1:1 deramiocel vs. placebo, double- blinded	Repeat peripheral IV infusion (4 infusions total; once every 3 months), 150M cells	Deramiocel: 8 Placebo: 12	04 Apr 2018/10 Mar 2020
HOPE- 2-OLE Ongoing	Pediatric and adult males with DMD who participated in the HOPE-2 study and completed the 12-month follow-up period	2	Open-labeled extension study of deramiocel	Repeat peripheral IV infusion (20 infusions in total; once every 3 months), 150M cells	Deramiocel: 13	05 Aug 2020/--
Supportive Safety Study						
HOPE- OLE Completed	Pediatric and adult males with DMD who were randomized to Usual Care treatment group of the HOPE-Duchenne study and completed the 12-month follow-up period	2	Open-labeled extension study of deramiocel	Repeat peripheral IV infusion (2 infusions total; once every 3 months), 75M cells	Deramiocel: 8	21 Jun 2018/ 06 Mar 2019
Other Studies						
HOPE-Duchenne Completed	Males (aged 12 years and older) with cardiomyopathy secondary to DMD	2	Open-labeled, randomized 1:1 deramiocel vs. usual care	Single intracoronary infusion, 75M cells	Deramiocel: 13 Usual care: 12	07 Jan 2016/ 14 Sep 2017

Study Number/ Status	Study Population	Phase	Study Design	Dosing Regimen	Patient Exposure	FVFP/LPLV
ALLSTAR[1] Completed	Adults with a history of MI, patent infarct-related artery status post percutaneous coronary intervention with stent placement,	1/2	P1: OL safety cohort followed by P2: randomized, double-blind, (2:1) placebo-controlled – cohort 1 no preexisting anti-HLA antibodies; cohort 2 with anti-HLA antibodies.	P1: 2 escalating dose levels (12.5 million CDCs [4 patients] and 25 million CDCs [10 patients] P2: single IC infusion of deramiocel (25 million CDCs)	P1: Deramiocel 14 P2: *Primary* Deramiocel 77/Placebo 44 *Exploratory* Deramiocel 13	P1: 13 Nov 2012/ 06 Oct 2014 P2: 16 Jan 2014/ 03 Jul 2017
DYNAMIC Completed	Patients with Dilated Cardiomyopathy	1	Single-arm, dose-escalation in 4 cohorts (3-5 patients per cohort)	Single intracoronary infusion, 37.5-75M cells	Deramiocel: 14	05 Dec 2014/ 24 Mar 2016
INSPIRE Completed	Adults with COVID-19 and compromised respiratory status	1	Randomized 1:1 deramiocel vs. placebo, double- blinded	Single IV infusion of 150M cells	Deramiocel: 28 Placebo: 27	15 Nov 2020/ 04 Feb 2022

CDCs = cardiosphere-derived cells; DMD = Duchenne muscular dystrophy; FPFV = first patient first visit; IP = investigational product; MI = myocardial infarction; OL = open label; OLE = open label extension

1 Only exposure data are included.

2 Exposure data and deaths included.

10.2 Cover Letter to IND 17800 SN0109 for HOPE-3 Protocol v9.0 and SAP v2.0

Capricor Therapeutics

IND 17800, SN 0109

26 September 2025

Vijay Kumar, M.D.
Acting Director, Office of Therapeutic Products
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Subject: IND 17800; Serial No. 0109
Deramiocel (CAP-1002; Human Allogeneic Cardiosphere-Derived Cells)
Protocol Amendment: Change in Protocol; Study HOPE-3
HOPE-3 Statistical Analysis Plan, version 2.0
Investigator's Brochure, Edition 10.0

Dear Dr. Kumar,

Reference is made to IND 017800 sponsored by Capricor, Inc. for deramiocel (code-name CAP-1002; human allogeneic cardiosphere-derived cells) indicated for the treatment of Duchenne muscular dystrophy (DMD).

Reference is also made to BLA STN BL 125842/0 for deramiocel for the treatment of cardiomyopathy in DMD submitted by Capricor, Inc. on 30 December 2024, the Complete Response letter (CRL) received on 09 July 2025, and the 13 August 2025 Type A post-action meeting (ID #21754) between FDA and Capricor to align on the most appropriate path forward for approval of deramiocel for treatment of cardiomyopathy in DMD following the CRL.

In accordance with 21 CFR 312.30(b), Capricor is submitting the following change in protocol for the ongoing Phase 3 study, HOPE-3:

Protocol number:	CAP-1002-DMD-04
Protocol title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Human Allogeneic Cardiosphere-Derived Cells for the Treatment of Duchenne Muscular Dystrophy (HOPE -3)
Amendment number:	9.0
Protocol date:	26 September 2025
Key Updates:	Prespecify the primary endpoint as mean percent change from baseline in Performance of the Upper Limb (PUL) 2.0 Total Score at Month 12 and the key secondary endpoint as mean change from baseline in left ventricular ejection fraction (LVEF) at Month 12, as measured by cardiac MRI and assessed centrally.

Capricor

Capricor had previously submitted protocol amendment 8.0 (Sequence 0105), for the ongoing and still blinded HOPE-3 study, proposing to switch the cardiac outcome measure of mean change from baseline in LVEF at Month 12, as measured by cardiac MRI and assessed centrally, from a key secondary to primary endpoint, and setting the neuromuscular outcome measure of mean change from baseline in functional capacity at Month 12, as assessed by Performance of Upper Limb (PUL) 2.0, from primary endpoint to secondary endpoint. The protocol amendment was submitted in response to the 09 July 2025 CRL, FDA Comment 1, recommending that Capricor conduct an adequate and well-controlled study, whose primary objective is evaluation of cardiac outcomes in deramiocel-treated patients with DMD cardiomyopathy.

Following the 13 August 2025 Type A post-action meeting and FDA's strong recommendation that Capricor maintain PUL as the primary endpoint and LVEF as a key secondary endpoint in the HOPE-3 study, Capricor has amended the HOPE-3 protocol to revert back to PUL as primary endpoint and LVEF as key secondary endpoint. The primary endpoint has been modified from *mean change* from baseline in PUL 2.0 Total Score at Month 12 to *mean percent change* from baseline in PUL 2.0 Total Score at Month 12. Percent change from baseline in PUL 2.0 is 90% powered to detect a treatment difference of 5 percentage points in decline rate between active and placebo, corresponding to a treatment difference of approximately 1.2 points on the raw scale. Other updates in the amended protocol include reordering of other secondary and exploratory endpoints, and providing clarifications and rationale for sample size calculations and thresholds for clinically meaningful differences in PUL 2.0 Total Score and LVEF outcome measures. Refer to HOPE-3 protocol amendment 9.0 clean and redlined (mark-up of the proposed changes) versions provided in this filing.

Furthermore, as requested by FDA at the Type A post-action meeting, Capricor is submitting the HOPE-3 Statistical Analysis Plan (version 2.0) outlining the planned statistical methods and procedures that will be used to analyze and interpret the outcome assessments collected in HOPE-3 that will serve as substantial evidence of effectiveness in support of the resubmission and approval of the BLA for the intended indication of treatment of cardiomyopathy in DMD.

The Investigator's Brochure, Edition 9.0, previously submitted with Sequence 0106, has been amended to update the description of the HOPE-3 study design and endpoints to be consistent with HOPE-3 protocol amendment 9.0. Refer to Investigator's Brochure, Edition 10.0, Section 5.1.1.1.4.