FDA Briefing Document

BLA# 125842/0

Drug: Deramiocel

Applicant: Capricor, Inc.

Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

07/29/2026

Office of Therapeutic Products (OTP) / Center for Biologics Evaluation and Review (CBER)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the BLA for deramiocel (human allogeneic cardiosphere-derived cells) for the treatment of cardiomyopathy in Duchenne muscular dystrophy to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AC	Advisory Committee
ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
ARNI	combination angiotensin receptor/neprilysin inhibitors
BLA	Biologics License Application
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDC	cardiosphere-derived cell
CI	confidence interval
cMRI	cardiac magnetic resonance imaging
DMD	Duchenne muscular dystrophy
DVA	Duchenne Video Assessment
EDC	explant-derived cell
EF	ejection fraction
FDA	Food and Drug Administration
IC	intracoronary
IL-6	interleukin-6
IND	investigational new drug
IP	investigational product
IV	intravenous
LGE	late gadolinium enhancement
LS	least-squares
LT-OLE	long-term open-label extension
LV	left ventricle
LVEF	left ventricular ejection fraction
MAR	missing at random
MMRM	mixed model for repeated measures
OLE	open-label extension
OTP	Office of Therapeutic Products
POC	proof-of-concept
PUL 1.2/2.0	Performance of Upper Limb version 1.2/2.0
SAE	serious adverse event
SAP	statistical analysis plan

1. Executive Summary and Draft Points for Discussion

1.1 Objective of the Advisory Committee Meeting

The Cellular, Tissue, and Gene Therapies Advisory Committee (AC) will meet on July 29, 2026, to discuss Biologics License Application (BLA) 125842 resubmitted by Capricor, Inc. for deramiocel for the proposed indication of treatment of cardiomyopathy in male patients with Duchenne muscular dystrophy (DMD). The Committee's input is sought on whether the results of pivotal Study HOPE-3 provide substantial evidence of effectiveness for deramiocel for the proposed indication.

1.2 Context for Issues to Be Discussed

DMD is a rare, severe, childhood-onset genetic disease characterized by progressive skeletal and cardiac muscle weakness with the major cause of mortality being cardiac disease and associated complications (heart failure, cardiac arrhythmias) due to dilated cardiomyopathy. The currently approved therapies for treatment of DMD have not been systematically studied for their effects on cardiomyopathy and, thus, their effect on cardiac disease progression is unknown. As such, there remains a high unmet medical need for safe and effective therapies targeting cardiomyopathy in DMD.

Deramiocel is a novel, investigational, allogeneic cellular product derived from cadaver donor hearts with a hypothesized anti-fibrotic, anti-inflammatory, immunomodulatory, and/or pro-angiogenic mechanism. The Applicant submitted clinical data from the phase 3 study HOPE-3 in this BLA resubmission to support substantial evidence of effectiveness for deramiocel for the treatment of cardiomyopathy in DMD. The original BLA submission for deramiocel was based on results from a phase 2 exploratory, randomized study, Study HOPE-2 and its open-label extension, Study HOPE-2-OLE. Results from these studies showed no evidence of effectiveness on skeletal or cardiac function (based on LVEF and other cardiac parameters). The original BLA received a Complete Response due to lack of substantial evidence of effectiveness and an unfavorable benefit-risk assessment.

Statutory Standards for Approval

As described in Section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and, for biologics, Section 351 of the Public Health Service Act, a product must be shown to be safe and effective for its intended use to support approval based on substantial evidence of effectiveness and evidence of safety. Substantial evidence of effectiveness is defined as clinical evidence generated from adequate and well-controlled (AWC) clinical investigations which include clinical trials that are scientifically robust to provide valid and reliable results in the proposed population or indication, per FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (June 2026) and FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023). Broadly speaking, AWC clinical investigations have several important features including: a clear statement of objectives with a scientific hypothesis defined prior to data collection; measures to minimize bias including randomization and blinding; comparison to an appropriate control group (placebo or other); a well-defined, and appropriately identified patient population; prospectively specified efficacy outcomes that are well-defined and reliable and reflect clinical benefit; and statistical methods that are pre-specified and scientifically justified. The analytical considerations are a critical

component of the overall assessment of the strength and validity of the clinical evidence and the statistical methodology (described in the study's statistical analysis plan) must be pre-specified and finalized prior to study completion and data unblinding (in blinded trials) to avoid bias and erroneous conclusions.

Substantial evidence of effectiveness generally requires at least two adequate and well-controlled (AWC) clinical investigations, each convincing on its own. When more than one AWC investigation is not feasible or practical, FDA may consider convincing evidence from one AWC clinical investigation together with confirmatory evidence (CE) to constitute substantial evidence of effectiveness. FDA also considers varying levels of scientific evidence in terms of quantity and quality to constitute substantial evidence of effectiveness based on the disease and therapeutic context. In serious and severely debilitating/life-threatening diseases with unmet medical needs where data collection and patient numbers pose significant limitations to study design and statistical considerations, the regulatory expectations take into account feasibility aspects, ethical considerations, the degree of unmet medical need, and practical constraints related to conducting clinical trials of certain designs. When the scientific evidence from adequate and well-controlled study(ies) is strong and enables valid and reliable conclusions on effectiveness, regulatory flexibility in applying the statutory standards for effectiveness is reasonable and warranted.

Clinical Benefit

Effectiveness must be based on scientifically robust, convincing, and reproducible evidence demonstrating that a drug provides benefit to patients with the disease, i.e., improves how patients feel, function, or survive. In certain cases, a surrogate endpoint, such as a laboratory or imaging biomarker, may be used for approval when strong clinical and other epidemiologic and mechanistic evidence supports its ability to predict clinical benefit in the intended population. Such validated surrogate endpoints can support traditional approval and are typically supported by strong clinical evidence and well-established/validated analytical methods that are fit-for-purpose and reliable for biomarker quantitation (e.g., laboratory assay, imaging methods).

Factors Affecting the Strength of Evidence of Effectiveness

FDA determines the strength of the evidence of effectiveness of a drug considering several critical factors, both independently and in combination as described in the FDA draft guidance on substantial evidence of effectiveness (June 2026). Such factors include: key clinical trial design elements (e.g., choice of control group, population selection, randomization, blinding, endpoint selection); the quality of trial conduct (e.g., completeness of follow-up, amount of missing data, protocol violations/deviations); aspects of the data analysis (e.g., statistical pre-specification, scientific support for analysis assumptions, adherence to pre-specified analytical plans and blinding plans); the clinical meaningfulness of the findings; the statistical persuasiveness of the results; and other aspects of the overall drug development program (e.g., number and quality of each trial conducted and their relative strength and directional convergence of the evidence, the biological plausibility of the drug's mechanism of action in the intended disease, the strength of the nonclinical evidence supporting the drug's mechanism and biological activity).

The overall persuasiveness of a trial's results is based on many different considerations. These include: the magnitude and clinical meaningfulness of the observed effect on the primary and other efficacy endpoints, whether the results on the different efficacy endpoints are directionally consistent and biologically plausible, whether the results are robust and consistent using different statistical assumptions and sensitivity analyses, the statistical significance/magnitude of the p-value (or of alternative measures such as the posterior probability of effectiveness in a Bayesian analysis).

Importantly, to contribute to a demonstration of substantial evidence of effectiveness, it is well established that the effect shown in the adequate and well-controlled trial must be, in FDA's judgment, clinically meaningful, i.e., reflect an improvement on how patients with the disease feel, function, or survive. This determination depends on the clinical relevance of the endpoint and the magnitude of the estimated treatment effect. For example, in a large trial, a small, statistically significant result may be detected; however, depending on the outcome being evaluated, that small treatment effect may not be clinically meaningful to patients with the disease. On the other hand, even small effects may be clinically meaningful when the effect is on survival or irreversible morbidity. The persuasiveness of the trial results also depends on the findings for additional relevant endpoints, as consistency across endpoints that reflect distinct and meaningful aspects of health increases confidence in the results. In addition, the robustness of findings to violations in statistical assumptions of the key analyses is important. For example, sensitivity analyses showing that conclusions hold up on all plausible missing data assumptions help support the strength of evidence from a trial.

1.3 Overview of Issues for Discussion

Study HOPE-3 was a phase 3, randomized, double blind, placebo controlled, 12-month study of deramiocel compared to placebo in males with DMD who were predominantly non-ambulatory and had an average age of 15 years old. The mean LVEF at baseline was 57%, and 5 patients (4.7%) had an LVEF <45%. The study was designed to demonstrate an effect on upper limb skeletal muscle function based on the change from baseline to month 12 in PUL 2.0 total score. A secondary objective was to assess the effect on left ventricular function based on the change from baseline to month 12 in left ventricular ejection fraction (LVEF). Additional secondary endpoints pertaining to the same clinical outcomes were also evaluated. The study did not meet its pre-specified primary and secondary efficacy endpoints showing no statistically significant difference between deramiocel and placebo at 12 months.

After completion of the randomized, double blind part of Study HOPE-3 and during Study HOPE-3-OLE (where all patients were treated with deramiocel), changes were made to the pre-specified statistical analysis plan (SAP), generating at least 2 additional versions. Those changes included modifications to the primary and key secondary endpoint definitions; the analytical methods; and the data imputation strategy for certain intercurrent events. FDA noted that the Applicant's final analyses presented in the BLA submission included additional statistical changes without an associated, updated SAP. The final version of the SAP (v. 3.0), dated November 24, 2025 was not submitted to FDA for review prior to BLA submission and was not discussed and consequently not agreed upon. In addition, the process for SAP changes outlined in the study's pre-specified blinding plan was not followed and the final clinical study protocol (Protocol 9.0) deviated from the associated SAP (v. 3.0). Lastly, the distinctive adverse event profile observed between treatment groups —hypersensitivity reactions seen in 42% of deramiocel-treated patients versus 15% of placebo-treated patients — raises the possibility that treatment

assignment could be inferred even under formal blinding conditions. This risk of functional unblinding was further extended by the open-label period of HOPE-3, during which additional treatment-related data accumulated and may have made treatment assignment more apparent. Given the *post-hoc* nature of the SAP changes, FDA considers all analyses implemented following study completion.

1.4 Draft Points for Discussion

1) Discuss whether the results on the pre-specified secondary endpoint of change from baseline to month 12 in left ventricular ejection fraction (LVEF) in Study HOPE-3, considered together with cardiac imaging results in Study HOPE-2, support a conclusion that deramiocel is effective in slowing the rate of decline in cardiac function in patients with DMD.

2) Discuss whether the results of Study HOPE-3 on the pre-specified primary and secondary endpoints assessing upper limb function and cardiac imaging parameters, considered together with results from Study HOPE-2, support a conclusion that deramiocel is effective in the treatment of DMD.

1.5 Draft Voting Questions

1) Does the available evidence from Study HOPE-3 provide substantial evidence of effectiveness of deramiocel for the treatment of cardiomyopathy in DMD?

2. Introduction and Background

2.1 Disease Background

2.1.1 Duchenne Muscular Dystrophy (DMD)

DMD is a rare, X-linked, genetic disease affecting predominantly males and resulting from variants in the *DMD* gene which encodes the protein dystrophin. DMD affects about 1 in 3,500 boys (Duan et al. 2021). Dystrophin is a critical protein that anchors the cytoskeleton inside myocytes to the extracellular matrix. Its function is important for mechanical stabilization, force transmission, membrane protection from damage during muscle contraction, and cell signaling. In the absence of functional dystrophin that occurs in DMD, progressive weakness of skeletal and cardiac muscles develops over many years. From a cardiac standpoint, dilated cardiomyopathy and cardiac conduction abnormalities are the primary causes of death in DMD (Nigro et al. 1990; Schultz et al. 2022). About one-third of affected boys also have cognitive and behavioral difficulties.

Although laboratory tests and muscle tissue may show evidence of muscle damage as early as birth, symptoms typically do not become clinically apparent until early childhood. The average age at diagnosis is around 5 years. The course of disease for individual patients is heterogeneous, but the overall pattern is consistent: weakness in the lower limbs leads to loss of ambulation, which overlaps with deterioration in the upper limbs, as well as declining respiratory and cardiac function. Limb weakness develops symmetrically, beginning in the muscles nearest the torso and over time also affecting muscles more

distally. Boys typically lose the ability to walk by age 12 or 13 years. In the past, patients often would die by late adolescence or their early twenties, from respiratory insufficiency or cardiomyopathy. Although both remain leading causes of mortality, the median life expectancy has increased to ~30 years, with some patients living into the fourth decade, primarily through improved respiratory and cardiac management (Wahlgren et al. 2022). Interventions such as physical and occupational therapy, nutritional support, psychosocial care, and surgical correction of scoliosis (to optimize lung expansion) have also contributed to the increased life expectancy in DMD (Wahlgren et al. 2022).

The mainstay of pharmacological treatment in DMD is oral corticosteroids, typically initiated in boys aged 4 years or older. Long-term corticosteroid administration has been shown to slow the decline of skeletal muscle function (Bushby et al. 2010; Escolar et al. 2011). The effect of corticosteroids on cardiac function or progression of cardiac disease in DMD is not well-characterized. Some cohort studies have suggested an association between corticosteroid use and slower decline in measures of left ventricular systolic function, but data on long-term cardiac outcomes from corticosteroid therapy is limited (Silversides et al. 2003; Biggar et al. 2006; Markham et al. 2008).

Upper Limb Weakness in DMD

Upper limb weakness first affects muscles at the shoulders, then at the elbows, and later in the hands and fingers, with overall decline generally progressing at a slower rate than in the lower limbs (Pane et al. 2018). Onset of upper limb weakness typically occurs as patients are losing the ability to walk (Janssen et al. 2016), and upper limb function becomes the primary determinant of independence and quality of life in those who are non-ambulatory. As the disease advances, patients may retain only distal hand and finger function, which remains critical for operating powered wheelchairs, communication devices, and other assistive technologies. Poorer respiratory status and cardiomyopathy may indirectly affect upper limb function, by impairing general health and endurance.

Several factors have been identified which broadly predict the rate of decline in upper limb function:

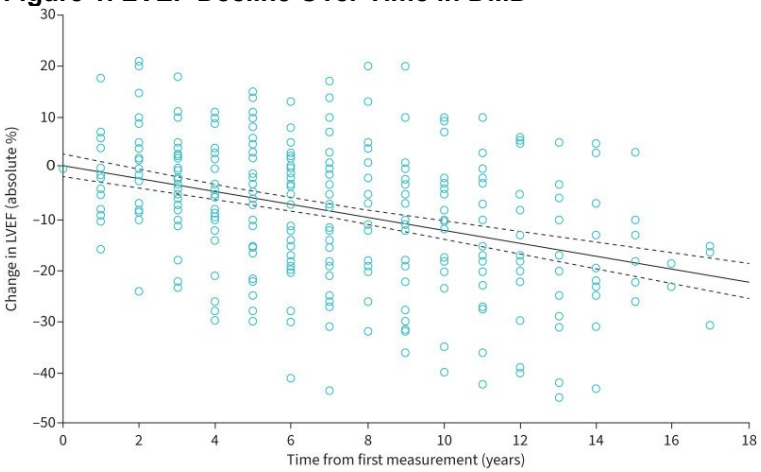
- Faster deterioration is seen in non-ambulatory patients compared to their ambulatory peers (Pane et al. 2018), and in patients with symptom onset at age < 2 years.
- Patients with higher entry-item scores on the PUL 2.0 assessment (described below) show slower rates of decline on PUL 2.0, as do patients with higher PUL 2.0 total scores at the time of loss of ambulation (Servais et al. 2015; Pane et al. 2018).

DMD Cardiomyopathy

Lack of functional dystrophin results in accumulation of damage in cardiac myocytes, and gradual replacement of these cells by fibrofatty tissue, followed by fibrosis, dilatation and thinning of the left ventricle. Because skeletal muscle weakness limits patients' physical activity, patients with DMD may not exhibit the typical clinical signs and symptoms seen in patients with cardiomyopathy, such as shortness of breath, fatigue, or dizziness (Feingold et al. 2017; Birnkrant et al. 2018; Buddhe et al. 2018). Cardiac imaging (either by echocardiography or cardiac magnetic resonance imaging [cMRI]) is an important tool used for early detection and long-term monitoring of cardiac status in DMD. In general, cardiac abnormalities first become apparent on imaging around age 14 years (Nigro et al. 1990; Connuck et al. 2008). As shown in Figure 1, LVEF progressively diminishes over many years (mean change ±

standard deviation was -10.0% ± 13.9%, occurring over 9.1 ± 5.1 years), with considerable variability observed in the rate of LVEF decline over time (Lechner et al. 2023).

Figure 1. LVEF Decline Over Time in DMD



Source: (Lechner et al. 2023).
The best-fitted line (black line) and 95% confidence intervals (dashed lines) are shown.
Abbreviation: DMD, Duchenne muscular dystrophy; LVEF, left ventricular ejection fraction

2.1.2 Clinical Management of DMD

FDA-approved drugs for treatment of DMD are shown in Table 1. These drugs are approved for the treatment of DMD in pediatric and adult patients regardless of *DMD* variant except the antisense oligonucleotide (ASO) products which target specific *DMD* variants. The four ASO products remain approved under accelerated approval and clinical benefit has not been verified. Approval was based on treatment effects on skeletal muscle function and not cardiac function in DMD patients and their impact on the heart in DMD is unknown.

Table 1. FDA-Approved Drugs for Treatment of Duchenne Muscular Dystrophy

Drug	Approval Year and Regulatory Pathway	Mechanism of Action	Indication/DMD Subpopulation
Emflaza (deflazacort)	2017 Traditional	Corticosteroid	≥ 2 years
Exondys 51 (eteplirsen)	2016 Accelerated	ASO	*DMD* mutation amenable to exon 51 skipping
Vyondys 53 (golodirsen)	2019 Accelerated	ASO	*DMD* mutation amenable to exon 53 skipping
Viltepso (viltolarsen)	2020 Accelerated	ASO	*DMD* mutation amenable to exon 53 skipping
Amondys 45 (casimersen)	2021 Accelerated	ASO	*DMD* mutation amenable to exon 45 skipping

Drug	Approval Year and Regulatory Pathway	Mechanism of Action	Indication/DMD Subpopulation
Agamree (vamorolone)	2023 Traditional	Novel corticosteroid	≥ 2 years
Elevidys (delandistrogene moxeparvovec)	2024 Traditional[a]	AAV-vector based gene therapy producing microdystrophin	Ambulatory, ≥ 4 years, except patients with exon 8/9 deletion
Duvyzat (givinostat)	2024 Traditional	HDAC inhibitor	≥ 6 years

Source: FDA
[a] Elevidys received accelerated approval in 2023 for treatment of ambulatory DMD patients aged 4 to 5 years. In 2024, Elevidys was granted traditional approval for DMD patients aged 4 years and older; a separate accelerated approval was also granted for non-ambulatory DMD patients aged 4 years and older. Due to three fatal cases of acute liver failure, FDA later removed non-ambulatory patients from the approved indication and restricted the indication to ambulatory DMD patients aged 4 years and older (November 25, 2025).
Abbreviations: AAV, adeno-associated virus; ASO, antisense oligonucleotide; DMD, Duchenne muscular dystrophy; HDAC, histone deacetylase

2.1.2.1 Management of DMD Cardiomyopathy

Management of cardiomyopathy in DMD patients aims to delay the development and progression of heart failure (Buddhe et al. 2018; Adorisio et al. 2020; Schultz et al. 2022). Because no therapies have been approved for DMD cardiomyopathy, clinicians rely primarily on standard drugs used for the treatment of heart failure in the general population.[1] Evidence for use of these drugs in DMD is based on relatively small studies demonstrating improvement on cardiac imaging parameters and other biomarkers; further research is needed to clarify their effect on clinical outcomes and quality of life, as well as to establish optimal timing of initiation and dosing (Raccah et al. 2021; Haddad et al. 2023). These medications include renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARB], and combination angiotensin receptor/neprilysin inhibitors [ARNI]), mineralocorticoid receptor antagonists, and beta blockers.

Use of an ACEi or ARB is recommended for DMD patients with reduced LVEF, in accordance with standard heart failure protocols (Feingold et al. 2017). ACEi may delay the onset or progression of DMD cardiomyopathy, and initiation of ACEi or ARB therapy may be considered for patients as young as 10 years of age, even without reduced LVEF (Duboc et al. 2005; Feingold et al. 2017; Silva et al. 2017; Aikawa et al. 2019). Sacubitril/valsartan, an ARNI, has been evaluated in only small case series; limited data suggests potential benefit in DMD patients with left ventricular systolic dysfunction (Lamendola et al. 2020).

The mineralocorticoid receptor antagonist eplerenone, used adjunctively with ACEi or ARB therapy, has been shown to attenuate the decline in left ventricular systolic function in DMD patients with preserved ejection fraction (Raman et al. 2015).

Beta blockers are a standard treatment for heart failure patients with left ventricular systolic dysfunction. A potential benefit in DMD cardiomyopathy is supported by limited evidence from small, nonblinded studies (Kajimoto et al. 2006; Matsumura et al. 2010). A small cohort study involving DMD

[1] Advanced heart failure therapies, such as mechanical circulatory support, in patients with DMD cardiomyopathy have been described in case reports and case series. Their use is limited by factors such as respiratory muscle weakness, kyphoscoliosis, and prospects for recovery and rehabilitation following surgery (Amodeo and Adorisio 2012).(Ryan et al. 2014; Adorisio et al. 2020).

patients with advanced dilated cardiomyopathy suggested that heart rate reduction with beta blockers and/or ivabradine was associated with fewer major cardiac adverse events (Adorisio et al. 2019).

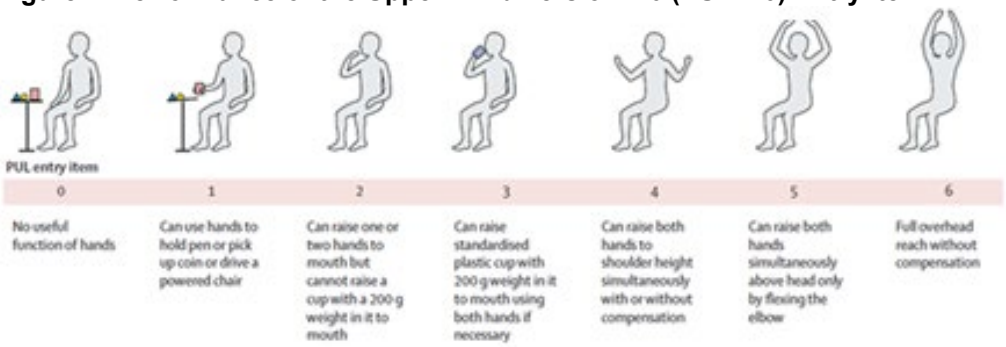
2.1.3 Upper Limb Function: Performance of the Upper Limb, Version 2.0 (PUL 2.0)

The PUL 2.0 was specifically developed for DMD, to enable clinicians to measure how well patients can use their arms and hands to carry out typical tasks of daily life. The clinician first administers an entry item (Figure 2), which establishes the patient's overall level of upper limb function. The entry item rating does not contribute to the total score.

The clinician then assesses the patient's ability to perform 22 items (Figure 3), testing function at the shoulder (6 items), elbow (9 items), and wrist/fingers (7 items). Each domain can be scored separately. Skills are graded as 0 (unable to perform), 1 (performs with modifications), or 2 (performs normally). The individual items may be summed to yield a total score of 0 to 42, with higher scores indicating greater function.

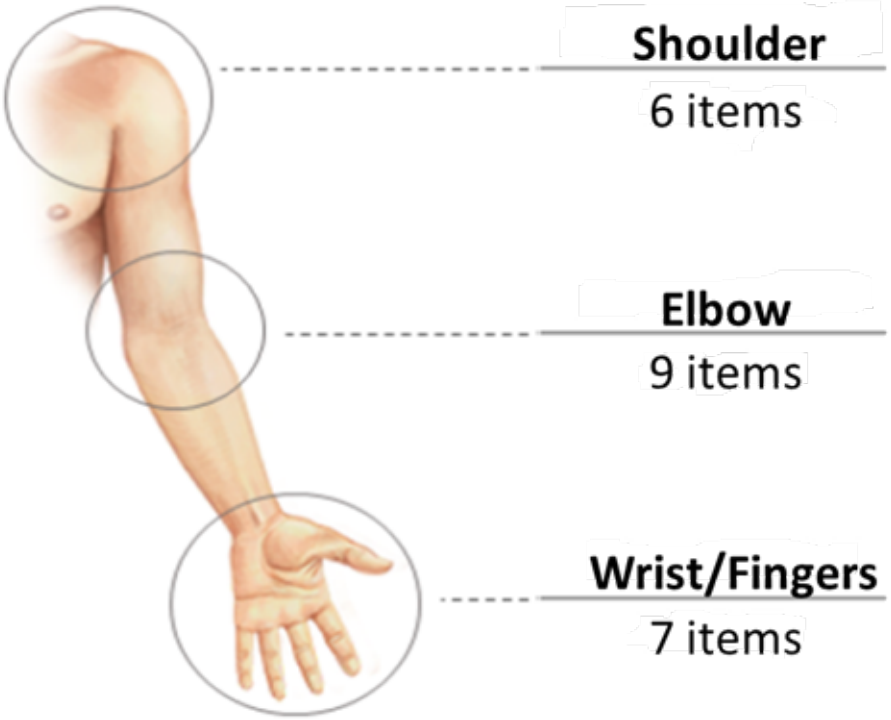
Results on the PUL 2.0 are to some degree effort-dependent – the effort by patients enrolled in a clinical study is likely to be greater than that of patients in settings such as a natural history study or a registry – so scores may be susceptible to bias when evaluated under open-label (unblinded) study conditions. In addition, administration of the PUL 2.0 is process-dependent: because of differences in training and standards of evaluation by administering clinicians, scores from different sources may vary to an extent that can affect overall scores. Because of these characteristics, results in clinical trials are most accurate when compared to a concurrent control group, in a study design incorporating randomization and blinding. Study HOPE-3 included all three of these design elements and, thus, use of this clinical outcome assessment to evaluate upper limb function is justified and scientifically appropriate.

Figure 2. Performance of the Upper Limb Version 2.0 (PUL 2.0) Entry Item



Source: Modified from McDonald et al (McDonald et al. 2022)
The PUL 2.0 entry item rates the patient's overall level of upper arm function on scale of 0 (no useful function of the hands) to 6 (full upper extremity overhead reach, without compensatory maneuvers). Because upper extremity weakness in DMD begins at the shoulders and progresses distally, patients able to carry out overhead reach are likely also able to perform tasks involving the elbows, wrists, and hands.
Abbreviations: DMD, Duchenne Muscular Dystrophy; Performance of Upper Limb version 2.0

Figure 3. Domains of the Performance of the Upper Limb Version 2.0 (PUL 2.0) Assessment



Source: Modified from Applicant
Abbreviation: Performance of Upper Limb version 2.0

Longitudinal natural history studies have consistently documented PUL 2.0 total score decline over time in DMD, but the rates of decline can be impacted by ambulatory status and stage of disease. A large multi-site study (Pane et al. 2018) reported a mean total PUL 2.0 change of −1.30 points at 12 months and −2.9 points at 24 months. When disaggregated by ambulation status, the same longitudinal framework revealed different trajectories, ambulant boys declined ~2.07 points over 24 months vs. ~4.36 points for non-ambulant boys. A recent longitudinal study followed 219 DMD patients for three years and reported similar findings based on ambulatory status (Coratti et al. 2025), highlighting that mixed-population analyses may underestimate decline in non-ambulant patients.

Other factors affecting PUL 2.0 trajectory include baseline functional status measured by entry item scores, DMD gene mutation type, and corticosteroid use.

2.1.4 Left Ventricular Ejection Fraction in DMD Cardiomyopathy

Because skeletal muscle weakness limits their activity, DMD patients may not exhibit the typical clinical signs and symptoms seen in other patients with cardiomyopathy (Feingold et al. 2017; Birnkrant et al. 2018; Buddhe et al. 2018).

Selecting endpoints for assessment of cardiac function is a considerable challenge in DMD clinical trials. The concomitant skeletal muscle weakness and the gradual course of cardiomyopathy in DMD limit the applicability of outcome measures commonly used in heart failure clinical trials involving the general population.

DMD patients with cardiomyopathy have diminished exercise capacity, making cardiac symptoms more subtle than in the broader population of patients with heart failure. Consequently, symptom-based or patient-reported outcome measures—such as the New York Heart Association (NYHA) or American Heart Association (AHA) functional classifications, or validated instruments such as the Kansas City Cardiomyopathy Questionnaire (KCCQ)—are of limited utility in DMD patients with cardiomyopathy. Similarly, assessments of exercise capacity, such as peak oxygen consumption (VO_2 peak), are difficult to administer and interpret in patients with significantly impaired ambulation. Furthermore, assessments of cardiovascular mortality or hospitalization due to cardiac causes would require extended follow up given the slow progression of cardiac disease in DMD, which may not be feasible. In addition, coronary artery disease is much less of a factor in DMD cardiomyopathy than in heart failure in the broader population and, thus, clinical endpoints related to myocardial ischemia are not suitable.

Cardiac imaging through echocardiography and cardiac MRI is routinely used in clinical practice to evaluate and monitor cardiac function in DMD. A few recent studies in DMD cardiomyopathy suggest that certain imaging parameters, considered alone or in combination, may be of prognostic value but the evidence is limited to enable any definitive conclusions (Florian et al. 2014; Lechner et al. 2023; Soslow et al. 2023; Starnes et al. 2024). A relationship between changes in one or more cardiac imaging markers, such as LVEF or LGE, and cardiac outcomes in DMD cardiomyopathy has not been extensively studied and is not currently established. In addition, the clinical meaningfulness of small changes in LVEF or LGE (or other imaging parameters) over a short period of time, such a 1-year's duration in a clinical trial, is unknown and must be considered within the context of the limitations and variability of the assessment tools used for cardiac parameters (echocardiogram, cardiac MRI).

In the deramiocel clinical program, there was considerable inter-rater variability in the ratings of cardiac MRI (with a mean discordance of 2.99-3.20 percentage points [minimum 0.02, maximum 12.67] at different timepoints between the 2 MRI raters). In addition, during Study HOPE-3, the MRI readings changed from 2+1 Consensus review paradigm with adjudication of discrepant readings (the pre-specified protocol) to a single reader for undetermined reasons (discussed in more detail below). Variability in MRI readings including variability from visit to visit and variability from rater to rater introduces noise in the measurement of cardiac parameters and severely limits the interpretation of any changes, especially when observed changes are small. In addition, in Study HOPE-3, missing cardiac MRI assessments introduce significant selection bias and further complicates the interpretation of results. Furthermore, a minority of patients (Cohort B treated with product manufactured in a different facility) had assessments of LGE as part of their cardiac MRIs limiting the strength of the LGE results and the interpretation of the LGE findings based on a small subgroup of the study population. As a result, interpreting LVEF changes alone or in combination with LGE changes (indicative of myocardial scarring) is limited due to the high degree of missing data in both measurements in Study HOPE-3. Given that LGE reflects the development of cardiac fibrosis from the underlying disease pathology, interpretation of LVEF or other cardiac imaging changes, especially small ones, considered together with LGE findings may provide a more accurate and complete picture of cardiac functional status. As such, interpreting the observations on LVEF, LGE, and other imaging parameters on cMRI in Study HOPE-3 is very challenging and limited. Furthermore, whether these observed changes relate to or reflect a benefit on slowing cardiac disease progression remains unknown.

There remains substantial uncertainty about whether and what magnitude of slowing the rate of decline of LVEF (or other cardiac imaging markers) reflects or predicts cardiac benefit in DMD cardiomyopathy

and in which patient subgroup(s) or stage of disease. The rate of progression of cardiomyopathy in DMD is highly variable, not linear, and may follow a different trajectory across the different stages of DMD. In addition, assessment of cardiac disease progression over time depends on several confounding factors including concomitant cardiac-targeted medications (used as standard-of-care management of the cardiac disease/heart failure in DMD) and FDA-approved drugs for DMD (which have not been studied in cardiomyopathy), genetic mutation type (deletion vs other), and associated co-morbidities. Given these uncertainties, assessing LVEF changes over a relatively short duration of follow up (1 year in Study HOPE-3) is not sufficient to provide confidence that any observed changes are real or that observing no change in LVEF over that 1 year represents a treatment effect vs the expected course of DMD cardiomyopathy which declines slowly over time.

2.2 Pertinent Drug Development and Regulatory History

2.2.1 Deramiocel

Deramiocel consists of allogeneic cells derived from specific regions of cadaver donor hearts obtained following a proprietary cell culture procedure. Explants from cadaveric donor hearts are cultured under conditions that promote the outgrowth of what the Applicant terms “Explant-Derived Cells” (EDCs), the drug substance. The EDCs are cryopreserved. Subsequently the EDCs are thawed and cultured in suspension under conditions that promote the formation of cardiospheres, which are self-assembling cell clusters. The cardiospheres are then collected, subjected to adherent culture, and expanded to produce cardiosphere-derived cells (CDCs). CDCs are harvested and formulated in a proprietary cryoprotectant and stored frozen in vapor phase liquid nitrogen at ≤ -140 °C. The drug product, deramiocel, is a suspension of CDCs. A single dose of deramiocel consists of two vials, each containing 75 million cells in 10 mL of the proprietary cryoprotectant. At the point of care, deramiocel is thawed, diluted 1:5 with 5% human serum albumin and administered by peripheral IV infusion. Each dose is derived from a single donor heart.

As indicated previously, during the clinical study under the IND, the manufacture of deramiocel was transferred from a facility in Cedars-Sinai in Los Angeles to a new commercial facility in San Diego. No significant differences in the product manufactured at the two sites were identified per analytical qualification data.

2.2.2 Mechanism of Action

The Applicant has proposed a composite mechanism of action for deramiocel, including anti-fibrotic, anti-inflammatory, immunomodulatory, and pro-angiogenic activities mediated through the secretion of exosomes and growth factors.

The Applicant referenced published literature and conducted *in vitro* studies assessing the biological activity of deramiocel or other CDC sources.[2] The literature demonstrated that CDCs secrete exosomes

[2] Related test articles used in nonclinical studies include CDCs isolated from patients with myocardial infarction or congestive heart failure, murine CDCs, and exosomes derived from patient- or murine-derived CDCs.

and growth factors,[3] and *in vitro* studies in which deramiocel-conditioned media was incubated with human fibroblast cells demonstrated a reduction in the expression of collagen variants (1A and 3A) compared to media controls. These collagen variants are thought to be involved in fibrosis, a process evident in DMD cardiomyopathy (Delfín et al. 2012). Although this data demonstrates CDCs secrete exosomes and growth factors, the specific role that these factors play in modulating DMD cardiomyopathy was not assessed in nonclinical studies. Finally, characterization of deramiocel in *in vitro* cultures demonstrated upregulation of interleukin-6 (IL-6) mRNA expression. Serum IL-6 has been shown to be elevated in patients with DMD, and published data demonstrate that inhibition of IL-6 signaling slows progression of muscular dystrophy in DMD mice compared to controls (Rufo et al. 2011; Wada et al. 2017). *In vitro* assays are generally limited in their ability to model important aspects of a disease like DMD cardiomyopathy because they don't replicate the complex interactions that occur in the human body, including the effects the immune system and microenvironment play on any complex cellular products. This makes the interpretation and clinical translation of such *in vitro* data very limited.

The Applicant has proposed that CDCs promote anti-fibrotic, anti-inflammatory, immunomodulatory, and pro-angiogenic effects through the secretion of exosomes and growth factors. However, nonclinical data regarding the impact of systemic administration of CDCs on cardiac function in the setting of DMD is limited, and the precise biological pathways by which CDCs may exert a beneficial effect in this patient population are not clear or well-defined. Prior nonclinical studies in mice have shown that the majority of CDCs distribute to extra-cardiac tissues following intravenous administration, and cardiac retention was low (<1%) (Bonios et al. 2011).

The Applicant conducted *in vivo* proof-of-concept (POC) studies in a murine model of DMD (female *C57BL/10ScSn-Dmd^{mdx}/J (mdx)* mice). *Mdx* mice are commonly used to model DMD due to their similar disease pathology that includes skeletal muscle necrosis. To justify the use of *mdx* mice to model DMD cardiomyopathy, the Applicant cited studies demonstrating that, compared to healthy mice, 10-month-old female *mdx* mice exhibit a comparable decrease in LVEF to that of the proposed DMD patient population (Tandon et al. 2015; Aminzadeh et al. 2018). A definitive POC study (Study #RD20171010RR) assessed the effect of healthy murine-derived CDCs on heart fibrosis and LVEF in *mdx* mice following IV administration of 2.5×10^5 cells/animal (human equivalent dose of $8.75\ x10^8$ cells/patient,[4] 5.83-fold higher than a single clinical dose). CDCs were administered once or twice (3 weeks apart). Compared to saline-administered control *mdx* mice, a single administration of CDCs resulted in a 20% increase in LVEF and a qualitative decrease in cardiac fibrosis (by histopathology) at 3 weeks post-administration. Assessment of skeletal muscle function also demonstrated a quantitative increase in the number of myofibers (by histopathology), a statistically significant increase in ex vivo soleus muscle force, and a non-significant increase in the distance traveled on a treadmill. Following a second administration at 3-weeks, assessment at 6 weeks did not demonstrate significant, additional improvement in skeletal muscle function; cardiac function (LVEF) was not assessed. This non-Good Laboratory Practice (GLP) study is not adequate to serve as confirmatory evidence due to its significant limitations, including the use of an analogous murine test article, an inappropriate saline-only control, and insufficient study design to demonstrate a dose response, particularly for cardiac endpoints.

[3] The following growth factors were released from human CDCs: angiopoietin-2, bFGF (basic fibroblast growth factor), HGF (hepatocyte growth factor), IGF-1 (insulin-like growth factor 1), SDF-1 (stromal derived factor 1), and VEGF (vascular endothelial growth factor).

[4] Extrapolation based on a body weight of 70 kg.

2.2.3 Deramiocel Clinical Development Program

Before initiating DMD-specific trials, the safety and biologic activity of CDCs were evaluated in adult patients with cardiac conditions using an intracoronary (IC) route of administration. The ALLSTAR study evaluated allogeneic CDCs in patients with myocardial infarction and ischemic left ventricular dysfunction, and the DYNAMIC study assessed CDCs in patients with dilated cardiomyopathy (Chakravarty et al. 2020; Makkar et al. 2020). The ALLSTAR study was a randomized, placebo-controlled, double-blind study of patients who were 4 weeks to 12 months after myocardial infarction, with LVEF ≤45% and LV scar size ≥15% of LV mass. Patients received an IC infusion of either deramiocel (90 subjects) or a placebo consisting of the same formulation but without CDCs (44 subjects), and the primary efficacy endpoint was the change in infarct (scar) size on contrast-enhanced cMRI at 12 months post-infusion. The study was stopped early due to concern for futility after a pre-specified interim analysis was performed, and the results did not demonstrate a reduction in scar size at 6 months. The DYNAMIC study was an open-label, dose-finding study of 14 patients with LVEF ≤ 35% by echocardiogram. The initial study design included enrollment of 28 additional patients for a randomized, placebo-controlled phase; however, this study did not proceed after review of the dose-finding results. Three additional studies generated supplementary safety data: ALPHA, REGRESS, and INSPIRE. ALPHA was an investigator-initiated trial which included subjects with pulmonary arterial hypertension, and CDCs were administered by central IV into the right ventricular outflow tract (Lewis et al. 2024). REGRESS was an investigator-initiated trial which included subjects with heart failure with preserved ejection fraction, and CDCs were administered by IC infusion. INSPIRE was a study of subjects with SARS-CoV2 infection and CDCs were administered by IV infusion.

The clinical development program for deramiocel in DMD is shown in Table 2 and consists of five clinical studies: Studies HOPE-Duchenne, HOPE-OLE, HOPE-2, HOPE-2-OLE, and HOPE-3 (which includes a randomized, blinded phase and open-label phases).

On December 31, 2024, the Applicant submitted an original BLA seeking traditional approval of deramiocel for the treatment of cardiomyopathy in patients with DMD, based on results from Studies HOPE-2 and HOPE-2-OLE (described below). FDA issued a Complete Response letter for the original BLA on July 9, 2025. A high-level summary of the HOPE-2 and HOPE-2-OLE results that formed the basis for the original BLA for deramiocel is provided below.

Study HOPE-2 Results (Original Deramiocel BLA Submission)

Study HOPE-2 was a Phase 2, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of IV deramiocel (150 million cells) administered every 3 months for 12 months (4 doses) in males ≥10 years old with DMD, the majority of whom were non-ambulatory. The primary efficacy endpoint was the change from baseline to Month 12 in score on the mid-level (elbow) domain of the Performance of the Upper Limb version 1.2 (PUL 1.2), an earlier iteration of the Performance of the Upper Limb assessment described above. The secondary efficacy endpoints included change from baseline in mid-level domain of the PUL 1.2 at Month 3, 6, and 9, and change from baseline in regional systolic left ventricular wall thickening, as determined by cardiac MRI, at Months 6 and 12. Exploratory efficacy endpoints included additional cardiac MRI measurements of left ventricular structure and function, such as left ventricular ejection fraction (LVEF) and left ventricular end-systolic and diastolic volumes (LVESV, LVEDV).

Although Study HOPE-2 was designed to enroll 84 patients, the Applicant terminated study enrollment after 20 patients (16 of whom completed the study) for administrative reasons after an interim analysis, and the data were unblinded to the Applicant at that time. Consequently, the study was not statistically powered to detect a treatment effect on the primary efficacy endpoint; no power calculations were performed for any of the secondary or exploratory endpoints related to cardiac imaging parameters.

After data unblinding, the Applicant modified the statistical analysis plan (SAP) for Study HOPE-2. The covariance structure in the model was changed, resulting in a violation of the normality assumption for model residuals according to the Applicant's *post hoc* criteria. The Applicant cited the violation of the normality assumption to change the primary analysis model for all efficacy endpoints by transforming the data from the original scale to percentile rank. The analyses on the transformed data appeared stronger than the prespecified analyses based on the original data. However, there was no evidence of non-normality under the prespecified covariance structure for many of the endpoints, including the primary efficacy endpoint. Moreover, percentile rank lacks clinical significance or a clear clinical interpretation. FDA therefore did not agree with the Applicant's *post hoc* analysis results of Study HOPE-2 data submitted in the BLA.

Based on the analysis model prespecified before data unblinding, Study HOPE-2 did not show a statistically significant treatment effect of deramiocel compared to placebo on either the primary efficacy endpoint or all the secondary efficacy endpoints. Because statistical significance was not shown for the primary efficacy endpoint, the secondary efficacy endpoints could not be formally tested statistically and therefore were considered by FDA as exploratory. The Applicant examined over 50 secondary and exploratory endpoints. Of the 26 cardiac endpoints, FDA's analysis based on the prespecified analysis model indicated that only three (LVEF, left ventricular end-systolic volume, and LVESVI) reached a nominal p-value <0.05, as seen in Figure 9 in the Appendix. Without pre-specification of hypothesis testing and multiplicity adjustment strategy to minimize the likelihood of obtaining false positive results, these findings may be spurious. In addition, these analyses may be biased because three randomized subjects (two who received placebo and one who received deramiocel) were excluded due to missing post-baseline assessments.

No overall consistency in treatment effect was apparent across the exploratory cardiac endpoints, as shown in Figure 9 in the Appendix. Notably, cardiac regimens were not standardized for the study subjects. The number and types of cardiac medications varied, both at baseline and during the study: multiple subjects were not on any cardiac therapies, while other subjects received up to 3 different classes of cardiac medications. Instances of adding or changing the dosage of concomitant cardiac medications occurred during the study.

Study HOPE-2-OLE Results (Original Deramiocel BLA Submission)

Study HOPE-2-OLE was a single-arm, open-label extension study in which subjects who had completed Study HOPE-2 (including those in the placebo group) were invited to receive deramiocel. The primary objective of Study HOPE-2-OLE was the assessment of safety and efficacy over 60 months.

A gap of approximately 1 year (although variable among patients) was present between the HOPE-2 and HOPE-2-OLE studies; during this period no subjects received deramiocel or underwent cardiac MRI assessments.

Study HOPE-2-OLE enrolled 13 subjects. Data derived from the Month 24 and Month 36 timepoints were submitted for review in the original BLA. The primary endpoints assessed safety and the change from baseline to Month 12 in PUL 2.0 total score. The secondary and exploratory efficacy endpoints were modified by the Applicant multiple times. The original protocol listed two secondary efficacy endpoints, both of which assessed skeletal muscle function via the PUL 2.0. No exploratory efficacy endpoints were included in the original protocol. Cardiac-related efficacy endpoints were added after study initiation, so subjects did not have baseline cardiac MRIs; instead, cardiac MRIs obtained at the end of Study HOPE-2 were used as baseline measurements for all analyses. The Applicant made major modifications to the statistical analysis plan throughout the study, and again after the last subject completed Month 36.

In Study HOPE-2-OLE, a minimal difference, neither statistically nor clinically significant, was observed in the change from baseline to Month 12 in PUL 2.0 total score between subjects previously randomized to receive deramiocel in Study HOPE-2 and subjects previously randomized to receive placebo. The Applicant submitted exploratory analyses of the PUL 2.0 data, comparing Study HOPE-2-OLE subjects to external controls (30 patients from Cincinnati Children's Hospital Medical Center). Cohort matching between the HOPE-2-OLE subjects and the external controls did not account for all important baseline variables which introduced significant confounding. As a result, FDA did not consider these analyses interpretable.

Out of 13 subjects who completed Study HOPE-2 and enrolled in Study HOPE-2-OLE, 10 subjects had LVEF measurements. The Applicant compared cardiac MRI measurements obtained in Study HOPE-2-OLE to external historical data from multiple sources, including from Vanderbilt University Medical Center, and submitted several *post hoc* analyses. The Applicant's propensity score matching between the HOPE-2-OLE subjects and the external controls was based on a small number of characteristics (age, LVEF, and the interaction between age and LVEF). The propensity score matching did not account for important clinical characteristics associated with outcomes related to cardiomyopathy, such as vital signs, physical exam findings, laboratory values (e.g., creatinine, hemoglobin), and medical history (e.g., prior heart failure hospitalizations, presence or absence of arrhythmias). All external control patients had received cardiac medications. Because the cardiac medication regimen was not standardized in either Study HOPE-2-OLE or among the external control patients, matching based on use of specific cardiac medication classes could not be performed. FDA determined that the analyses of cardiac parameters based on comparison to the external control patients were not interpretable.

Efficacy Conclusions: Original BLA Submission

Although the original BLA submission was intended to support an indication of treatment of cardiomyopathy in DMD, the Applicant clarified during the interactive BLA review process that Studies HOPE-2 and HOPE-2-OLE were not designed to evaluate deramiocel for the treatment of cardiomyopathy in DMD, either as a standalone therapy or as an add-on therapy to standard guideline-directed medical regimens.

Study HOPE-2 was not powered to show a treatment effect on skeletal muscle function, because of the early termination of enrollment.

The exploratory, *post-hoc* analyses of clinical data from Studies HOPE-2 and HOPE-2-OLE lacked scientific validity and were susceptible to substantial bias.

Overall, Studies HOPE-2 and HOPE-2-OLE did not provide substantial evidence of effectiveness of deramiocel and a Complete Response Letter was issued to the Applicant, detailing the study deficiencies.

Table 2. Deramiocel Clinical Development Program in DMD

Study	Study Design	Intervention	Route of Administration	Number of Patients	Study Population	Duration of Follow-Up (Number of Infusions)	Status
HOPE-Duchenne	Randomized, open-label, exploratory	Deramiocel 75M cells (25M per coronary artery) vs. usual care; single dose	IC	25 (13 deramiocel; 12 usual care)	Male DMD patients with cardiomyopathy	12 months (1 infusion)	Completed
HOPE-OLE	Open-label extension of HOPE-Duchenne; uncontrolled	Deramiocel 75M cells; 2 doses (Day 1 and Month 3)	IV	8 deramiocel	Male DMD patients from HOPE-Duchenne usual care arm	6 months (2 infusions)	Completed
HOPE-2	Multicenter, randomized, double-blind, placebo-controlled Phase 2	Deramiocel 150M cells vs. placebo, Q3M	IV	20 (8 deramiocel; 12 placebo)	Male DMD patients ≥10 years with skeletal muscle impairment (PUL entry item score 2–5); ambulatory and non-ambulatory	12 months (4 infusions)	Completed
HOPE-2-OLE	Open-label extension of HOPE-2; uncontrolled; external natural history comparators used	Deramiocel 150M cells, Q3M	IV	13	Male DMD patients who completed HOPE-2; all non-ambulatory at OLE entry	Up to ~60 months / up to 20 infusions (data available through 36 months / 13 infusions)	Ongoing
HOPE-3 (blinded phase)	Multicenter, randomized, double-blind, placebo-controlled, two-cohort, Phase 3	Deramiocel 150M cells vs. placebo, Q3M	IV	106 (54 deramiocel; 52 placebo)	Male DMD patients aged 10–22 years; ambulatory and non-ambulatory (84.9% non-ambulatory); PUL entry item score 2–6, total PUL ≤40	12 months (4 infusions)	Completed
HOPE-3 OLE/LT-OLE	Open-label extension of HOPE-3; uncontrolled, unblinded	Deramiocel 150M cells, Q3M	IV	All HOPE-3 completers eligible, irrespective of initial treatment assignment	Same population as HOPE-3 blinded phase	OLE: 12 months (4 infusions); LT-OLE: Q3M until commercially available	Ongoing

Source: Adapted from Tabular Listing of All Clinical Studies (module 5.2) and FDA review
Abbreviations: CDCs, cardiosphere-derived cells; DMD, Duchenne muscular dystrophy; IC, intracoronary; IV, intravenous; LT-OLE, long-term open-label extension, M, million; Q3M, every 3 months; OLE, open-label extension; PUL, Performance of the Upper Limb

2.2.4 Pertinent Regulatory History

Table 3 summarizes key regulatory milestones and interactions between FDA and the Applicant.

Table 3. Key Regulatory History

Date	Milestone	Topic
April 21, 2015	Orphan Drug Designation granted	-
July 5, 2017	Rare Pediatric Disease Designation granted	Indication: treatment of DMD.
November 24, 2017	IND 17800 allowed to proceed	-
January 29, 2018	RMAT Designation granted	Indication: treatment of DMD.
August 2, 2024	Type B Pre-BLA meeting	FDA recommended that a future BLA submission with an indication of "treatment of patients with DMD" include the results of the HOPE-3 clinical study (Cohort A). FDA did not consider data from the HOPE-2 and HOPE-2-OLE studies to be sufficient to support a broad indication. Summary data of the potential effects of deramiocel on cardiac function were discussed. FDA was open to reviewing the data in support of a cardiac claim and recommended that any future BLA submission include more detailed information on the cardiac effects of deramiocel, including individual subject-level data. The *post hoc* Statistical Analysis Plan addendum was discussed. The FDA statistical review team provided a detailed discussion of concerns regarding the *post hoc* analyses conducted by the Applicant.
December 31, 2024	Original BLA submission	Studies HOPE-2, HOPE-2-OLE
July 9, 2025	Complete Response Letter	Study HOPE-2 failed to meet the pre-specified primary (PUL 1.2) and any key secondary efficacy endpoint (cardiac measures on MRI) and did not provide evidence of effectiveness. The findings from *post hoc* and exploratory analyses of cardiac function from the nonrandomized HOPE-2-OLE study also did not provide substantial evidence of effectiveness.
August 13, 2025	Type A meeting	The Complete Response Letter and the clinical development of deramiocel were discussed. The Applicant proposed to change the primary endpoint of Study HOPE-3 to change from baseline in LVEF. FDA disagreed with changing the primary endpoint, as the study was already under way. FDA stated that change from baseline in LVEF could potentially be considered a key secondary endpoint, and requested additional information to support the Applicant's proposed change from a secondary endpoint to a key secondary endpoint.
June 18, 2025	Randomized, double-blind period of Study HOPE-3 completed	
September 26, 2025	Statistical Analysis Plan (SAP) 2.0* and Study Protocol 9.0 Submitted	FDA comment or discussion not solicited; some previous FDA comments not incorporated; no FDA concurrence obtained;

Date	Milestone	Topic
November 24, 2025	SAP 3.0* created by Applicant	Not submitted to FDA for review and comment, No FDA concurrence
November 25, 2025	Database lock and data unblinding for Study HOPE-3	
December 29, 2025	BLA resubmission	Study HOPE-3 (missing documents)
January 13, 2026	Incomplete Response Letter	The submission was deemed incomplete due to multiple missing documents, including a complete clinical study report, all versions of the clinical protocol and Statistical Analysis Plan, and narrative summaries.
February 20, 2026	BLA resubmission	Study HOPE-3 with requested additional data and information for a complete submission

Source: FDA
**SAP 2.0, SAP 3.0: prepared by the Applicant and not aligned with the Applicant's approved blinding plan
Abbreviations: SAP, statistical analysis plan; BLA, biologics license application; DMD, Duchenne muscular dystrophy; IND, investigational new drug; LVEF, left ventricular ejection fraction; OLE, open-label extension; PUL, Performance of Upper Limb; RMAT, regenerative medicine advanced therapy

3. Summary of Issues for AC Discussion

3.1 Efficacy Summary

Deramiocel was studied in two randomized studies in patients with DMD, Studies HOPE-2 and HOPE-3. This briefing document and the BLA resubmission focus on the results of Study HOPE-3. Data from Study HOPE-2 and its open-label extension, Study HOPE-2-OLE, were submitted to support the original BLA for deramiocel which received a Complete Response Letter due to lack of evidence of effectiveness.

3.2 Efficacy Evaluation

3.2.1 Study HOPE-3

3.2.1.1 Study Overview

Study HOPE-3 was a Phase 3, multicenter, randomized, double-blind, 12-month placebo-controlled study designed to assess the efficacy and safety of deramiocel administered as four intravenous (IV) infusions, once every 3 months, in males with DMD. The study enrolled 106 males with DMD, aged 10 years or older with the majority being non-ambulatory and with LVEF > 55%. Upon completion of the initial double-blind, placebo-controlled Phase 3 study, each patient was eligible to receive up to four additional IV infusions of deramiocel, administered once every 3 months during a 12-month open-label extension (OLE) period (Month 12 - Month 24). Patients who completed Month 24 of Study HOPE-3-OLE were subsequently eligible to continue deramiocel in a long-term open-label extension (HOPE-3-LT-OLE) period, until commercial availability, termination of the trial at the Applicant's decision, or withdrawal of consent. Efficacy data from the HOPE-3-OLE and HOPE-3-LT-OLE periods were not included in the BLA re-submission.

3.2.1.2 Study Population

Key Inclusion Criteria

- Males at least 10 years of age at the time of consent.
- Clinical and genetic diagnosis of DMD based on clinical and phenotypic manifestations consistent with DMD
- Performance of the Upper Limb entry item score 2-6 and total PUL score ≤ 40.
    - For Cohort A only: Enrollment of patients with PUL entry score 6, Exon 44 skipping amenable, and/or Exon 3 through 7 deletions will be capped at no more than 10% of the total study population (approximately 6 patients with these specific entry characteristics).
- If ambulatory, subjects must take > 10 seconds for the 10-meter walk/run (i.e., velocity < 1 meter/second).
- If non-ambulatory, loss of independent ambulation between 10th and 18th year birthday (standing unassisted or ability to take, at most, several steps independently is not considered ambulation).
- Treatment with a systemic glucocorticoid for at least 12 months prior to randomization. The dose must remain stable for at least 6 months prior to randomization with the exception of either weight-based dose adjustment or a decrease in steroid dose of ≤ 10% for toxicity. For patients on chronic deflazacort, treatment with an equivalent dose of prednisone or prednisolone for a period of ≤ 30 days to bridge lack of availability of deflazacort during the 6 months prior to randomization is acceptable.

Key Exclusion Criteria

- LVEF ≤35% prior to randomization (cMRI performed during screening, which will serve as baseline).
- Elbow-flexion contractures > 30° in both extremities.
- Body mass index (BMI) > 45.
- Percent predicted forced vital capacity (FVC%) < 35% within 6 months prior to randomization.
- Inability to perform consistent PUL 2.0 measurement within ±2 points without shoulder domain or within ±3 points with shoulder domain during paired testing at screening.
- Risk of near-term respiratory decompensation in the judgment of the Investigator, or the need for initiation of day and night non-invasive ventilator support as defined by serum bicarbonate ≥ 29 mmol/L at screening.
- Initiation of treatment with an FDA-approved exon skipping therapy for the treatment of DMD and/or non-weight-based dose adjustments within 12 months prior to randomization.
- Inability to undergo a cMRI.
    - For Cohort B Only – Subjects with a known hypersensitivity to gadolinium may forgo the late gadolinium enhancement (LGE) assessment but must complete a cMRI without contrast.
    - For Cohort B Only – Subjects who are unable to tolerate gadolinium due to renal insufficiency as measured by an estimated Glomerular Filtration Rate (eGFR) less than 60 mL/min/1.73m^2 may forgo the LGE assessment but must complete a cMRI without contrast.

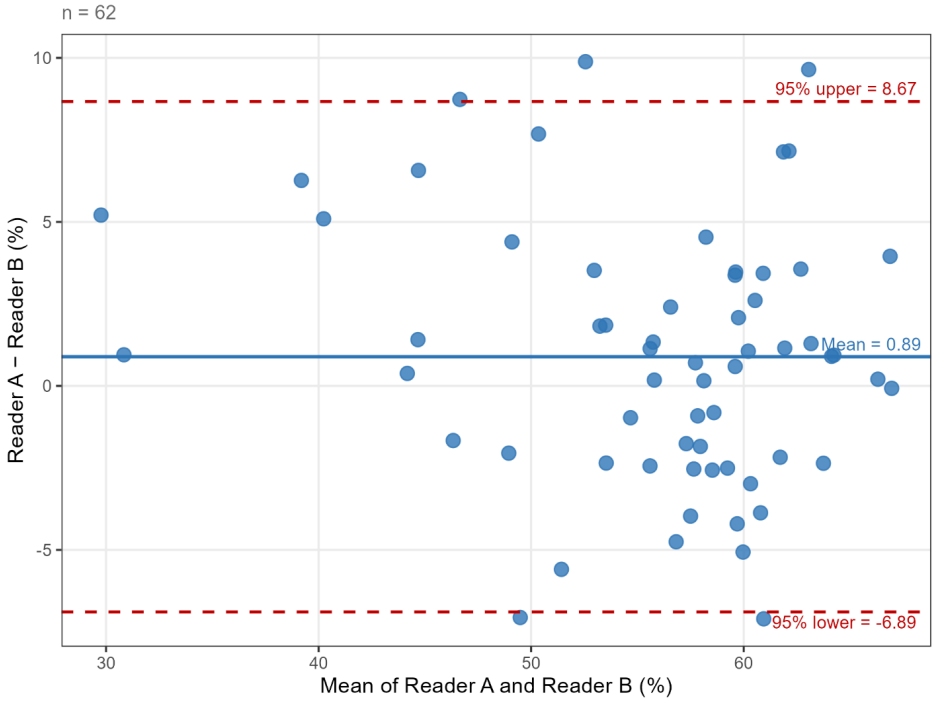
- For Cohort B: Subjects with PUL entry score 6, Exon 44 skipping amenable, or Exon 3 through 7 deletions are excluded from participation.

3.2.1.3 Cardiac MRI Data Collection

Patients in HOPE-3 underwent cMRI for the assessment for the assessment of cardiac structure and function. An Imaging Review Charter details the independent, central review of cMRI. This document includes a protocol for a 2+1 Consensus review paradigm, which states that each timepoint will be centrally reviewed by two independent reviewers (Reader A and Reader B). If the two reads disagree, as defined by pre-specified criteria, then a consensus review will be triggered, and an adjudicator reviewer (Reader C) will select the final read. The criteria for triggering a consensus review include "either Read A or Read B LVEF or LVESV or LGE data not available", in addition to other criteria. The Applicant stated that during adjudication activities, it was identified that Reader B had provided results for only 62 of 82 subjects in the LVEF analysis dataset, due to an image-transfer configuration issue associated with the imaging platform. Rather than applying the pre-specified 2+1 review paradigm to cases where both Reviewer A and Reviewer B data were available, the imaging dataset uses reads from only a single reviewer (Reviewer A).

An Imaging Variability Analysis Report generated by the Applicant includes an analysis of the cMRI data from the two central readers (Reader A and Reader B) at screening and Month 12. There were 62 subjects with paired reads at both timepoints. For LVEF measurements, the mean absolute difference was 2.99% at screening and 3.20% at Month 12. The coverage probability, or the proportion of cases with an absolute difference of ≤5%, was 0.85 at screening and 0.77 at Month 12. Estimates of the inter-reader interclass correlation coefficient (ICC) were also provided: the ICC (95% CI) at screening was 0.89 (0.80, 0.93) and the ICC (95% CI) at Month 12 was 0.88 (0.77, 0.93). There were no repeat reads conducted, so an intra-reader variability assessment was not performed. The Figure 4 and Table 4 below show the inter-rater variability on cardiac MRI readings.

Figure 4. Bland-Altman Plot for Pairwise Reading Comparison of LVEF (%) at Month 12



Source: Adapted from Applicant's Figure 2, Imaging Variability Analysis Report version 1.0 (April 2, 2026)

Table 4. Absolute Difference in LVEF Between Reader A and Reader B - Screening / Month 12

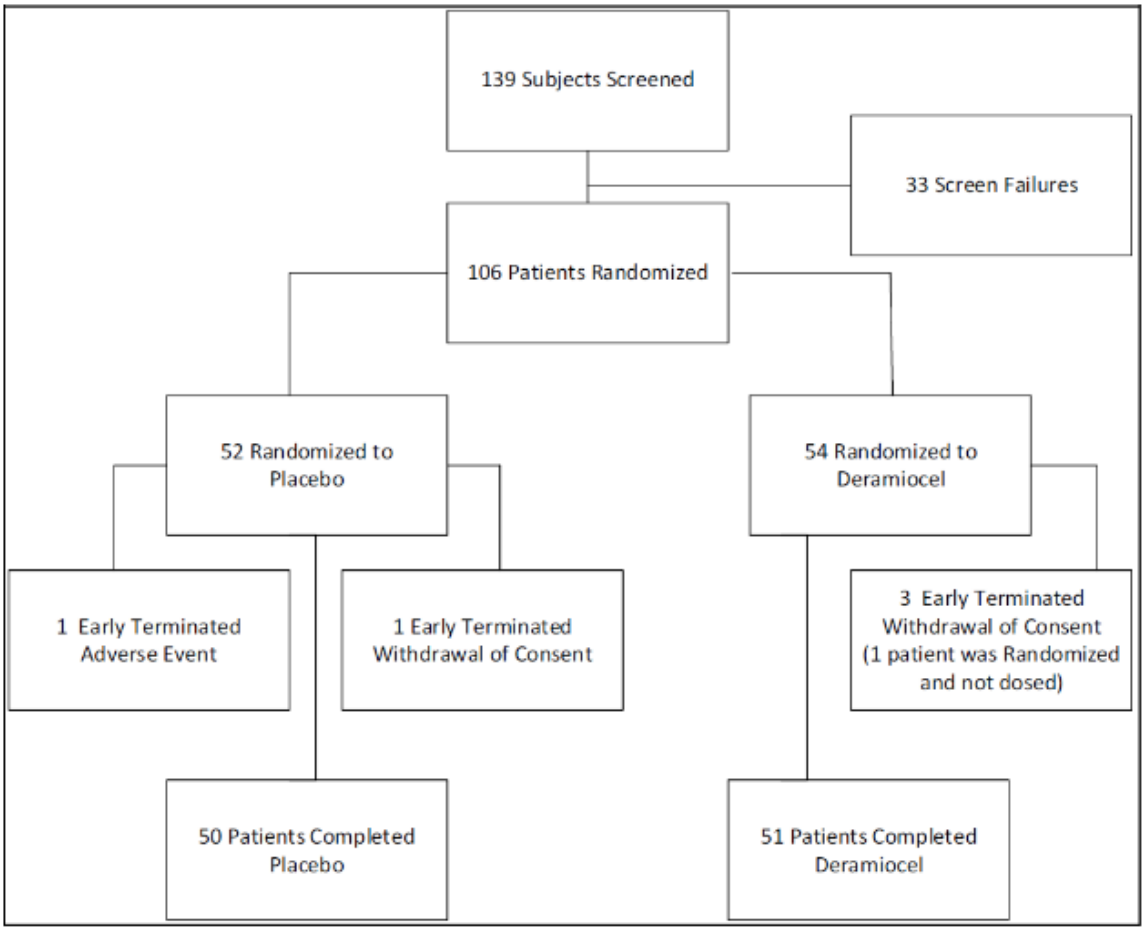
Parameter	Reader A vs Reader B Screening	Reader A vs Reader B Month 12
LVEF (%)		
n	62	62
Mean difference	2.99	3.2
Standard deviation	2.57	2.48
Median	2.56	2.47
Minimum	0.02	0.07
Maximum	12.67	9.88
Coverage probability	0.85	0.77

Source: Adapted from Applicant's Table 2, Imaging Variability Analysis Report version 1.0 (April 2, 2026)
n is the number of subjects with paired reads at the given timepoint. Coverage probability is the proportion of cases with absolute difference ≤5%.
Abbreviations: LVEF, left ventricular ejection fraction; n, number of subjects in sample; vs, versus

3.2.2 Subject Disposition

Figure 5 illustrates the subject disposition for Study HOPE-3, including screening (n=139), enrollment (n=106), randomization (54 in deramiocel group, 52 in placebo group), and completion of the 12-month randomized, double-blind phase of the study (51/54 in deramiocel group, 50/52 placebo group). There was a 5% discontinuation rate.

Figure 5. Subject Disposition, Study HOPE-3



Source: HOPE-3 Clinical Study Report, section 10.1, Figure 3

3.2.3 Baseline Population Characteristics

The mean age was 14.5 years (range: 10 to 22 years) in the placebo group and 15.4 years (range: 10 to 22) in the deramiocel group. Most subjects fell within the 12–18 years age range. All subjects were male. The race distribution was predominantly white across both treatment groups. Mean BMI was similar across groups. Overall, baseline demographic characteristics were reasonably balanced between the placebo and deramiocel groups.

Baseline characteristics of the study population are summarized in Table 5. The distribution of genotypes was similar across treatment groups, with *DMD* deletions being the most common mutation.

“Slow progressor” was defined as a subject meeting any of the following criteria: a PUL entry-item score of 6 in at least 2 of the 3 screening/baseline visits; exon 44 skipping-amenable; exons 3 through 7 deletions; or gene mutations known to be potentially associated with Becker’s Muscular Dystrophy and/or a mild dystrophy phenotype (e.g., exon 51-55 duplication). Most subjects were classified as "non-slow progressors." An imbalance in slow progressor status was observed between treatment groups: 9.6% of placebo subjects (n=5) were classified as slow progressors, compared to 1.9% of deramiocel subjects (n=1).

Cardiomyopathy was defined by the Applicant as any one of the following criteria: 1) medical history from the preferred term list (Cardiomyopathy; Congestive Cardiomyopathy; Dilated Cardiomyopathy; Myocardial Fibrosis; Cardiac Dysfunction; Left Ventricular Dysfunction), 2) LVEF ≤ 55% at Screening, or 3) Number of affected LGE segments >0 (on cMRI) at Screening. The sources, quality, clinical assessments, and completeness of the medical history data supporting this definition is unclear and could not be verified by FDA. In addition, LVEF between 45-55% represents normal left ventricular ejection fraction and does not represent by itself a definition of cardiomyopathy. Lastly, 27 of the 106 (25%) enrolled patients had assessment of LGE on cMRI (cohort B) and, thus, this criterion cannot be applied consistently across the whole trial population. The threshold of LGE segments >0 on cMRI appears arbitrary and was not justified by the Applicant as a reflection (as a standalone) of cardiomyopathy. The presence of LGE on cMRI signifies cardiac scarring and fibrosis but does not indicate whether cardiomyopathy is present. Therefore, FDA does not agree with the Applicant's definition of cardiomyopathy for the enrolled patient population and, as a result, it is unclear whether the patient population in Study HOPE-3 had DMD with associated cardiomyopathy. Based on the baseline cardiac characteristics, the population had a normal LVEF at baseline on average.

Overall, baseline medical characteristics were reasonably balanced between the placebo and deramiocel groups with the exception of "slow progressor" status and baseline LGE on cMRI.

Table 5. Baseline Population Characteristics, Study HOPE-3

Characteristic	Placebo (N=52)	Deramiocel (N=54)
Baseline PUL 2.0 entry item score, n (%)	-	-
2	2 (3.8)	2 (3.7)
3	26 (50.0)	24 (44.4)
4	8 (15.4)	7 (13.0)
5	15 (28.8)	18 (33.3)
6	1 (1.9)	3 (5.6)
Baseline PUL 2.0 entry item score group, n (%)	-	-
2, 3	28 (53.8)	26 (48.1)
4, 5, 6	24 (46.2)	28 (51.9)
Baseline PUL 2.0 Total Score	-	-
Mean (SD)	26.5 (6.70)	27.6 (7.36)
Median (min, max)	25.3 (15.7, 39.7)	27.5 (12.7, 39.0)
DMD mutation type, n (%)	-	-
Deletion	33 (63.5)	34 (63.0)
Non-deletion[a]	19 (36.5)	20 (37.0)
"Slow progressor" indicator for PUL outcomes, n (%)[b]	-	-
Not "slow progressor"	47 (90.4)	53 (98.1)
"Slow progressor"	5 (9.6)	1 (1.9)
Baseline LVEF (%)	-	-
n	46	45
Mean (SD)	59.3 (6.11)	55.3 (7.74)
Median (min, max)	59.3 (47.4, 74.0)	55.9 (36.5, 71.1)
Baseline LVEF Group, n (%)	-	-
<45%	0 (0)	5 (9.3)
≥45%	46 (88.5)	40 (74.1)
Missing	6 (11.5)	9 (16.7)

Characteristic	Placebo (N=52)	Deramiocel (N=54)
Baseline ambulatory status	-	-
Non-ambulatory	44 (84.6)	46 (85.2)
Ambulatory	8 (15.4)	8 (14.8)
Baseline cardiac medications, n (%)[c]	-	-
Yes	48 (92.3)	50 (92.6)
No	4 (7.7)	4 (7.4)
Cardiomyopathy per Applicant's definition[d], n (%)	-	-
No	14 (26.9)	13 (24.1)
Yes	38 (73.1)	41 (75.9)
Baseline late gadolinium enhancement (LGE) on cMRI[e]	-	-
N (only cohort B patients)	14	13
Mean (SD)	1.9 (2.68)	3.1 (3.88)
Median (min, max)	0.5 (0, 9)	2.0 (0, 11)
Part-time use of manual/power wheelchair or scooter, n (%)	47 (90.4)	46 (85.2)
Transitioned to fulltime use of manual/power wheelchair or scooter, n (%)	43 (82.7)	44 (81.5)

Source: FDA Reviewer
[a] Non-deletion includes duplication, point mutation, intron splice and other.
[b]"Slow progressor" was defined as a patient meeting any of the following criteria: a PUL entry-item score of 6 in at least 2 of the 3 screening/baseline visits; exon 44 skipping-amenable mutation; exons 3 through 7 deletions; or gene mutations known to be potentially associated with Becker's Muscular Dystrophy and/or a mild dystrophy phenotype (e.g., exon 51-55 duplication).
[c]Baseline cardiac medications include agents acting on the renin-angiotensin system, beta blocking agents, SGLT-2 inhibitors with an indication for cardiac treatment, and diuretics (including mineralocorticoid receptor antagonists).
[d]Cardiomyopathy was defined as any of the following criteria: 1) medical history from the preferred term list (Cardiomyopathy; Congestive Cardiomyopathy; Dilated Cardiomyopathy; Myocardial Fibrosis; Cardiac Dysfunction; Left Ventricular Dysfunction), 2) LVEF ≤ 55% at Screening, or 3) Number of affected LGE segments >0 (on cMRI) at Screening (Source: HOPE-3 CSR, Table 11).
[e]Baseline late gadolinium enhancement (LGE) was defined as the number of positive LGE segments. LGE was measured for Cohort B only.
Abbreviations: ITT, intent-to-treat; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; N, number of subjects in the specified group, or the total sample; n (%), number of subjects with the specified characteristic; SD, standard deviation

3.2.4 Efficacy Analysis

3.2.4.1 Efficacy Endpoints

The study's pre-specified primary efficacy endpoint was change from baseline in PUL 2.0 total score to Month 12. The pre-specified key secondary efficacy endpoint was change from baseline to Month 12 in LVEF measured by cMRI (assessed centrally). Other prespecified secondary endpoints included: change from baseline in LV end-systolic volume, indexed at Month 12; change from baseline in LV end-diastolic volume, indexed at Month 12; change from baseline in mid+distal PUL 2.0 at Month 12; and change from baseline in "Duchenne Video Assessment (DVA) Eat 10 bites" at Month 12, among others.

3.2.4.2 Statistical Analysis Plan

Pre-Specified SAP (Version 1)

The pre-specified statistical analyses for Study HOPE-3 are described in SAP version 1 (dated July 19, 2022), which is the first version created prior to substantial data collection begun (first subject first visit for Study HOPE 3 on June 22, 2022) and the version based on which Study HOPE-3 was designed and powered. SAP 1.1 was the very first version with additional versions (SAP 1.2-1.8) created which contain minor modifications. SAP versions 1.5, 1.6, and 1.7 were submitted to FDA. SAP 1.1 is used for the FDA analyses and for the efficacy evaluation of deramiocel as this SAP version contains the pre-specified analytical methodology and statistical assumptions which form the basis for the Study HOPE-3 design

and powering for efficacy based on the primary efficacy endpoint of change from baseline to month 12 in PUL 2.0 total score.

According to SAP 1.1, the primary efficacy endpoint of change from baseline to Month 12 in PUL 2.0 total score was to be analyzed using a mixed model repeated measures (MMRM) approach. The dependent variable was change from baseline in PUL 2.0 score, and the model included treatment, investigative site, visit, and treatment-by-visit interaction, as well as baseline score and baseline score by visit interaction. An unstructured covariance structure was to be used. The primary comparison was the difference between deramiocel and placebo at Month 12. Due to the introduction of a separately randomized second cohort using product manufactured in the San Diego facility, FDA included "cohort" as a covariate in its analysis model; SAP 1.1 was prepared prior to the manufacturing shift and therefore did not include this covariate. An analogous model was used for the secondary efficacy endpoints, including LVEF, using change from baseline to Month 12.

No imputation was planned to be performed for any efficacy endpoint and the MMRM analysis was to use all available data to estimate the mean treatment effect assuming all missing data were Missing at Random (MAR).

The primary efficacy analysis set included all subjects who were randomized and had a PUL entry score of 2, 3, 4, or 5 and had a change from baseline outcome for the PUL 2.0.

The study was designed to provide 90% power to detect a 1.5-point difference in mean change from baseline to Month 12 in PUL 2.0 total score assuming a total sample size of 68 subjects (34 per group), and a standard deviation of 1.71. This was based on SAP 1.1.

Post-Study SAP Modifications

After completion of the randomized, double-blind period of Study HOPE-3 on June 18, 2025, the Applicant implemented major changes to the SAP over several different versions. Although the Applicant provides justifications for these changes, FDA does not agree that the scientific rationale for those changes was supported and considers the changes unwarranted based on the study's design, powering, and original statistical assumptions. The final SAP was created directly by the Applicant which deviated from the documented blinding and statistical implementation/drafting plan (described below). Given these uncertainties and plan deviations, FDA considers the Applicant's analyses based on the post-study SAP versions to be *post-hoc* and exploratory.

SAP Versions

The Applicant created versions SAP 2.0 (submitted to FDA, no discussion held, no agreement reached, did not incorporate some previous FDA comments) and SAP 3.0 (not submitted to FDA and not discussed with FDA). The clinical study report (CSR) for Study HOPE-3 submitted in the BLA included analyses that further deviated from SAP 3.0 (these analyses are referred to as modified SAP 3.0 below); these deviations were not submitted to FDA or agreed upon prior to the BLA resubmission.

The SAP modifications in versions 2.0 and 3.0 included substantial changes to: 1) the primary and secondary efficacy endpoint definitions (PUL 2.0 and LVEF respectively), 2) the data imputation strategy for intercurrent events, and 3) the statistical analysis models. SAP 3.0 which the Applicant considers as the final SAP was created/finalized one day prior to database lock/data unblinding of Study HOPE-3 (as

shown in Table 6). In addition, the Applicant's pre-specified, approved blinding plan states that "the blinded biostatistics team [at Pentara Corporation] will develop the study Statistical Analysis plan." However, SAP versions 2.0 and 3.0 were created directly by the Applicant.

Bioresearch Monitoring (BIMO) inspection assignments were issued for the Sponsor and one domestic clinical investigator site, which participated in Studies HOPE-2 and HOPE-3. While the Applicant inspections are ongoing at the time of this briefing document preparation, preliminary review of audit trails and site records revealed the Applicant deviated from the pre-specified, approved blinding plan and the statistical programming and biostatistics functions were transferred from the outside, independent vendor to an in-house biostatistical team in October 2023.

A timeline of the key changes to the efficacy endpoints and the statistical analysis plan is summarized in Table 6 below.

Table 6. SAP Changes; Study HOPE-3

Date	Milestone	Key SAP content
June 22, 2022	First subject first visit	Start of Study HOPE-3
July 19, 2022 (SAP 1.1) June 8, 2023 (SAP 1.5 submitted to FDA on June 9, 2023)	SAP 1.1* to SAP 1.5*	Primary endpoint: **change from baseline to Month 12 in PUL 2.0 total score** • Model[a]: mixed model repeated measures (MMRM) with treatment, cohort, investigative site, visit, treatment-by-visit interaction, baseline score, baseline score by visit interaction as model covariates; an unstructured covariance structure to model within patient errors • Missing data and intercurrent event (IE) handling: the MMRM would use all available data in estimation • Baseline score: first non-missing score prior to the time of first IP administration on Day 1 Key secondary endpoint: **change from baseline to Month 12 in LVEF** • An analogous model as primary efficacy endpoint was used
December 6, 2023	SAP 1.7	Primary endpoint: **change from baseline to Month 12 in PUL 2.0 total score** • Model[a]: MMRM with treatment, cohort, investigative site, visit, treatment-by-visit interaction, slow progressor and its interactions with visit and treatment, baseline score, baseline score by visit interaction as model covariates; an unstructured covariance structure to model within patient errors • Missing data and intercurrent event (IE) handling: composite strategy for the intercurrent events of death or adverse event leading to study discontinuation, whereby the worst observed value among all subjects at that visit would be assigned • Baseline score: first non-missing score prior to the time of first IP administration on Day 1 Key secondary endpoint: **change from baseline to Month 12 in LVEF** • An analogous model as primary efficacy endpoint was used
June 18, 2025	Last subject last visit	Completion of randomized, double-blind period of Study HOPE-3

Date	Milestone	Key SAP content
September 26, 2025	SAP 2.0**	Primary endpoint: **percent change from baseline to Month 12 in PUL 2.0 total score** • Model[b]: MMRM with treatment, cohort, investigative site, visit, treatment-by-visit interaction, baseline score; heterogeneous first-order autoregressive (ARH[1]) to model within patient errors • Missing data and intercurrent event (IE) handling: composite strategy for the intercurrent events of death or adverse event leading to study discontinuation, whereby the worst observed value among all subjects at that visit would be assigned • Baseline score: first non-missing score prior to the time of first IP administration on Day 1 Key secondary endpoint: **change from baseline to Month 12 in LVEF** • An analogous model as primary efficacy endpoint was proposed
November 24, 2025	SAP 3.0**	Primary endpoint: **percent change from baseline to Month 12 in PUL 2.0 total score** • Model[b]: MMRM with treatment, cohort, investigative site, visit, treatment-by-visit interaction, baseline score; ARH[1] to model within patient errors • Missing data and intercurrent event (IE) handling: composite strategy for the intercurrent events of death or adverse event leading to study discontinuation, whereby the worst observed value among all subjects at that visit would be assigned; removed all post-use data for subjects who used prohibited medication • Baseline score: average of all screening visits and day 1 Key secondary endpoint: **ranked change from baseline to Month 12 in LVEF** • Model: analysis of covariance (ANCOVA) with treatment, cohort, slow progressor indicator, indicator for screening LVEF greater than or equal to 45%, baseline LVEF and age at baseline.
November 25, 2025	Database lock, data unblinding	-
February 3, 2026	HOPE-3 Clinical study report (CSR) in BLA	Primary endpoint: **percent change from baseline to Month 12 in PUL 2.0 total score** • Model: include an additional term, slow progressor indicator, which should be removed based on specified criteria Key secondary endpoint: **ranked change from baseline to Month 12 in LVEF** • Model: include an unspecified interaction term between baseline LVEF and age at baseline

Source: FDA review team
*SAP 1.1-SAP 1.8: prepared by Pentara Corporation (CRO) according to Applicant's approved blinding plan
**SAP 2.0, SAP 3.0: prepared directly by the Applicant and not aligned with the Applicant's approved blinding plan
[a]: because HOPE-3 consisted of two cohorts that were randomized separately, for statistical rigor, FDA's analyses modified the original model based on SAP 1.1 to include cohort as a covariate, similar to SAPs 2.0 and 3.0.
[b]: "slow progressor" should be removed from the statistical model based on the Applicant's criteria: "if cell sizes fall below 2 subjects per treatment arm for categorical variables, that variable will be omitted from the model."
Abbreviations: FDA, U.S. Food and Drug Administration; IP, investigational product; LVEF, left ventricular ejection fraction; PUL, Performance of Upper Limb; SAP, statistical analysis plan

Change in Primary Endpoint Definition (PUL 2.0)

In SAP versions 2.0 and 3.0, the primary endpoint was modified from change from baseline to Month 12 in PUL 2.0 total score (pre-specified in SAP 1) to percent change from baseline to Month 12. The Applicant fitted the MMRM model using percent change from baseline as the dependent variable and then converted results back to the raw scale by multiplying the mean baseline PUL 2.0 total score by the estimated mean difference in percent change. FDA does not consider the conversion of raw change to percent change and then back to raw change to have been scientifically justified, as it adds complexity and reduces accuracy. In FDA's view, the change from baseline can be directly modeled using the MMRM, as was specified in all SAP and protocol versions prior to study completion.

The Applicant cited inherent heterogeneity of functional ability in the DMD population to support this change. However, this heterogeneity was known at the time of HOPE-3 study design and the study design had already addressed baseline heterogeneity through randomization stratification and inclusion of baseline PUL total score as a covariate.

As described in ICH E9, *Statistical Principles for Clinical Trials*, "the decision to transform key variables prior to analysis is best made during the design of the trial on the basis of similar data from earlier clinical trials", not after trial completion, and "the decision on whether and how to transform a variable should be influenced by the preference for a scale that facilitates clinical interpretation." Revising an endpoint after data collection raises concerns about data driven endpoint selection and compromises the integrity of a confirmatory trial.

From a clinical standpoint, there is no corresponding clinical interpretation for a percent change from baseline (relative change) in PUL 2.0 total score as the clinical meaningfulness associated with a certain percent change in the PUL 2.0 total score is unknown, not established, and not studied in DMD. Published studies in DMD patients have assessed changes in PUL 2.0 score (change from baseline) and not percent change from baseline. In addition, based on the structured items and scoring (points) of PUL 2.0, a patient's upper limb function is reflected in their score (points) on each category (shoulder, elbow, wrist/fingers) and in the total PUL 2.0 score with changes in score used for tracking the disease trajectory over time and assessing the severity of upper limb functional impairment. The PUL 2.0 instrument is structured and validated to assess and yield scores in each domain and a total score, also in points, and not a percent in change in points. As such, a change from baseline in PUL 2.0 score is a clinically interpretable metric reflecting progression of skeletal muscle disease in DMD patients with at least a 1 point change representing a clinically relevant change in function. Lastly, Study HOPE-3 was designed and specifically powered to detect a 1.5-point difference in the mean change from baseline to Month 12 in PUL 2.0 total score and not a percent change in PUL 2.0 score. Based on these considerations and uncertainties pertaining to a relative (percent) change in PUL 2.0 score, the FDA considers the pre-specified definition for the study's primary efficacy endpoint (change from baseline in PUL 2.0 total score) to reflect a clinically meaningful outcome measure that is fit for use in this study and directly interpretable.

Change in Key Secondary Endpoint Definition (LVEF)

In SAP version 3.0, the key secondary endpoint definition for LVEF was revised from change from baseline to ranked change from baseline to Month 12. The analysis of covariance (ANCOVA) on ranks model used for this endpoint definition did not use all available data; it excluded all Month 6 data and

subjects who did not have both baseline and Month 12 data observed, whereas the pre-specified MMRM model in SAP 1.1 did use all available data. Specifically, the ANCOVA on ranks model requires both baseline and Month 12 data to be included and, thus, using the ANCOVA model for the LVEF analysis results in excluding a total of 23 randomized subjects representing 22% of the randomized study population in Study HOPE-3. Excluding 22% of the population from the LVEF analysis violates the intention to treat principle in this randomized study and compromisess the integrity of the results. In addition, the revised LVEF analysis did not adjust for randomization stratification factors, which could increase the risk of imbalance in an already potentially biased sample. Rank-based analyses are also unstable statistically as very minor numerical changes can result in large swings in rank.

The Applicant has indicated that the decision to change to ANCOVA on ranked change was informed by Study HOPE-2 which was completed in March 2020. However, this rationale was known at the time of HOPE-3 study design but the change was not instituted until one day before data unblinding for HOPE-3. As described in ICH E9, *Statistical Principles for Clinical Trials*, "the decision to transform key variables prior to analysis is best made during the design of the trial on the basis of similar data from earlier clinical trials", not after trial completion, and "the decision on whether and how to transform a variable should be influenced by the preference for a scale that facilitates clinical interpretation." Revising an endpoint after data collection raises concerns about data-driven endpoint selection and compromises the integrity of the study.

Importantly, a ranked change in LVEF has no clinical interpretation or correlation and is not used as part of cardiac imaging measurements or tracking of LVEF (or other cardiac parameter) changes over time in DMD or other cardiac diseases. Change in LVEF on cardiac imaging constitutes the standard measurement and metric used both in clinical practice and in clinical research to track LVEF changes over time in cardiac disease in general and in DMD cardiomyopathy. In the absence of a credible scientific rationale for utilizing a ranked change to quantify LVEF changes and to capture cardiac benefit, a ranked change in LVEF is not a clinically interpretable or scientifically reasonable evolution for this endpoint. Lastly, characterization of LVEF changes through a ranked change definition would not be fit for inclusion in a label or for communication of the study's findings or clinical progress to patients and, thus, it lacks clinical utility and practical use. Therefore, the FDA analyses use the change from baseline in LVEF as specified in the original SAP.

Change in Data Imputation Strategy

SAP 1.1 specified that all missing data would be assumed missing-at-random (MAR), with the MMRM analysis using all observed data. However, SAP 3.0 considered for the Applicant's analyses included two important changes to the data imputation strategies that influence the study results significantly.

First, SAP 3.0 included a composite strategy for handling the intercurrent events of death or AE-related discontinuations, whereby the worst observed value among all subjects at that visit would be assigned. In addition, a new data imputation strategy for prohibited medication use was introduced in SAP 3.0 whereby all data observed after use of prohibited medication were excluded from the analyses, a strategy that was not included in the SAP previously. The reason for addition of the latter in SAP 3.0 is unclear. Regarding the imputation assumptions, assigning the worst observed score to a subject who discontinued due to an AE is not scientifically reasonable (e.g., a subject on placebo who withdraws due

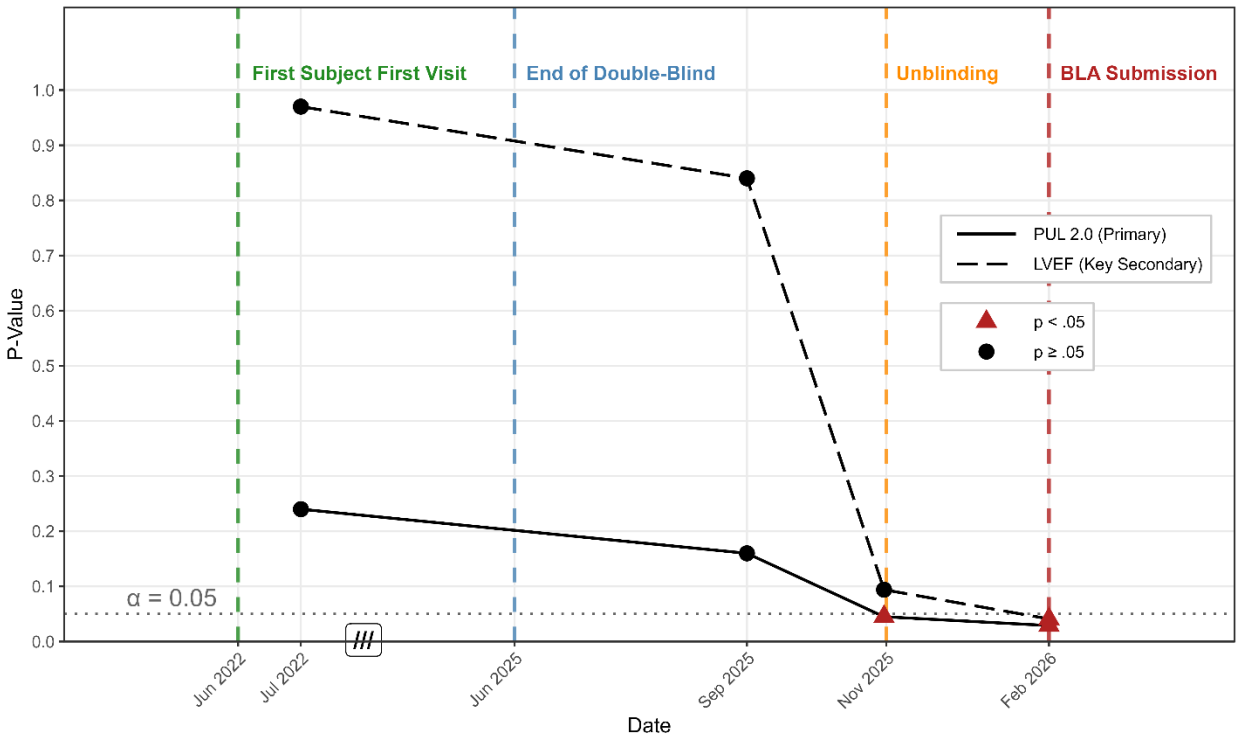
to an AE would be expected to continue a placebo-like trajectory after discontinuation rather than experience the worst observed decline).

These two changes affected only 2 placebo subjects (one who discontinued due to an AE and another who used a prohibited medication). Meanwhile, data for deramiocel-treated subjects who discontinued from the study were assumed MAR — implying they retained the same treatment effect as completers — as the reasons for withdrawal for such subjects were recorded as "withdrawal of consent." As a result, these data imputation strategies in SAP 3.0 disproportionately influenced the results from the two placebo subjects and their handling had a large influence on the study results and conclusions. Overall, the study conclusions lacked robustness to deviations from missing data handling from a very small number of subjects. The Applicant and FDA have different views on which version of the SAP is most appropriate to use. However, regardless of which version is used, this level of sensitivity of the conclusions to missing data handling raises serious questions about whether there is substantial evidence of effectiveness.

Potential Functional Unblinding

A related concern is the potential for functional unblinding. A distinctive adverse event profile was observed for the treatment groups in Study HOPE-3, raising the possibility that treatment assignment for some subjects could have been inferred even if efficacy outcome data may have been formally blinded. This concern is further compounded by the study's open-label treatment period: upon completing the 12-month randomized, double-blind period, subjects were eligible to cross over to open-label treatment, generating a substantial body of additional data from which treatment assignment could potentially be inferred. For instance, in Study HOPE-3, hypersensitivity reactions occurred in 22 of 53 subjects (41.5%) in the deramiocel group and in 8 out of 52 subjects (15.4%) in the placebo group. Eleven placebo subjects who did not have hypersensitivity reactions during the double-blind period developed hypersensitivity reactions during the open-label treatment. Under these circumstances, SAP modifications made after data collection are at risk of being data-driven regardless of the formal blinding status due to the presence of functional unblinding. For this reason, non-pre-specified SAP changes made after study completion (as in SAP 2.0 and 3.0), even if made under seemingly "blinded" conditions, have a high risk of bias and compromisee the study's integrity. Analyses of the data based on these modified SAP versions can be misleading and lead to erroneous conclusions about product efficacy as they deviate significantly from the study's original design, statistical assumptions, and study powering that enables statistical hypothesis testing. The post-study SAP changes led to a dramatic increase of the statistical significance of the results, most prominently on LVEF, as shown in Figure 6 below and discussed in more detail in Section 3.2.4.3 and Section 3.2.4.4. The fact that the study results differ substantially based on the different SAP versions puts in question the robustness and consistency of the observed changes across statistical approaches and compromises the interpretability of the study results based on post-study statistical methods.

Figure 6. Statistical Significance (p-value) Evolution Across SAP Versions of Study HOPE-3



Source: FDA review team
SAP 1.1 was dated July 19, 2022. SAP 2.0 was dated September 26, 2025. SAP 3.0 was dated November 24, 2025. The CSR in the BLA was dated February 3, 2026.
SAP 1.1: prepared by Pentara Corporation (CRO) according to Applicant's approved blinding plan
SAP 2.0, SAP 3.0: prepared by the Applicant and not aligned with the Applicant's approved blinding plan
SAP 2.0: A composite strategy was specified for the intercurrent events of death or adverse event leading to study discontinuation, whereby the worst observed value among all subjects at that visit would be assigned. One placebo subject was affected.
SAP 3.0: A composite strategy was specified for the intercurrent events of death or adverse event leading to study discontinuation, whereby the worst observed value among all subjects at that visit would be assigned; introduced the strategy of removing all post-use data for subjects who used prohibited medication. Two placebo subjects were affected.
Abbreviations: LVEF, left ventricular ejection fraction; PUL 2.0, Performance of Upper Limb version 2.0; SAP, statistical analysis plan

As described in ICH E9, *Statistical Principles for Clinical Trials*, strict adherence to a clinical study's pre-specified SAP is critical to preserve the scientific validity of the results (September 1998; February 2020). Amending analytical methodologies, altering endpoint definitions, or adjusting covariate models or missing data handling strategies after the trial has concluded creates a high risk of bias and inflation of the Type 1 error rate, increasing the probability of misleading results and false conclusions. Furthermore, any analyses executed outside the parameters of a pre-specified SAP constructed prior to study completion are generally considered by the scientific community and by regulatory agencies as exploratory and hypothesis-generating only. As such, analyses based on modified post-study SAP versions (whether or not those analyses were based on blinded or unblinded data) and containing significant modifications to important statistical parameters compromise the study's interpretability.

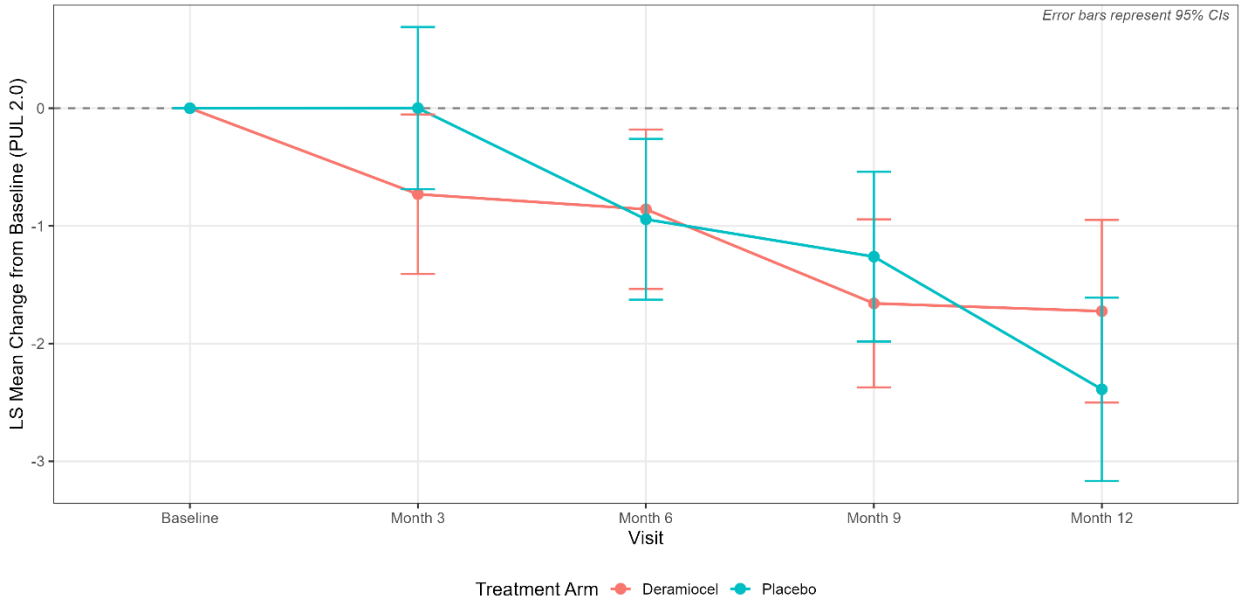
In the Applicant's briefing document, the Applicant presented supportive results from analyses based on SAPs version 1.7 and 2.0. We note that these analyses deviate in important ways from their respective analysis plans as actually described in these SAPs. For SAP 2.0, the Applicant included a "slow progressor" term and its interactions with visit and treatment for both the primary and key secondary endpoints. These covariates should have been removed according to the Applicant's own criteria in the

SAPs, since there was only one slow progressor in the treatment group. Additionally, in these analyses, the Applicant censored one placebo subject who initiated prohibited medication. However, this intercurrent event strategy was not introduced until SAP 3.0 and should not have been used. Furthermore, for both sets of analyses, the Applicant included an additional age-by-baseline interaction term in the LVEF analyses that was not pre-specified in either SAP 1.7 or 2.0. Therefore, these results should be interpreted with caution.

3.2.4.3 Primary Efficacy Endpoint Results: Change from Baseline in PUL 2.0 Total Score

There was no statistically significant or clinically meaningful difference in the pre-specified primary efficacy endpoint of mean change from baseline to month 12 between the two groups in PUL 2.0 total score. Based on the MMRM analysis using all available data as pre-specified in SAP 1.1, the least-squares (LS) mean change in PUL 2.0 Total Score from baseline to Month 12 was -1.73 (95% CI: -2.50, -0.95) for deramiocel and -2.39 (95% CI: -3.17, -1.61) for placebo. **The difference in LS mean change in PUL 2.0 total score from baseline to Month 12 was 0.66 (95% CI: -0.45, 1.77; p-value: 0.24).** Figure 7 shows the adjusted mean change from baseline in PUL 2.0 total score for both treatment groups.

Figure 7. Adjusted Mean Change From Baseline to Month 12 in PUL 2.0 Total Score (SAP 1.1)



Source: FDA analysis
SAP 1.1 analysis model adjusts for treatment, investigative site, visit, treatment-by-visit interaction, baseline score, and baseline score by visit interaction.
The HOPE-3 study initially used deramiocel prepared in the manufacturing facility in Los Angeles. When manufacturing was shifted to the San Diego facility, patients who received deramiocel prepared in San Diego were added to the study as a second cohort. FDA agreed with this change, which was made after SAP 1.1. The FDA Chemistry, Manufacturing, and Controls team considers deramiocel manufactured at the two facilities to be equivalent. However, because the study now consisted of two cohorts that were randomized separately, for statistical rigor, FDA's analyses modified the original model based on SAP 1.1 to include "cohort" as a covariate.
Abbreviations: LS, least-squares; CI, confidence interval; PUL 2.0, Performance of Upper Limb version 2.0; SAP, statistical analysis plan

In the BLA submission, the Applicant presented post-hoc analyses from an MMRM analysis based on SAP 3.0. The Applicant reported a LS mean percent change of -3.86% for deramiocel versus -8.41% for placebo, which corresponds to a between-group difference of 4.55 percentage points (95% CI: 0.47, 8.63; p-value = 0.029). Although the Applicant presents version 3.0 as the final SAP, the Applicant's

analyses presented in the clinical study report did not follow the analyses described in SAP 3.0. The Applicant included a "slow progressor" indicator in the model, which should have been excluded according to their own criteria (only one slow progressor in the deramiocel group). The inclusion of this variable lowered the p value for the comparison between deramiocel and placebo.

Among the 106 randomized subjects, one placebo and three deramiocel subjects did not complete Month 12. The reason for withdrawal for the placebo subject was recorded as due to an adverse event, and missing data from this subject were imputed with worst observed among all subjects. The reason for withdrawal for all three deramiocel subjects was recorded as "withdrawal of consent" and missing data from these three subjects were assumed to be missing-at-random, i.e., these subjects had the same treatment effect as the completers, although the cause of withdrawal of consent for these three treated subjects is unknown. The Applicant also discarded available data from Month 6 to Month 12 for another placebo subject who completed the study and whose improved PUL 2.0 scores the Applicant attributed to prohibited medication use – a new strategy introduced in SAP 3.0. To assess the robustness of these results, FDA analyzed the data under the missing data and intercurrent event handling pre-specified in SAP 1.1 and the analysis model from SAP 3.0. The mean difference was 2.53% (95% CI: -1.48%, 6.53%; p-value: 0.21). Thus, the Applicant's results lack robustness to missing data assumptions for a very small number of subjects, suggesting lack of treatment effect, as shown in Table 7 and in Table 12 in the Appendix. The data imputation strategies in SAP 3.0 (used for the Applicant's analyses) disproportionally influenced the data from the 2 placebo subjects and had a substantial effect on the study results which indicates lack of robustness of the results.

Table 7 shows the mean difference in change from baseline to Month 12 in PUL 2.0 total score based on the prespecified MMRM model in SAP 1.1, SAP 2.0, SAP 3.0, and the Applicant's post hoc analyses submitted in this BLA. Note that analyses "with Data Imputation" mean that one placebo subject who withdrew due to an AE had the worst value observed among all subjects imputed for Months 3, 6, 9, and 12, and another placebo subject who took prohibited medication had observed data from Months 6, 9, and 12 removed. Analyses "without Data Imputation" include all available data included and no data imputation, as prespecified in SAP 1.1. In Table 7, all analyses across the different SAP versions were independently verified by FDA and are presented for comparison.

Table 7. Primary Efficacy Endpoint (PUL 2.0 Total Score) Results Across SAP Versions

Parameter	Pre-specified Analysis (SAP 1.1)[a]	SAP 1.1 With Data Imputation[a] (FDA Analysis)	SAP 2.0 Without Data Imputation (FDA Analysis)	SAP 2.0 With Data Imputation (FDA Analysis)	SAP 3.0 Without Data Imputation (FDA Analysis)	SAP 3.0 With Data Imputation (FDA Analysis)	SAP 3.0 Modified in CSR (Applicant Analysis)
Document date	Jul 19, 2022	July19, 2022	Sep 26, 2025	Sep 26, 2025	Nov 24, 2025	Nov 24, 2025	February 3, 2026
Endpoint Definition	***change* from baseline**	*change* from baseline	*percent* change from baseline	*percent* change from baseline	*percent* change from baseline	*percent* change from baseline	***percent* change from baseline**

Parameter	Pre-specified Analysis (SAP 1.1)[a]	SAP 1.1 With Data Imputation[a] (FDA Analysis)	SAP 2.0 Without Data Imputation (FDA Analysis)	SAP 2.0 With Data Imputation (FDA Analysis)	SAP 3.0 Without Data Imputation (FDA Analysis)	SAP 3.0 With Data Imputation (FDA Analysis)	SAP 3.0 Modified in CSR (Applicant Analysis)
Sample size	Treated: 53 Placebo: 51	Treated: 53 Placebo: 52	Treated: 53 Placebo: 51	Treated: 53 Placebo: 52	Treated: 53 Placebo: 51	Treated: 53 Placebo: 52	Treated: 53 Placebo: 52
Mean difference (95% CI)	**0.66 (-0.45, 1.77)**	0.92 (-0.21, 2.04)	2.38% (-1.78%, 6.54%)	3.74% (-0.44%, 7.93%)	2.53% (-1.48%, 6.53%)	4.16% (0.09%, 8.23%)	**4.55% (0.47%, 8.63%)**
p-value	**0.24**	0.11	0.26	0.08	0.21	0.045	**0.029**

Source: FDA analysis
[a]The HOPE-3 study initially used deramiocel prepared in the manufacturing facility in Los Angeles. When manufacturing was shifted to the San Diego facility, patients who received deramiocel prepared in San Diego were added to the study as a second cohort. FDA agreed with this change, which was made after SAP 1.1. The FDA Chemistry, Manufacturing, and Controls team considers deramiocel manufactured at the two facilities to be equivalent. However, because the study now consisted of two cohorts that were randomized separately, for statistical rigor, FDA's analyses modified the original model based on SAP 1.1 to include "cohort" as a covariate.
"With Data Imputation": one placebo subject who withdrew due to AE had the worst value observed among all subjects imputed for Months 3, 6, 9, and 12; another placebo subject who took prohibited medication had observed data from Months 6, 9, and 12 removed.
"Without Data Imputation": all available data included and no data imputation.
Abbreviations: CI, confidence interval; CSR, clinical study report; PUL 2.0, Performance of Upper Limb version 2.0; SAP, statistical analysis plan

A number of subgroup analyses were performed for PUL 2.0, as shown in Table 8. None of the subgroups achieved nominal statistical significance. Although the study was not powered to detect treatment effects in any of the subgroups, the overall trend across the subgroups is consistent with a lack of treatment effect for deramiocel. For some subgroups, the observed treatment effects in the subgroup and its complement are in opposite directions, which is consistent with what would be expected under an overall null result and further calls into question the reliability of any apparent subgroup effects.

Table 8. Subgroup Analyses for Change From Baseline in PUL 2.0 (SAP 1.1)

Subgroup	Deramiocel (N=54)	Placebo (N=52)	Mean Difference Deramiocel-Placebo (95% CI)	Nominal p-value
Cohort A (N=61)[a]	30	31	-0.09 (-1.50, 1.32)	0.90
Cohort B (N=45)[a]	23	20	1.75 (-0.30, 3.79)	0.092
Ambulatory (N=16)	8	8	-0.43 (-3.98, 3.11)	0.80
Non-ambulatory (N=90)	45	43	0.77 (-0.40, 1.94)	0.19
Slow progressors (N=6)	1	5	-	-
Non-slow progressors (N=100)	52	46	0.92 (-0.21, 2.05)	0.11

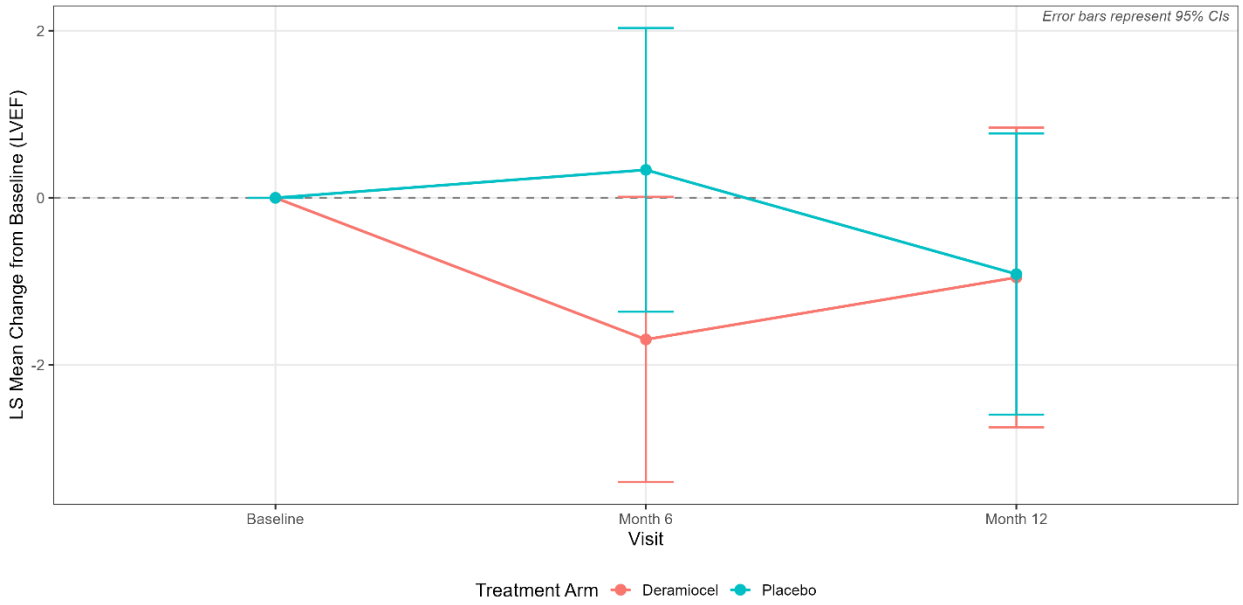
-: model did not converge; N: total of subjects in each subgroup; total number of treated N=54; total number of placebo N=52. [a]The [a]HOPE-3 study initially used deramiocel prepared in the manufacturing facility in Los Angeles. When manufacturing was shifted to the San Diego facility, patients who received deramiocel prepared in San Diego were added to the study as a second cohort. FDA agreed with this change, which was made after SAP 1.1. The FDA Chemistry, Manufacturing, and Controls team considers deramiocel manufactured at the two facilities to be equivalent.
Abbreviations: CI, confidence interval; N, number of subjects in the specified group, or the total sample; PUL 2.0, Performance of Upper Limb version 2.0; SAP, statistical analysis plan

3.2.4.4 Key Secondary Efficacy Endpoint Results: Change From Baseline in LVEF

There was no statistically significant difference between the two groups in change from baseline to Month 12 in LVEF. Based on the MMRM analysis as prespecified in SAP 1.1, the LS mean change from

baseline in LVEF was -0.95% (95% CI: -2.75%, 0.84%) for deramiocel and -0.91% (95% CI: -2.60%, 0.77%) for placebo. The between-group **LS mean difference was -0.041 percentage points (95% CI: -2.58%, 2.49%; p-value: 0.97)**. Figure 8 shows the adjusted mean change from baseline in LVEF for both treatment groups.

Figure 8. Adjusted Mean Change from Baseline to Month 12 in LVEF (SAP 1.1)



Source: FDA analysis
SAP 1.1 analysis model adjusts for treatment, investigative site, visit, treatment-by-visit interaction, baseline score, and baseline score by visit interaction.
The HOPE-3 study initially used deramiocel prepared in the manufacturing facility in Los Angeles. When manufacturing was shifted to the San Diego facility, patients who received deramiocel prepared in San Diego were added to the study as a second cohort. FDA agreed with this change, which was made after SAP 1.1. The FDA Chemistry, Manufacturing, and Controls team considers deramiocel manufactured at the two facilities to be equivalent. However, because the study now consisted of two cohorts that were randomized separately, for statistical rigor, FDA's analyses modified the original model based on SAP 1.1 to include "cohort" as a covariate.
Abbreviations: CI, confidence interval; LS, least-squares; LVEF, left ventricular ejection fraction; SAP, statistical analysis plan

In the BLA, the Applicant presented post-hoc analyses from an ANCOVA on ranks model based on SAP 3.0 but with modifications. The Applicant reported a LS mean ranked change of 57.47 for deramiocel versus 45.82 for placebo, which corresponds to a between-group difference in ranked change of 11.65 (95% CI: 0.47, 22.82; p-value: 0.041). For this, the Applicant did not follow the analyses in SAP 3.0 as the analyses included an additional interaction term not described in SAP 3.0 (Table 9). In addition, because only subjects who had both baseline and Month 12 data could be included in the ANCOVA analysis, the Applicant's analysis excludes nearly 22% of the randomized subjects, which introduces substantial bias and compromises the validity of these results.

Furthermore, compared to the prespecified MMRM analysis, the Applicant's analysis excluded 6 additional subjects (5 treated and 1 placebo) due to missing Month 12 data. This exclusion was important. The placebo subject who was excluded had shown a 9.93 percentage point increase in LVEF from baseline at Month 6. Three of the five treated subjects excluded showed large decreases in LVEF at Month 6 (2 subjects had close to 5 percentage points and one subject had 15 percentage points decrease in LVEF); one treated subject had a 0.37 percentage point decrease in LVEF; one treated subject had a 2.2 percentage point increase in LVEF. In other words, the exclusion removed a placebo

subject who was doing well and removed multiple treated subjects who were not. This exclusion favors the deramiocel group and introduces bias into the comparison.

As with the PUL 2.0 analyses, the Applicant's results for LVEF were influenced by the imputation and censoring strategy applied to the two placebo subjects. To assess the robustness of these results, FDA analyzed the data under the missing data and intercurrent event handling pre-specified in SAP v1.1 with the analysis model from SAP 3.0 without the unspecified interaction term. The mean difference was 6.88 (95% CI: -4.29, 18.05; p-value: 0.22). Again, the Applicant's results show lack of robustness to missing data assumptions for a small number of subjects, suggesting lack of treatment effect, as shown in Table 9 and Table 13 in Appendix.

Table 9 shows the mean difference in change from baseline to Month 12 in LVEF based on the prespecified MMRM model in SAP 1.1, SAP 2.0, SAP 3.0, and the Applicant's post hoc analyses submitted in this BLA submission. Note that analyses "with Data Imputation" mean that one placebo subject who withdrew due to an AE had the worst value observed among all subjects imputed for Months 6 and 12, and another placebo subject who took prohibited medication had observed data from Months 6 and 12 removed. Analyses "without Data Imputation" include all available data included and no data imputation, as prespecified in SAP 1.1. In Table 9, all analyses across the different SAP versions were independently verified by FDA and are presented for comparison.

Table 9. Key Secondary Efficacy Endpoint (LVEF) Results Across SAP Versions

Parameter	Pre-specified Analysis (SAP 1.1)[a]	SAP 1.1 With Data Imputation[a] (FDA Analysis)	SAP 2.0 Without Data Imputation (FDA Analysis)	SAP 2.0 With Data Imputation (FDA Analysis)	SAP 3.0 Without Data Imputation (FDA Analysis)	SAP 3.0 With Data Imputation (FDA Analysis)	SAP 3.0 Modified in CSR (Applicant Analysis)
Document date	Jul 19, 2022	Jul 19, 2022	Sep 26, 2025	Sep 26, 2025	Nov 24, 2025	Nov 24, 2025	February 3, 2026
Endpoint Definition	**change from baseline**	change from baseline	change from baseline	change from baseline	*ranked* change from baseline	*ranked* change from baseline	***ranked* change from baseline**
Sample size	Treated: 44 Placebo: 45	Treated: 44 Placebo: 45	Treated: 44 Placebo: 45	Treated: 44 Placebo: 45	Treated: 39 Placebo: 44	Treated: 39 Placebo: 44	Treated: 39 Placebo: 44
Mean difference (95% CI)	**-0.041% (-2.58%, 2.49%)**	1.08% (-1.55%, 3.71%)	-0.37% (-2.87%, 2.13%)	0.74% (-1.87%, 3.35%)	6.88 (-4.29, 18.05)	9.51 (-1.64, 20.65)	**11.65 (0.47, 22.82)**
Nominal p-value[b]	**0.97**	0.42	0.77	0.57	0.22	0.09	**0.041**

Source: FDA analysis

[a] The HOPE-3 study initially used deramiocel prepared in the manufacturing facility in Los Angeles. When manufacturing was shifted to the San Diego facility, patients who received deramiocel prepared in San Diego were added to the study as a second cohort. The FDA Chemistry, Manufacturing, and Controls team considers deramiocel manufactured at the two facilities to be equivalent. However, because the study now consisted of two cohorts that were randomized separately, for statistical rigor, FDA's analyses modified the original model based on SAP 1.1 to include cohort as a covariate.

[b] When a clinical study fails to achieve statistical significance on the primary endpoint, p-values for secondary endpoints may be calculated mathematically but lack scientific meaning and may be misleading. Such calculations therefore are designated as "nominal p-values."

"With Data Imputation": one placebo subject who withdrew due to AE had the worst value observed among all subjects imputed for Months 6 and 12; another placebo subject who took prohibited medication had observed data from Months 6 and 12 removed.
"Without Data Imputation": all available data included and no data imputation.

Abbreviations: CI, confidence interval; CSR, clinical study report; FDA, U.S. Food and Drug Administration; LVEF, left ventricular ejection fraction; SAP, statistical analysis plan

A number of subgroup analyses were performed for LVEF, as shown in Table 10. None of the subgroups achieved nominal statistical significance, and the overall trend is consistent with a lack of substantial evidence of effectiveness for deramiocel. Some subgroups are very small, and notably, for some subgroups the observed treatment effect and its complement are in opposite directions —

consistent with an overall null result — suggesting the findings are exploratory and hypothesis-generating only. For example, in the documented cardiomyopathy subgroup (N=79), the mean difference was 0.85 (95% CI: -2.31, 4.01), whereas in the complementary non-cardiomyopathy subgroup, the treatment effect was in the opposite direction with a mean difference of -1.26 (95% CI: -7.14, 4.62). These subgroup results may also be confounded by selection bias from excluding a large number of subjects with missing data.

Table 10. Subgroup Analyses for Change From Baseline to Month 12 in LVEF (**SAP 1.1**)

Subgroup	Deramiocel **(N=54)**	Placebo **(N=52)**	**Mean Difference Deramiocel-Placebo (95% CI)**	**Nominal p-Value**
Cohort A (N=61)[a]	25	29	0.08 (-2.96, 3.12)	0.96
Cohort B (N=45)[a]	19	16	-0.88 (-6.22, 4.47)	0.74
Cardiomyopathy at baseline (Applicant's definition) (N=79)	35	32	0.85 (-2.31 4.01)	0.59
Without documented cardiomyopathy (N=27)	9	13	-2.18 (-7.89, 3.53)	0.43
Ambulatory (N=16)	6	7	2.84 (-2.37, 8.05)	0.25
Non-ambulatory (N=90)	38	38	-0.29 (-3.03, 2.46)	0.83
Slow progressors (N=6)	0	4	-	-
Non-slow progressors (N=100)	44	41	0.60 (-1.83, 3.04)	0.62

Source: FDA analysis
-: model did not converge; N: total of subjects in each subgroup; total number of treated N=54; total number of placebo N=52.
[a] The HOPE-3 study initially used deramiocel prepared in the manufacturing facility in Los Angeles. When manufacturing was shifted to the San Diego facility, patients who received deramiocel prepared in San Diego were added to the study as a second cohort. FDA agreed with this change, which was made after SAP 1.1. The FDA Chemistry, Manufacturing, and Controls team considers deramiocel manufactured at the two facilities to be equivalent.
Abbreviations: CI, confidence interval; FDA, U.S. Food and Drug Administration; LVEF, left ventricular ejection fraction; SAP, statistical analysis plan

3.2.4.5 Other Secondary Endpoints

Study HOPE-3 included multiple other secondary efficacy endpoints. Because the primary efficacy endpoint did not show statistical significance, the secondary efficacy endpoints cannot be tested with Type 1 error control; however, the observed trends are consistent with the null findings in the primary and key secondary efficacy endpoints. We note that the Applicant also revised the ordering and contents of the secondary efficacy lists after trial completion. When multiple statistical tests are conducted within a single study, the probability of observing at least one statistically significant result (p value <0.05) by chance alone increases substantially, even in the absence of a true treatment effect. Thus, all secondary efficacy endpoint analyses are exploratory in nature and hypothesis generating only, and no statistical inference can be drawn.

Table 11. Other Secondary Efficacy Endpoints (SAP 1.1)

Endpoints: Change From baseline to Month 12	Deramiocel **(N=54)**	Placebo **(N=52)**	**Treatment Difference (deramiocel-Placebo) (95% CI)**	**Nominal p-Value**
LV end-systolic volume, indexed	43	45	1.46 (-0.99, 3.92)	0.24
LV end-diastolic volume, index	43	45	4.78 (0.69, 8.87)	0.02
Mid and distal PUL 2.0	53	51	0.74 (-0.10, 1.59)	0.08
Mid-level PUL 2.0	53	51	0.69 (0.007, 1.36)	0.048
Duchenne video assessment (DVA)-eat 10 bites	49	43	-5.65 (-11.89, 0.59)	0.08
Creatine kinase-MB (CKMB) (absolute)	49	40	-2.61 (-22.27, 17.04)	0.79
Patient Global Impression of Severity (PGI-S)	51	50	-0.25 (-0.60, 0.09)	0.15

Source: FDA analysis
N=total number of subjects; total number of treated N=54; total number of placebo N=52.
Abbreviations: CI, confidence interval; LV, left ventricular; PUL 2.0, Performance of Upper Limb version 2.0; SAP, statistical analysis plan

Of these, two endpoints focused on measurements of late gadolinium enhancement (LGE), a biomarker which is detected by cMRI that indicates areas of fibrosis and damaged myocardium. Detection of LGE by cMRI requires use of a gadolinium-based contrast agent and was only measured in patients within Cohort B (45 subjects). The secondary endpoints which incorporate LGE include change in the number of segments of myocardial scarring as observed by LGE at Month 12, and change in the percentage of myocardial scarring as observed by LGE at Month 12. Studies of the prognostic value of LGE in the DMD population have generally focused on the percentage of myocardial scarring, which is a more clinically meaningful assessment of the extent of scarring than the number of segments. Observational studies of patients with DMD have not demonstrated evidence of an association between increasing number of LGE segments and death or any other clinical outcomes. The percentage-based assessment of myocardial scar by LGE did not demonstrate a nominally statistically significant difference based on the Applicant's final SAP, with a mean difference of -3.87 ranks (p value: 0.20) without data imputation and a mean difference of -4.82 ranks (nominal p value: 0.092) with data imputation. Most importantly, the results of endpoints related to LGE are challenging to interpret due to missing LGE measurements for over 50% of patients.

3.2.4.6 Efficacy Conclusions

Study HOPE-3 did not show a statistically significant or clinically meaningful treatment effect of deramiocel on the pre-specified primary and key secondary endpoints of change from baseline to Month 12 in PUL 2.0 total score and on change from baseline to Month 12 in LVEF respectively. Similarly, no treatment effect was observed across the remaining secondary endpoints and no differences were seen between deramiocel and placebo in several clinically relevant subgroups for either PUL 2.0 total score or LVEF at month 12.

The Applicant has implemented multiple modifications in the SAPs for Study HOPE-3. The results for primary/secondary/exploratory endpoints based on these SAPs are in some cases considerably different from each other. Major changes were made across SAP versions in endpoint definitions, statistical analysis methods, and data imputation strategies rendering very different results for the primary and secondary endpoints. In addition, analyses contained within the BLA submission and in the Applicant's briefing document use statistical methods that do not align with the specified methods in the respective or referenced SAPs 1.7 or 2.0 or 3.0. Therefore, these analyses should be interpreted with caution.

Considering the Applicant's analyses based on SAP 3.0 or the modified statistical analyses contained in the CSR for Study HOPE-3, the observed results on PUL 2.0 percent change from baseline range from 2.53% to 4.55% with p-values between 0.21 and 0.029. Similarly, the analyses on PUL 2.0 percent change from baseline to month 12 using SAP 2.0 (with and without data imputation) yield highly variable results ranging from 2.38% to 3.74% with p values ranging from 0.26 to 0.08. Given the wide variability of both the magnitude of the effects and the statistical significance across the statistical methods used, these observed differences are difficult to interpret. Also, given those analyses were specified *post-hoc*, the results should be interpreted with caution. In addition, the clinical meaningfulness of a 2-4% change in PUL 2.0 total score can have very different interpretations depending on the severity (score) of a patient's upper limb impairment at baseline as this metric represents a relative change in the total score and not an absolute change which is readily interpretable and has been extensively studied in DMD patients.

Regarding the Applicant's results on LVEF using the Applicant's analyses from SAP 2.0, the mean change from baseline in LVEF ranged from -0.37% to 0.74% with p values ranging grom 0.57-0.77 representing essentially no treatment difference between deramiocel and placebo with non-significant p values. When considering the mean ranked change in LVEF as in SAP 3.0, this ranged from 6.88 to 11.65 with p values between 0.22 to 0.041 indicating lack of robustness of the results and widely shifting statistical significance, calling into question the validity of the conclusions. Importantly, a mean ranked change in LVEF is a metric that is not interpretable from a clinical standpoint and its meaning in terms of an effect on cardiac function is unclear. As changes in cardiac imaging parameters are routinely measured and reported in clinical practice and in clinical research as an (absolute) change from baseline, a ranked change from baseline appears unfit for measurement of changes in LVEF or other cardiac imaging parameters over time.

Lastly, based on the available nonclinical and mechanistic evidence (from published literature and generated in the deramiocel nonclinical program), it is unclear how much deramiocel administered IV distributes to the cardiac muscle and the skeletal muscles compared to the rest of the body and whether the amount that reaches the heart is sufficient to exert therapeutic benefit. Deramiocel's proposed therapeutic mechanism of action (acting through exosomes and growth factors) is not targeted or specific enough to make this mechanism biologically plausible as a disease-modifying therapy in DMD or DMD cardiomyopathy.

3.3 Safety Overview

The safety evaluable population in Study HOPE-3 included 105 out of 106 randomized subjects, as one subject who was randomized to deramiocel withdrew consent prior to receiving any study treatment. Of the 105 subjects in the safety population, 53 received deramiocel and 52 received placebo. One subject in each group received only a single infusion at baseline, and the remaining subjects received 4 doses. Completion rates of the full infusion were 92.3%-94.2% in the placebo group and 84.9%-92.5% in the deramiocel group across the four dose visits.

There were 6 serious adverse events (SAEs) reported in the randomized, double-blind portion of Study HOPE-3, including 5 SAEs in 5 subjects who received placebo, and 1 SAE in 1 subject who received deramiocel. Of the 5 SAEs in subjects who received placebo, 1 was considered related to the investigational product (IP), a Grade 4 life-threatening anaphylactic reaction which occurred at the time of the first infusion. This anaphylactic reaction may have been secondary to the product excipients used in deramiocel as the placebo contained all excipients except the cardio-sphere cells. The subject was discontinued from the study as a result. The SAE in a subject who received deramiocel was considered related to the IP, a Grade 2 infusion-related reaction which occurred at the time of the second infusion (Month 3). Treatment was temporarily interrupted, and the subject received anti-allergy medications and IV fluids. The subject continued to receive treatment in the study.

Hypersensitivity reactions[5] were the most frequently observed adverse events: 22 of 53 subjects (41.5%) in the deramiocel group and 8 of 52 subjects (15.4%) in the placebo group experienced any kind of hypersensitivity reaction in Study HOPE-3. In addition, "immune sensitization syndrome" (including the following events: pyrexia, arthralgia, rash, white blood cell count increased starting on second day after an infusion) was suspected in 1 subject in the deramiocel group.

4. Conclusions

FDA recognizes the serious nature of DMD and the associated cardiomyopathy which has a substantial impact on patients' daily lives and causes early mortality. FDA is aware of the limitations of the currently available therapies for treatment of DMD and recognizes the high unmet need for additional safe and effective therapies. In addition, as there are no FDA-approved products shown to be effective in slowing the cardiac function decline in DMD, there is an urgent need for cardiac-targeted therapies addressing DMD cardiomyopathy.

[5] Hypersensitivity reactions include treatment-emergent adverse events related to IP or to administration procedure classified as tachycardia, pyrexia, allergic reaction to excipient, anaphylactic reaction, hypersensitivity, heart rate increased, tachypnea, throat irritation, throat tightness, rash, or flushing.

In the deramiocel clinical development program, two randomized, double-blind, placebo-controlled studies were conducted in DMD patients with skeletal muscle impairment, Studies HOPE-3 and HOPE-2.

Study HOPE-2 along with its open-label extension, Study HOPE-2-OLE, formed the basis for the original BLA submission for deramiocel. Study HOPE-2 was terminated early and, therefore, was not powered to demonstrate a treatment effect of deramiocel on the primary efficacy endpoint of change from baseline to month 12 in PUL 1.2. The results from Study HOPE-2 and HOPE-2-OLE did not demonstrate a statistically significant treatment difference between deramiocel and placebo on upper limb skeletal muscle decline or cardiac imaging findings (LVEF, LGE, and others) on cardiac MRI. The original BLA received a Complete Response due to lack of substantial evidence of effectiveness.

Study HOPE-3 was designed and statistically powered to demonstrate a treatment difference between deramiocel and placebo on the change from baseline to month 12 in PUL 2.0 total score. The results demonstrate that this pre-specified primary efficacy endpoint was not met. Similarly, no statistically significant difference was observed between deramiocel and placebo on the change from baseline in LVEF at month 12. Changes in other cardiac imaging parameters (LV volumes, LGE) showed small and variable changes of unclear clinical significance. The results on cardiac imaging parameters taken together are difficult to interpret and do not appear to provide conclusive evidence of a favorable effect of deramiocel on slowing the decline of cardiac function in the studied population.

Overall, Study HOPE-3 demonstrates small and variable changes in measures of upper limb skeletal muscle function and in several cardiac imaging parameters that did not reach statistical significance and are, thus, difficult to interpret. After extensive analyses of the submitted data both in the original BLA and in the BLA resubmission, the FDA review team was unable to identify a subpopulation that may potentially derive benefit from deramiocel. The results of Study HOPE-3 considered together with Study HOPE-2 do not conclusively provide evidence that deramiocel is effective in slowing the decline of upper limb function or cardiac function in DMD.

For an investigational product to receive approval, there must be convincing and substantial clinical evidence that the product is effective in the proposed population and indication, and the observed benefits must outweigh the observed risks of the product in its intended use. The submitted data from Study HOPE-3, considered together with the results from Study HOPE-2, does not provide substantial evidence of effectiveness for deramiocel in DMD. Considering the observed safety risks, which include hypersensitivity reactions including anaphylaxis, the benefit-risk assessment for deramiocel appears unfavorable in the absence of evidence of effectiveness.

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Guidances for Industry

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6. Appendix

Table 12. Analysis Results for the Primary Endpoint Across Missing Data Assumptions, HOPE-3

SAP Version[a]	Placebo Sample Size	Deramiocel Sample Size	Mean Difference	p-Value
SAP 1.1[b]	52	53	0.92	0.11
SAP 1.1*[b]	51	53	0.76	0.17
SAP 1.1**[b]	51	53	0.66	0.24
SAP 2.0	52	53	3.74%	0.079
SAP 2.0*	51	53	3.07%	0.13
SAP 2.0**	51	53	2.38%	0.26
SAP 3.0	52	53	4.16%	0.045
SAP 3.0*	51	53	3.34%	0.085
SAP 3.0**	51	53	2.53%	0.21

Source: FDA Reviewer
[a] SAP v1.1, SAP v2.0, and SAP v3.0 were dated July 19, 2022, September 26, 2025, and November 24, 2025, respectively. The double-blind period ended on June 18, 2025.
[b] FDA analysis included cohort as covariate in analysis model.
* One placebo subject who withdrew due to AE was imputed with the worst value observed among all subjects for Months 3, 6, 9 and 12. This analysis removed these imputed values.
** One placebo subject who withdrew due to AE was imputed with the worst value observed among all subjects for Months 3, 6, 9 and 12. This analysis removed these imputed values. Additionally, another placebo subject who completed the double-blind phase had observed data from Months 6, 9, and 12 removed due to prohibited medication use. This analysis filled in the observed data for this subject.
Abbreviations: AE, adverse event; SAP, statistical analysis plan

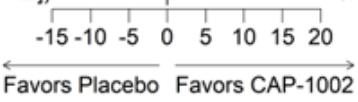
Table 13. Analysis Results for the Key Secondary Endpoint Across Missing Data Assumptions, HOPE-3

SAP Version[a]	Placebo Sample Size	Deramiocel Sample Size	Mean Difference	p-Value
SAP 1.1[b]	45	44	1.08	0.42
SAP 1.1*[b]	44	44	0.42	0.73
SAP 1.1**[b]	45	44	-0.04	0.97
SAP 2.0	45	44	0.74	0.57
SAP 2.0*	44	44	0.09	0.94
SAP 2.0**	45	44	-0.37	0.77
SAP 3.0	44	39	9.51	0.09
SAP 3.0*	43	39	7.76	0.17
SAP 3.0**	44	39	6.88	0.22

Source: FDA Reviewer
[a] SAP v1.1, SAP v2.0, and SAP v3.0 were dated July 19, 2022, September 26, 2025, and November 24, 2025, respectively. The double-blind period ended on June 18, 2025.
[b] FDA analysis included cohort as covariate in analysis model.
* One placebo subject who withdrew due to AE was imputed with the worst value observed among all subjects for Months 6 and 12. This analysis removed these imputed values.
** One placebo subject who withdrew due to AE was imputed with the worst value observed among all subjects for Months 6 and 12. This analysis removed these imputed values. Additionally, another placebo subject who completed the double-blind phase had observed data from Months 6 and 12 removed due to prohibited medication use. This analysis filled in the observed data for this subject.
Abbreviations: AE, adverse event; SAP, statistical analysis plan

Figure 9. Study HOPE-2: LSM Difference in Change From Baseline at Month 12 in Cardiac MRI Parameters (N=17, not ITT)

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



Source: FDA Reviewer
Note: MMRM model with an UN covariance structure was used with change from baseline at Month 6 and 12 as the dependent variable, and visit, treatment, baseline measurement, site and stratification of entry item score of the PUL 1.2 at screening as main effects and the interaction between treatment and visit.
p-value: all nominal p value, i.e., no multiplicity adjustment
Abbreviations: CI, confidence interval; ED, end-diastolic; ES, end-systolic; ITT, intent-to-treat; LSM, least squares mean; LV, left ventricular; MRI, magnetic resonance imaging; N, number of subjects in the specified group, or the total sample