U.S. FOOD & DRUG ADMINISTRATION

Cellular, Tissue, and Gene Therapies Advisory Committee

BLA 125842
Deramiocel (CAP-1002)

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

Applicant: Capricor, Inc.

Center for Biologics Evaluation and Research | FDA

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Introductory Remarks

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Purpose of the Advisory Committee

Obtain expert input into the available evidence of effectiveness for deramiocel for the treatment of cardiomyopathy in patients with Duchenne Muscular Dystrophy (DMD)

Today's Agenda

- Introductory Remarks
- Applicant presentation
- Open public hearing
- FDA presentation
- Advisory Committee Discussion

BLA 125842: Deramiocel

- Allogeneic cellular therapy derived from cadaveric donor hearts
- Proposed mechanism: paracrine signaling through secretion of exosomes/growth factors
- Proposed Dosage: 1.5×10^8 cells IV every 3 months
- Proposed indication: treatment of cardiomyopathy in patients with DMD

Duchenne Muscular Dystrophy (DMD)

- Rare and serious neuromuscular disease of childhood onset
- *DMD* gene variants/deletions cause dystrophin deficiency in skeletal/ respiratory/ cardiac muscles
- Chronic, progressive, contraction-induced muscle damage
- Severe skeletal muscle weakness, respiratory insufficiency, cardiomyopathy
- Highly heterogeneous progression
- Core prognostic factors: *DMD* mutation type; genetic modifier mutations; corticosteroid therapy (overall); cardiac medication therapy (cardiomyopathy)

Cardiomyopathy in DMD

- Contraction-induced myocardial damage: myocardial fibrosis; ventricular thinning (dilated cardiomyopathy)
- Slow & variable rate of cardiac function decline
- Cardiac imaging abnormalities appear before any clinical symptoms starting in teenage years (mean 15 y)
- Heart failure, arrhythmias are life-threatening
- Pharmacologic management aims to slow onset and progression of cardiac decline
  - Corticosteroids
  - Standard cardiac medications: ACEi, ARBs, β-blockers, MRA, SGLT-2 inhibitors

Clinical Studies Relevant to Evaluation of Efficacy

Study	Design	Population	Regulatory Context
HOPE-3 (OLE ongoing) N =106	**Randomized, double blind, placebo-controlled (followed by OLE) 12 months**	**DMD with skeletal muscle impairment**	**BLA resubmission (randomized phase)**
HOPE-2 (terminated early) N=20	Randomized, double blind, placebo-controlled 12 months	DMD with skeletal muscle impairment	Original BLA, 2024 (Complete Response)
HOPE-2-OLE (ongoing) N=13 (deramiocel)	Single-arm, open-label (dosing ~1 year after HOPE-2 end) 60 months	Previously in HOPE-2	Original BLA, 2024 (Complete Response)

DMD, Duchenne muscular dystrophy; OLE, open-label extension

Study HOPE-3

- Phase 3, randomized (1:1), double-blind, placebo-controlled, 12-month study
- 106 males with DMD and skeletal muscle impairment
  - Mean age 15 years; 85% non-ambulatory; upper limb impairment (PUL 2.0) mean baseline LVEF 57% (normal)
- Pre-specified primary endpoint: **change from baseline in PUL 2.0 total score**
  - Statistically powered at 90% to demonstrate 1.5-point difference between groups in PUL 2.0 total score (SAP v1)
- Pre-specified key secondary endpoint: **change from baseline in LVEF (cardiac MRI)**
- Endpoint definitions and statistical methods modified after randomized phase ended

LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PUL, performance of the upper limb; SAP, statistical analysis plan

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Regulatory Approval Framework

Scientific & Regulatory Considerations

Statutory Standard for Approval

- Substantial evidence of effectiveness (SEE) and evidence of safety
- SEE defined as clinical evidence from adequate and well-controlled (AWC) clinical investigations (studies)
- One AWC clinical investigation with confirmatory evidence can provide SEE
- Same standard in common and rare diseases
- Same standard for traditional approval and accelerated approval

Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 505(d); Public Health Service Act, Section 351 (biologics);
FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (June 2026)

Adequate and Well-Controlled Study

- Clear, pre-specified protocol
- Valid comparison to a control group
- Standardized population selection
- Comparability of groups (e.g., randomization)
- Measures to minimize bias (e.g., blinding)
- Prospectively specified, well-defined efficacy endpoints
- Pre-specified and appropriate statistical analysis plan

21 CFR 314.126

Critical Statistical Analysis Elements

- Pre-specified analyses and analytical methods (statistical analysis plan)
- Scientifically rigorous statistical methodology
- Robust approach to limit false positive results
- Major post-study changes risk validity of results and could lead to erroneous conclusions

ICH E9: Statistical Principles for Clinical Trials (September 1998)
FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (June 2026)

Single AWC Study With Confirmatory Evidence

- Framework for FDA's assessment of effectiveness
- Single AWC study provides primary evidence of effectiveness
- Confirmatory evidence independently substantiates the primary evidence

FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (June 2026)

Evaluation of Primary Evidence of Effectiveness

- Likelihood that results are real and did not occur by chance/other influence
  (p value; statistical significance)
- Magnitude of observed effect on primary and other endpoints
- Clinical meaningfulness of effect (considering the endpoint and effect size)
- Results on other relevant endpoints (consistency of results)
- Robustness (consistency) of results using different statistical methodologies

FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (June 2026)

Confirmatory Evidence of Effectiveness

- Different sources can provide confirmatory evidence

- Mechanistic evidence (animal data); pharmacodynamic evidence (early phase trials); clinical evidence from related diseases or related products; evidence from natural history of disease

- Strength and amount of CE required depends on strength of primary evidence from AWC study

FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (June 2026)

Benefit-Risk Assessment

- Therapeutic Context
- Evidence on Benefits and Risks
- Uncertainties about Benefits and Risks
- Regulatory Options to Manage Risks and Reduce Uncertainties

FDA Guidance for Industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023)

Focus of Today's Advisory Committee Discussion

- The advisory committee will hear perspectives from the Applicant, public, including patients, and the FDA review team

- We ask the advisory committee to consider all perspectives and provide their independent, expert assessment of the available clinical evidence from Study HOPE-3 of deramiocel for treatment of cardiomyopathy in patients with DMD

CTGTAC Discussion Topic 1

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

CTGTAC Discussion Topic 2

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

CTGTAC Voting Question

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