# Deramiocel heart-derived cellular therapy in advanced Duchenne muscular dystrophy (HOPE-3): a phase 3, randomised, double-blind, placebo-controlled trial

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## Summary

**Background** Duchenne muscular dystrophy (DMD) is an X-linked genetic disease of skeletal and cardiac muscle that leads to loss of ambulation and premature death due to progressive myopathy and cardiomyopathy. Deramiocel, a heart-derived cellular therapy consisting of human allogeneic cardiosphere-derived cells, improved cardiac and skeletal muscle function in phase 1–2 studies of DMD. Our aim was to assess the efficacy and safety of deramiocel in advanced DMD and support the findings of HOPE-2.

**Methods** HOPE-3, a phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled study, included participants aged 10 years or older with DMD. Investigational product was infused intravenously every 3 months in outpatient settings. Skeletal and cardiac function was evaluated at 12 months. The primary endpoint was total Performance of the Upper Limb 2.0 (PUL2.0) percentage change from baseline. The trial is registered with ClinicalTrials.gov (NCT05126758).

**Findings** Between June 22, 2022, and May 28, 2024, 139 participants were screened, of whom 106 were randomly assigned to deramiocel (n=54) or placebo (n=52), and included in the intention-to-treat population. The primary endpoint showed significant improvements in the deramiocel group versus placebo. For total PUL2.0, least-squares mean percentage change at 12 months favoured deramiocel by 4·55% (95% CI 0·47–8·63; p=0·029). The safety profile of deramiocel was similar to that of placebo.

**Interpretation** Deramiocel safely slows disease progression in advanced DMD, preserving skeletal muscle function. Administered quarterly in a simple outpatient regimen, deramiocel is a promising treatment for DMD, agnostic to the precise underlying genetic lesion.

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## Introduction

Duchenne muscular dystrophy (DMD) is an X-linked genetic disease of skeletal and cardiac muscle that leads to loss of ambulation and premature death due to progressive myopathy and cardiomyopathy.[1,2] Most therapeutic clinical trials have focused on young ambulatory boys with DMD. To gauge disease severity in late-ambulatory and non-ambulatory patients, who now constitute a majority of the DMD population, a validated functional scale (Performance of Upper Limb 2.0 [PUL2.0])[3,4] can quantify skeletal muscle impairment, whereas cardiac magnetic resonance (CMR) methods characterise DMD cardiomyopathy, the leading cause of death.[5–7] CMR imaging evaluates left ventricular function but also detects myocardial scarring and fibrofatty replacement[8] using late gadolinium enhancement (LGE).[9,10] CMR measures of left ventricular ejection fraction (LVEF) and LGE are both strongly predictive of survival in DMD.[11,12] While clinical tools allow for precise monitoring of disease progression, effective treatments for advanced DMD are scarce.

Deramiocel is an investigational cellular suspension consisting of human allogeneic cardiosphere-derived cells (CDCs) originally developed to treat cardiomyopathy. CDCs survive only 1–2 weeks after transplantation but have persistent anti-inflammatory, anti-fibrotic, and immunomodulatory properties (appendix pp 3–7).[13] While present, CDCs act by secreting paracrine factors that modulate macrophage and fibroblast function resulting in long-lasting therapeutic benefits.[14] Preclinical studies revealed that CDCs improve both cardiac and skeletal muscle in models of DMD, with sustained benefits after repeated administrations.[15] The discovery that CDCs work by secreting extracellular vesicles (nanosized lipid bilayer particles replete with specific bioactive RNA cargo) rationalised the systemic benefits of local cell administration and led to preclinical

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See Online for appendix

## Research in context

### Evidence before this study

Despite the expansion of molecular and clinical research in the four decades since the identification of the genetic basis of Duchenne muscular dystrophy (DMD), outcomes for affected boys and young men remain uniformly poor, with median life expectancy younger than 30 years. Cardiomyopathy is the most frequent cause of death. Despite treatment with guideline-directed medical therapy for heart failure, the cardiomyopathy continues to progress inexorably. Other than corticosteroids, which have limited effects on cardiomyopathy, no therapeutic intervention has been shown to slow the decline of upper limb function. Genetic therapies, while mechanistically attractive, did not provide convincing evidence of clinical benefit, particularly in DMD cardiomyopathy. A unique approach using allogeneic cardiac derived cellular therapy has been shown to deliver anti-fibrotic activity and functional benefit preclinically and in early clinical evaluation of DMD (HOPE-Duchenne; HOPE-2 trials). Deramiocel, the name of this cellular therapy product, is a suspension of allogeneic cardiosphere-derived cells administered, following pre-medication with corticosteroids and antihistamines, every 3 months by outpatient intravenous infusion. A search of the US National Library of Medicine PubMed database was done on May 24, 2026, for relevant related publications. All searches were filtered on publication date "10 years" and article type "randomized controlled trial". The terms ["Duchenne" AND "cardiosphere cell therapy"] identified four reports of studies in the deramiocel programme (NCT03406780, NCT02485938, NCT03145298, and NCT01458405). The terms ["Duchenne" AND "stem cell therapy"] revealed no reports. Using the terms ["Duchenne" AND "PUL"] yielded two studies from the deramiocel programme: one large phase 3 study of tadalafil, which missed both primary and secondary endpoints but included Performance of Upper Limb (PUL) as exploratory (NCT01865084), and a device study in which no therapeutic benefit on PUL was identified (Netherlands Trial Register 3857). The terms ["Duchenne" AND "cardiomyopathy"] identified three reports from the deramiocel programme: one long-term open-label follow-up study to a negative randomised study of perindopril and bisoprolol as cardiomyopathy prophylaxis, a non-inferiority study of spironolactone versus eplerenone (NCT02354352), a negative study of enalapril and metoprolol (DRKS-number 00000115; EudraCT number 2009-009871-36), and a post-hoc subgroup analysis of a randomised study of tamoxifen (NCT03354039).

### Added value of this study

This multicentre, randomised, double-blind, placebo-controlled, phase 3 study recruited patients with DMD who were either late-ambulatory, defined as having a 10 m walk or run time of 10 s or greater, and thus predicted to lose significant upper limb function and ambulation within 2 years, or non-ambulatory with preserved hand-to-mouth function. All participants were treated with stable doses of corticosteroids and the majority received standard-of-care heart failure medications. At 12 months of follow up, the prespecified, type I error controlled primary endpoint was significant, supporting previous clinical evidence that deramiocel slows progression of skeletal myopathy (Performance of the Upper Limb 2.0). The key secondary endpoint of left ventricular ejection fraction (LVEF) did not reach statistical significance, although the difference favoured deramiocel. Prespecified subgroup analysis of LVEF in the population with documented cardiomyopathy at baseline did favour deramiocel with nominal significance. Two further secondary endpoints, late gadolinium enhancement, a measure of fibrofatty replacement of myocardial tissue, and a total global statistical test, showed nomimal significance. Deramiocel was safe and well tolerated. This is the first phase 3 trial in advanced DMD to meet a primary efficacy endpoint.

### Implications of all the available evidence

Deramiocel delays disease progression, with benefits on skeletal and cardiac muscle, in patients with advanced DMD. Delay in the progression of upper limb functional decline is likely to maintain independence and quality of life by preserving the abilities to transfer, turn, and self-feed. The observed slowing of cardiomyopathy progression in DMD is predicted to reduce mortality in this devastating paediatric genetic disease, a conjecture worth testing in future long-term registry studies. Deramiocel is the first manufactured cell therapy product shown to be efficacious in phase 3 testing for any genetic disease.

validation of intravenous infusion as an alternative to intracardiac delivery.[16] The HOPE-2 trial of deramiocel in advanced DMD—the first to use intravenous cell delivery and repeat sequential dosing of a cell therapy to treat a genetic disease—showed stabilisation of upper limb function and improved heart function relative to placebo without restriction by genotype, meeting the primary endpoint with 71% slowing of decline in mid-level PUL2.0.[17] In parallel, deramiocel improved LVEF and left ventricular volumes versus placebo. A follow-up open-label extension study (HOPE-2 OLE, NCT04428476) revealed sustained benefits in upper limb and cardiac function over 3 years relative to external natural history control groups[18] with no serious safety concerns over 3 years. Our aim was to assess the efficacy and safety of deramiocel in boys and young men with advanced DMD and support the findings of HOPE-2.

## Methods

### Study design

This phase 3, randomised, double-blind, placebo-controlled trial was carried out at 20 investigational sites in the USA. The study was approved by the ethics committee at each site and conducted in accordance with

Good Clinical Practice guidelines and principles of the Declaration of Helsinki. Oversight was provided by an independent data safety monitoring board. The trial is registered with ClinicalTrials.gov (NCT05126758).

The protocol amendment and regulatory history, and the study protocol and the statistical analysis plan, are included in the appendix (pp 48, 50, 197). In July, 2025, the sponsor received a complete response letter from the US Food and Drug Administration (FDA) for Biologics License Application 125842 which relied on phase 2 data[17] only. Subsequent alignment at an FDA type A post-action meeting in August, 2025, led to important and final protocol changes in version 9.0 (September, 2025) which was implemented at Independent Review Boards (IRBs) and study sites. In this amendment, the primary endpoint reverted to total PUL2.0 (from a proposed primary endpoint of LVEF in protocol version 8.0 that was neither implemented nor submitted to IRBs based on FDA guidance). In protocol version 9.0 the analysis for the primary endpoint was also modified from absolute to percentage change from baseline in total PUL2.0 based on updated literature and guidance from subject matter experts. Following these changes and finalisation of the statistical analysis plan (version 3.0, Nov 23, 2025), database lock and unblinding procedures were conducted on Nov 25, 2025, in a controlled and compliant manner. In February, 2026, the sponsor completed a Biologics License Application resubmission, which incorporated safety and efficacy data from the present phase 3 study, HOPE-3.

### Patients

Male patients aged 10 years or older with genetically confirmed DMD, who had PUL2.0 entry item score 2–6 (appendix p 10) and total PUL2.0 score ≤40 (ie, at least a 2-point decrement from the ceiling value; normal upper limb function PUL2.0 score is 42), either non-ambulatory or late-ambulatory (with 10 m walk or run time of >10 s), and receiving chronic and stable corticosteroids were eligible for inclusion. LVEF ≤35%, forced vital capacity percentage predicted <30%, and severe elbow contractures (30°) were exclusionary. All participants provided written informed consent. All inclusion and exclusion criteria can be found in the appendix (pp 103–105).

### Randomisation and masking

Patients were randomly assigned (1:1) to deramiocel or placebo. To reduce baseline imbalances, randomisation was stratified according to PUL2.0 entry-level score (either 2 or 3, or 4–6). The allocation sequence was generated by an independent unblinded statistician from the CRO and was loaded into a validated randomisation and trial supply management (RTSM) system before enrolment of the first participant. Participants were screened, consented, and enrolled by site investigators or their delegates. Once eligibility was confirmed, participants were randomised and treatment assignment was issued automatically by the RTSM system. Allocation was concealed from participants, caregivers, investigators, site staff, outcome assessors, and sponsor personnel for the duration of the trial. The only individuals with access to individual assignments were sponsor Quality Assurance representatives responsible for the clinical supply management of the trial and were firewalled from the clinical study teams.

Masking was maintained throughout the study for patients, investigators, site personnel, clinical and imaging assessors, and sponsor staff. Deramiocel and placebo were identical in appearance, packaging, and labelling, with no treatment-identifying information. No incidents occurred during the conduct of the protocol that were known to compromise masking. Periodic monitoring visits and data audits confirmed adherence to masking procedures and data integrity.

### Procedures

Patients received intravenous infusions of deramiocel ($1{\cdot}5\times10^8$ CDCs) or placebo on day 1 and every 3 months thereafter for 12 months between July 13, 2022, and June 18, 2025. The study population was divided into two cohorts by protocol amendment: cohort A, administered clinical trial product, and cohort B, the intended commercial product. Prespecified analysis pooled both cohorts, except for the LGE, which was only performed in cohort B. Placebo vials contained identical volumes and concentrations of buffer and excipients as deramiocel vials and used identical packaging and storage.

Pretreatment with high-dose oral corticosteroids and oral or intravenous histamine antagonists was identified as salutary in previous studies and was used here (appendix p 14). CMR assessments were managed by Medpace (Cincinnati, OH, USA), which oversaw centralised image evaluation masked to treatment allocation and timepoint. CMR images deemed technically inadequate before unmasking were excluded from analysis; given the paired nature of the analysis, uninterpretable images at either timepoint sufficed to exclude a participant from the cardiac analysis.

Deramiocel is derived from donated human hearts, eligible but not used for transplantation (appendix pp 8–9). Donor hearts are obtained from organ procurement organisations. Donors aged 60 years or younger and of any race and ethnicity or sex are screened to ensure the absence of risk factors for, or clinical evidence of, infection or communicable diseases. The number of donor hearts that satisfy donor eligibility requirements for human cells, tissues, and cellular and tissue-based products is surprisingly high, and the donor heart supply has not been found, and is not anticipated, to be limiting for deramiocel drug product supply. The heart is used to create explants, placed into primary culture using proprietary media from which

explant-derived cells are harvested to produce the drug substance. Each drug substance lot is release-tested for use as the critical starting material for production of the deramiocel drug product. Drug substance vials are thawed, initially cultured in suspension to create cardiospheres, and then cultured adherently for five passages in proprietary media to preferentially expand CDCs. Critical process parameters with defined performance attributes and in-process controls are used throughout the expansion process to ensure consistent production. CDCs are harvested, formulated, and filled to create the drug product, each lot of which is tested for release using assays of viability, identity, purity, potency, and sterility, ensuring reproducible production of high-quality deramiocel. Potency is assessed using two confirmatory assays: a cell-based assay to show the anti-fibrotic activity of extracellular factors released by CDCs, and mRNA sequencing to verify the unique CDC gene expression profile and correlate the profile to that of clinically efficacious CDCs from the HOPE-2 studies.[19] Using current procedures (which can be further scaled out), a single donor heart can produce 400–800 doses of deramiocel drug product, which can treat about 100–200 patients for 1 year. Thus, there is expected to be ample supply of deramiocel for the treatment of DMD. In the HOPE-3 trial, deramiocel was derived from donors aged 22–50 years, of both male and female sex, and of either Caucasian or Hispanic ethnicity.

### Outcomes

The primary objective of HOPE-3 was to evaluate skeletal muscle full upper limb function, with the primary endpoint being the mean percentage change from baseline to month 12 in PUL2.0 total score[3,20] (appendix pp 11–12) measured by trained therapists before each infusion and at endpoint. The secondary objective of the study was to evaluate cardiac function, with the key secondary endpoint being the change from baseline to month 12 in LVEF. CMR data were acquired by standardised protocols at baseline, 6-month and 12-month visits. CMR analysis was done in a core laboratory by one image analyst, masked to site and previous CMR results. All studies were reviewed for technical quality by a paediatric cardiologist with 15 years' experience reading DMD CMR images (appendix p 13).

Secondary endpoints that were type I error-controlled included mean percentage change from baseline in mid-level (elbow domain) PUL2.0; change in the number of segments of the heart with myocardial scarring by LGE at month 12 relative to baseline (for cohort B only, by protocol amendment); and a global statistical test (total Global Statistical Test) that combines the PUL2.0 total score, LVEF, and a Patient Global Impression of Severity (PGI-S) as described in the appendix (pp 31–32). Other secondary endpoints included the Duchenne Video Assessment (DVA) Eat 10 Bites score, LVEF in the prespecified cardiomyopathy population, left ventricular end-systolic volume index by CMR, LGE by percentage scarring, a cardiac global statistical test and creatine kinase-myocardial band (CK-MB).

We used masked analysis of the DVA Eat 10 Bites score as a confirmatory endpoint; this tool records patients during independent eating and measures participant ease of movement through identification of compensatory movement patterns, providing a clinically meaningful activity of daily living (appendix pp 34–36).

Adverse events were recorded at each visit. Serious adverse events and treatment-emergent adverse events, related to investigational product or its administration, including hypersensitivity reactions and acute respiratory decompensation, were listed separately.

### Statistical analysis

The study was powered at 90% with 49 patients per group to detect a treatment difference of 1·1, equivalent to 34% slowing of disease progression, in the PUL2.0 total score at an $\alpha$=0·05 level after 12 months of treatment, based on a model-adjusted mean change from baseline of −3·33 (SD 1·71) from the HOPE-2 trial.[17] All analyses were performed on the intention-to-treat (ITT) population with prespecified statistical methods. A gatekeeping procedure was used to control the overall type I error rate across the first five endpoints, with hierarchical testing proceeding through each successive prespecified endpoint. Study-wise $\alpha$ was controlled at 0·05, and all hypothesis tests were two-sided. For PUL2.0, mean percentage change from baseline was analysed using a mixed model with repeated measures. Percentage change from baseline was calculated as absolute change from baseline divided by baseline score at the participant level. Mixed model with repeated measures included the fixed, categorical effects of treatment, cohort, investigative site (using pooled sites), visit, treatment-by-visit interaction, as well as baseline PUL2.0 total score and an indicator variable for whether the participant is a known slow progressor (appendix p 37).

LVEF was analysed using a ranked analysis of covariance (ANCOVA) model. Both the dependent variable (change from baseline) and the baseline values were ranked separately before analysis. The model included fixed effects for treatment group, cohort, and slow-progressor status, as well as an indicator variable for screening LVEF ≥45%. Continuous covariates included baseline LVEF, and age at baseline. Analyses of the other type I error controlled secondary endpoints is detailed in the appendix (p 26).

### Role of the funding source

The funder of the study developed the study design with the first author, provided oversight of data collected by investigators through a contract research organisation, was involved in data analysis along with an outsourced data management contract research organisation, and was involved in data interpretation and writing of the

report along with the first author and study investigators and co-authors. The sponsor placed no restrictions on publication of study results.

## Results

Between June 22, 2022, and May 28, 2022, 139 participants were screened, of whom 106 were randomly assigned to deramiocel (n=54) or placebo (n=52), and included in the ITT population with 61 participants in cohort A and 45 in cohort B (figure 1). A prespecified interim futility analysis was done when 30 participants had completed month 6, and was reviewed by the data safety monitoring board, which resulted in continuation of the study due to a predefined futility boundary. Five individuals terminated participation early, one due to an adverse event and four withdrew consent. One participant was not dosed following randomisation and was excluded from the safety population. Those with evaluable CMR at baseline and 12 months (n=83; reasons for exclusion shown in the appendix [p 29]) were included in an ITT population for LVEF and other non-LGE endpoints. Among the 44 participants consented for gadolinium administration, 22 had evaluable paired sets of baseline and 12-month LGE images, with exclusions before unmasking due to inadequate CMR image quality (appendix p 29). Baseline demographic characteristics were broadly similar between groups (table 1).

The mean percentage changes in total PUL2.0 over 12 months are shown in figure 2A. The between-group least-squares mean difference of 4·55 (SE ±2·06; 95% CI 0·47–8·63; p=0·029), reveals preservation of upper limb function by deramiocel. The absolute difference on the PUL2.0 scale corresponds to a 1·2-point advantage for participants receiving deramiocel relative to placebo (figure 2A). This represents about a 54% reduction in disease progression (calculated as $(placebo_{CFB} - treatment_{CFB}) / placebo_{CFB} \times 100\%$, where CFB represents the change from baseline value). A prespecified sensitivity analysis for the absolute change in total PUL2.0 over 12 months in treated versus placebo was conducted and yielded p=0·0503 for change in upper limb function, favouring deramiocel. Patient-level PUL2.0 data at 3-month increments are provided in the appendix (pp 27–28).

The primary endpoint prespecified for hypothesis testing (type I error-controlled) showed improvements in the deramiocel group versus placebo (figure 3A). The key secondary endpoint did not reach statistical significance.

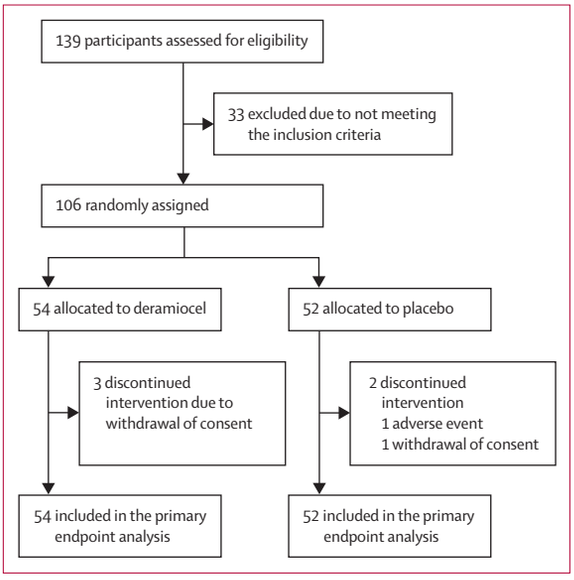


*Figure 1:* **Trial profile**

| | Deramiocel (n=54) | Placebo (n=52) | Overall (n=106) |
|---|---|---|---|
| Age, years | 15·0 (10–22) | 14·0 (10–22) | 15·0 (10–22) |
| Sex | | | |
| Male | 54 (100%) | 52 (100%) | 106 (100%) |
| Ethnicity | | | |
| Hispanic or Latino | 5 (9·3%) | 6 (11·5%) | 11 (10·4%) |
| Not Hispanic or Latino | 49 (90·7%) | 46 (88·5%) | 95 (89·6%) |
| Race | | | |
| Asian | 5 (9·3%) | 7 (13·5%) | 12 (11·3%) |
| Black or African American | 2 (3·7%) | 1 (1·9%) | 3 (2·8%) |
| Native Hawaiian or other Pacific Islander | 0 | 1 (1·9%) | 1 (0·9%) |
| White | 43 (79·6) | 38 (73·1) | 81 (76·4) |
| Multiple | 1 (1·9) | 2 (3·8) | 3 (2·8) |
| Not reported | 3 (5·6) | 2 (3·8) | 5 (4·7) |
| Unknown | 0 | 1 (1·9) | 1 (0·9) |
| Randomisation PUL2.0 entry item score | | | |
| 2, 3 | 25 (46·3%) | 23 (44·2%) | 48 (45·3%) |
| 4, 5, 6 | 29 (53·7%) | 29 (55·8%) | 58 (54·7%) |
| Baseline total PUL2.0 score | 27·6 (7·36) | 26·5 (6·69) | 27·1 (7·03) |
| Slow progressor indicator* | 1 (1·9%) | 5 (9·6%) | 6 (5·7%) |
| Ambulatory at baseline | 8 (14·8%) | 8 (15·4%) | 16 (15·1%) |
| Baseline corticosteroid use | | | |
| Prednisone | 16 (29·6%) | 7 (13·5%) | 23 (20·7%) |
| Deflazacort | 39 (72·2%) | 43 (82·7%) | 82 (77·4%) |
| Once daily | 43 (79·6%) | 39 (75·0%) | 82 (77·4%) |
| Intermittent regimen | 10 (18·5%) | 12 (23·1%) | 22 (20·8%) |
| Baseline use of genetic medication | | | |
| Exon-skipping drugs | 14 (25·9%) | 12 (23·1%) | 26 (24·5%) |
| Ataluren | 0 | 1 (1·9%) | 1 (0·9%) |
| Microdystrophin gene replacement | 1 (1·9%) | 0 | 1 (0·9%) |

Data are median (range), n (%), or mean (SD). PUL2.0=Performance of Upper Limb 2.0. *Participants with a baseline PUL2.0 entry item score of 6 (on two or three screening or baseline visits), or had documented slow progressor genotypes, were classified as positive for the Slow Progressor Indicator. The following genotypes were considered as slow progressor: exon 44 skippable mutations, exon 3–7 deletions, and other genotypes identified as slow progressor (appendix p 37).

*Table 1:* **Demographic and disease characteristics of the intention-to-treat population**

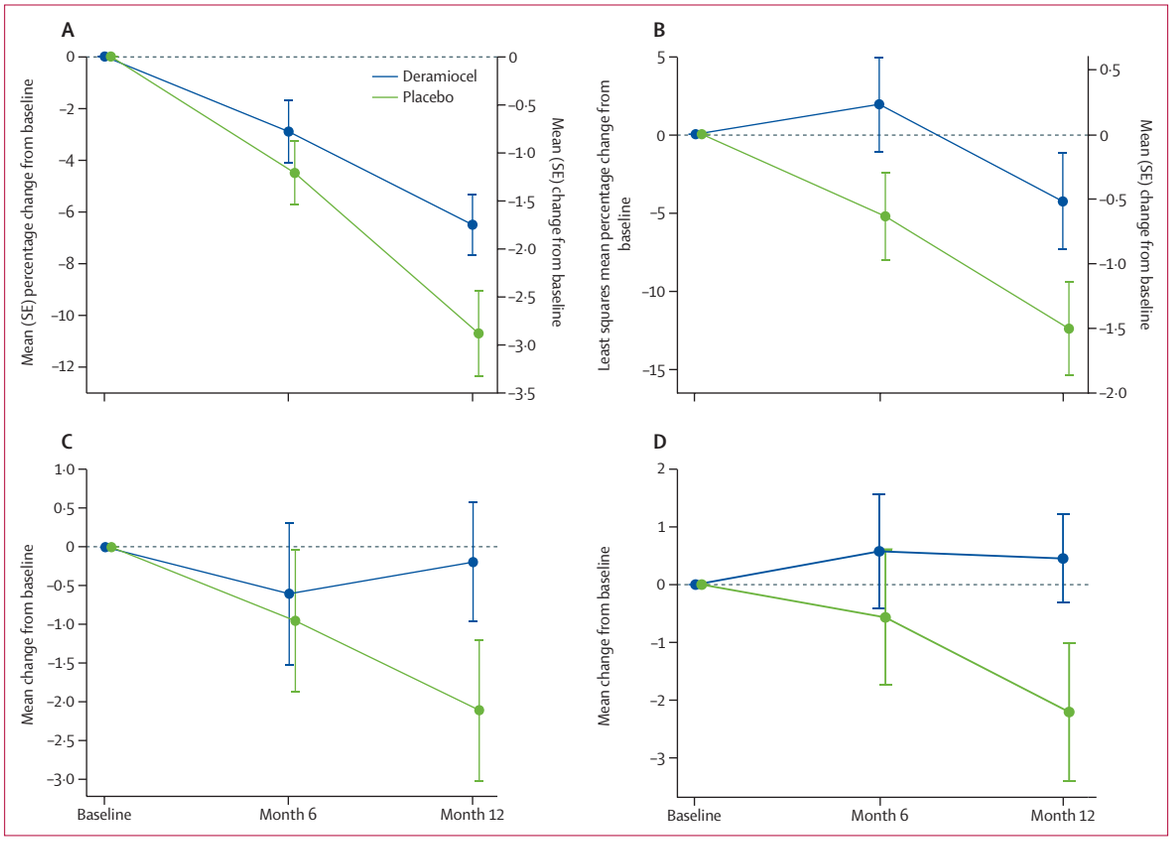


***Figure 2:*** **Change from baseline in musculoskeletal and cardiac endpoints up to month 12**
(A) PUL2.0 total score for the ITT population. (B) PUL2.0 mid-level score for the ITT population. (C) Left ventricular ejection fraction for the ITT population. (D) Left ventricular ejection fraction for the cardiomyopathy population. Each graph shows observed mean changes from baseline at baseline, month 6, and month 12 in the deramiocel (blue) and placebo (green) with accompanying standard errors (indicated by error bars). Panels (A) and (B) show the musculoskeletal measures of PUL2.0 total and mid-level scores, respectively, in the ITT population. Both panel (A) and (B) feature dual y axes, the left showing the mean observed percentage change and the right showing the observed raw mean change on the absolute scale. Panels (C) and (D) feature observed raw mean change from baseline in left ventricular ejection fraction for the ITT population and the cardiomyopathy population, respectively. PUL2.0=Performance of the Upper Limb 2.0. ITT=intention-to-treat.

At 12 months, the deramiocel-treated group versus placebo showed a least-squares mean ranked change in LVEF of 57·47 ranks (SE ±9·43), compared with 45·82 ranks (SE ±8·92) in the placebo group, with a between-group difference of 9·51 (SE ±5·60; 95% CI –1·64 to 20·65; p=0·0935; figure 3A). The secondary endpoints of PUL 2.0 mid-level, total global statistical test and LGE segments were then tested nominally and they all yielded statistical significance (figure 3A). Because the prespecified key secondary endpoint (change from baseline to 12 months in LVEF measured by cardiac MRI) did not reach statistical significance, p values for subsequent endpoints in the fixed-sequence hierarchy are unadusted or nominal and are presented for descriptive purposes only. Other secondary endpoints are represented in figure 3B. The 12-month change in the DVA Eat 10 Bites and LVEF in the prespecified cardiomyopathy population both favoured deramiocel with nominal statistical significance.

Participants randomly assigned to deramiocel showed significant stabilisation in the mean percentage change from baseline to month 12 in mid-level PUL2.0 score compared with placebo, with a between-group least-squares mean difference of 8·12 (SE ±3·03; 95% CI 2·12–14·11; p=0·008; figure 2B). The absolute difference on the PUL2.0 scale corresponds to 1·0-point advantage (figure 2B), reflecting 65% slowing of disease progression relative to placebo. The real-world effect of the PUL2.0 difference was further supported by analysis of the DVA Eat 10 Bites score (appendix pp 34–36). At month 12, deramiocel-treated participants had a least-squares mean DVA Eat 10 Bites score of 1·68 (SE ±3·31) compared with 9·52 (SE ±2·99) in the placebo group. The between-group difference of –7·84 (SE ±3·25) reached nominal statistical significance (p=0·0176), supporting a clinically meaningful reduction in the rate of mid-level upper limb functional deterioration (appendix pp 37).

Mean baseline LVEF for deramiocel-treated participants was 54·4% compared with 59·6% for placebo participants, an imbalance that is not expected to affect 12-month trajectory (table 2).[15] 93% had

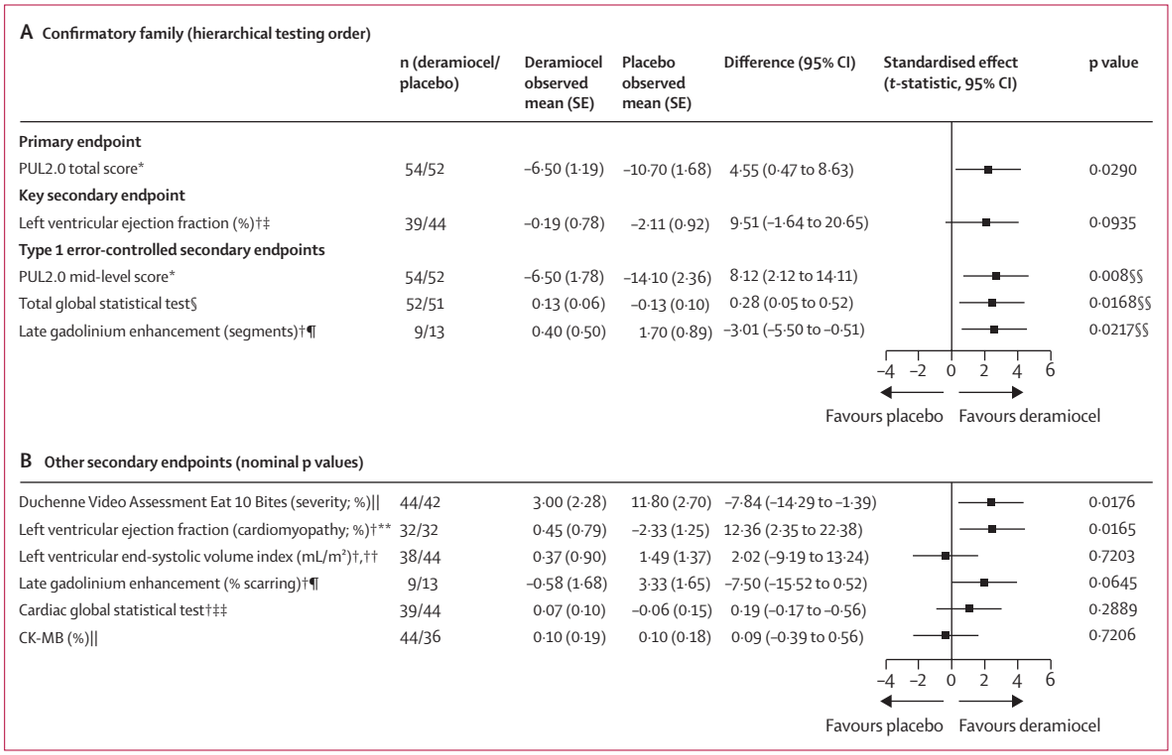


***Figure 3*: Forest plot of treatment effects at month 12 for the primary, key secondary, and other prespecified secondary efficacy endpoints**
(A) Confirmatory family in the prespecified hierarchical (fixed-sequence) testing order that controls the family-wise type I error rate. (B) Other prespecified secondary endpoints, tested nominally. Points are standardised treatment effects, plotted so that values to the right of the reference line favour deramiocel; each is the treatment difference divided by its standard error, signed towards clinical benefit, with whiskers spanning ±1·96. Standardisation places endpoints measured on different scales on a common axis. Tabulated treatment differences and 95% CIs are on each endpoint's analysis scale–native units for most endpoints, and the rank scale for endpoints analysed by rank ANCOVA (LVEF, LVEF [cardiomyopathy], and left ventricular end-systolic volume index). All reported p values and 95% CIs come from the prespecified covariate-adjusted models and are not adjusted for multiplicity. Analysis population and reduced CMR or cohort B subsets are indicated per endpoint by the n (deramiocel/placebo) column and footnotes. LVEF=left ventricular ejection fraction. PUL2.0=Performance of the Upper Limb 2.0. ITT=intention-to-treat. LGE=late gadolinium enhancement. CK-MB=creatine kinase-myocardial band. CMR=cardiac magnetic resonance. *Treatment difference in percentage change from baseline in PUL2.0 total score and mid-level score were analysed using a prespecified mixed model with repeated measures that included treatment, cohort, pooled sites, visit, treatment-by-visit interaction, slow or non-slow progressor status, and baseline score. †Physical limitations and image quality affected the sample size of the ITT set for CMR outcomes. ‡The prespecified analysis for left ventricular ejection fraction used an ANCOVA on ranks of change from baseline at month 12, with terms for treatment group, cohort, slow progressor indicator, an indicator for screening LVEF greater than or equal to 45%, along with baseline LVEF, and age at baseline. A prespecified Hodges–Lehmann shift estimate is included to provide interpretability of the treatment difference presented in ranks. §Total global statistical test was constructed using standardised change scores at the participant level from the three endpoints of PUL2.0 total score, LVEF, and Patient Global Impression of Severity score representing the domains of feels, functions, and survives. An ANCOVA model was prespecified to produce the reported treatment difference with the model terms of treatment group, cohort, slow progressor indicator, age at baseline, and baseline value. ¶Only a subset of patients was included for tissue characterisation using LGE, reported as both the number of segments and the percentage of myocardial scarring. The model for LGE was the same as that used for LVEF. ||Duchenne Video Assessment (Eat 10 Bites severity percentage) and CK-MB were analysed using a prespecified mixed model with repeated measures with the same model terms as the PUL2.0 analysis, applied to change from baseline rather than percentage change from baseline. **Follows the same prespecified analysis for LVEF (ANCOVA on ranks), but with a subgroup of patients with documented cardiomyopathy at baseline. ††Indexed left ventricular end-systolic volume followed the same prespecified ANCOVA on ranks described for LVEF, with baseline indexed end-systolic volume substituted as the baseline covariate; the treatment difference is therefore presented on the rank scale. ‡‡The Cardiac Global Statistical Test was constructed in the same manner as the Total Global Statistical Test, using participant-level standardised change scores from LVEF, indexed left ventricular end-systolic volume, and indexed left ventricular end-diastolic volume, and analysed with the same prespecified ANCOVA model. §§p values are nominal.

concomitant use of cardiac medications at baseline, whereas 41% had changes to cardiac medication class during the trial. Both baseline cardiac medications and changes therein were well balanced across treatment groups and sensitivity analyses for LVEF (appendix p 30) indicate that these potential confounders did not meaningfully influence the following result. For LVEF, at month 12, the deramiocel-treated group versus placebo showed a least-squares mean ranked change in LVEF of 57·47 ranks (SE ±9·43), compared with 45·82 ranks (SE ±8·92) in the placebo group, with a between-group difference of 9·51 (SE ±5·60; 95% CI −1·64 to 20·65; p=0·0935). The absolute mean change in LVEF percentage with a treatment benefit of 1·92-percentage points in LVEF over 1 year is shown in figure 2C. This translates to 91% slowing of cardiac functional decline for deramiocel-treated participants relative to placebo.

The ITT analysis (figure 2C) includes 19 participants with no previous evidence of cardiomyopathy. When

| | Deramiocel (n=39) | Placebo (n=44) | Overall (n=83) |
|---|---|---|---|
| Age, years | 16 (10–22) | 14 (10–22) | 15 (10–22) |
| Sex | | | |
| Male | 39 (100%) | 44 (100%) | 83 (100%) |
| Slow progressor indicator | 0 | 3 (6·8%) | 3 (3·6%) |
| LVEF percentage at baseline | | | |
| Mean (SD) | 54·36 (7·60) | 59·62 (5·96) | 57·15 (7·24) |
| Median (range) | 55·17 (36·54–69·26) | 59·54 (48·05–73·98) | 57·53 (36·54–73·98) |
| Cardiomyopathy | 32 (82·1%) | 32 (72·7%) | 64 (77·1%) |
| Baseline LVEF group | | | |
| <45% | 5 (12·8%) | 0 | 5 (6·0%) |
| ≥45% | 34 (87·2%) | 44 (100%) | 78 (94·0%) |
| Age at start of cardiac medications | | | |
| n | 37 | 41 | 78 |
| Mean (SD) | 12·86 (2·95) | 11·58 (2·93) | 12·19 (2·99) |
| Median (range) | 13·0 (6·3–19·3) | 11·3 (5·1–17·3) | 12·15 (5·1–19·3) |
| Baseline cardiac medication type | | | |
| Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors | 37 (94·9%) | 40 (90·9%) | 77 (92·8%) |
| Beta-Adrenoceptor blockers | 17 (43·6%) | 17 (38·6%) | 34 (41·0%) |
| Sodium-glucose cotransporter 2 inhibitors | 3 (7·7%) | 2 (4·5%)* | 5 (6·0%) |
| Mineralocorticoid receptor atagonists | 21 (53·8%) | 29 (65·9%) | 50 (60·2%) |
| No cardiac medication | 2 (5·1%) | 3 (6·8%) | 5 (6·0%) |
| Ambulatory at baseline | 6 (15·4%) | 6 (13·6%) | 12 (14·5%) |

Data are median (range) or n (%), unless otherwise stated. LVEF=left ventricular ejection fraction. *SGLT2 inhibitors in the placebo group were prescribed for type 2 diabetes and not for cardiac care.

***Table 2:*** **Demographic and disease characteristics of the cardiac-evaluable population**

| | Deramiocel (n=53) | Placebo (n=52) | Overall (n=105) |
|---|---|---|---|
| Acute respiratory decompensation within 2 h following investigational product administration | 0 | 0 | 0 |
| Hypersensitivity reaction | 22 (41·5%), 55 | 8 (15·4%), 18 | 30 (28·6%), 73 |
| Immune sensitisation syndrome | 1 (1·9%), 2 | 0 | 1 (1·0%), 2 |
| TEAEs related to investigational product or administration procedure | 44 (83·0%), 265 | 19 (36·5%), 51 | 63 (60·0%), 316 |
| TEAEs related to investigational product | 44 (83·0%), 259 | 16 (30·8%), 44 | 60 (57·1%), 303 |
| TEAEs related to administration procedure | 23 (43·4%), 54 | 9 (17·3%), 22 | 32 (30·5%), 76 |
| TEAE severity of grade 3 or higher | 1 (1·9%), 4 | 3 (5·8%), 3 | 4 (3·8%), 7 |
| Serious TEAEs | 1 (1·9%), 1 | 5 (9·6%), 5 | 6 (5·7%), 6 |
| All-cause mortality | 0 | 0 | 0 |

Date are n (%), E. n (%)=number and percentage of participants with adverse events. E=number of events. TEAEs=treatment-emergent adverse events.

***Table 3:*** **Adverse events according to grade (safety population)**

| | Placebo (n=52) | Deramiocel (n=53) | Overall (n=105) |
|---|---|---|---|
| Any treatment-emergent adverse events | 43 (82·7%) | 50 (94·3%) | 93 (88·6%) |
| Infections and infestations | 23 (44·2%) | 22 (41·5%) | 45 (42·9%) |
| Musculoskeletal and connective tissue disorders | 15 (28·8%) | 18 (34·0%) | 33 (31·4%) |
| Injury, poisoning, and procedural complications | 14 (26·9%) | 14 (26·4%) | 28 (26·7%) |
| Gastrointestinal disorders | 14 (26·9%) | 17 (32·1%) | 31 (29·5%) |
| General disorders and administration site conditions | 12 (23·1%) | 28 (52·8%) | 40 (38·1%) |
| Respiratory, thoracic, and mediastinal disorders | 11 (21·2%) | 22 (41·5%) | 33 (31·4%) |
| Nervous system disorders | 5 (9·6%) | 35 (66·0%) | 40 (38·1%) |
| Cardiac disorders | 5 (9·6%) | 14 (26·4%) | 19 (18·1%) |

Data are n (%).

***Table 4:*** **Adverse events by Medical Dictionary for Regulatory Activities class**

analysing a prespecified subpopulation (64 [77·1%] of 83) with confirmed evidence of cardiomyopathy at baseline (by medical history, LVEF <55%, or presence of LGE on baseline CMR), the mean change in LVEF at 12 months was 0·45 (SD 4·44) for deramiocel and –2·33 (SD 7·08) for placebo and mean difference of 2·79 (SD 5·91; figure 2D). The difference between treatment and placebo was 12·36 ranks (95% CI 2·35–22·38; nominal p=0·0165). Thus, in participants with pre-existing cardiomyopathy, LVEF at 12 months trended higher than it had been at baseline, corresponding to 119% slowing of disease progression. Neither the left ventricular end systolic volume index nor the cardiac global statistical test (a composite score of LVEF, left ventricular end systolic volume index, and left ventricular end diastolic volume index) showed any evidence of treatment difference (figure 3B).

When LGE was measured at baseline and month 12, study participants showed a least-squares mean change of –0·4 (SE ±0·5) in the deramiocel group compared with 1·7 (SE ±0·89) in placebo, representing a between-group difference of –3·01 in the number of affected myocardial segments (95% CI –5·50 to –0·51; p=0·022) in favour of deramiocel (figure 3). When LGE was assessed as percentage of myocardial scar, a similar pattern was observed, with 12-month change from baseline of –0·58 (SE ±1·68) relative to 3·33 (SE ±1·65; 95% CI –15·52 to 0·52; p=0·0645; figure 3B). Thus, the progression of myocardial scar over 1 year was markedly attenuated by deramiocel relative to placebo. No between-group difference was seen in plasma levels of high sensitivity troponin I or T, or CK-MB throughout the study, consistent with the poor correlation of such biomarkers with the CMR-graded severity of DMD cardiomyopathy.

The composite global statistical test consistently favoured deramiocel over placebo; the deramiocel-treated

group showed a least-squares means total global statistical test of 0·13 (SE ±0·06), compared with –0·13 (SE ±0·1) in the placebo group, and a between-group difference of 0·28 (Z score) (95% CI 0·05–0·52; p=0·0168; figure 3; appendix p 31). The standalone PGI-S score is presented in the appendix (p 32).

No new safety signals emerged relative to the HOPE-2, and HOPE-2 OLE trials.[17] 594 treatment emergent adverse events were reported by month 12 (table 3; table 4; appendix pp 16–24) with incidences for deramiocel to placebo of 94·3% to 82·7% with risk-ratio of 1·14 (95% CI 0·99–1·31). 98% of adverse events were mild to moderate in severity and 23% were related to hypersensitivity. Hypersensitivity reactions (appendix p 15) were more frequent among deramiocel-treated participants (41·5%) versus placebo (15·4%). The most frequently reported adverse events (≥10% incidence) were headaches (35·2%), cough (15·2%), pyrexia (14·3%), nausea (12·4%), and tachycardia (12·4%), which predominantly resolved within 24–48 h. More placebo recipients experienced at least one grade 3 or higher treatment-emergent adverse event. Two participants had treatment-related serious adverse events (appendix p 25). One, receiving deramiocel, had a grade 2 (moderate) infusion-related reaction during the second infusion, which resolved rapidly with conservative management; the participant continued treatment per protocol with no recurrence. A second participant in the placebo group had a grade 4 anaphylactic reaction during baseline infusion requiring epinephrine, and brief monitoring in the outpatient infusion facility with resolution. The adverse event was presumably due to an allergic reaction to an excipient included in both the placebo and deramiocel preparations. No deaths occurred in the study.

## Discussion

HOPE-3 is, to our knowledge, the first phase 3 trial of systemic non-autologous cell therapy in a genetic disease, and the first phase 3 registration trial in late-ambulant and non-ambulant DMD participants. This pivotal trial supports the findings of the HOPE-2 trial;[17] both studies showed preservation of upper limb function and cardiac function relative to placebo. New data on LGE provide tissue-level characterisation of the cardiac benefits conferred by cell therapy and reveal that reductions in myocardial fibrosis underlie the cardiac functional benefits evident in the preserved LVEF. Deramiocel intravenous infusions were generally well tolerated, with no participants experiencing acute respiratory decompensation, immune sensitisation syndrome, or mortality. A pre-treatment regimen of high-dose oral corticosteroids, H1 and H2 blockers, prevented severe infusion-related hypersensitivity-like reactions, but the occurrence of mild-to-moderate hypersensitivity reactions with deramiocel treatment necessitates medically supervised administrations at an infusion centre. Therefore, deramiocel offers meaningful therapeutic benefits for both skeletal and cardiac muscle in advanced DMD, with manageable safety and tolerability. Deramiocel was associated with more treatment-related and hypersensitivity events than placebo, although most were mild or moderate. Serious treatment-emergent adverse events occurred more frequently in placebo recipients. No known long-term safety concerns were identified.

Previous work showed that CDCs secrete extracellular vesicles replete with non-coding RNAs that modulate innate immunity and reduce fibrosis.[21,22] As a result, injured muscle tissue pivots from scarring towards healing and regeneration. Although CDCs are heart-derived, their benefits are not heart-restricted; they recruit general mechanisms pertinent to skeletal muscle as well.[16,22,23] In the context of DMD, deramiocel does not address the underlying dystrophin deficiency, but, by modulating maladaptive inflammatory and fibrotic pathways in DMD,[16,23] disease progression is attenuated. It is particularly encouraging that deramiocel shows efficacy even in advanced DMD, in which tissue damage is already extensive. Early initiation of CDC therapy in *mdx* mice (a well validated model of DMD) leads to striking long-term preservation of muscle function,[24] giving good reason to wonder if the benefits of deramiocel might be even greater if it were started earlier in the disease process—a conjecture worth testing in future trials.

The therapeutic effects of deramiocel are not subtle. The 1·2-point difference seen in the total PUL2.0 score at 12 months, in the context of a highly heterogeneous disease in which PUL score might continuously decline over one to two decades, indicates a clinically relevant delay in disease progression. A 54% reduction in mean skeletal-muscle disease progression over 12 months, if sustained, would be equivalent to delaying approximately 1 year of untreated progression over 2 years. The effects on cardiomyopathy progression are also encouraging. Here we find 119% slowing of mean cardiac disease progression (ie, full preservation or slight improvement) in those with cardiomyopathy at baseline. These values align with the 107% slowing seen with deramiocel in the 12-month HOPE-2 trial and 99% slowing over 3 years observed in the HOPE-2 OLE study, both representing stabilisation of cardiomyopathy progression not seen with other cardiac therapeutics in DMD.[25]

Preservation of upper limb function—the main therapeutic objective in HOPE-3—yielded significant clinical benefits in advanced DMD. Notably, the 1·0-point treatment effect in the mid-level domain corresponds to either preservation or delay in partial or full loss of elbow function. It is noteworthy that the change in total PUL across our placebo patients over 1 year (–2·72 points; SD ±3·18) was almost identical to the change in total PUL reported in a large natural history cohort of non-ambulatory participants with DMD (–2·7 annualised,

–8·09 over 36 months, with baseline score of 24·3 points), showing that our study population shows typical DMD upper extremity disease progression.[4]

It is worth noting that the PUL2.0 instrument is relatively new, and our understanding of its clinical relevance is still developing. PUL2.0 is known to rapidly deteriorate in the shoulder or upper domain in those with higher baseline scores.[4] Here, we emphasised the importance of considering baseline scores when interpreting meaningful changes in PUL2.0 by evaluating percentage change from baseline. This analytic approach, although novel for PUL2.0, is widely used in other clinical endpoint analyses, and might reflect disease progression more faithfully in heterogeneous neuromuscular disease cohorts. Although the minimal clinically important difference for percentage change in PUL2.0 has not been established, the prespecified choice of percentage change in baseline PUL2.0 as an analysis strategy recognises the clinical meaningfulness of 1-point changes in PUL in patients with more severe upper limb impairment and lower baseline values[26] concomitant with expected large declines in the upper dimension domain over short intervals in patients with higher baseline scores.[4] Mean percentage change allows evaluation of meaningful treatment effects on the PUL in a wide functional range of patients without over-weighting one domain set of functions over those of another domain depending on the baseline functional status of the patient. Importantly, a prespecified sensitivity analysis for the absolute change in total PUL2.0 over 12 months also showed a clear trend to a treatment effect of deramiocel on the primary endpoint (p=0·0503). As in the HOPE-2 trial, we found mid-level (elbow) PUL to be the most responsive PUL subdomain, consistent with its intermediate rate of decline between the significantly faster upper (shoulder) domain[4] and the more slowly progressive loss of lower (hand) domain function. Changes in the mid-level PUL are particularly relevant, as they are highly associated with quality-of-life indicators such as the ability to eat independently. This is the most important activity to support good quality of life in DMD (as determined by parent caregivers), and the second most important activity next to repositioning self at night by non-ambulatory DMD patients. The 12-month treatment effect of deramiocel on the novel DVA Eat 10 Bites, which measures a real-world vital activity requiring the ability to use the arm with mid-level elbow flexion, supports the clinical meaningfulness of the treatment effect measured by the PUL2.0 and portends a major potential favourable effect of deramiocel on maintenance of independence.[27]

There are no approved DMD-specific therapies for cardiomyopathy, the leading cause of death in patients with DMD. Current recommendations suggest the use of generic guideline-directed medical therapy, based on clinical trials of adult patients with ischaemic and non-ischaemic heart failure and reduced LVEF. The patient population, pathogenesis, and disease course of such patients are all unlike those of DMD cardiomyopathy. In DMD, irreversible fibrosis and fibrofatty replacement of the myocardium[8,26] mirrors the histological progression of the skeletal myopathy.[28] Such histological changes in the heart underlie deteriorating cardiac function.[29] Due to the limitations of symptom assessment in non-ambulatory patients, cardiac imaging has become the primary mode of assessing cardiomyopathy in DMD. Such imaging is now performed routinely for prognostic and monitoring purposes,[9,30] with CMR preferred over echocardiography in advanced DMD due to improved precision and technical ease. The association between a decline in systolic function and all-cause mortality provides additional context to the present results. For every 3% decline in LVEF, risk of death increases by 32% (hazard ratio 1·32).[12] Thus, there is good reason to believe that the 1-year treatment difference of 2·79% in LVEF with deramiocel in those with defined cardiomyopathy is clinically meaningful. Of note, this subset of patients with pre-existing cardiomyopathy showed the greatest benefit, consistent with the finding that LVEF decline begins after scar burden begins to accumulate.[9]

Loss of dystrophin leads to myocardial inflammation and damage, which eventually results in cardiomyocyte death and fibrofatty replacement. LGE imaging identifies and quantifies the extent of this fibrofatty replacement. The observed stabilisation of LGE reflects preservation of viable myocardium, resulting in maintained global contractile function as assessed by LVEF. These findings, which are consistent with the known anti-inflammatory and anti-fibrotic mechanisms of deramiocel, are sufficiently dramatic to be expected to result in a mortality benefit.[11,12]

No treatment differences were observed in change from baseline in left ventricular end systolic volume index or the cardiac global statistical test. Indexed ventricular volumes depend on both a CMR-based measure and an estimate of body surface area derived from height and weight. Calculation of the body surface area is problematic in non-ambulant DMD patients, where height is generally estimated from ulnar length, not standing height, and weight measurements are complicated by limited mobility. Thus, indexing to body surface area makes it difficult to assess changes in cardiac volumes over time. By contrast, LVEF, a dimensionless ratio of the absolute end-systolic and end-diastolic volumes in a single image set of the cardiac cycle, is independent of body surface area indexation. Hence, for this patient population, LVEF is generally regarded as a more reliable endpoint to assess DMD cardiomyopathy.

We acknowledge several limitations to this study. Sample sizes of phase 3 trials in rare diseases such as DMD are usually modest and similar to HOPE-3, and trial durations are limited by the ethics of placebo-exposure with compelling phase 2 data. In DMD, there

has been limited ability of shorter duration trials of less than 12–18 months to show clear treatment effects with the exception of corticosteroids. Therefore, based on previous HOPE-2 results, we designed the HOPE-3 trial to test the effect of deramiocel on upper limb function measured by the PUL after 12 months and not earlier. A trial duration longer than 12 months would likely capture larger skeletal muscle treatment effects in both the total or mid-level PUL.

Our broad genetic inclusion criteria, enrolling DMD patients with diverse mutations, resulted in significant and expected heterogeneity of disease progression. We stratified by PUL entry-level score and excluded participants with ceiling scores and PUL entry scores of 1. This provided sufficient enrichment of upper limb disease progression to measure a 12-month treatment effect. Although baseline imbalances were small and largely addressed by stratification by PUL2.0 entry criteria (except for an excess of slow progressors in the placebo group), baseline values for LVEF were slightly higher in placebo, and more patients had documented cardiomyopathy at baseline in the deramiocel group. However, previous CMR natural history data suggest the expected rate of decline would be similar among patients in this age and LVEF range.[12] Moreover, the direction of the imbalance, with LVEF being about 5% lower in participants randomly assigned to deramiocel, would have predicted faster progression of underlying cardiomyopathy in the deramiocel group, rather than the observed preservation of left ventricular function. Missing data on the primary endpoint were minimal, and CMR data exclusions were due to limited CMR image quality in some patients; prespecified comprehensive adjudication of CMR image quality was performed before database lock. Finally, reported findings in HOPE-3 have largely focused on prespecified primary, key secondary, and type I error-controlled secondary endpoints. It is anticipated that the effect of deramiocel on other prespecified secondary and exploratory endpoints, including patient-reported outcomes, will be in future publications.

In conclusion, deramiocel significantly slows DMD progression with a favourable safety profile. Both the preservation of upper limb function and the attenuation of cardiomyopathy have not been shown in the advanced DMD population. The fact that deramiocel is agnostic to the precise underlying DMD genotype makes it broadly applicable. These findings reinforce deramiocel as a safe, effective, and promising therapy for individuals living with DMD. Longer follow-up is needed to establish durability, long-term safety, and effects on clinically important cardiac outcomes.

#### Contributors

Individual author contributions are described in the appendix (pp 38–43). Study conceptualisation was done by CMM, CV, JHS, KAE, MT, EMa, LM, and EMe. Data were collected by CMM, HCP, SA, PSG, CT, AV, LR-P, KG, SMB, ASV, STI, CGL, SJP, NEB, KMo, RJB, KDM, RJS, ECS, JAE. Data curation was done by KMo, NH, and MSA. Formal statistical analysis was performed by KMo, NH, MB, KCB, JS, and MSA. Funding acquisition was done by LM. Study investigation was done by CMM, CV, JHS, KAE, NH, MB, KCB, MT, EKH, HCP, SA, PSG, CT, AV, LR-P, KG, SMB, ASV, STI, CGL, SJP, NEB, KMo, RJB, KDM, RJS, ECS, JAE, and MSA. Study methodology was developed by CMM, MB, KCB, and MSA. Project administration was done by CMM, KMo, MB, KCB, MT, KNH, HCP, SA, PSG, CT, AV, LR-P, KG, SMB, ASV, STI, CGL, SJP, NEB, KMo, RJB, KDM, RJS, ECS, JAE, and MSA. Resources were managed by CMM, KMo, NH, HCP, SA, PSG, CT, AV, LR-P, KG, SMB, ASV, STI, CGL, SJP, NEB, KMo, RJB, KDM, RJS, ECS, and JAE. Software implementation and oversight were don't by CMM, MB, and MSA. Study supervision was done by CMM, KMo, NH, MB, KCB, and MSA. Visualization of study data was done by CMM, CV, JHS, KMo, NH, MB, KCB, and MSA. Writing of the original draft was done by CMM, CV, JHS, KMo, NH, MB, MSA, and EMa. Review and editing was done by all authors. KMo, NH, MB, KCB, and MSA directly accessed and verified the data for validation purposes. CMM had final responsibility to submit the data for publication. All authors had access to the data and had final responsibility for the decision to submit for publication.

#### Declaration of interests

CMM served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; received grants from and served as site principal investigator for Avidity Biosciences, Edgewise Therapeutics, Insmed, and Italfarmaco, NS Pharma, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics, and Solid Biosciences; has received grants from California Institute for Regenerative Medicine, Muscular Dystrophy Association, Parent Project Muscular Dystrophy, Shriners Hospitals for Children, Department of Defense, National Institute of Disability Independent Living and Rehabilitation Research, and the US National Institutes of Health (RO1HD35714, 2P01HD033988–06A1, R01NS043264, R01AR061875, R01AR062380, U01NS061799–01A2, P50AR060836, U10NS077422, U01AR065113–01, U24NS107209–01, U24 NS107209, R01DK129793–01, and R01DK125794–01A1); has received consultancy fees from Catalyst Pharmaceuticals, Capricor Therapeutics, Catabasis, Dyne, Edgewise Therapeutics, Italfarmaco, NS Pharma, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics, and Solid Biosciences; and served on advisory boards for Avidity Biosciences, Catalyst Pharmaceuticals, Edgewise Therapeutics, Entrada Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics, Solid Biosciences, and Roche. ASV served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Biogen, Argenx, and Blue Oak Nutraceuticals; received payment for expert testimony as medical legal consultant; received support for attending meetings or travel from Argenx and Muscular Dystrophy Association; holds a leadership or fiduciary role for Sjogren's Foundation; and owns stock or stock options from Blue Oak Nutraceuticals. LR-P served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; served as site principal investigator for Sarepta Therapeutics, Scholar Rock, Genentech, Biohaven, Novartis, PTC Therapeutics, and NS Pharma; received consulting fees and served on advisory boards for Sarepta Therapeutics, Scholar Rock, IFT Therapeutics, Catalyst Pharmaceuticals, Mando Therapeutics, Novartis, Dyne Therapeutics, and Solid Biosciences; and received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Scholar Rock. RJB served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; served as site principal investigator for Ionis Pharmaceuticals; and received consulting fees and served on the Scientific Advisory Board for Sarepta Therapeutics, Biogen, Novartis, Precision BioSciences, Solid Biosciences, Scholar Rock, and BridgeBio Pharma. KMo served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the

study; received support for attending meetings or travel from Capricor Therapeutics; participated on a data safety monitoring board or advisory board for Solid Biosciences, Catalyst Pharmaceuticals, and Sarepta Therapeutics; and holds a leadership or fiduciary role at American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM). AV served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; and received consulting fees from Capricor Therapeutics, Biogen, Novartis, PTC Therapeutics, Sarepta Therapeutics, Scholar Rock, Pfizer, Catalyst Pharmaceuticals, Lupin, Entrada Therapeutics, Avidity Biosciences, Solid Biosciences, REGENXBIO, Insmed, Keros Therapeutics, Precision BioSciences, Gruenenthal, Mesoblast, and Italfarmaco. CGL served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; served as site principal investigator for Sarepta Therapeutics, Dyne Therapeutics, Biohaven, Avidity Biosciences, and Novartis; received consulting fees from Sarepta Therapeutics, Genentech, and Italfarmaco; and received payment for expert testimony from Stanford University. SA served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; served as site principal investigator for Sarepta Therapeutics, Dyne Therapeutics, and Satellos Bioscience; received consulting fees from ITF Therapeutics; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Dyne Therapeutics; received support for attending meetings or travel from Dyne Therapeutics; and holds a leadership or fiduciary role as a Board of Director for American Board of Physical Medicine and Rehabilitation as well as a Board Director for Parent Project Muscular Dystrophy. STI served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; and received support for attending meetings or travel from Capricor Therapeutics. KDM served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; served as site principal investigator for PTC Therapeutics, Sarepta Therapeutics, Edgewise Therapeutics, and Italfarmaco; received support for attending meetings or travel from Sarepta Therapeutics; participated on a data safety monitoring board or advisory board for Dyne Therapeutics, Edgewise Therapeutics, and Avidity Biosciences; and holds a leadership or fiduciary role on the Research Advisory Committee for Muscular Dystrophy Association. ECS served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Avidity Biosciences, Catalyst Pharmaceuticals, Precision BioSciences, Boehringer Ingelheim, Quince Therapeutics, Entrada, and Italfarmaco; and participated on a data safety monitoring board or advisory board for Solid Biosciences and Edgewise Therapeutics. SJP served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; served as site principal investigator for CSL Behring, Scholar Rock, Pfizer, Sarepta Therapeutics, Satellos Bioscience, Catalyst Pharmaceuticals, PTC Therapeutics, Biogen, Avexis, Solid Biosciences, and FibroGen; received clinical grant support from Muscular Dystrophy Association, Parent Project Muscular Dystrophy, and Cure SMA; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from the American Academy of Neurology; received support for attending meetings or travel from Capricor Therapeutics, Muscular Dystrophy Association, Parent Project Muscular Dystrophy, Cure SMA, and the American Board of Psychiatry and Neurology; participated on a data safety monitoring board or advisory board for Solid Biosciences, Catalyst Pharmaceuticals, Sarepta Therapeutics, Entrada Therapeutics, Novartis, and Dyne Therapeutics; and holds a leadership or fiduciary role as a Committee Member on the American Board of Psychiatry and Neurology. NEB, SMB, JAE, KG, PSG, HCP, and CT served as site principal investigators for Capricor Therapeutics; and received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study. RJS served as site principal investigator for Capricor Therapeutics; received reimbursement for travel for study-related meetings and their institutions received payment for the conduct of the study; received research funds from Novartis, Sarepta Therapeutics, Genentech, Argenx, Biohaven, Catalyst Pharmaceuticals and Biogen; and received consulting fees and served on Medical Advisory Board for RegenXBio and Scholar Rock. MT was employed on this study by Medpace and owns equity in Capricor Therapeutics. EMa is an inventor of several patents licensed by Capricor Therapeutics, and owns founder's equity in Capricor Therapeutics. JHS received grants or contracts from Ametris (R61HL180327/R33, R01HL167969, R01HL164995, R01FD006649, and R01FD006371); received consulting fees from Capricor Therapeutics, Boehringer Ingelheim, Catalyst Pharmaceuticals, Dyne Therapeutics, Keros Therapeutics, Medpace, NS Pharma, Sarepta Therapeutics, Secretome Therapeutics, Sardocor, and Wave Life Sciences; received support for attending meetings or travel from Capricor Therapeutics; participated on a data safety monitoring board or advisory board for Sardocor, Solid Biosciences, ITF Therapeutics, Sarepta Therapeutics, and Boehringer Ingelheim; holds a leadership or fiduciary role as the Chair and Chair Ex Officio of Pediatric and Congenital Heart Disease Section of the Society for Cardiovascular Magnetic Resonance (SCMR PCHD), Steering Committee and Abstract Chair of SCMR Scientific Sessions Planning Committee; and owns stock or stock options from Secretome Therapeutics. CV received payments made to Cincinnati Children's Hospital Medical Center for cardiac natural history in DMD; received consulting fees either directly or to their employer as well as reimbursement for travel from Capricor Therapeutics; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Capricor Therapeutics; and received support for attending meetings or travel from Capricor Therapeutics. KNH received consulting fees as a masked second reader for CMR analysis from Capricor Therapeutics. JS received consulting fees either directly or to their employer as well as reimbursement for travel from Capricor Therapeutics. EMe received grants or contracts from Sarepta Therapeutics; received consulting fees from PTC Therapeutics, Sarepta Therapeutics, Edgewise Therapeutics, Santhera, Roche, Dyne Therapeutics, Solid Biosciences, Avidity Biosciences, Entrada Therapeutics, and NS Pharma; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sarepta Therapeutics, Santhera, Roche, and Dyne Therapeutics; participated on a data safety monitoring board or advisory board for Sarepta Therapeutics, Santhera, Roche, PTC Therapeutics, Dyne Therapeutics, Solid Biosciences, Avidity Biosciences, Entrada, Edgewise Therapeutics, and NS Pharma. EKH received payment through UC Davis for study site clinical trial operations; received grants or contracts from Sarepta Therapeutics, NS Pharma, Insmed, Santhera, Solid Biosciences, and Parent Project Muscular Dystrophy; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sarepta Therapeutics and Santhera; received support for attending meetings or travel from Parent Project Muscular Dystrophy; and holds a leadership or fiduciary role on the Scientific Advisory Board for Parent Project Muscular Dystrophy, the Executive Committee for Cooperative International Neuromuscular Research Group, and the Clinical Certification Committee for World Duchenne Organization. KMa, NH, MB, KCB, KAE, MSA, and LM are full time employees of and hold equity in Capricor Therapeutics.

#### Data sharing

The funder will make available individual anonymised participant data that underlie the results reported in this Article to academic researchers who provide a methodologically sound proposal (as determined by the study funder) to achieve specific study objectives beginning 12 months and ending 36 months after publication. Investigator access will be covered by a data-use agreement. Proposals should be directed to datarequests@capricor.com.

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**References**

1 Hoffman EP, Brown RHJ Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell* 1987; **51:** 919–28.

2 Duan D, Goemans N, Takeda S, Mercuri E, Aartsma-Rus A. Duchenne muscular dystrophy. *Nat Rev Dis Primers* 2021; **7:** 13.

3 Mayhew A, Mazzone ES, Eagle M, et al, and the Performance of the Upper Limb Working Group. Development of the performance of the upper limb module for Duchenne muscular dystrophy. *Dev Med Child Neurol* 2013; **55:** 1038–45.

4 Coratti G, Pane M, Paolucci S, et al. Upper limb progression in Duchenne muscular dystrophy: Insights from a 36-month longitudinal study using the PUL2.0. *J Neuromuscul Dis* 2025; **13:** 293–303.

5 Van Ruiten HJ, Marini Bettolo C, Cheetham T, et al. Why are some patients with Duchenne muscular dystrophy dying young: an analysis of causes of death in North East England. *Eur J Paediatr Neurol* 2016; **20:** 904–09.

6 Broomfield J, Hill M, Guglieri M, Crowther M, Abrams K. Life expectancy in Duchenne muscular dystrophy: reproduced individual patient data meta-analysis. *Neurology* 2021; **97:** e2304–14.

7 Kieny P, Chollet S, Delalande P, et al. Evolution of life expectancy of patients with Duchenne muscular dystrophy at AFM Yolaine de Kepper centre between 1981 and 2011. *Ann Phys Rehabil Med* 2013; **56:** 443–54.

8 Sunthankar SD, George-Durrett K, Crum K, et al. Comprehensive cardiac magnetic resonance T1, T2, and extracellular volume mapping to define Duchenne cardiomyopathy. *J Cardiovasc Magn Reson* 2023; **25:** 44.

9 Tandon A, Villa CR, Hor KN, et al. Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in Duchenne muscular dystrophy. *J Am Heart Assoc* 2015; **4:** e001338.

10 Raucci FJJ Jr, Xu M, George-Durrett K, et al. Non-contrast cardiovascular magnetic resonance detection of myocardial fibrosis in Duchenne muscular dystrophy. *J Cardiovasc Magn Reson* 2021; **23:** 48.

11 Menon SC, Etheridge SP, Liesemer KN, et al. Predictive value of myocardial delayed enhancement in Duchenne muscular dystrophy. *Pediatr Cardiol* 2014; **35:** 1279–85.

12 Soslow JH, Xu M, Slaughter JC, et al. Cardiovascular measures of all-cause mortality in Duchenne muscular dystrophy. *Circ Heart Fail* 2023; **16:** e010040.

13 Smith RR, Barile L, Cho HC, et al. Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens. *Circulation* 2007; **115:** 896–908.

14 Marbán E. A mechanistic roadmap for the clinical application of cardiac cell therapies. *Nat Biomed Eng* 2018; **2:** 353–61.

15 Aminzadeh MA, Rogers RG, Fournier M, et al. Exosome-mediated benefits of cell therapy in mouse and human models of Duchenne muscular dystrophy. *Stem Cell Reports* 2018; **10:** 942–55.

16 Rogers RG, Fournier M, Sanchez L, et al. Disease-modifying bioactivity of intravenous cardiosphere-derived cells and exosomes in *mdx* mice. *JCI Insight* 2019; **4:** e125754.

17 McDonald CM, Marbán E, Hendrix S, et al, and the HOPE-2 Study Group. Repeated intravenous cardiosphere-derived cell therapy in late-stage Duchenne muscular dystrophy (HOPE-2): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2022; **399:** 1049–58.

18 McDonald C, Villa C, Tian C, et al. Multi-modal benefits of deramiocel (CAP-1002) in late-stage patients with DMD: a new treatment approach to target skeletal and cardiac muscle pathogenesis (HOPE-2-OLE Trial–36-month data). *Neuromuscular Disorders* 2024; **43:** Suppl 1.

19 Li Y, Nice JB, Kozinova M, et al. A novel in vitro potency assay demonstrating the anti-fibrotic mechanism of action of CDCs in deramiocel. *Biomedicines* 2025; **13:** 2652.

20 Pane M, Coratti G, Brogna C, et al. Upper limb function in Duchenne muscular dystrophy: 24 month longitudinal data. *PLoS One* 2018; **13:** e0199223.

21 Ibrahim AG-E, Cheng K, Marbán E. Exosomes as critical agents of cardiac regeneration triggered by cell therapy. *Stem Cell Reports* 2014; **2:** 606–19.

22 Marbán E. Deconstructing regenerative medicine: from mechanistic studies of cell therapy to novel bioinspired RNA drugs. *Circ Res* 2024; **135:** 877–85.

23 Gallet R, Dawkins J, Valle J, et al. Exosomes secreted by cardiosphere-derived cells reduce scarring, attenuate adverse remodelling, and improve function in acute and chronic porcine myocardial infarction. *Eur Heart J* 2017; **38:** 201–11.

24 Rogers RG, Antich J, Fournier M, et al. Long-term preservation of muscle function and structure by repeated administration of cardiosphere-derived cells in *mdx* mice. *Stem Cell Reports* 2025; **20:** 102468.

25 Bourke JP, Bueser T, Quinlivan R. Interventions for preventing and treating cardiac complications in Duchenne and Becker muscular dystrophy and X-linked dilated cardiomyopathy. *Cochrane Database Syst Rev* 2018; **10:** CD009068.

26 Breaux A, Lang SM, Wittekind S, et al. Cardiac histopathology in Duchenne muscular dystrophy demonstrates diffuse fibrofatty replacement of the myocardium. *J Am Heart Assoc* 2024; **13:** e033862.

27 Gillman A, Ciobanu T, Barrett L, et al. A patient-centered qualitative evaluation of meaningful change on the NSAA and PUL in Duchenne muscular dystrophy. *Front Neurol* 2025; **16:** 1509174.

28 Forbes SC, Arora H, Willcocks RJ, et al. Upper and lower extremities in Duchenne muscular dystrophy evaluated with quantitative MRI and proton MR spectroscopy in a multicenter cohort. *Radiology* 2020; **295:** 616–25.

29 Starnes JR, Xu M, George-Durrett K, et al. Rate of change in cardiac magnetic resonance imaging measures is associated with death in Duchenne muscular dystrophy. *J Am Heart Assoc* 2024; **13:** e032960.

30 Wittlieb-Weber CA, Knecht KR, Villa CR, et al. Risk factors for cardiac and non-cardiac causes of death in males with Duchenne muscular dystrophy. *Pediatr Cardiol* 2020; **41:** 764–71.