Cardiac Effects of Deramiocel in Duchenne Muscular Dystrophy

Randomized Placebo controlled (HOPE-3) Phase-3 Trial Results and Natural History Comparison

Jonathan H Soslow, MD, Craig M. McDonald, MD, Chet Villa, MD, Michael Taylor, MD, PhD Kan N. Hor, MD, Larry Markham, MD, Christopher Spurney, MD, Katheryn Gambetta, MD, Nazia Husain, MD, Frank Raucci, MD PhD, Brian Soriano, MD, Michael Binks, MD, Nathaniel Hogan, PhD, Kati Maharry, PhD, Adam Sullivan, PhD, HOPE-3 Investigators, DMD Cardiac Care Consortium, Mark S. Awadalla, BS, Linda Marbán, PhD

Monroe Carell Jr. Children's Hospital at Vanderbilt

Capricor

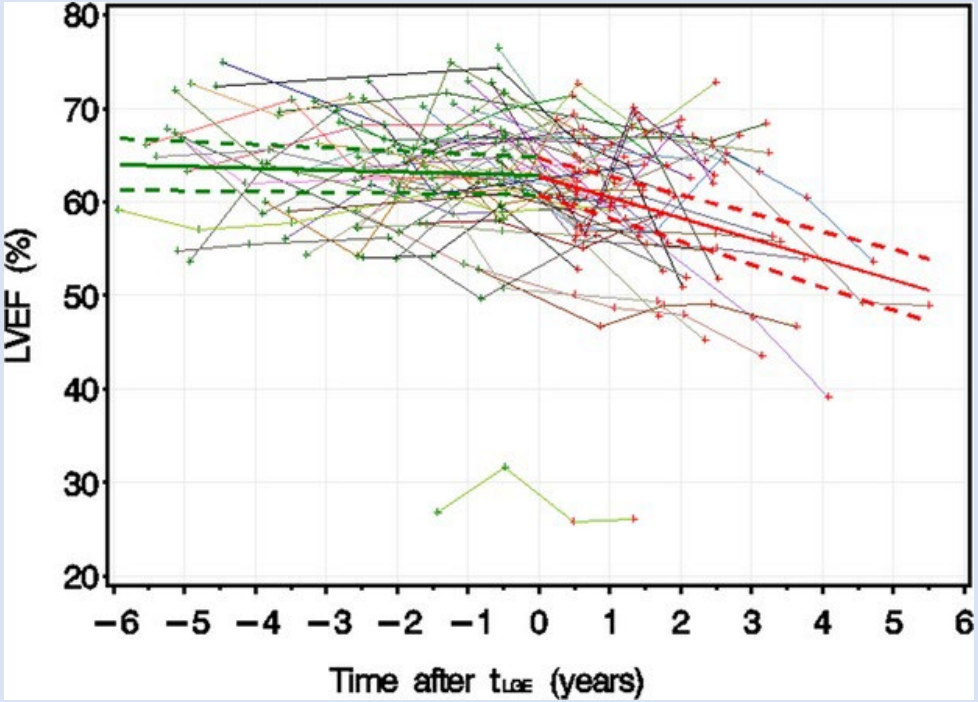
Disclosures

- Disclosures relevant to this talk
  - Consultant for Capricor
- Additional Disclosures
  - Consultant for Boerhinger Ingelheim, Dyne, Medpace, Sarepta, Secretome
  - Adboards: Bridgebio, Catalyst, Insmed, Solid
  - DSMB: Dyne, Sardocor
- Current Funding
  - NIH/NHLBI R01HL164995
  - NIH/NHLBI R01HL167969
  - NIH/NHLBI R61HL180327/R33
  - DoD GRANT14478340 (PI Soslow)/GRANT14478461 (PI Tamaroff)
  - DoD GRANT14478676 (PI Soslow)/ GRANT14478434 (PI Befliore-Oshan)
  - Fighting Duchenne Foundation Endowment
  - Ametris

Background

- Duchenne muscular dystrophy (DMD) is a devastating X-linked disease that results in progressive skeletal muscle weakness and cardiomyopathy
- Dystrophin protein stabilizes the sarcolemma during muscle contraction
  - Absence of dystrophin results in inflammation, fibrosis, and eventual myocyte death with fibrofatty replacement
- Improvements in supportive care have extended life expectancy to a median of 28 y/o and unmasked the cardiovascular phenotype
- *Cardiomyopathy is now the leading cause of death in DMD*
  - There are no approved therapies specifically for DMD cardiomyopathy

DMD-Cardiomyopathy



Tandon et al., 2015

Presence of LGE signals the onset of cardiomyopathy progression

Prior to LGE

No significant decline

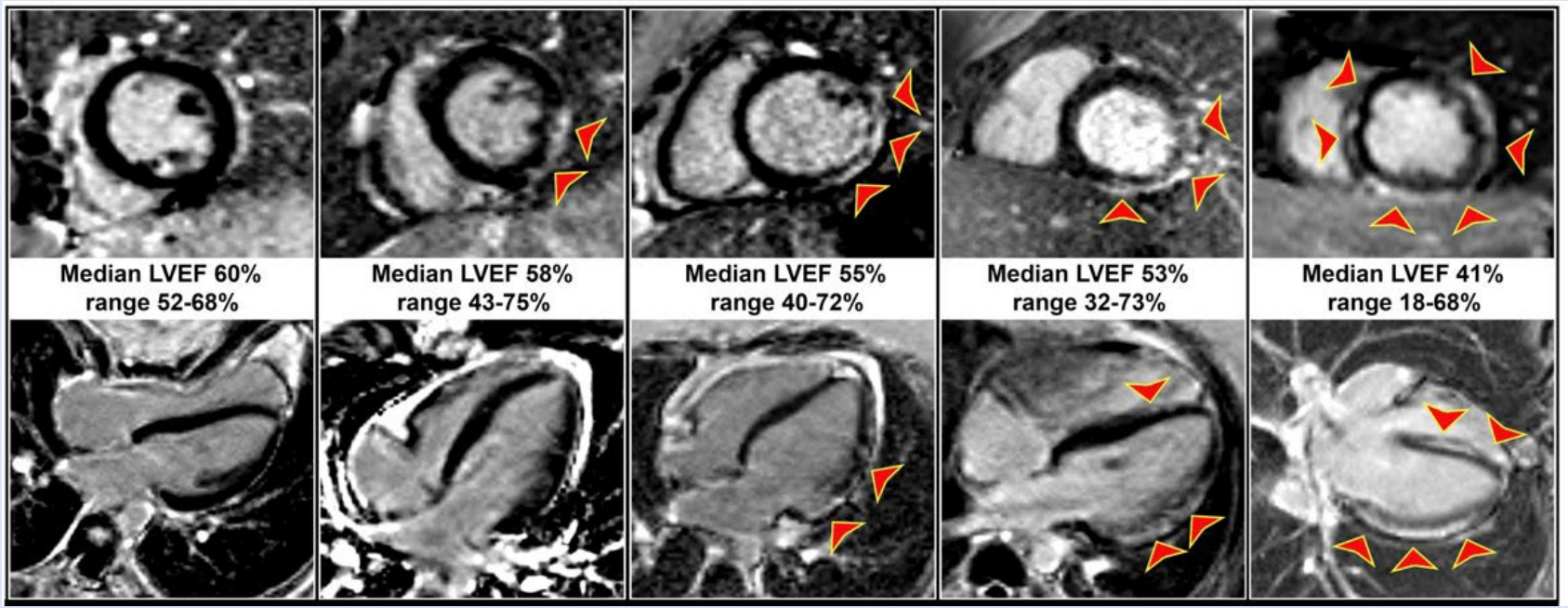
Post LGE

Steeper, accelerated decline.

2.2% per year.

DMD-Cardiomyopathy

LGE burden increases as LVEF declines.

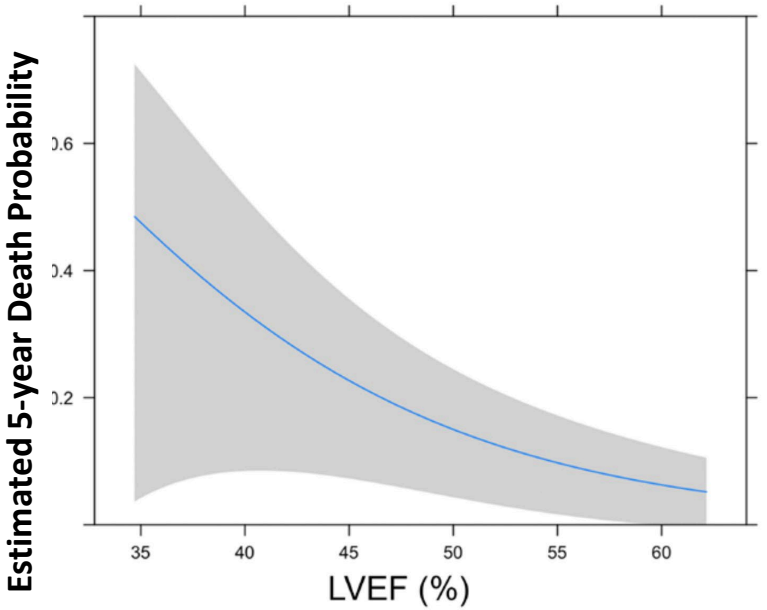


Top row: short-axis views · Bottom row: long-axis views · Red arrowheads mark LGE (scar). Groups span median LVEF 60% → 41%.

DMD-Cardiomyopathy Mortality

Model for All-Cause Mortality Based on First Available Visit that Included a Cardiac MRI

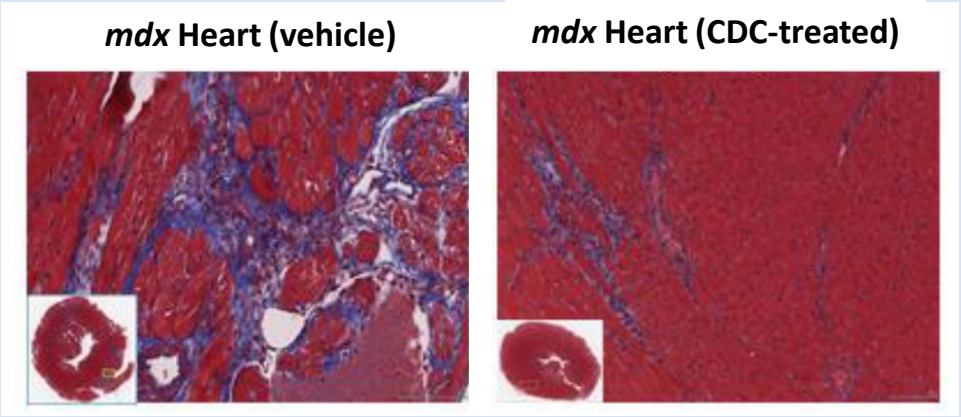
Measure	N	Number of events	Hazard ratio, confidence interval	*P* value
LV ejection fraction per 3% decrease	78	15	1.32 (1.12–1.55)	<0.001
LV end diastolic volume indexed per 4 mL/m² increase	77	14	1.20 (1.09–1.32)	<0.001
LV end systolic volume indexed per 2 mL/m² increase	77	14	1.12 (1.06–1.19)	<0.001

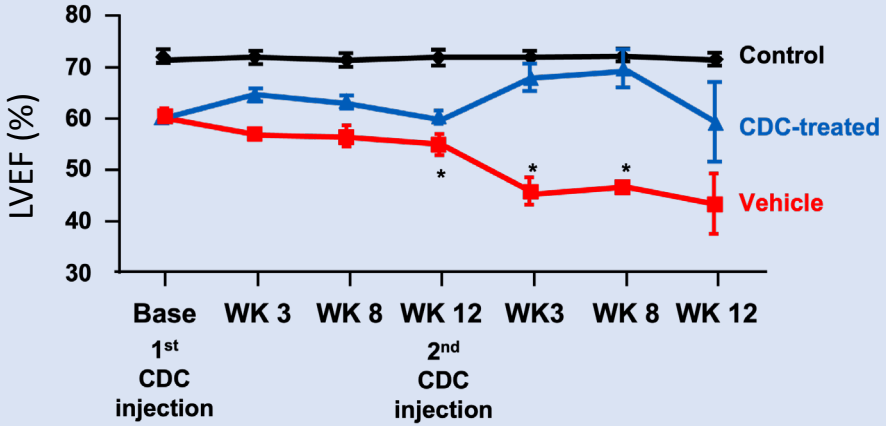


Soslow, J.H. *et al*. *Circ.: Hear. Fail.* 2023.

Deramiocel

- Cardiosphere derived cells (CDCs) are stromal cells cultured from cardiac tissue explants.[1]
- CDCs are not stem cells and do not engraft.
- They exert their anti-fibrotic and anti-inflammatory effects through the release of exosomes.



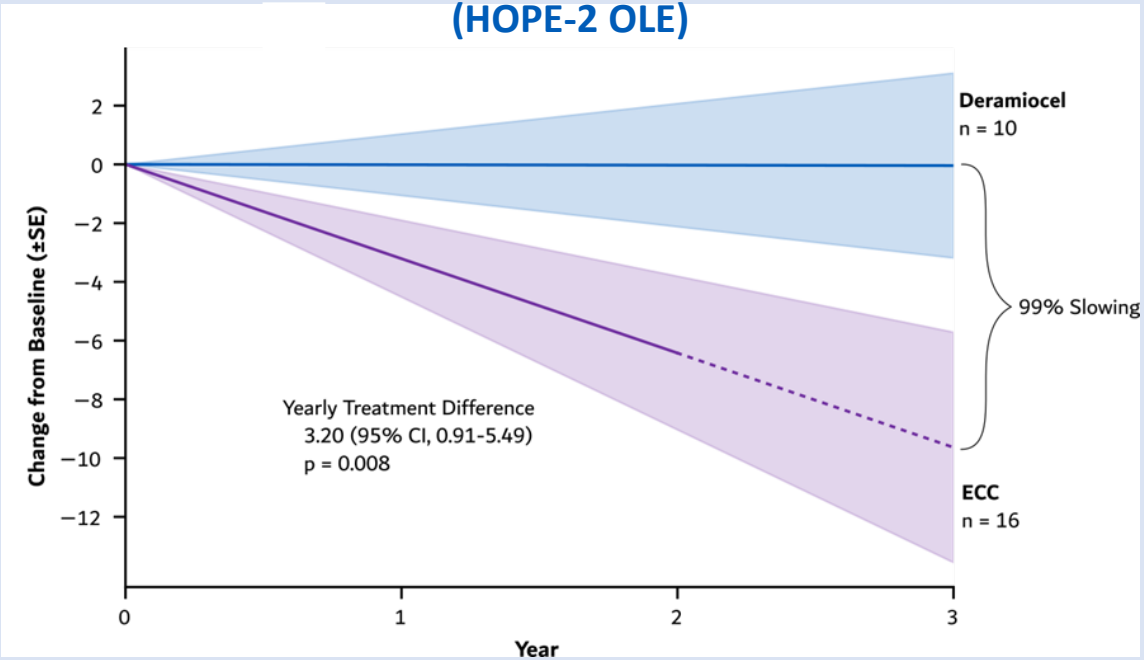


1. Marbán, E. *Circ. Res,* 2024.
2. Rogers, R. G. *et al. JCI Insight* **4**, 2019. Rogers, R. G. *et al. Stem Cell Rep,*2025.
3. Chimenti, I. *et al. Circ. Res,* 2010, Walravens, A.-S. *et al. Sci. Rep,* 2021.
4. Rogers, R. G. *et al. JCI Insight,* 2019.
5. Aminzadeh et al., *Stem Cell Rep,* 2018

Deramiocel - HOPE-2 and HOPE-2 OLE

- Phase 2 studies of deramiocel in DMD suggest a durable clinically and statistically significant benefit in both musculoskeletal and cardiac domains
  - HOPE-2- randomized, double blind, PBO controlled (n=20)[1]
  - HOPE-2 open label extension (n=10)[2]

LVEF comparison with matched external control group (HOPE-2 OLE)



1. McDonald, C. M. *et al. Lancet,* 2022.
2. McDonald, C. *et al. eClinical Medicine,* 2026.

Objectives

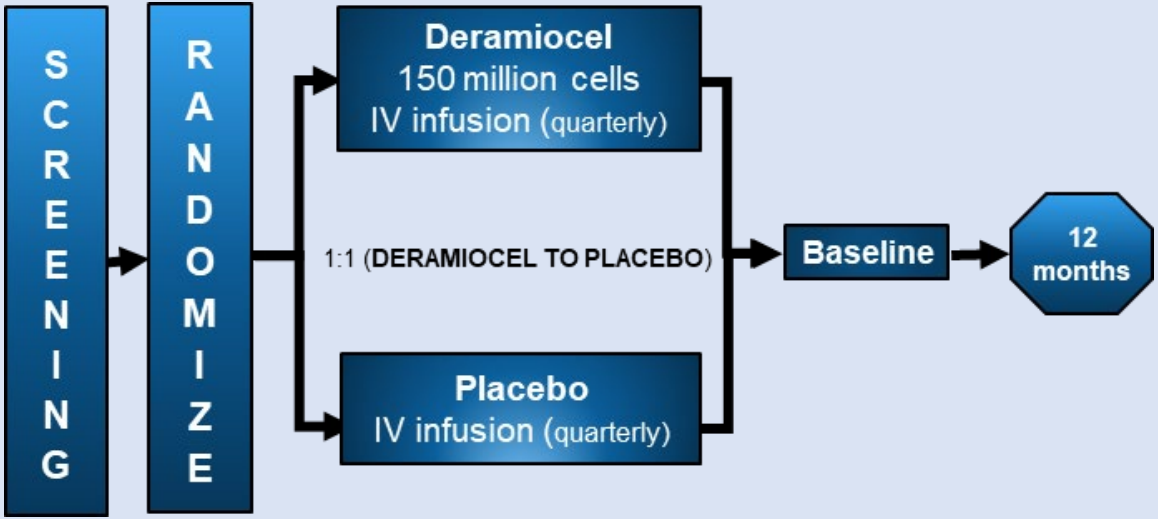
- ***Hypothesis 1:*** Deramiocel preserves left ventricular ejection fraction (LVEF) and stabilizes the progression of late gadolinium enhancement (LGE) versus placebo.

- ***Hypothesis 2:*** Similar treatment benefits are confirmed against a propensity-matched natural-history cohort of untreated DMD.

HOPE-3 Pivotal Phase 3 Trial

Study Design

- Phase 3: randomized (1:1), double-blind, placebo-controlled study
- Conducted in the United States at 20 clinical sites
- Primary results published: McDonald *et al., Lancet*, 2026.



HOPE - 3
DUCHENNE CLINICAL TRIAL

Endpoints

- **Primary efficacy endpoint**[1]: PUL v2.0
- **Key secondary endpoint**[1]: left ventricular fraction (LVEF)
- **Secondary endpoints**[1]: mid-level PUL v.2.0, GST and LGE
- **Secondary endpoints**[2]: LVEF in Cardiomyopathy

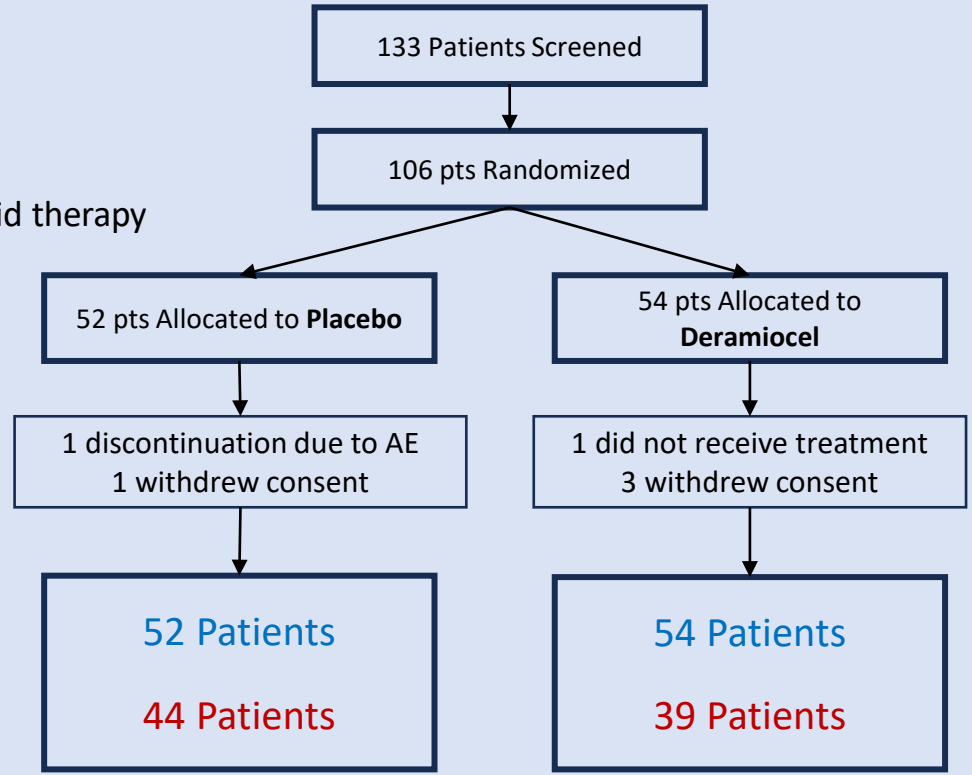
ClinicalTrials.gov ID: NCT05126758 [1]Type-I error controlled [2]Not type-I error controlled

HOPE-3 Pivotal Phase 3 Trial

Patients

Key Entry Criteria

- Ages ≥ 10 who are late or non-ambulatory
- LVEF ≥ 35%
- All patients on background stable corticosteroid therapy



OUTCOME MEASURES

Primary PUL 2.0 (ITT=106)

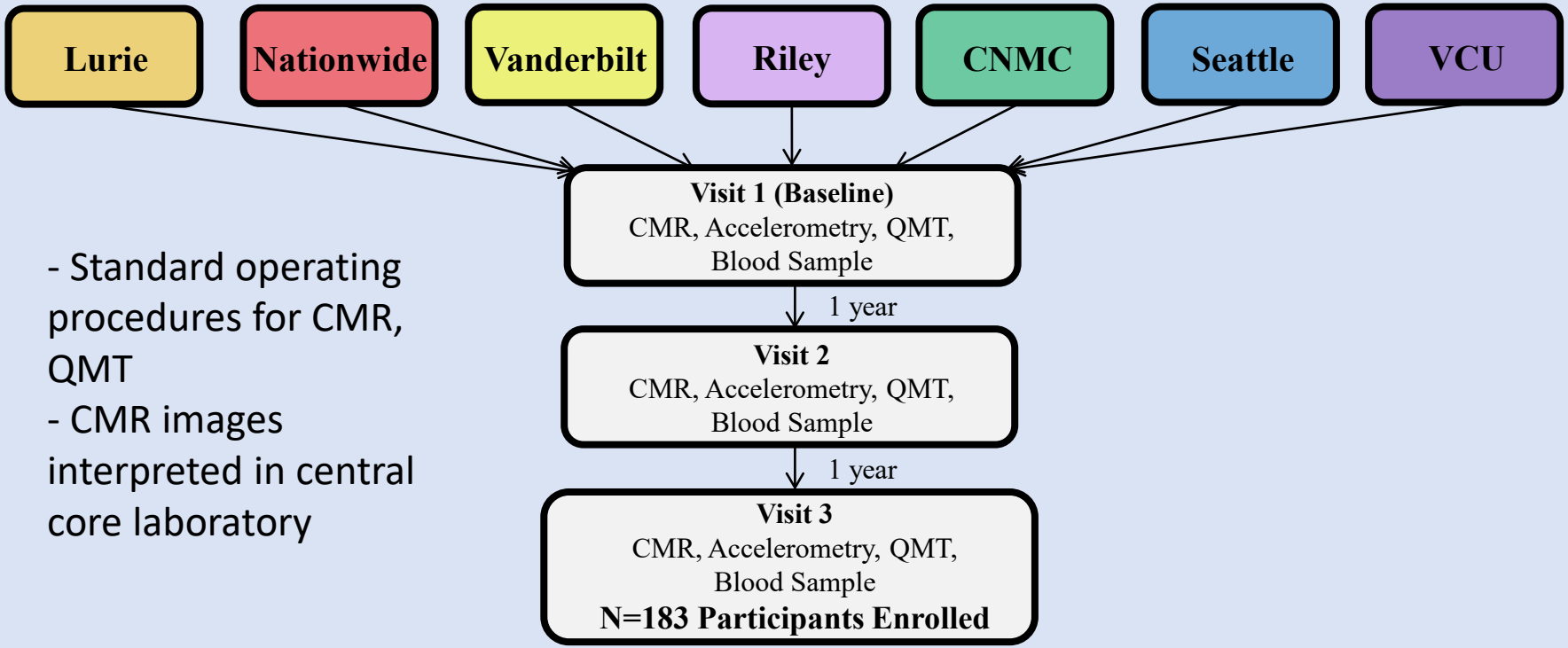
Key Secondary LVEF* (ITT=83)

*Population for LVEF required centrally analyzable baseline and 12-month images

External Comparison Cohort

DMDCCC Natural History Study (prospective, NHLBI and FDA funded)

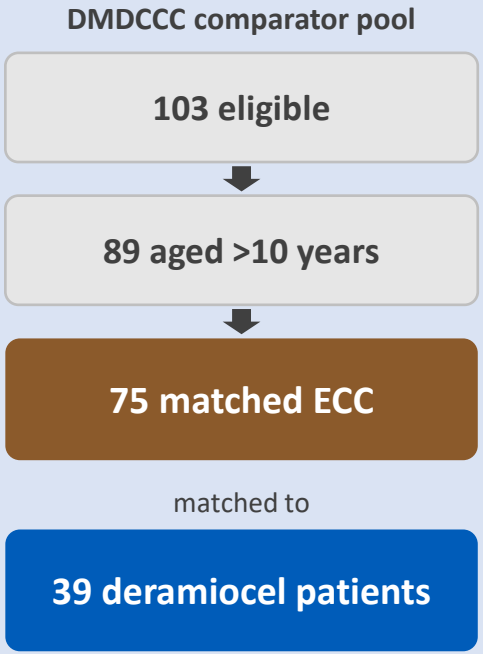
First patient in: 2/21/14; last patient out: 12/15/25



- Standard operating procedures for CMR, QMT
- CMR images interpreted in central core laboratory

Propensity-Matching

- **Comparator:** DMDCCC natural history study — DMD patients on cardiac medication with baseline and 12-month CMR
- Matched to the 39 deramiocel patients on **age, baseline LVEF, and their interaction**
- Up to 5 comparators per treated patient (caliper 0.25 SD) → **75 matched patients**; analyses weighted by match weight



ECC CMRs read at DMDCCC sites, not the HOPE-3 core lab. ECC = external comparator cohort.

Statistical Analysis

- **Deramiocel vs placebo** (Pre-specified)
  - Primary analysis comparing PUL - HOPE-3 primary-publication model (MMRM)
  - 12-month change in LVEF - HOPE-3 primary-publication model (Rank ANCOVA)
  - Secondary analysis of 12-month change in LVEF in cardiomyopathy subgroup (Rank ANCOVA)
  - Secondary analysis of change in LGE-positive segments at 12 months(ANCOVA)
- **Deramiocel vs ECC**, weighted by match weight (all post-hoc)
  - 12-month change LVEF (Rank ANCOVA)
  - 12-month change in LVEF in cardiomyopathy subgroup (Rank ANCOVA)
  - 12-month change in LGE-positive segments vs the LVEF-matched ECC with LGE at both visits (ANCOVA)
- Report p-values from the above models
- Figures demonstrate unranked LS-mean difference (deramiocel − comparator)

Baseline Characteristics

	Placebo (n=44)	Deramiocel (n=39)	Matched ECC (n=75)
Age, years, median (range)	14 (10–22)	**16 (10–22)**	16 (10–25)
Baseline LVEF, %, mean (SD)	59.6 (5.96)	**54.3 (7.60)**	52.1 (8.80)
Baseline LVEF, %, median (range)	60 (48–74)	**55 (37–69)**	54 (18–74)
Cardiomyopathy, n (%)	32 (72.7)	**32 (82.1)**	60 (87.4)
Non-ambulatory, n (%)	38 (86.4)	**33 (84.6)**	57 (79.6)
Ambulatory, n (%)	6 (13.6)	**6 (15.4)**	18 (20.4)
Cardiac medication at baseline, n (%)			
ACE inhibitor / ARB / ARNI	40 (90.9)	**37 (94.9)**	74 (99.3)
Beta blocker	17 (38.6)	**17 (43.6)**	23 (31.5)
MRA	29 (65.9)	**21 (53.8)**	36 (45.9)
SGLT2 inhibitor	1 (2.3)	**4 (10.3)**	0 (0.0)
No cardiac medication	3 (6.8)	**2 (5.1)**	0 (0.0)

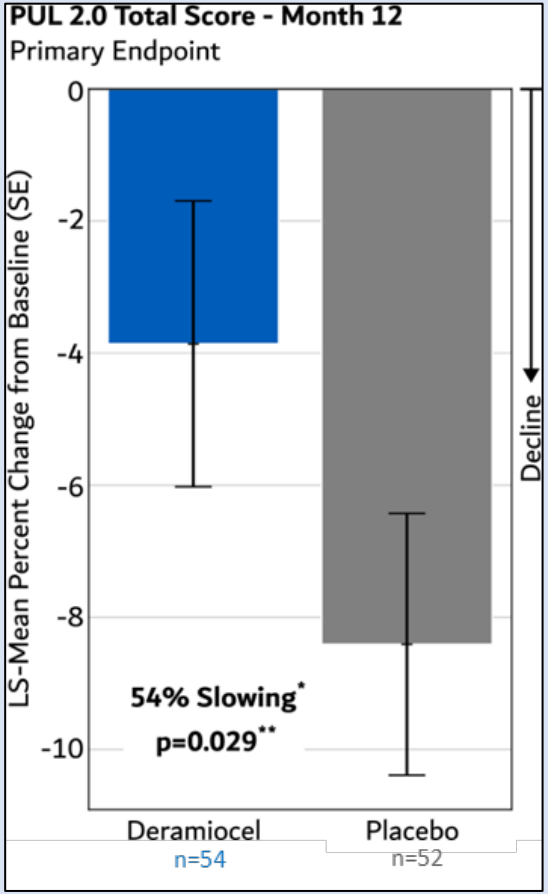
Cardiac ITT population: patients with centrally reviewed, evaluable CMR LVEF at baseline and 12 months. Matched ECC: DMDCCC natural history patients propensity-matched to deramiocel; statistics weighted by match weight, n = matched patients. Cardiac medication: taking or prescribed on the day of the baseline CMR (ECC: DMDCCC taking_* fields); cardiac medication at baseline was an ECC eligibility criterion. Ambulatory status: HOPE-3 ADSL; ECC visit 1. Cardiomyopathy: LVEF <55% or any LGE.

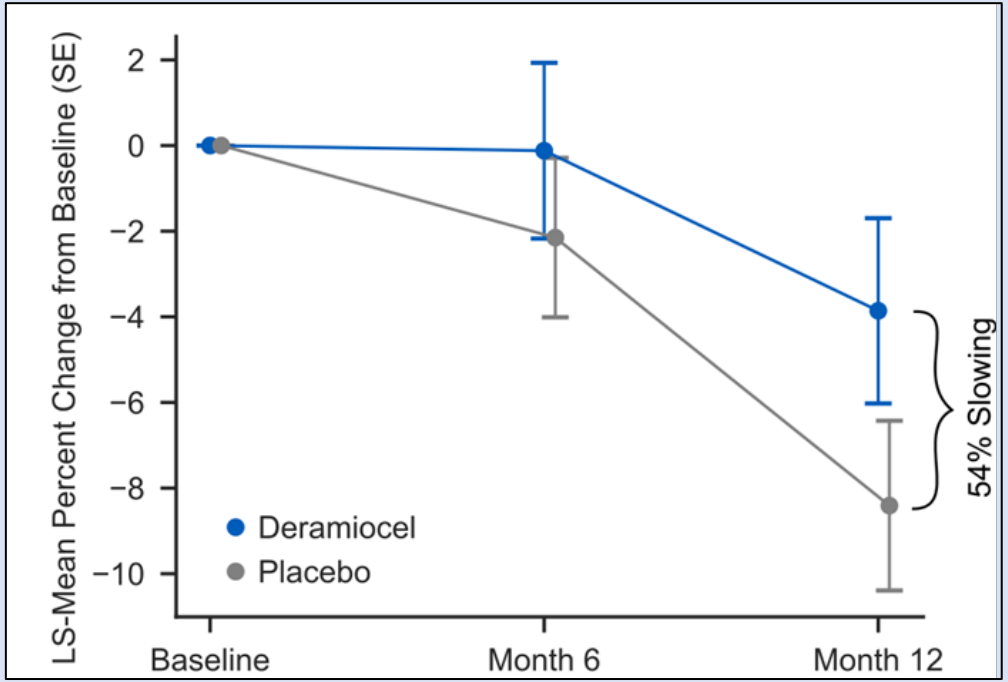
Safety

	Placebo n=52, n (%)	Deramiocel n=53, n (%)	Overall n=105[1], n (%)
Any TEAEs	43 (82.7)	**50 (94.3)**	93 (88.6)
TEAEs related to IP or administration procedure	19 (36.5)	**44 (83.0)**	63 (60.0)
TEAEs related to IP	16 (30.8)	**44 (83.0)**	60 (57.1)
TEAEs related to administration procedure	9 (17.3)	**23 (43.4)**	32 (30.5)
TEAEs related to IP or administration procedure, by maximum severity			
Mild (grade 1)	15 (28.8)	**19 (35.8)**	34 (32.4)
Moderate (grade 2)	3 (5.8)	**25 (47.2)**	28 (26.7)
Severe (grade 3)	0	**0**	0
Life-threatening (grade 4)	1 (1.9)	**0**	1 (1.0)
Fatal (grade 5)	0	**0**	0
TEAEs leading to death	0	**0**	0
Any serious TEAEs	5 (9.6)	**1 (1.9)**	6 (5.7)
Serious TEAEs related to IP or administration procedure	1 (1.9)	**1 (1.9)**	2 (1.9)

[1] Safety population (n=105)

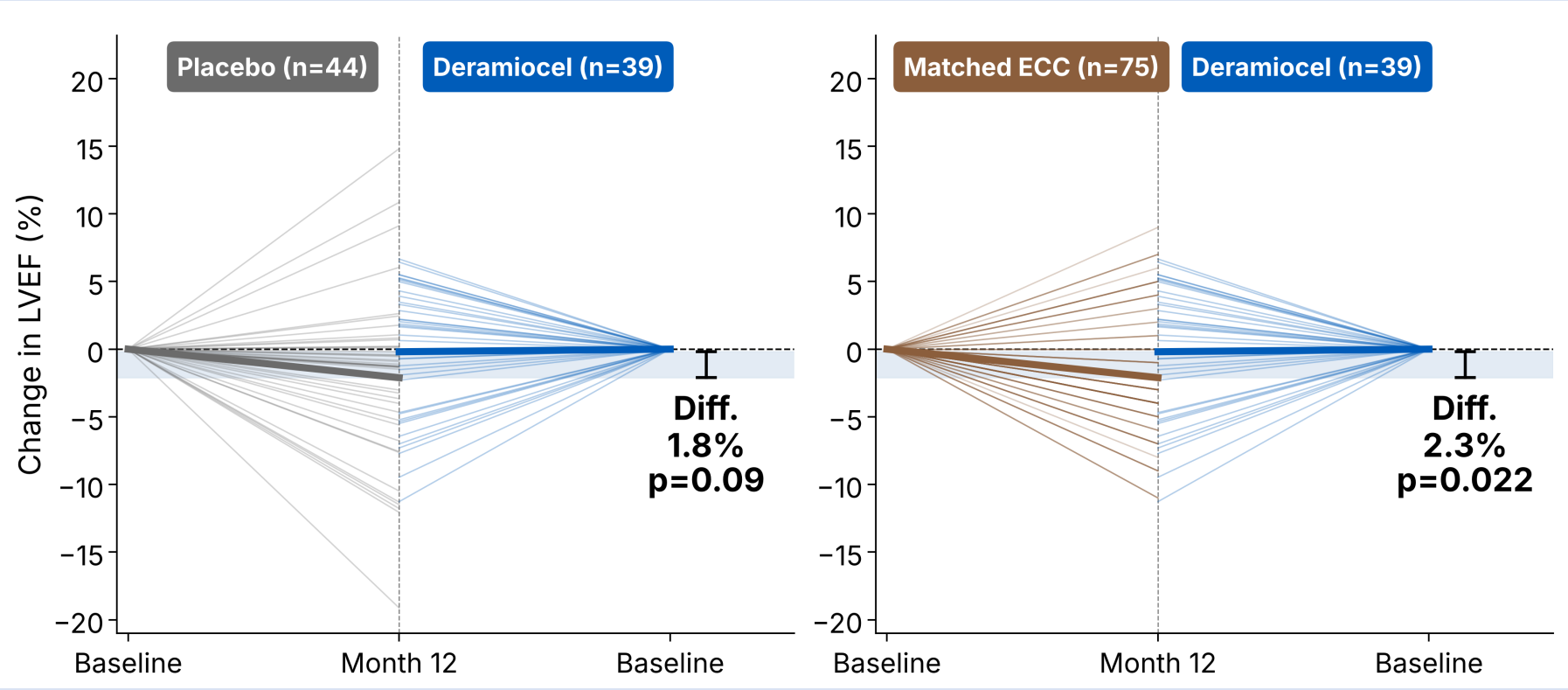
Primary Endpoint: PUL 2.0 at 12 months





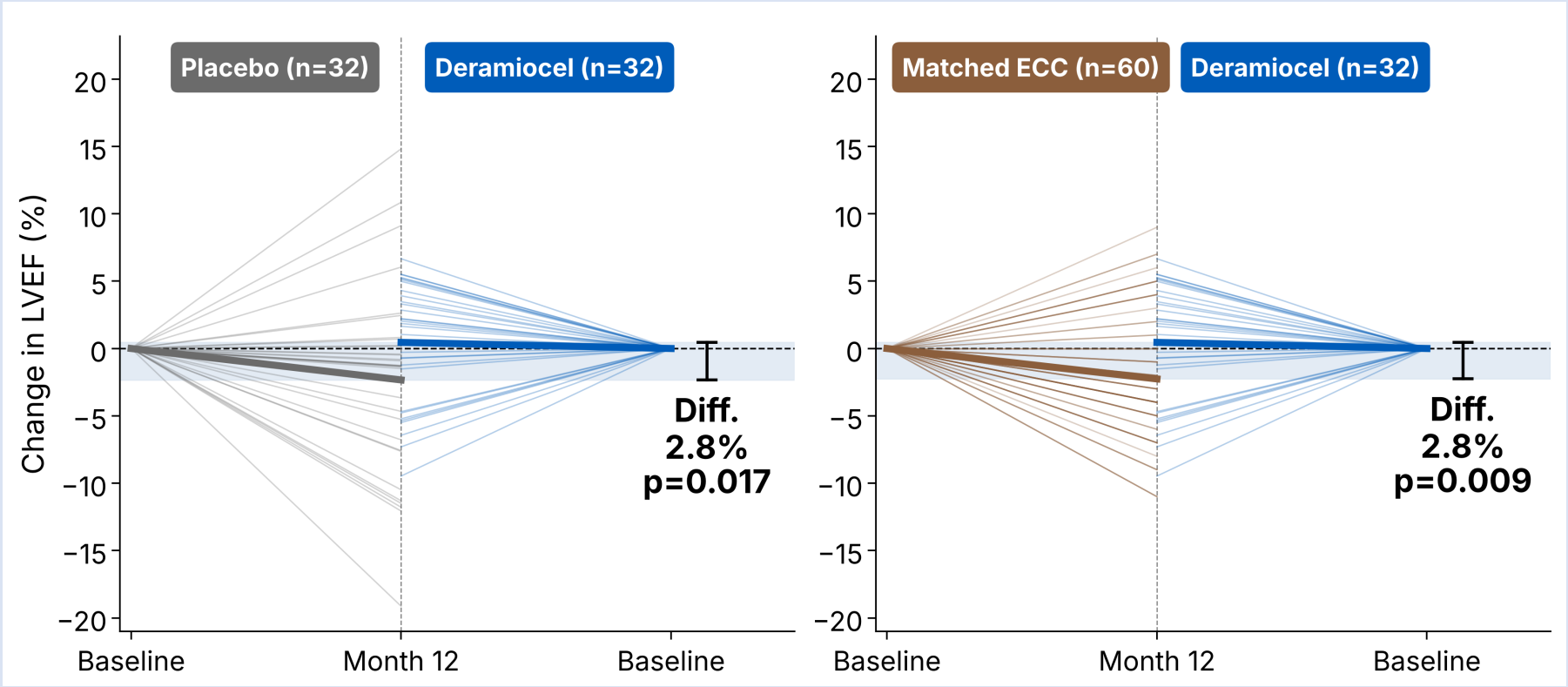
Deramiocel treatment difference = 1.2 points (54% slowing); p=0.029

Key Secondary Endpoint: LVEF 12 months



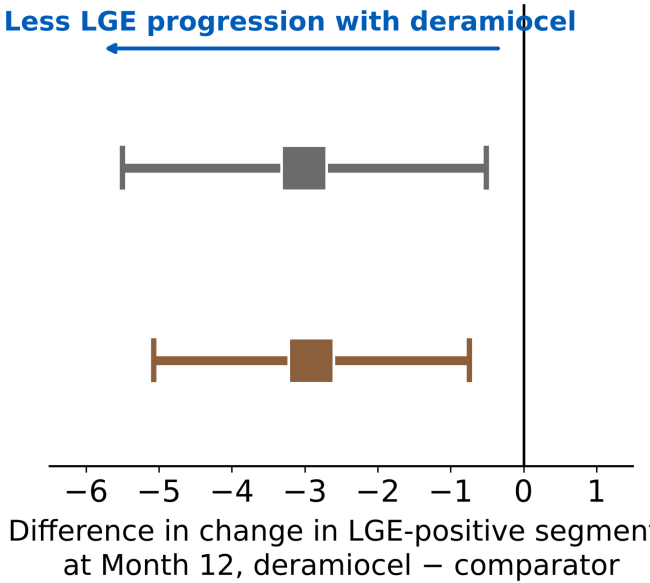
Thin lines: individual patients; bold line: weighted mean change. Diff. = LS-mean difference (deramiocel − comparator); p from rank ANCOVA. ECC weighted by match weight.

Secondary Endpoint: Cardiomyopathy Subgroup



Thin lines: individual patients; bold line: mean change (ECC weighted by match weight). Vs placebo: observed mean difference and nominal rank-ANCOVA p, as reported in the Lancet. Vs matched ECC: LS-mean difference, weighted rank ANCOVA p (post hoc). Cardiomyopathy subgroup not type-I-error controlled.

Secondary Endpoint: LGE



	Difference (95% CI)	p
vs Placebo Randomized, HOPE-3 (9 vs 13)	**−3.0 (−5.5 to −0.5)**	**0.022**
vs Matched ECC Natural history, weighted (9 vs 62)	**−2.9 (−5.1 to −0.7)**	**0.009**

Lancet LGE ANCOVA (baseline, age, LVEF stratum, baseline LVEF, age × baseline LVEF), unranked; ECC weighted by match weight. Nominal p-values.

Conclusions

- Deramiocel stabilized LVEF in patients in the HOPE-3 trial
  - Larger effect in the cardiomyopathy subgroup
- Treatment benefits were confirmed when compared with propensity score matched patients from the DMDCCC NHS
- Anti-fibrotic activity was demonstrated by stabilization of LGE in DMD, which is consistent with the known mechanism of action of Deramiocel and the preclinical data

Acknowledgements

- **Thank you to all the patients and families who participated in the HOPE-3 Study**
- HOPE-3 Investigators (20 sites) and Coordinators
- Members of the DMDCCC