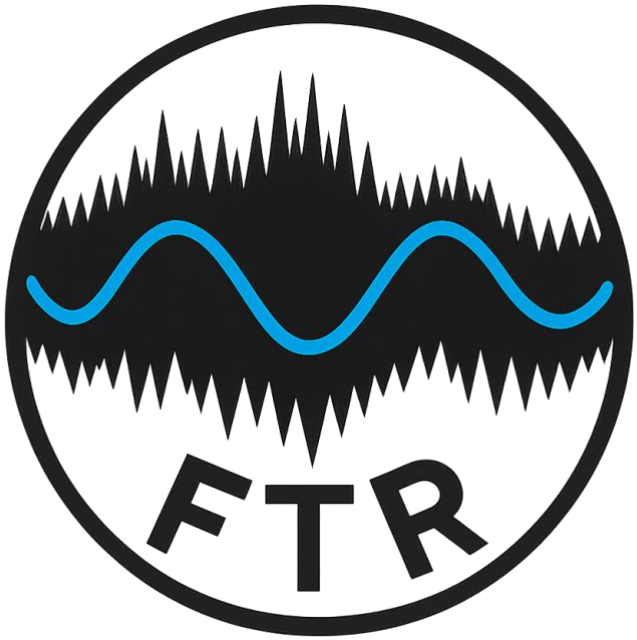
Star sign Capricor: when astrology does drug development



Fourier Transform Research

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Executive Summary

Capricor Therapeutics (NASDAQ:CAPR) is expected to announce the results of a phase III clinical trial of its only asset, Deramiocel (CAP-1002), in Duchenne Muscular Dystrophy in Q42025.

In this work, we present an air-tight case challenging the safety and efficacy of Deramiocel as a treatment for Duchenne Muscular Dystrophy.

Capricor has changed the stated mechanism of action multiple times throughout the development of deramiocel, and they have failed to characterize the cell product leading up to this pivotal readout. We do not find the assembled data compelling or rooted in the scientific process.

The repeated failure of deramiocel in cardiac indications clearly show that it has little effect on human tissue, and the purported HOPE-2 efficacy signal was spurious and likely confounded by concomitant medication. Beyond these cardiac readouts we have found clear baseline imbalances in the functional readouts for DMD which confound the stated pre-specific primary endpoints in HOPE-2 and HOPE-3.

We also believe the safety signals of this product are not discussed enough publicly. We have found an alarmingly high rate of anaphylaxis and severe immune mediated reactions as a result of taking this allogeneic cell product. Worse still, are Capricor's attempts to *hide* this data from their published works.

They have yet to demonstrate clear efficacy signals and the FDA issued a CRL in July of 2025, requiring Capricor to finally unblind themselves to the HOPE-3 topline data which they have had available to them for over a year, and which they have continuously punted since they first said they would publish it in Q42024.

Capricor has been (unsuccessfully) developing Deramiocel for the past 15 years across 8 indications, and Duchenne Muscular Dystrophy may be the last. Upon the announcement of Phase III failure, the stock price should convert to the company's cash value or below, representing a >60% decline from its current price of ~$5.80 per share (landing near $2).

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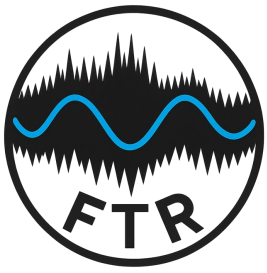


Company History

Capricor Therapeutics (NASDAQ: CAPR) is a clinical-stage biotechnology company developing cell- and exosome-based medicines, best known for deramiocel (CAP-1002), an allogeneic cardiosphere-derived cells (CDCs) therapy for Duchenne muscular dystrophy (DMD). The company's scientific roots trace to the laboratory of cardiologist-scientist Eduardo Marbán, MD, PhD, who first isolated and characterized CDCs in academia; Capricor's wholly owned operating subsidiary, Capricor, Inc., was founded in 2005 on this work and later moved with Marbán from Johns Hopkins to Cedars-Sinai. In November 2013, Capricor, Inc. completed a reverse merger with Nile Therapeutics, after which the combined public entity was renamed Capricor Therapeutics.

Early development focused on cardiac indications. After promising first-in-human data (CADUCEUS), Capricor's Phase II ALLSTAR trial in post-MI patients failed to meet its scar-reduction endpoint in 2017, prompting Janssen Biotech, Inc. not to exercise its option on CAP-1002; Capricor retained full rights and pivoted to DMD, where they believed CDCs would be able to address skeletal and cardiac muscle decline.

In DMD, Capricor reported "positive signals" across the HOPE clinical program, including HOPE (Phase I/II) and HOPE-2 (Phase II), with The Lancet publication in 2022 describing slowed deterioration in upper-limb function and supportive cardiac measures after repeated IV dosing of CAP-1002[1]. The company has also advanced an exosome platform (CAP-2003), derived from CDCs, as a next-generation therapeutic approach.

Regulatory interactions have been active in 2025. The FDA issued a Complete Response Letter (CRL) in July 2025 for deramiocel; Capricor has since engaged the agency and, per a September 25, 2025 update, prepared a resubmission supported by HOPE-3 data, with topline results guided for mid-November 2025 and then revised again to a few weeks after the Q3 ER in mid-November.

Capricor is led by co-founder Linda Marbán, PhD (Chief Executive Officer since 2013), with Eduardo Marbán serving as scientific founder and long-time advisor; Executive Chairman Frank I. Litvack, MD, is a cardiologist-entrepreneur with decades of device and biotech leadership. Recent additions include industry veteran Michael Binks, MD, as Chief Medical Officer (2025), reflecting a build-out toward late-stage development and potential commercialization.

Deramiocel (CAP-1002)

Deramiocel is the lead candidate for Capricor, which is made from Cardiosphere-derived Cells (CDCs) to treat cardiac injury. This product comes from harvesting heart cells from an organ donor, culturing them in vitro, and injecting them intravenously (as is the case in Phase III) or via intracoronary catheter (as in previous trials) to the patient as an allogeneic cell product.

This approach has been tried in Myocardial Infarction, Heart Failure with Preserved Ejection Fraction, COVID-19, Ventricular Dysfunction, Univentricular Heart Disease, Dilated Cardiomyopathy, Pulmonary Hypertension, and now Duchenne Muscular Dystrophy. Despite the many clinical failures no clear clinical efficacy has ever been shown.

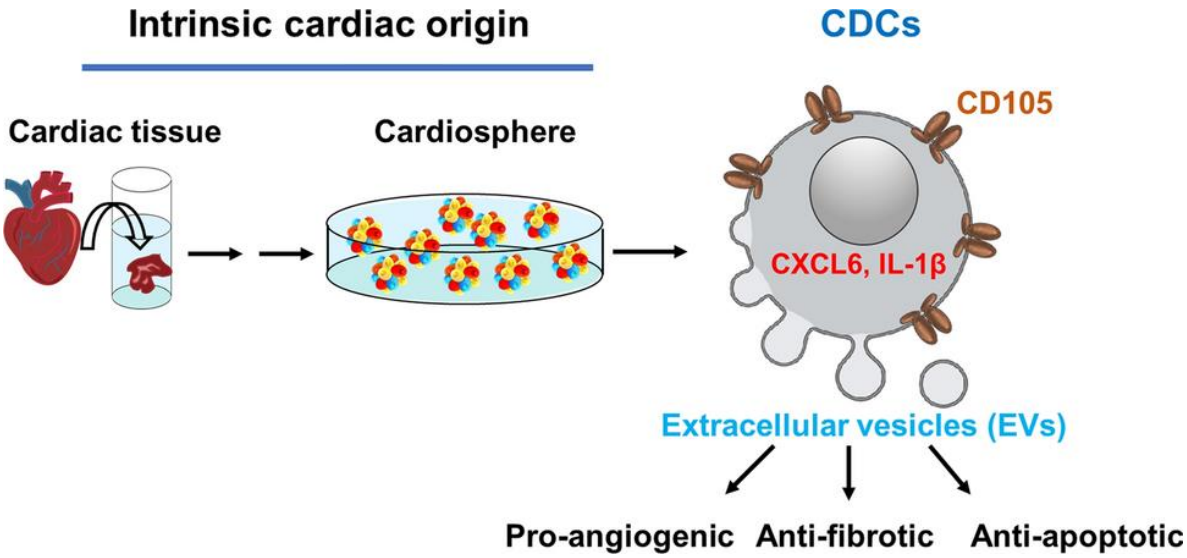
Cardiosphere-derived Cells (CDCs)

To further understand Deramiocel and its potential as a therapeutic agent, a deeper understanding of CDCs is necessary. The first use of the term 'cardiosphere' was coined in a 2004 paper by Messina et al. describing the isolation and long-term self-renewal of undifferentiated self-adherent clusters of cells obtained from murine and human cardiac tissue[2]. In parallel, the early 2000s saw an intense push to regenerate injured tissues using stem and progenitor cells, with cardiology becoming one specialty with significant activity given the unmet need in treating myocardial infarction.

This led to several clinical studies during the early 2000s with mixed results, largely using either skeletal myoblasts or autologous bone-marrow mononuclear cells injected directly into the heart muscle or delivered locally within the coronary circulation of animal models[3,4]. In 2007, Eduardo Marbán, reported on CDCs grown from percutaneous endomyocardial biopsies[5]. In the introduction of their paper four of the first five citations (and 7 in total) are from the work of Anversa and state "recent evidence that the adult mammalian heart contains endogenous, cardiac-committed stem cells." as they describe why they began the program that led to deramiocel.

However the field now views this predicate work much differently. A large body of Anversa-affiliated work underpinning claims of robust, self-renewing c-kit$^+$ cardiac stem cells has been repudiated or retracted including the SCIPIO trial report in *The Lancet* and multiple basic/translational papers after institutional investigations. Additionally, a settlement was reached between Anversa and colleague's former hospital and the U.S. Government related to federal grant fraud and research misconduct. These events substantially undermine the field's original "resident cardiac stem cell" premise.

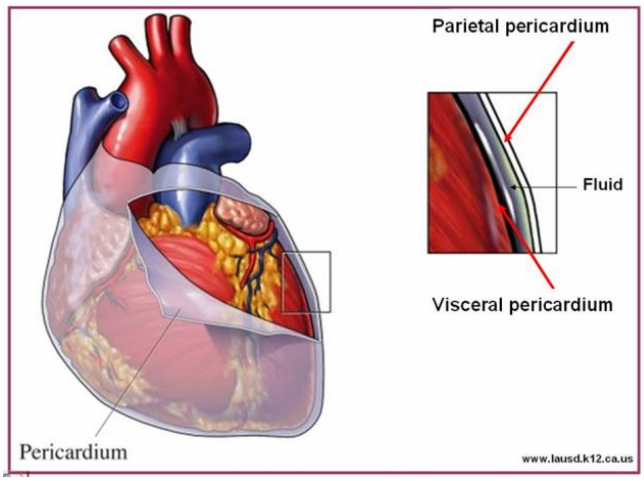
In parallel, neutral reassessments and lineage-tracing studies from independent groups concluded that c-kit labeling largely marks non-myocyte lineages and contributes minimally to new cardiomyocytes, further eroding the biological basis for the original regeneration narrative[6,7]. Against this backdrop, the Marbán/Capricor CDC platform emphasis shifted from direct remuscularization towards paracrine mechanism, including extracellular vesicles (EVs) as putative effectors (e.g. CDCs and/or their EVs) as *signalers* rather than durable "stem cells" engrafting to rebuild myocardium which can be seen in the figure below.

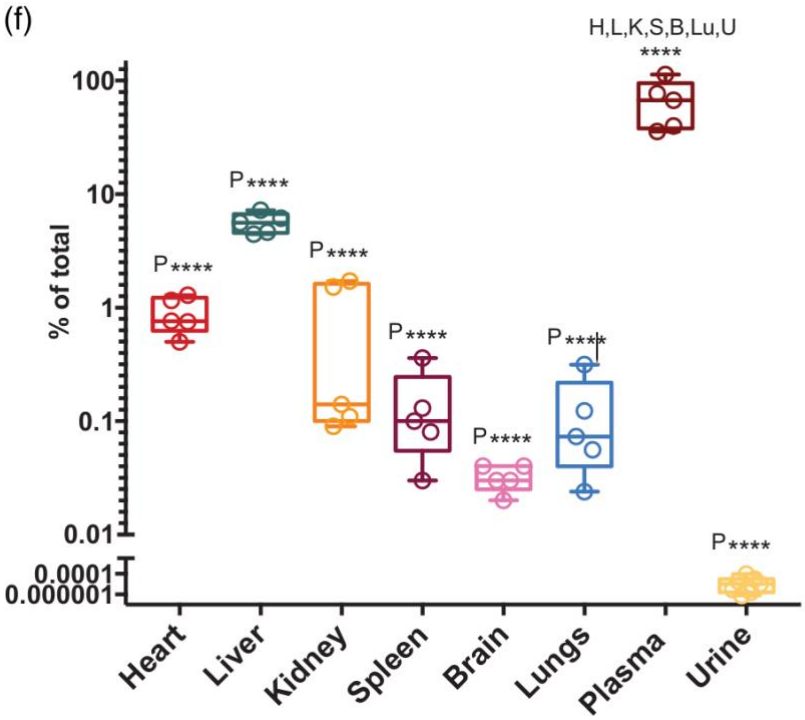


Mechanism of Action

Capricor's deramiocel has a rather purportedly multi-faceted mechanism of action. Firstly, it relies on what we would describe as a Russian-doll-like drug delivery mechanism by injecting CDCs which contain exosomes which contain the payload which happens to coincidentally act upon cardiac and skeletal muscle tissue.

This is very difficult to imagine working in principle since 1. there is no intrinsic tropism for CDCs to heart tissue 2. the pericardium envelopes the heart and 3. it is therefore not readily permeable. Further in biodistribution studies by Marban and colleagues show that CDCs primarily do not end up in heart tissue.





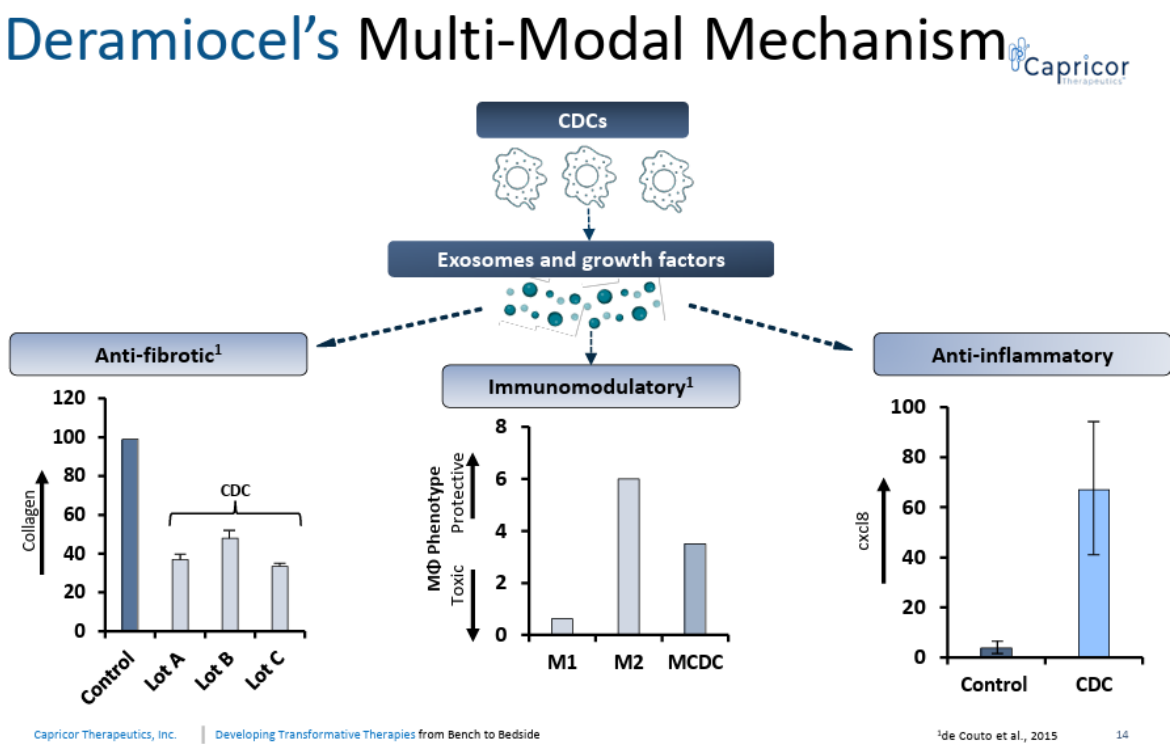
Here work from the Marban lab shows that approximately 1% of CDCs sequester on the heart in an animal model after injection[8]. The overwhelming majority of cells are simply circulating in serum. Within a matter of days these cells are lysed and no longer circulating in vivo. Once lysed their exosomes will be exposed within serum, and we know they have incredibly short half-lives. Matsumoto et al. tell us that exosome half-life is as low as 7 **minutes**, meaning that within an hour 0.3% of

exosomes remain intact in circulation. Once the exosomes are lysed their payload will be cleared quite quickly in serum via natural pathways.

Further, exosomes do not contain a homogenous distribution of payload(s) as many different payloads exist within CDCs. They do not contain homogenous payload amounts (sometimes several copies of an oligo, sometimes they are empty, sometimes one copy). We also do not have a sense of retention at the site of injury. How long do cells stay on/ in the heart?

The lack of tropism to the heart, coupled with the nested payload delivery mechanism therefore requires substantial numbers of CDCs to act upon local cardiac tissue to resolve injury. We contend that this is well above the injected fraction, even in best case estimates. More on this in the following PK analysis.

But let's ignore this for now. Let's consider the current deramiocel MoA as proposed by Capricor.

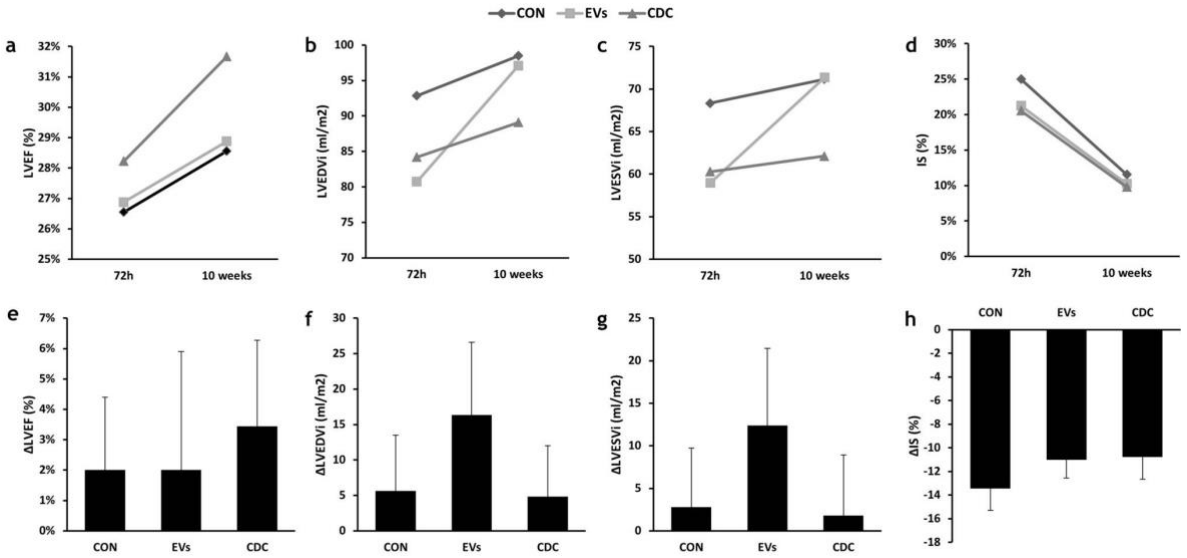


They assert that the therapy, through exosomes and growth factors contained within the cell, are anti-fibrotic, immunomodulatory and anti-inflammatory.

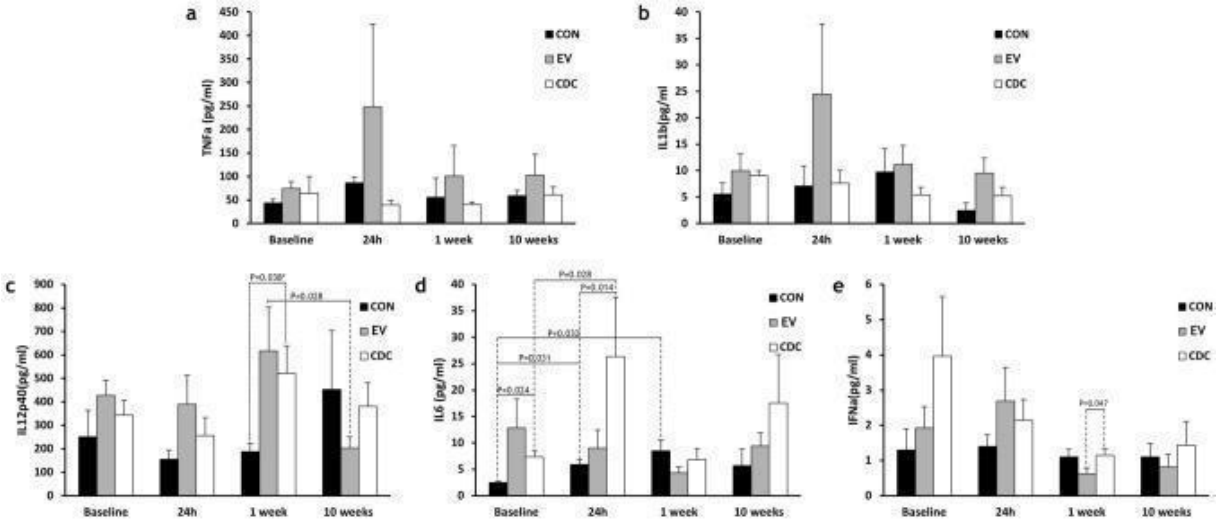
First, the claim of anti-inflammatory activity conferring clinical benefit. CDCs have been studied in many models by many different researchers but few are able to demonstrate efficacy that Capricor claims for cardiac tissue. In particular, we see this Spanish group was unable to observe a difference in efficacy for CDCs or extracellular

vesicles (exosomes) compared to placebo when injected directly into the pericardial sac on the heart of swine post-infarct.

Below we can see that there is no difference to the functional activity of the heart in CDC vs placebo group. In particular, we note the remarkably comparable outcome for placebo and treatment arms in LVEF, the primary endpoint in the upcoming HOPE-3 clinical trial.

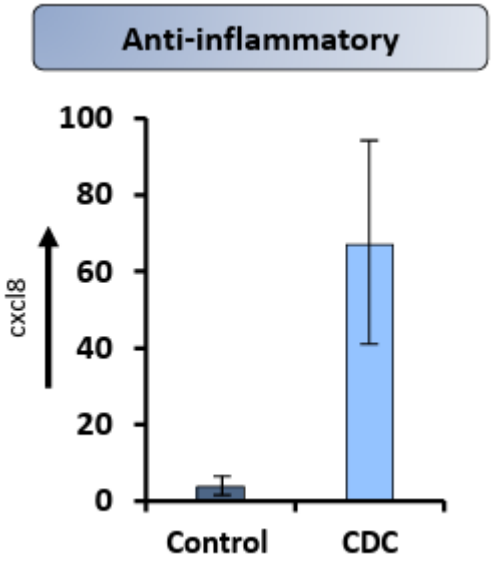


Next, we see the notably consistent readouts for known inflammatory cytokines such as TNFa, IL1b, IL6, IFNa and IL12. For an agent to be anti-inflammatory one would expect to see reductions in known inflammatory signalling cytokines.



In this study they were unable to observe any differences between several markers on the panel and thus were unreported, in particular, IL-8. We note this because you may remember that Capricor's slide deck above cites IL-8 as a key marker.

We find this strange, because increased IL-8 is ostensibly pro-inflammatory via recruitment of neutrophils to the site of inflammation which produce ROS and secrete proteases. We would also expect to see a suppression of NF-kB, but other studies have shown that CDCs do not downregulate NF-kB. So, unfortunately, Capricor's own slide deck seems to contradict the point it's trying to make in demonstrating a chart of the gene CXCL8 being upregulated by CDCs compared to some control.

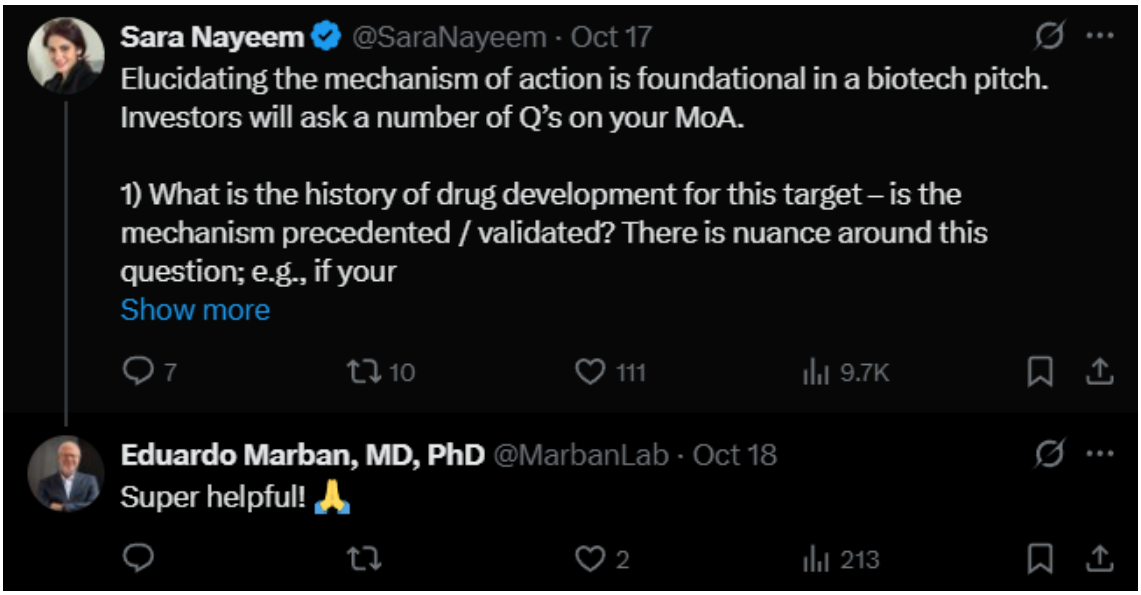


Worse yet, IL-6 gene expression is upregulated in CDCs, according to Capricor's in vitro batch release studies for CAP-1002[9]. CXCL6, is a small cytokine belonging to the CXC chemokine family which elicits its chemotactic effects by interacting with CXCR1 and CXCR2 which are pro-inflammatory chemokine receptors. It has also been found to be a valid marker for Capricor's CDCs[10]. Using single-cell RNA sequencing (sc-RNAseq), several chemokines (CXCL6, CXCL1, CXCL8, CXCL3, CXCL5, CXCL2), interleukins (IL1B, IL1A, IL24, IL6, IL32, IL6ST, IL11, IL1R1) and TGFB1/TGFB2 were found, suggesting that CDCs secrete immunomodulatory molecules[11]. As we noted previously in the figure above by Marban and colleagues, IL-1B and IL-6 if anything are slightly overexpressed in CDCs groups and are pro-inflammatory.

Moreover, a Spanish group preclinical study has confirmed the potential pro-inflammatory effects of CDCs[12]. Cristiomo et al, as well as a Brazilian group Kasai-Brunswick et al. found these cells to be of limited value in infarction and cardiac failure showing no clinical improvement in these animal models[12,13].

All of this paints a very confusing picture on the MoA. We would recommend Sara Nayeem's post on X for further guidance on this topic, which co-founder Dr. Marban

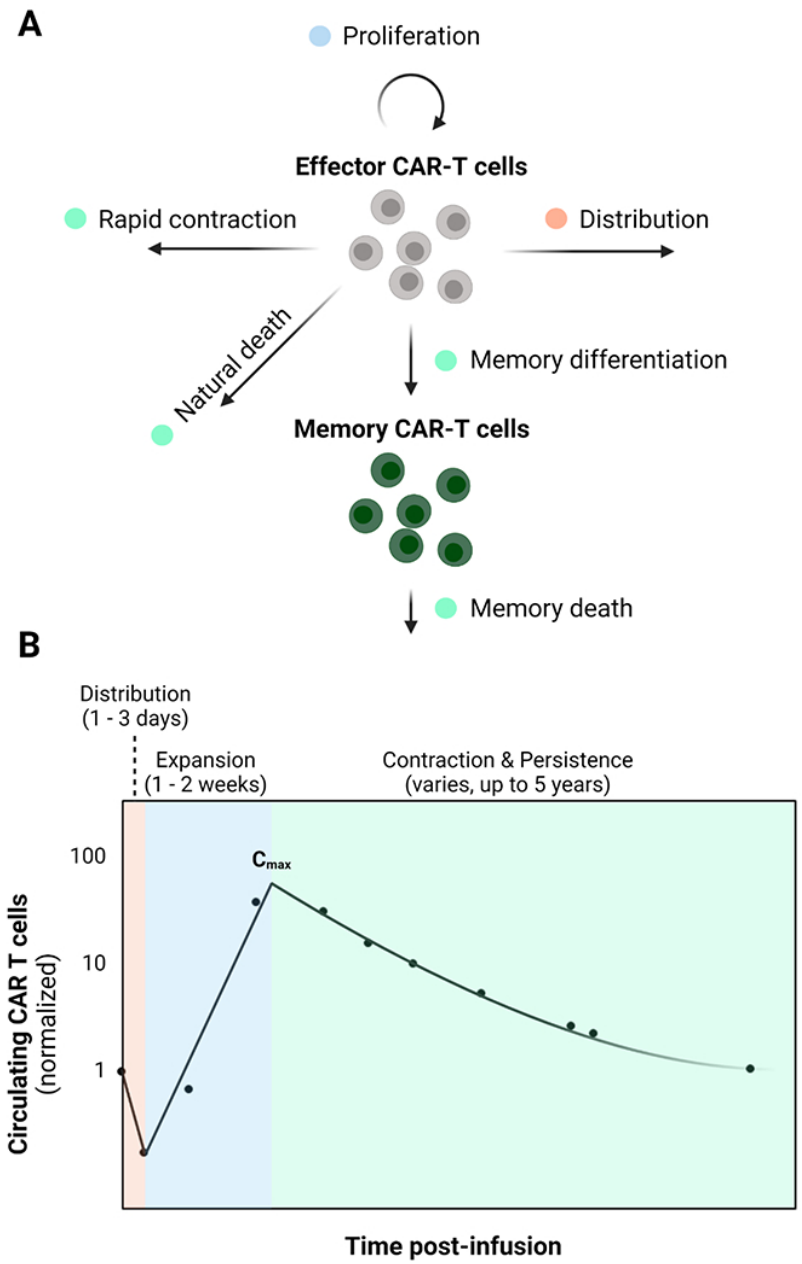
seems to agree with! This is encouraging, and we hope the MoA can be elucidated before BLA resubmission.



Pharmacokinetics/ Pharmacodynamics

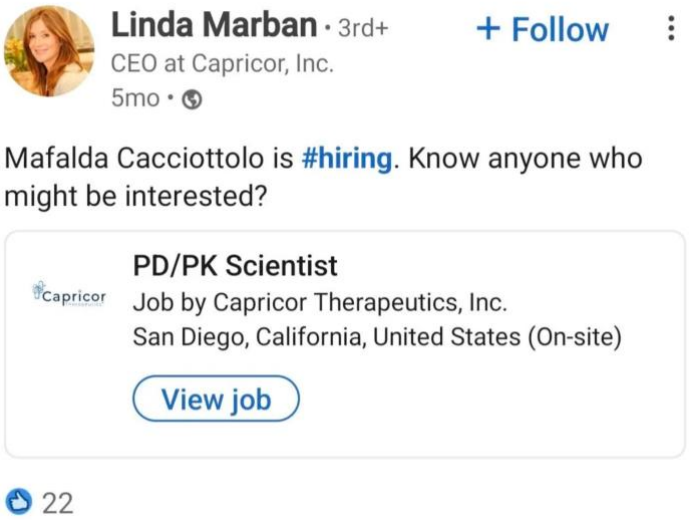
Moving onto the pharmacokinetics of deramiocel, we find there to be a lack of pharmacokinetic analysis and we are also troubled as it is a purportedly registrational data package. Quantifying cellular counts and activity in vivo is critical to demonstrating biological plausibility, and there is no lack of technology to this end with flow cytometry based PK models being widely employed in industry.

We can look to Qi et al. 2022 for an example of how the CAR-T field approaches the problem of pharmacokinetics in cellular therapy[14].



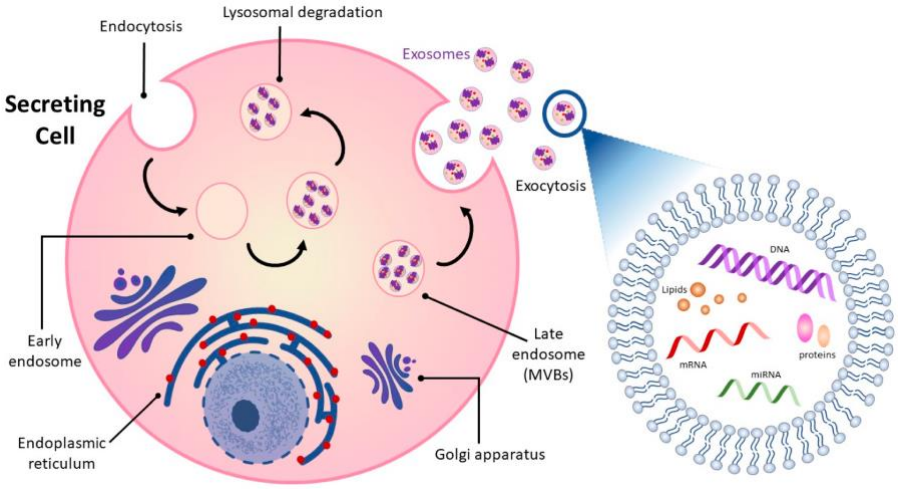
Beyond the cells themselves, simply making an attempt to quantify the exosome species in CDCs would go a long way towards meaningfully convincing the public of this product's efficacy *in vivo*.

We can also consider the FDA guidance page on Cell and Gene therapies. In particular, we note the guidance on Potency Assurance for Cellular and Gene Therapy Products. So it is certainly possible and ostensibly required for a company like Capricor to have gone through this exercise as they prepare for a pivotal readout. We note that they are interested in investigating this issue with a recent job posting:



However the lack of such data going into a BLA resubmission is genuinely surprising for a publicly traded company. PK/PD data in our opinion is something that is established with initial phase 1 data, not after nearly a dozen clinical trials.

Moving onto the PK analysis we conducted; we mentioned previously that an apt analogy to the CDC MoA here is a Russian doll. This is because CDCs are said to carry exosomes, which carry payloads, which act upon the cardiac tissue and reduce inflammation.



This of course brings up a question of: why not deliver the payload more efficiently? Why not directly couple an oligo, or a chemokine, or any payload of interest to a well known carrier like an antibody and drug the patient with that instead?

We note the language from Capricor suggesting that the future directions of the company may be in leveraging exosomes. Engineered variants may see some

improved utility but wild type exosomes have not been found to have drug-like properties.

As we noted previously, they have a heterogeneous distribution of payload with many exosomes containing nothing, and some carrying more than one copy of the desired payload. Further, they have a 7 minute half-life (or 2-4 minutes, according to Morishita 2017) making them unable to circulate in vivo for extended periods of time and engage a target of interest[15,16]. This is extremely problematic as we established earlier, since the payload will be dropped to no effect if not immediately adjacent to target tissues, and even then, we predict very little actual drug makes its way into any cells.

Lastly, they lack any tropism for a cell type and therefore must be proximal to the site of interest (extracellular, intracellular, whatever the target is) to have any activity.

But let us again suspend our disbelief, let us consider the case of a miRNA payload Y-RNA. We assume that ~1% of CDCs end up at the heart (we will not model for the permeability issue with the pericardium). Then, let's use Dr. Marban's estimate of payload uptake in the heart shown previously for healthy conditions (~1%), and even their more generous estimate of uptake under injured heart conditions (~10%), despite DMD patients not fitting this categorization explicitly.

Then, let's model for:

- f_{heart} fraction of CDCs near the heart[17]
- $N_{CDC,\,IV}$ Number of cells injected through IV
- s the exosome secretion rate per cell cg[18,19]
- c cargo per EV distribution
- u fraction of EVs taken up by the heart cells[8]
- ε fraction of payload acting upon the cell
- T effective interaction time

From here we have a model:

$$Functional\ copies\ in\ heart\ =\ N_{CDC,IV}\ \cdot f_{heart} \cdot s \cdot c \cdot u \cdot \varepsilon \cdot T$$

With this we can assign values to each variable:

Variable	**Definition**	**Value**	**Reasoning**
$N_{CDC,IV}$	Number of cells injected through IV	$1.5x10^8$ cells	HOPE-2 dose
f_{heart}	fraction of CDCs	0.01 (1%)	Bonios et al 2011

	near the heart		rat PET study
s	the exosome secretion rate per cell	60 EV/cell hr	Chiu 2021 single-cell data, Kaluri review 2020
c	cargo per EV distribution	1 copy per EV	Generous mid-point of various studies
u	fraction of EVs taken up by the heart cells	0.10 (10%)	DUST method study Ciullo 2022
ε	fraction of payload acting upon the cell	0.10 (10%)	Typical cytosolic escape efficiency estimate
T	effective interaction time	24h	Pre-clin dwell ranges

Running this math yields 2.16 x 10^7 copies. So 21m functional cargo molecules delivered to the myocardium.

With this model, we can assume that there is an amount of payload required to act upon the cells in the heart to cause an effect. We propose that this is 9x10^9 copies. This is because we assume that 3x10^6 macrophages in the area of the left ventricle would require 3x10^3 copies per cell.

Thus, we can calculate target engagement:

$$Efficacy\ fraction\ = \frac{2.16x10^7}{9x10^9} = 0.0024\ = 0.24\%$$

This result is quite problematic from a PK perspective, for many reasons. Giving even 10x the dose would suggest that only 2.4% of the efficacy dose is achieved locally in the heart, even 100x going to 24% is quite low.

We would also suggest that our model is *generous* in many our assumptions given the literature for each variable- in particular, the cargo per EV could reasonably be lowered to 0.1 copy per EV given that many EVs contain no cargo, and we are unsure about the copy number being high given the lack of data to support that notion.

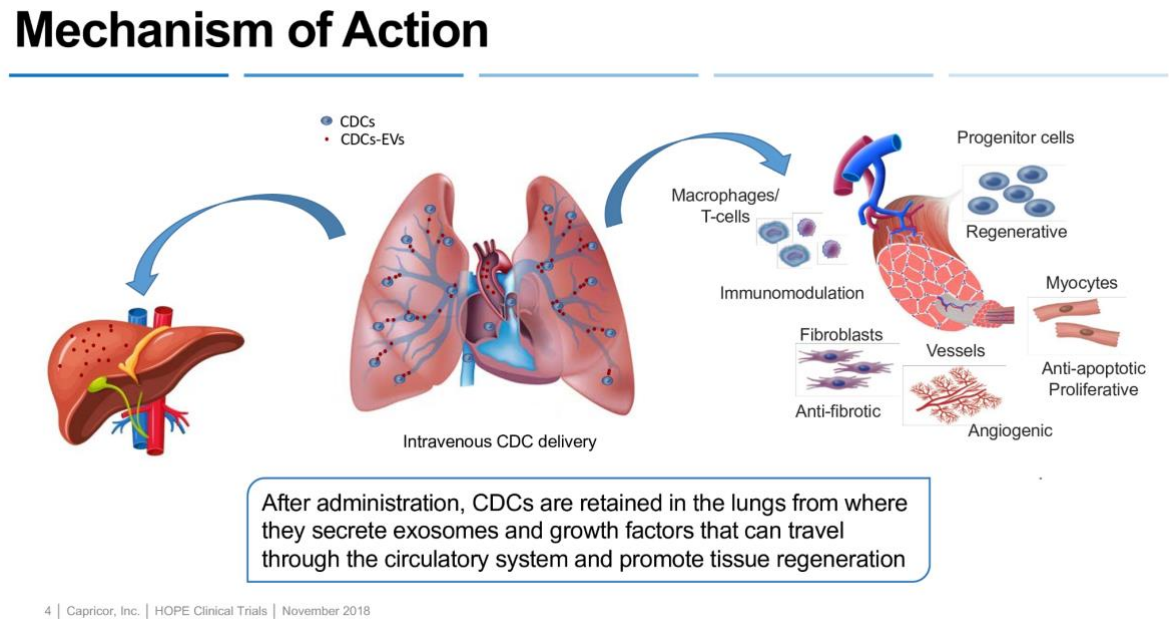
Further, these are deceased patients (organ donors) they are harvesting cells from and then culturing in vitro. We assume at least some apoptosis and no circulation of blood to the tissue and thus without the full repertoire of endogenous cellular

machinery available from circulation we're unsure that these cells could continue producing their exosome payloads. Indeed we have not seen characterization data for the exosomes contained within the CDCs made by Capricor.

Beyond this, the fraction of the EVs taken up by the heart cell could be significantly lower than 10%, which was inferred from the Marban et al DUST study which purports a higher uptake due to acute injury in patients. DMD patients likely do not possess this acute injury phenotype, nor do we have measurements showing they do, therefore as per the same study this could safely be assumed to be 1% not 10%, reducing the payload delivery another 10 fold.

Therefore we have no strong evidence that the dosing in the trial would act upon the cardiac tissue and cause a clinically meaningful effect, let alone the entire skeletal muscle system which could require 100-1000x more dosing of CAP-1002 to be effective by our calculations.

However it seems that even Capricor acknowledges these issues of biodistribution in earlier versions of their presented material, like this slide deck from 2018, where they argue that the localization of CDCs in the lungs is a good thing, and which turns them into a "factory" for paracrine signalling.



Of course, this does not make sense given what we know about the half-life of exosomes, their payloads, and the lack of any binding moiety against the target tissue. If Capricor tries to argue that they bring systemic anti-inflammatory+anti-

fibrotic+immunomodulatory benefit to patients to heal patients they would require doses of deramiocel unseen in the clinic and perhaps impossible to produce.

Thus there is no compelling rationale for the several proposed mechanisms of action and it is simply not possible for deramiocel to have a clinically meaningful effect on DMD patients.

Pre-clinical Work

A review of the preclinical research is notable for the use of female mdx mice as a DMD model of disease. Indeed, much of Marban's preclinical motivation for using CDCs in DMD stems from their work in mdx mice[20–22]. However, it is known the mdx C57BL/10ScSn-Dmd has a milder phenotype and doesn't fully replicate the human DMD severity particularly the more advanced non-ambulant patients.

This is because mice can compensate for missing dystrophin with utrophin whereas in humans this is limited. Consequently therapies often appear more effective in these mdx mice than they would in a truly severe dystrophic context such as mdx/utrn -/- mice. It is telling how some therapies show benefits if given early in mdx mice yet fail to help "aged" mdx mice with more advanced pathology. For instance, in one study by Chun et al, direct injection of vessel-derived stem cells prevents dilated cardiomyopathy if given prior to development of DCM but in more advanced mice such as non-ambulant DMD patients, it lead to no functional improvement in echocardiography and actually exacerbated some features of DCM[23].

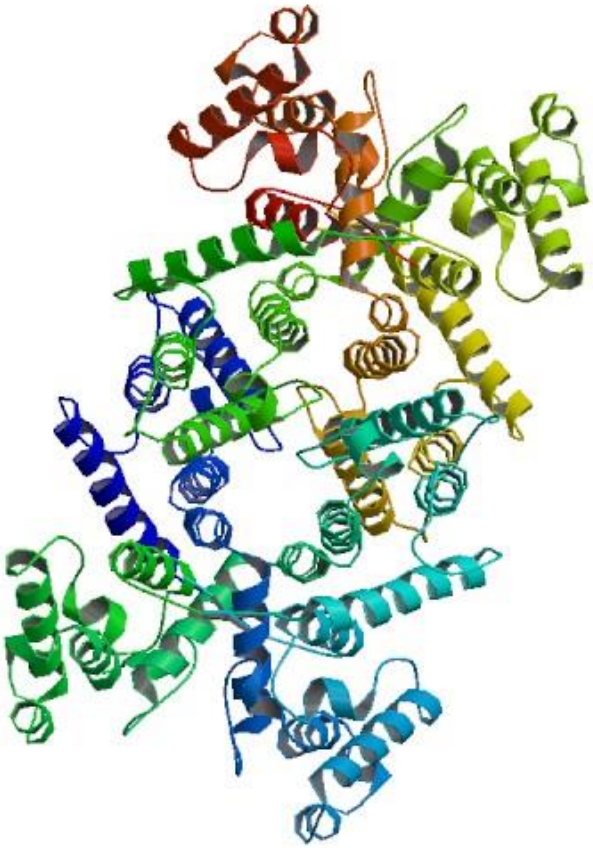
More broadly, guidelines regarding the use of mouse models of DMD have been published. In one such guideline, it recommends the use of male mdx where possible which makes intuitive sense as this is an X-linked disease. However, in their seminal preclinical paper justifying the switch from intracoronary to systemic administration of CDCs for DMD rather than post-MI, the Marban used female mdx mice which raises suspicion about their findings[21].

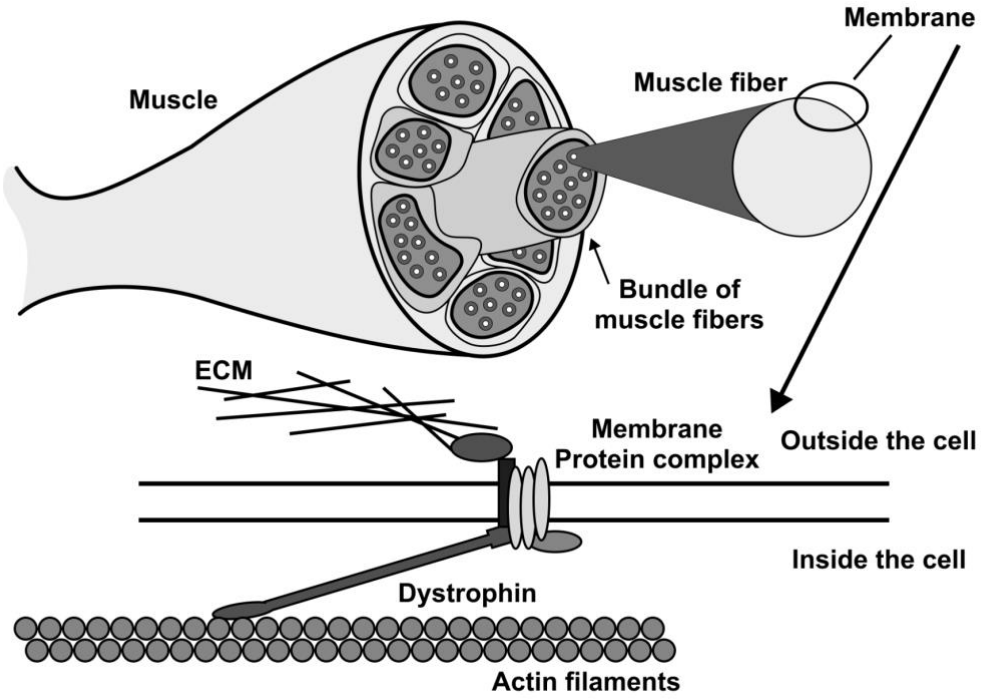
Beyond this, we see that other groups have failed to replicate the work of Marban and Capricor, such as the Spanish and Brazilian groups we mentioned earlier.

Duchenne Muscular Dystrophy & Functional Treatments

To take a quick step back, Duchenne muscular dystrophy (DMD) is caused by mutations or deletions in any of the 79 exons encoding the large dystrophin protein, which is essential for maintaining the muscle fibers' cell membrane integrity and their ability to function normally. Dystophin is essentially a molecular spring or shock absorber by protecting the muscle fibers from damage during contraction via

the actin filaments. These mutations alter its ability to act as a spring and thus lead to systemic muscular impairments.





Despite many industry efforts, only corticosteroids and a histone deacetylase inhibitor (givinostat) have conclusively demonstrated benefit in controlled trials. These improve functional endpoints, but not ventricular function or height.

Failures are just as important to understand the disease, so we have compiled a list of drugs that failed to show definitive evidence of benefit in controlled trials (despite some being approved).

Therapy / Mechanism	**NCT number(s)**
Eteplirsen, Drisapersen (exon 51 skipping)	NCT01396239; NCT01540409; NCT02255552; NCT01462292; NCT01254019
Viltolarsen (exon 53 skipping)	NCT04060199
PF-0693992, Elevidys (AAV9 micro-dystrophin)	NCT04281485; NCT05096221
Talditercept alfa, Domagrozumab (myostatin inhibition)	NCT03039686; NCT02515669; NCT02310763
TAS-205 (PGD2 inhibition)	NCT02752048

IGF-1	NCT01207908
Pamrevlumab (connective tissue growth factor inhibitor)	NCT04371666; NCT04632940
Edasalonexent (NF-κB inhibition)	NCT03917719; NCT03703882; NCT02439216
Tadalafil (PDE5 inhibition)	NCT01865084
L-citrulline and Metformin	NCT05291091
Idebenone (Electron carriage in the mitochondrial electron transport chain)	NCT01027884

In addition, a range of stem cell therapies including bone marrow derived autologous cells (NCT01834066), myoblasts transplantation (NCT02285673), mesangioblast transplantation, and human umbilical cord mesenchymal stem cells transplantation have been tried in small DMD clinical trials with poor results.

It is important to re-iterate that these prior cell transplant strategies have failed in DMD, even in studies where they are injected locally in the skeletal muscle. Thus there is little biological rationale supporting the idea that giving intravenous cell therapy derived from cardiac tissue will meaningfully improve patient outcomes in DMD. Particularly as the therapy is not regenerating skeletal muscle or improving dystrophin function in patients.

We are willing to consider that there may be *some* therapeutic properties to EVs secreted by CDCs. But we lack compelling pharmacokinetic data to conclude that there is a pharmacologically relevant amount of these so-called therapeutic payloads contained in CDCs delivered by Capricor. It may also be that these clinically relevant doses are in fact toxic.

Even on the notion of improving cardiac outcomes for patients (reducing LVEF degradation), we doubt that CAP-1002 is meaningfully improving patient outcomes. With the significant immunogenicity concerns we find its use unethical when several other classes of drugs exist to help delay cardiomyopathy in patients.

These include ACE inhibitors, Angiotensin II receptor blockers (ARBs), Mineralocorticoid receptor antagonists (MRAs) and beta blockers to name only the most commonly used and trial validated options. Many of these options are used off-label as they do not have an FDA approval in DMD specifically, but the clinical trial

data is quite clear. They have clearly established a clinical benefit to DMD patients and their use is endorsed by:

- DMD Care Considerations 2018[24–26]
- 2018 & 2023 Neuromuscular and Cardiology consensus guidelines
- American Heart Association Scientific Statement on Cardiac Involvement in Neuromuscular Disease (Feingold et al., Circulation 2017) [27]
- Adult North Star Network (ANSN) Consensus Guideline for Adults With DMD (2021)[28]
- ACTION Muscular Dystrophy Committee Consensus – "Cardiac treatment for Duchenne muscular dystrophy" (Cardiology in the Young, 2025) Cardiology in the Young[29]
- Parent Project Muscular Dystrophy (PPMD) "Duchenne Muscular Dystrophy Standards of Care 2018" summary
- Adorisio et al. 2020 – "Duchenne Dilated Cardiomyopathy: Cardiac Management" (J Clin Med)[30]

As such, we believe it would be unethical if patients enrolled in a DMD study with a novel agent while not receiving the SOC which clearly includes these agents. Unfortunately, we don't know precisely which concomitant medications patients in this study are on since Capricor has not published their use on both the HOPE-2 and HOPE-3 trials despite collecting this data.

We believe the purported benefit observed on cardiac endpoints are largely attributable to the use of these other well established cardioprotective agents as we will discuss in more detail below.

Review of Clinical Data

Having been through 11 clinical trials and two in DMD, much information can be gathered from the available data. We thought it appropriate to give a quick rundown of the initial few trials, and a long breakdown of the HOPE-2 trial leading into this HOPE-3 readout.

ALLSTAR Trial (NCT01458405)

This was a 12-month randomized, double-blind, placebo-controlled phase I/II trial of Deramiocel after Myocardial Infarction and Ischemic Left Ventricular Dysfunction (n=135) conducted by Capricor in partnership with Janssen Pharmaceuticals. The study was terminated for futility, and Janssen promptly terminated their partnership and returned Deramiocel to Capricor. The intervention was administered through a single intracoronary infusion of 25 million CDCs.

The results were as follows:

Endpoint	p value	Notes
Myocardium Mass Infarct Size (@ 12 months)	0.65	
LVEF	0.63	Favored placebo
LVEDV (@ 12 months)	0.62	
LSESV (@ 12 months)	0.91	
Scar Tissue (@ 12 months)	0.78	
Viable Mass (@ 12 months)	0.83	
Function of region receiving Deramiocel (@ 12 months)	No Change	
6MWT (@ 12 months)	0.46	
MLHFQ (@ 12 months)	0.92	
SF-36 (@ 12 months)	No Change	
NT-proBNP (@ 12 months)	0.48	

As we can see, they failed to impart any clinical benefit in any measured category of interest.

ALPHA Trial (NCT03145298)

This was a randomized, double-blind, placebo-controlled phase I study of Deramiocel in Pulmonary Hypertension (n=26).

The results were as follows:

Endpoint	Effect	Notes
6MWT	No Change	
DLCO	No Change	
Creatinine	No Change	
BNP	No Change	
MRI RVEDV, RVEDVI, RVEF	No Change	
Echo RV FAC, TAPSE	No Change	
R H Cath PA Sys, PA Mean, CI, PVR, RAP	No Change	

Here we see a similar failure. Why do we show these trial results? Because they show that deramiocel has never been able to show clinical benefit in heart-related conditions.

HOPE Trial (NCT02485938)

This was the first phase II randomized, standard-of-care-controlled, open-label study of Deramiocel conducted in DMD patients (n=25). The primary endpoint was a mixture of clinical laboratory, hematological and ECG parameters, vital signs, and number of patients with clinically significant change from baseline in cardiac physical examinations – at months 6 and 12. Other pre-specified endpoints include LVEF, circumferential strain, PUL total score (including and excluding shoulder), among others. Here, 25 million Deramiocel CDCs were administered directly into each of the three left ventricle cardiac territories (anterior, lateral, inferior/posterior, totaling 25 million CDCs each) via catheter, totalling 75M CDCs in this one time injection.

The results are summarized below:

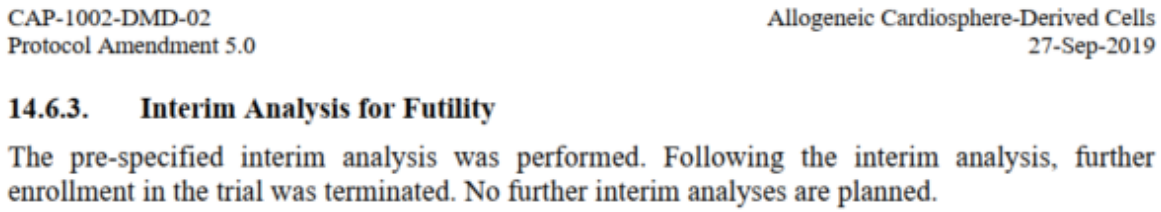
Endpoint	Effect	Notes
Systolic & Dystolic blood pressure	No Change	
Heart rate, respiratory rate, temperature	No Change	
ECG Parameters	No Change	
Ventricular rate	No Change	
LVEF, LVEDV, LSESV	No Change	
LGE Scar Tissue Mass	No Change	
LV LGE	No Change	
Circumferential Strain	No Change	
Peak expiratory flow, FEV1, predicted FVC, FVC	No Change	
Predicted forced expiratory flow (25%-75% of FVC)	No Change	
PODCI (parent and participant responses)	No Change	
DMD biomarkers	No Change	
6WMT (n=4)	p=0.0008	Favored placebo
Pediatric quality of life inventory total summary score	Stat sig	
PUL excluding shoulder (@ 6 months)	p=0.3399	
PUL excluding shoulder (@ 12 months)	p=0.2674	
PUL including shoulder (@ 12 months)	p=0.07	Favored placebo

Overall, these results show no clinical benefit to the drug arm in any metric measured. Given that these cells were infused directly into the coronary arteries, it is difficult to imagine a more direct delivery method for the EVs of the CDCs to work upon the cardiac tissue. Thus these results substantially undermine the hypothesis that CDCs offer a clinical benefit to cardiac function in DMD patients.

HOPE-2 Trial (NCT03406780)

HOPE-2 is the study we will spend the most time discussing as it is the most recent clinical trial and most relevant as it was the sole study used for Capricor's BLA submission which was recently given a CRL. It is also the study used as the basis for launching the HOPE-3 study, which will be reported soon and used to supplement the BLA submission and seek approval once more.

HOPE-2 was a randomized, double-blind, placebo-controlled study of Deramiocel in DMD patients (n=20), this time with repeated IVinfusions of the drug. Patients received 150M CDCs (double HOPE dose) every 3 months for 4 total doses. The trial was designed and powered for enrollment of 80 patients, but after enrollment hit 20 patients, Capricor cited financial constraints and stopped taking more patients onto the study. This raises many concerns as it was therefore not adequately powered to show a change and this is a smaller study than the original HOPE study. It is also interesting to note that this cut to enrollment was **after** an interim futility analysis.

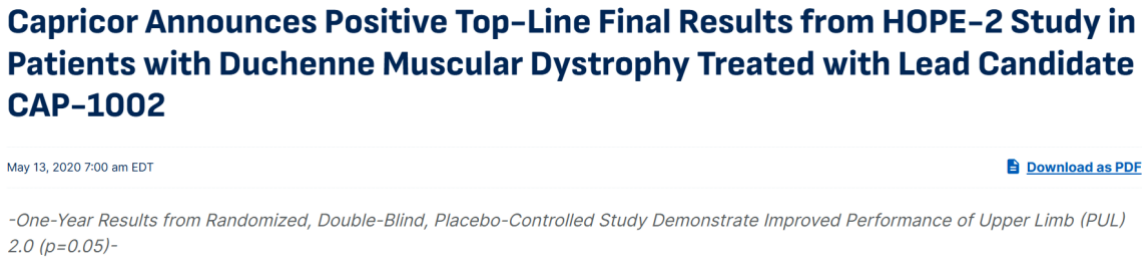


CAP-1002-DMD-02 Allogeneic Cardiosphere-Derived Cells
Protocol Amendment 5.0 27-Sep-2019

14.6.3. Interim Analysis for Futility

The pre-specified interim analysis was performed. Following the interim analysis, further enrollment in the trial was terminated. No further interim analyses are planned.

The May 13, 2020 topline initially reported a p=0.05 exactly stat sig on PUL2.0, which was a secondary endpoint. But the primary endpoint mid-PUL1.2 failed to hit stat sig, reaching p=0.08.



Capricor Announces Positive Top-Line Final Results from HOPE-2 Study in Patients with Duchenne Muscular Dystrophy Treated with Lead Candidate CAP-1002

May 13, 2020 7:00 am EDT Download as PDF

-One-Year Results from Randomized, Double-Blind, Placebo-Controlled Study Demonstrate Improved Performance of Upper Limb (PUL) 2.0 (p=0.05)-

Top-Line Efficacy Data:

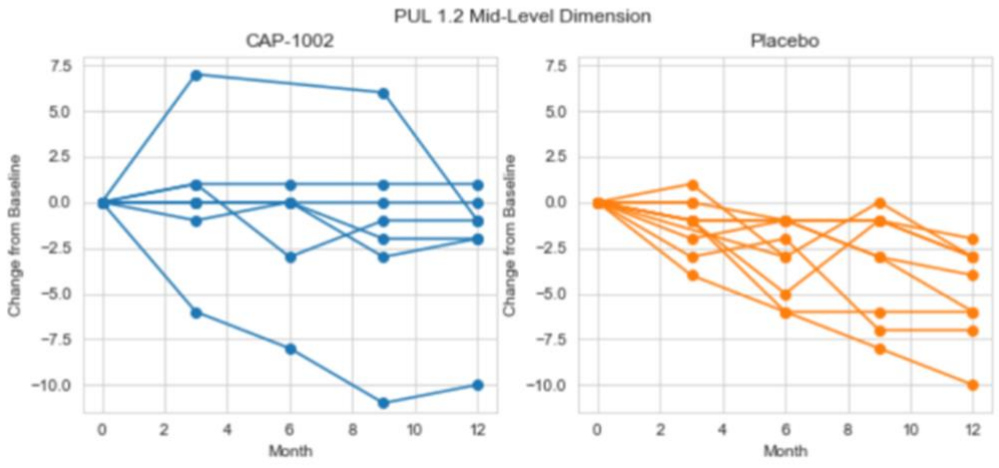
	12-month Time-point		
	CAP-1002 n=8	Placebo n=12	p-value
Upper Limb Function			
Mid-level PUL (version 1.2)	-2.1 (3.63)	-4.9 (2.57)	p=0.08
Shoulder + Mid + Distal PUL (version 1.2)	-2.3 (3.86)	-6.4 (3.84)	p=0.03
Shoulder + Mid + Distal PUL (version 2.0)	-1.3 (2.14)	-3.7 (1.50)	p=0.05

This is interesting because we wanted to see if we could replicate these results from the known data. We started by looking at the raw data found in the appendix of the HOPE-2 study, using the spaghetti plots.

Baseline PUL

Figure S7. PUL 1.2 mid-level Dimension (Spaghetti Plots of Raw Scores vs. Time).

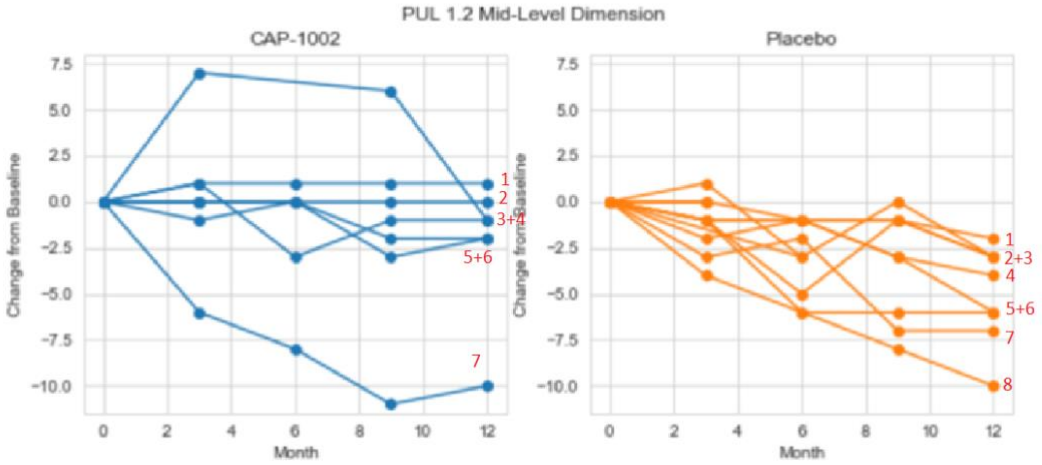
Spaghetti plots of PUL 1.2 mid-level raw scores vs. time for CAP-1002 (Blue on left) and placebo (orange on right).



With this labelling, and knowing that PUL values are reported in integers we can reduce this “guessing game” to a brute forceable math problem.

Figure S7. PUL 1.2 mid-level Dimension (Spaghetti Plots of Raw Scores vs. Time).

Spaghetti plots of PUL 1.2 mid-level raw scores vs. time for CAP-1002 (Blue on left) and placebo (orange on right).



Looking at the 12m endpoint we are aiming to read their data off the graph and replicate the values required to generate a p-value of 0.08. We know the drug arm has n=8 patients being evaluated and the placebo arm has n=12. We also know the mean and SD reported at -2.1 (3.63) for CAP1002 and -4.9 (2.57) for placebo. We can easily identify 7 lines going into the drug arm and 8 going into the pbo arm.

We went ahead and determined the integer values for all 7 patients in pbo arm and 8 pbo arm patients, and tried to fill in the gaps to reproduce the values reported by Capricor. Since we know the finite set of integers which are possible, filling in the missing value is a matter of trying a number between 1 and -2. The only number that works even close is -2 which yields a reasonable mean to match but SD is off. Similarly, we can repeat this process with the pbo arm and find a set which works for mean but not SD. It is mathematically impossible to arrive at the SD values they report given the mean they report with it.

	CAP1002 12m	published	pbo 12m	published
	1		-2	
	0		-2	
	-1		-2	
	-1		-3	
	-2		-3	
	-2		-4	
	-2		-6	
	-10		-6	
			-7	
			-7	
			-7	
			-10	
n=	8		12	
mean	-2.125	-2.1	-4.917	-4.9
SD	3.140	3.63	2.499	2.57
p-value			0.067	0.08
rank order p-value			0.0133	0.014

So this is weird for a few reasons. We can't replicate their data from their own plots, indicating that at least one of these numbers they shared is wrong. We don't know which one, but at least one is wrong. If your numbers are wrong, your integrity is in question.

It's especially weird, because on Sep 24, 2021 they changed the p-value to 0.04 on PUL2.0, and declared that the PE was actually mid-PUL1.2 with p=0.014, per the PR and Lancet paper. This is using the new, post-hoc, % rank order statistical scheme.

Capricor Therapeutics Announces Positive Final Data From its Phase 2 HOPE-2 Trial in Patients with Duchenne Muscular Dystrophy Treated with CAP-1002

September 24, 2021 7:00 am EDT

Download as PDF

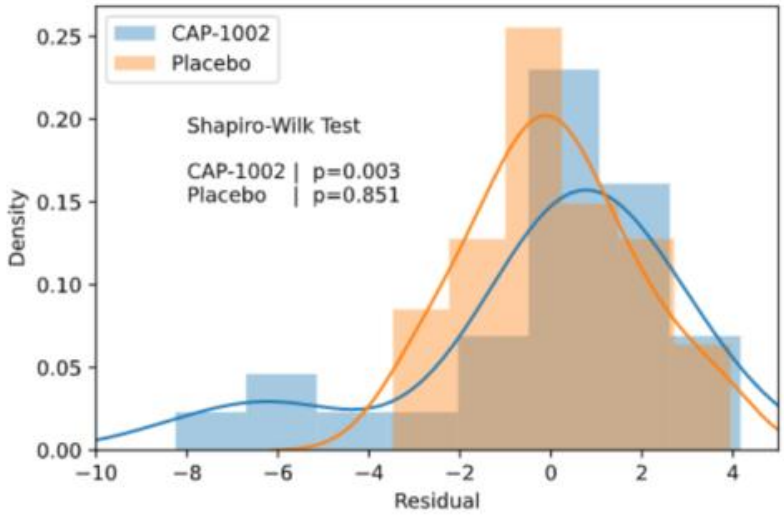
–Trial Met its Primary Efficacy Endpoint of Mid-level Performance of Upper Limb (PUL) v1.2 (p=0.01)–

–Additional Positive Endpoints of Full PUL v2.0 (p=0.04) and Cardiac Endpoint of Ejection Fraction (p=0.002)–

Why did they do this? They suggest that due to a normality violation in the cohort, a % rank method was better to use to account for the "extreme" outliers present in the drug arm.

Figure S2. Histogram of MMRM Residuals of PUL 1.2 mid-level.

Residuals are broken out by Placebo (orange) and CAP-1002 (blue). Lines are a guide to the eye, and do not represent a fitted distribution. Results of Shapiro-Wilk test are given as a p-value for each treatment arms in the annotation.



Indeed, the Shapiro-Wilk test supports this claim as the data shows a failure to align with normality in the drug arm. However we would remind the reader that Capricor halted the study and reduced total enrollment to 20 instead of the planned 84. We would also remind the reader that baseline imbalances exist on the basis of PUL entry score in the HOPE-2 study, and quite possibly for cardiac medication as well.

	CAP-1002 group (n=8)	Placebo group (n=12)

Ambulatory status		
Non-ambulatory	7 (88%)	11 (92%)
Ambulatory	1 (13%)	1 (8%)
PUL entry score		
4–5	2 (25%)	6 (50%)
2–3	6 (75%)	6 (50%)

This statistical change to % rank order took the mid-PUL1.2 readout from not stat sig, to stat sig.

We also want to note that the disease baseline difference likely introduced a floor effect on the drug arm as the lower entry score relates more closely with patients who are late-stage non-ambulatory patients.

This is important specifically in the context of the PUL1.2 score as it is extremely sensitive to loss of function in the elbow (the difference between entry 2-3 and 4-5). Thus, patients who are lower (2-3) have already lost elbow function are unlikely to see a dramatic loss of score in the 12m period as compared to stage 4-5 patients who have yet to lose such functionality. Scores 2-3 compare to roughly 25-40 on the 74pt scale, and 4-5 are roughly 45-55 on the same scale.

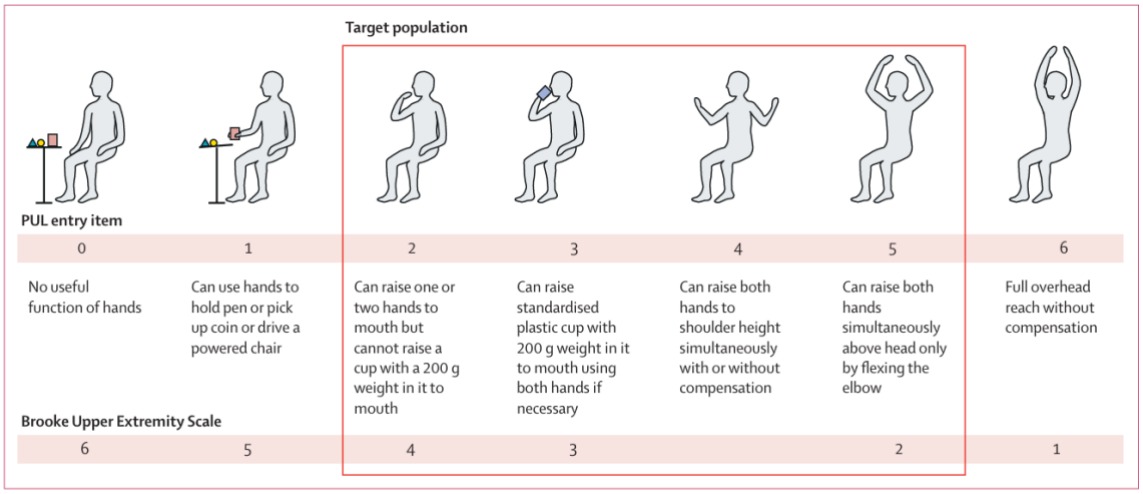


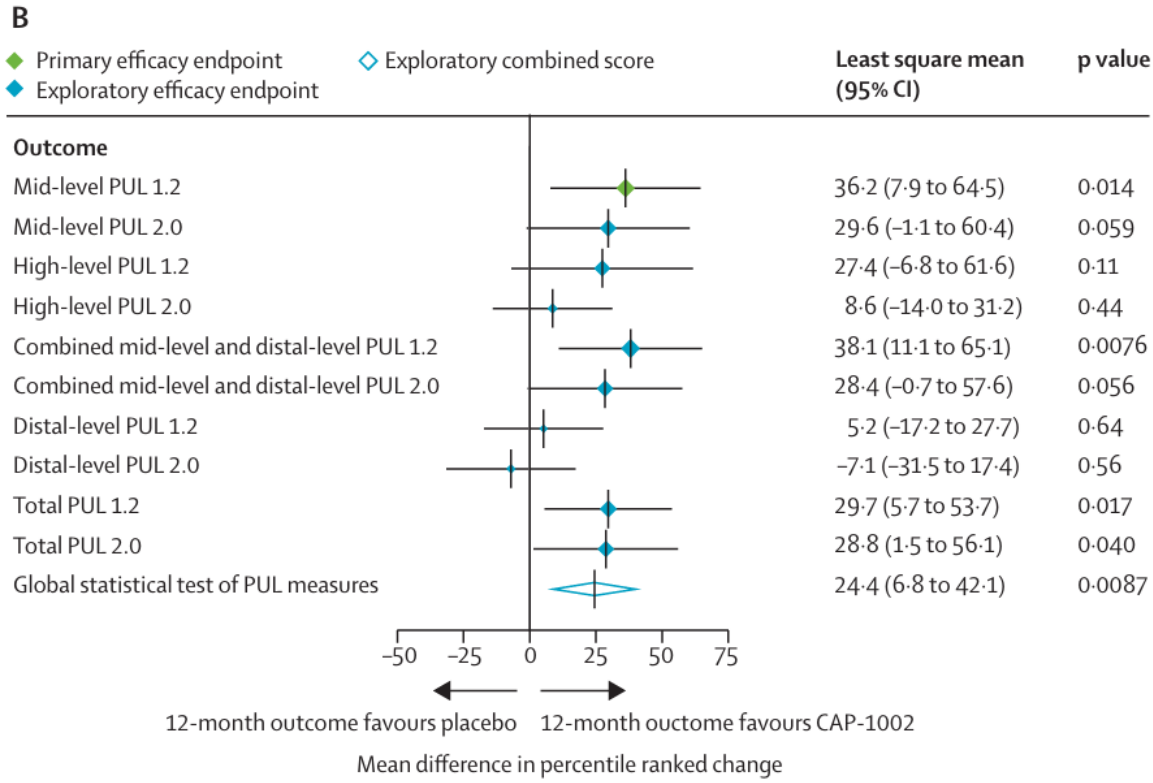
Figure 1: **PUL entry items**
Brooke Upper Extremity Scale values are also shown for comparison. PUL=Performance of Upper Limb.

The total combined PUL1.2 scale itself ranges from 0-74, with shoulder being up to 16pts, elbow being 34(!) pts, and wrist/ distal being 24 pts. Obviously, loss in elbow function will show the most impact to overall score and in particular the mid-level PUL1.2 portion which is the primary endpoint of the HOPE-2 trial.

Therefore this is a clear imbalance at baseline favoring the drug arm as it introduces a floor effect (less room to fall) compared to the placebo arm with patients on the verge of losing mid-level functionality.

Because we are only examining changes from baseline the graphs look worse than they otherwise would if we account for baselines in an ANCOVA model or if enrollment had been permitted to continue and achieve normality in both arms.

We can actually prove that the baseline is imbalanced at specifically the mid-level PUL capability by comparing PUL1.2 and PUL2.0. These tests are quite similar, but the key difference is in the fact that 2.0 introduces more range to patients who've lost elbow functionality. Thus later stage patients are more accurately captured in the 2.0 system as compared to the 1.2 system.



And here from the Lancet paper we see that in every single PUL2.0 metric CAP-1002 fares worse when compared to PUL1.2 scores. So we believe that a baseline imbalance accounts for all of the observed difference between the drug and pbo arm in this particular metric.

LVEF and Baseline Medications

Beyond the functional assessment by PUL, we considered the improvements noted to cardiac endpoints. We were curious about these especially because we see that the

clinicaltrials.gov page was not updated to include these cardiac endpoints after the September 2019 update.

Outcome Measures

Primary Outcome Measures	1. Change in the mid-level (elbow) dimension of the Performance of the Upper Limb (PUL) The PUL includes functional tasks that relate to activities of daily living that are very important for quality of life. The PUL has been validated for the assessment of upper limb motor function in individuals with DMD. [Time Frame: Month 12]
Secondary Outcome Measures	1. Change in the mid-level (elbow) dimension of the PUL The PUL includes functional tasks that relate to activities of daily living that are very important for quality of life. The PUL has been validated for the assessment of upper limb motor function in individuals with DMD. [Time Frame: Months 3, 6, and 9] 2. Change in regional systolic left ventricular wall thickening as assessed by cardiac MRI Systolic thickening is thought to be a principal mechanism of cardiac output generation in people with DMD. [Time Frame: Months 6 and 12]

But then did include these updates finally in the Jan 2025 update. The 2019 update to the SAP increased the number of discrete endpoints from just 3 to over 25 (over 50 with repeat sampling every 3m), but by 2025 they had reduced this to just under 20. This is of course problematic because a fundamental rule of statistical testing in a randomized controlled study is that you can't test too many hypotheses without incurring Type-1 error. Thus, by testing so many different hypotheses you are bound to hit on at least one. They explicitly state in the SAP that these results are nominal and not multiplicity adjusted; therefore they are only hypothesis generating and not approvable.

Besides the dubious statistical inferences we can draw from HOPE-2 cardiac endpoints we also must consider the baseline use of medications in the HOPE-2 study. This is important as we consider cardiac endpoints because heart medication can significantly alter the outcomes for patients.

As we had mentioned previously, some medicines have already demonstrated clinically validated cardioprotective benefits. Multiple agent classes are already recommended in DMD including ACE inhibitors, Angiotensin II receptor blockers (ARBs), Mineralocorticoid receptor antagonists (MRAs) and beta blockers. These drugs have meaningfully improved LVEF outcomes for patients. Kisel et al in 2023 reminds us that DMD patients in ACEi and beta blockers had much slower LVEF decline over a follow up period of over 11yrs on avg, with an average decline of 4.3% and 5.73% respectively[31]. That's pretty good! Annualized, that's 0.39% and 0.52% for

each. Many more studies replicate the findings that these agents are cardioprotective.

But what about patients on HOPE2?

Sadly, we do not know their concomitant medications as they are not stated in the Lancet paper nor the appendix. This data is collected as per the HOPE-2 study protocol, and this data was also collected and published in the original HOPE study. However it appears to have not been disclosed in the HOPE-2 study despite its obvious importance in ruling out baseline imbalances for cardioprotective agents.

Without knowing that there is parity for baseline medications we can not rule out the possibility that there is an imbalance and it has contributed to the difference observed in LVEF between the two arms.

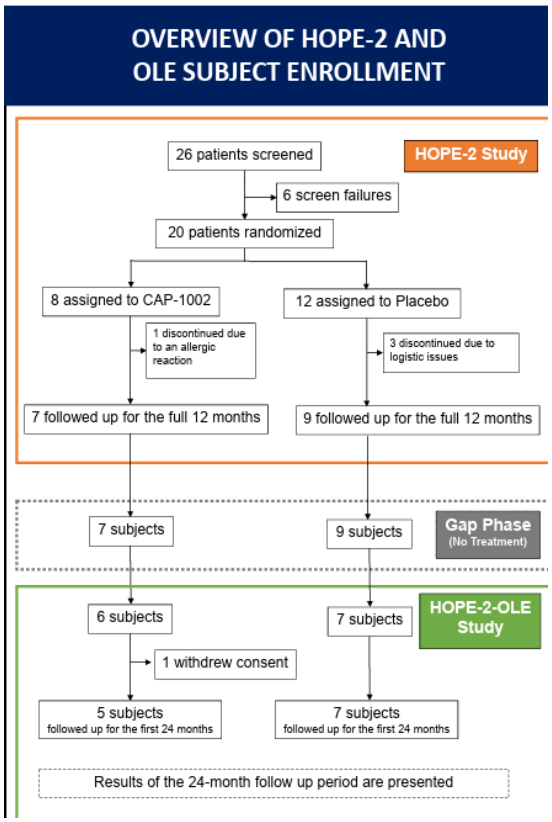
Outside of these baseline issues with concomitant medications we can note that the measurement of LVEF can have some variance and on such a small data set that this can introduce a potential source of error. The literature shows us that cardiac MRI in DMD has reproducible LVEF measurements with ~2–3% inter-reader variability, meaning that true treatment-related preservation of LVEF in the range of 1–3% per year can be statistically masked without sufficient sample size[32,33]. This is yet another element by which we remain unconvinced of the data presented by Capricor.

Safety and Immunogenicity

Beyond the issues with efficacy identified above, we find it quite troubling to observe a consistent report of serious safety issues and inconsistent grading of the severity of AEs reported publicly. Per the Study Protocol (Amendment 5.0) , in the HOPE-2 trial 3 (37.5%) patients with immune reactions were observed, including a grade 3 compared to 0 in the placebo arm. This grade 3 reaction was attributed to the DMSO excipient present in the formulation, and the injury was deemed life threatening, requiring hospitalization. A second patient experienced an allergic reaction which was not deemed life-threatening but which did require hospitalization.

On the open label extension (OLE) phase of the trial, a grade 3 event was determined to be an anaphylactic reaction which was considered life-threatening and required hospitalization. These issues persisted throughout the OLE, where they report that 4/13 (31%) have grade 3-4 AEs! This is remarkable because some of these patients had been exposed previously to the therapy and developed reactions *de novo* to the

treatment. Thus there is no effective mechanism currently used by Capricor to predict who may develop such a life-threatening reaction to the therapy.



OVERVIEW OF ADVERSE EVENTS/SAFETY IN OLE

AE Categories	CAP-1002 (N=13) n (%)
Any TEAE[1]	12 (92.3%)
TEAE by maximum severity[2]	
Mild or Moderate (≤ Grade 2)	8 (61.5%)
Severe or life-threatening or disabling (Grade 3 or 4)	4 (30.8%)
Death	0
TEAE related to IP or administration procedure[3]	9 (69.2%)
TEAE related to IP[3]	8 (61.5%)
TEAE related to administration procedure	7 (53.8%)
Any SAE related to IP or administration procedure	0

AE: adverse event; IP: investigational product; IV: intravenous; TEAE: treatment-emergent adverse event defined as an AE occurring after the initiation of the IV catheter placement for the initial dose of IP.

1. A total of 95 TEAEs occurred by Month 24 in HOPE-2-OLE.
2. Each Subject is counted once by the worst severity. AEs with missing severity are counted as "severe".
3. Each Subject is counted once by the greatest relationship to IP or administration procedure, ie, "probable or possible". AEs with missing relatedness to the IP or IP administration will be considered to have "possible" relatedness. A total of 23 events were considered as related to IP, and 21 related to administration procedure.
4. AEs with missing seriousness are counted as "serious".

The attribution of one anaphylactic reaction is a bit different than the language outlined in Study Protocol Amendment 4.0, which counted two patients as having

anaphylactic reactions. With 1 out of 8 (12.5%) having the reaction, and now 2 out of 15 (8+7) (13%), the rate is consistent over the HOPE-2 study and OLE.

No severe allergic reactions were reported in any CAP-1002 trial that required the administration of a single intracoronary dose only. Two subjects, one enrolled in the HOPE Open Label extension (HOPE-OLE) trial and another in the HOPE-2 trial, experienced an anaphylactic reaction during the second intravenous administration of investigational product (CAP-1002 in HOPE-OLE and CAP-1002 or placebo in HOPE-2). Both events required discontinuation of the infusion, were considered life-threatening and required hospitalization. Both subjects were observed overnight and discharged without any sequelae on the following day. Further information about the allergic reactions is found in the Investigator's Brochure and Section 13.2.1.3.	Consistency with Investigator's Brochure	5.6.3. Repeat Administrations

This of course led to a change in the protocol to minimize the risk of anaphylaxis by prophylactically administering other medications to patients at the investigator's discretion.

Prior to each IP infusion, medication(s) will be administered to the subject as determined by the Investigator based on the pre-treatment guidelines (see Section 21.2) and/or institutional protocols to minimize the risk of potential severe allergic reactions such as anaphylaxis.	To minimize the risk of a potential severe allergic reaction to IP.	7.1. Overall Trial Design

And by the time Amendment 5.0 came out, they realized they didn't like the word "anaphylactic", so they simply scratched it out and grouped the incidents with the acute allergic reaction patient.

Safety and Pharmacovigilance		
~~Two~~ *Three* subjects, one enrolled in the HOPE Open Label extension (HOPE-OLE) trial and *two subjects* ~~*another*~~ in the HOPE-2 trial, experienced an *acute allergic* ~~anaphylactic~~ reaction during *or after* the second intravenous administration of investigational product (CAP-1002 in HOPE-OLE and CAP-1002 or placebo in HOPE-2).	Administrative update for inclusion of third acute allergic reaction	5.6.3 Repeat Administration

Similarly, they didn't like the word "severe" so they scratched it out and replaced it with "acute".

Description of Change	**Rationale / Justification**	**Section(s) Affected**
To date, significant immune system adverse events have been identified in ~~two~~ *three* subjects, who experienced ~~severe~~ *acute* allergic reactions to CAP-1002 or placebo.	Administrative update for inclusion of third acute allergic reaction	13.2.1.3 Expected Adverse Events

They didn't like the wording of this patient reaction either so they just removed it.

~~Both allergic reactions occurred within the first two minutes of the second infusion of IP. While the subject in the HOPE-OLE trial experienced no allergy-related symptoms during the first infusion, the subject in the HOPE-2 trial reported tightness in his throat during the first infusion.~~	Administrative update for inclusion of third acute allergic reaction	13.2.1.3 Expected Adverse Events
A second subject in the HOPE-2 trial experienced an acute allergic reaction during and after the administration of the third IP infusion, which required hospitalization, but was not considered life-threatening. This subject was pre-medicated using the guidelines outlined in Section 21.2 and completed the third IP infusion with no interruption.	Administrative update for inclusion of third acute allergic reaction	13.2.1.3 Expected Adverse Events

Just so we're clear on this point, after the first infusion this patient reported that they had a (mild) symptom of an anaphylactic reaction to the investigator. Capricor then continued treatment for this patient, and even though they took the extra allergy/

immunosuppressive medications prior to infusion three, the patient *still* developed an anaphylactic reaction and was hospitalized.

On a personal level, we are deeply troubled by Capricor's behavior in this regard. Outright removing words like "anaphylactic" and "severe" from the documentation is unethical and we hope patients enrolled in HOPE-3 had the risks of anaphylactic reactions communicated to them prior to enrollment.

Screening

Patients can make antibodies at any time against the CAP-1002 therapy because CDCs are intrinsically immunogenic to many people. This is because they have proteins on their cell surface which trigger immune reactions. This is like organ donation or stem cell transplants where we usually have patients on immunosuppressants, sometimes forever. The risk of immunological rejection is present and the consequences are quite significant for some people.

Diving into the protocol adjustments a bit more we note that patients are screened and followed for donor-specific anti-HLA antibodies (DSAs) to try to mitigate the immunogenicity risk. If a patient has such antibodies, they will almost assuredly have an immune reaction to the therapy and so they are screened out up-front and should be when a patient tests positive.

To test for this they are using a single-antigen bead (SAB) on the Luminex platform, and assessing the mean fluorescence intensity (MFI) at a central lab. This allows them to see how much a patient's serum 'lights up' the assay, and whether that changes over time.

What's important to know here is that while Capricor can mitigate most patients who *present* with DSAs to a particular lot of CAP-1002 but they can't stop or predict patients who will develop DSAs *de novo* against the therapy. This is precisely what leads to the immune reaction they report in their study, and as we see it can be quite a serious adverse event.

Thus, we believe this potentially significant adverse reaction is understated in the discourse of this agent. As the value calculus of this therapy (like any other) will be relative to existing therapies, we believe the risk of immunogenicity should preclude any chance of approval given the middling efficacy results on both functional movement endpoints like PUL, and the likely confounded cardiac endpoints like LVEF.

Since the company has not mentioned any changes to the formulation it stands to reason that the AEs will continue in the HOPE-3 trial, and we would expect 30-35% to have these grade 3-4 reactions.

Thus with this significant safety risk and well established competitor molecules with established safety and efficacy, we believe deramiocel has a 0% chance of approval in DMD.

HOPE-3

Lastly, as we wrap up the evaluation of the clinical trials by Capricor we want to go over the imminent readout for HOPE-3. This is a double blind, placebo controlled, 1:1 randomized ph3 trial with two cohorts and one dosing regimen, same as HOPE-2 (Q3M). Cohort A will have ~58 patients and uses a deramiocel lot made in Los Angeles, CA whereas Cohort B will have ~44 patients enrolled and drug arm patients receiving the product made at their site in San Diego, CA. Patients can also enroll in the OLEs but we'll focus on the initial readout.

Primary endpoint here is total PUL2.0 at 12m, and the key secondary endpoint seems to be LVEF as assessed by cMRI at 12m. They still list an additional 9 secondary endpoints, we believe in an effort to inflate the probability of hitting on one by virtue of type 1 error.

Interestingly they removed the PUL2.0 readout at 24m in January 2025.

We believe that for several reasons the results shown in the HOPE-2 trial are nearly impossible to replicate in the HOPE-3 trial:

- Primary endpoint is now the total PUL2.0 score at 12m, less sensitive to loss of elbow function like mid-PUL1.2
- Unlikely to show a difference between drug and placebo when baselines are balanced in larger n ph3 study
- Regression to the mean
- Cardiac endpoints like LVEF are unlikely to show difference between drug and placebo when baseline concomitant medications are balanced

Beyond these efficacy endpoints, we believe the risk of anaphylactic reactions and dropouts will remain high, confirming deramiocel has an unsafe drug profile for broader use in the market.

Due to the baseline confounding, poor biological rationale, and no demonstrable pharmacokinetic or pharmacodynamic efficacy we predict near zero separation on the PUL2.0 score at 12m, and similar for LVEF at 12m. We also expect Capricor to indulge themselves in spurious sub-group analyses but even so it will be nearly impossible to show a clinical benefit without confounding the analyses.

Even so, they can only be so creative. We are looking for something like: analyzing patients from Cohort A vs Cohort B and calling one a "bad" batch. Analyzing biomarker subgroups. Analyzing a so-called low PUL entry vs high PUL entry. They

may simply remove the poor responders entirely from their topline. They may try to run a MAR based imputation scheme to favorably analyze patients who dropped out due to toxicity. All of these are spurious post-hoc adjustments with the simple intention to hide the reality that the results are not significant.

Lastly, we would add that the biggest wild card in our analysis is the possibility of fraudulent activity.

We believe the risks always outweigh the rewards in the context of fraudulently reporting clinical trial results, particularly a phase 3 result which will immediately be submitted for FDA review.

We also note that an investigator on the HOPE-3 clinical trial, Dr. Han Phan, was personally issued a warning letter (WL) from the CDER branch of the FDA for problematic data reporting on a clinical trial.

> - **Atlanta, Georgia, United States, 30329**
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> |---|---|
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> | Facility: | Rare Disease Research, LLC |
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There is a distinction between a Form 483 and a Warning Letter, the latter being more serious as it is issued in response to the infractions noted in the 483 after the recipient has had the opportunity to respond. This particular WL issued to Dr. Phan is quite scathing. In particular, they note:

- Specifically, at least 11 of the 29 subjects whose records were reviewed during the inspection had additional items administered beyond what was needed to establish the (b)(4) for the (b)(4) assessments at Baseline.
- It is impossible to retrospectively account for all instances of noncompliance for the 42 enrolled subjects at your site, because of the inadequate and inconsistent documentation of the assessments.

- As a result, your failure to follow the instructions for establishing a (b)(4) for required assessments raises significant concerns about the interpretability of the study data.
- Although there was a site assessor who is no longer employed on site, other assessors have not undergone retraining.
- One of the primary efficacy endpoints for Protocol (b)(4) was the (b)(4) as measured by the (b)(4) assessments. Your failure to correctly administer and score the protocol-required (b)(4) assessments for this (b)(4) study raises significant concerns about the validity and integrity of the data collected at your site.

We believe that since a site investigator has received a WL there will be more scrutiny applied by the FDA to this particular readout. As the consequences of fraud have undoubtedly been communicated to Dr. Phan and the Capricor team this should preclude the possibility of such activity.

The Capricor team has also begun communicating about their work on their next program with exosomes, and so we expect them to rip off the HOPE-3 bandaid soon and focus on that asset going forward without risking the probing eyes of the FDA or SEC in the way Cassava Sciences did.

CRL

In July 2025 Capricor Therapeutics received a CRL (Complete Response Letter) for their BLA (Biologics License Application) of Deramiocel in Duchenne Muscular Dystrophy (DMD). We applaud CBER for rejecting an unsubstantiated application with significant concerns on efficacy, safety, and manufacturing.

Given this CRL which included the ph2 data, the company has now, finally after having access to topline data for over a year, pivoted to the ph3 data. This is in an effort to resubmit the BLA with the HOPE-3 results and try to convince the FDA that deramiocel deserved an approval in DMD. Some highlights:

Lack of efficacy

The FDA notes that HOPE-2 did not meet its pre-specified primary endpoint (change in PUL 1.2 mid-level at 12 months) and also failed its pre-specified secondaries. The agency also rejected Capricor's post-hoc cardiac analyses from HOPE-2 and the non-randomized HOPE-2-OLE as insufficient to establish efficacy. On this basis they have the full authority to reject the drug and this is the primary basis from which they issued the CRL.

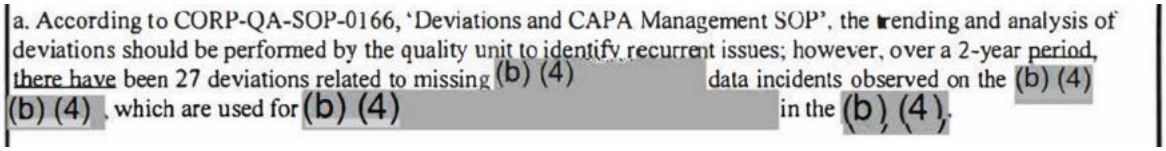
50 secondary end points

The BLA included ~50 secondary/exploratory endpoints (including 26 post-hoc cardiac MRI endpoints) without a pre-specified multiplicity plan. FDA noted that the few nominal signals could be spurious due to inflated Type 1 error, and overall effects were not consistent across cardiac measures. We would add that this is clearly an attempt to obtain a statistically significant results on the basis of type 1 error.

Manufacturing concerns

Largely redacted from CRL, but an additional form 483 from May 2025 notes troubling findings:

- Qualification/validation gaps: an area/process lacked adequate qualification under dynamic conditions, and simulations did not replicate actual manufacturing layout/conditions.
- Trending/analysis of deviations by QA not effectively performed; 27 deviations tied to missing instrument/data entries called out.
- Nonconforming products and Corrective Action Reports left past due or lacked extensions **for over 2 years.** Some of these were in direct contradiction to Capricor's own established SOP(s) (SOP CORP-QA-SOP-0166).
- ALCOA+ documentation deficiencies- corrections lacking proper notation
- Site not maintained in a state of good repair. [redacted] found on the inside of the [redacted] inside the ISO manufacturing room.


a. According to CORP-QA-SOP-0166, 'Deviations and CAPA Management SOP', the trending and analysis of deviations should be performed by the quality unit to identify recurrent issues; however, over a 2-year period, there have been 27 deviations related to missing (b) (4) data incidents observed on the (b) (4) (b) (4) , which are used for (b) (4) in the (b) (4).

Despite these concerns, the FDA did not issue a warning letter after a subsequent visit in June but we note that the CRL from July did highlight some manufacturing issues though they were not required to issue the CRL.

We believe there remains substantial work to be done with respect to CQA testing, batch testing, and other critical manufacturing validation that will be required to substantiate a ready-for-market product. This is somewhat evidenced by the very recent publication by Capricor which attempts to satisfy some of the FDA guidance on cell therapy products by coupling manufacturing runs to a so-called mechanism of action[34].

However, Capricor routinely invokes multiple MOAs when describing their product and we have yet to see any evidence coupling anti-inflammatory or immunomodulatory properties with the manufactured lots even in a contrived *in*

vitro assay let alone a more robust *ex vivo* model of cardiac tissue from DMD patients, or, actual clinical trial data free of confounders. In fact the opposite seems to be true as we showed IL6 and IL8 upregulation in CAP-1002 lots, which are pro-inflammatory signals.

Conclusion

Given this totality of evidence we believe the HOPE-3 clinical trial results will show no difference between drug and placebo arm.

The notion of CDCs as therapeutic agents is largely built on fraudulent data. Marban's colleagues in the field have brought great shame on their institution and have wasted tax payer money by fraudulently presenting pre-clinical data to gain funding and reputational benefits.

The inability of researchers worldwide to replicate the data of Dr. Marban further underscores this point- we could not find CDC research with a pre-clinical benefit that did not have Dr. Marban as a listed author. Indeed, those which did not include Dr. Marban showed no difference between CDCs and placebos.

Further, the biological rationale for CDCs in DMD is lacking as they do not enhance dystrophin production or function and the purported poly-MOA lacks clear causal relationship at the pre-clinical and clinical stage. We have no dose-dependent response (or attempts to show one), no molecular interaction between one or more payloads within the CDCs and cells in the patient's body, no macrophage polarization data, nor any characterization of the pharmacodynamics of deramiocel and its contents. This is deeply troubling for a phase 3 product.

The clinical data remains unconvincing. As we noted, the HOPE-2 trial was clearly confounded by baseline imbalance for disease severity, leading to spurious functional readouts. But even the cardiac endpoints are likely to be similarly confounded on the basis of concomitant medicines which Capricor has categorically refused to publish in the public domain.

The safety data is deeply problematic and their deliberate efforts to remove words like "anaphylactic" and "severe" from the clinical documentation genuinely concerns us. Their way of accounting for patients who explicitly had an anaphylactic reaction and who were hospitalized shows that the team is willing to engage in unethical behavior in order to cast themselves in a more favorable light at the expense of patients.

Particularly as the DMD community already has multiple agents with demonstrable cardiac protection, and some exciting new agents improving functional outcomes, the risk associated with deramiocel makes it clear that it has no place in the continuum of care.

The FDA is clearly aware of this situation. They already issued a CRL with good reason, and we believe they have many more reasons they left redacted including the manufacturing issues which we believe are substantial and will necessarily preclude Capricor from obtaining approval in this patient population.

We believe the HOPE-3 trial readout is imminent and will make it clear the deramiocel has no place on the market. As such, we believe the market will then value this asset at $0, bringing the total value of the company to its cash.

Based on the Q3 10Q, we note that CAPR has $98.5m in cash, with 45.7m shares outstanding. This means they have roughly $2.18 in cash as of Sep 30, 2025. If we factor in ⅔ of Q4 expenses being spent, this yields a pro-forma cash of $81.3m and $1.78 per share.

References

1. McDonald, C. M. *et al.* Repeated intravenous cardiosphere-derived cell therapy in late-stage Duchenne muscular dystrophy (HOPE-2): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet* **399**, 1049–1058 (2022).
2. Messina, E. *et al.* Isolation and Expansion of Adult Cardiac Stem Cells From Human and Murine Heart. *Circ. Res.* **95**, 911–921 (2004).
3. Menasché, P. *et al.* Myoblast transplantation for heart failure. *The Lancet* **357**, 279–280 (2001).
4. Strauer, B. E. *et al.* Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans. *Circulation* **106**, 1913–1918 (2002).
5. Smith, R. R. *et al.* Regenerative Potential of Cardiosphere-Derived Cells Expanded From Percutaneous Endomyocardial Biopsy Specimens. *Circulation* **115**, 896–908 (2007).
6. Chien, K. R. *et al.* Regenerating the field of cardiovascular cell therapy. *Nat. Biotechnol.* **37**, 232–237 (2019).
7. Zhou, B. & Wu, S. M. Reassessment of c-Kit in Cardiac Cells: A Complex Interplay Between Expression, Fate, and Function. *Circ. Res.* **123**, 9–11 (2018).
8. Ciullo, A. *et al.* Biodistribution of unmodified cardiosphere-derived cell extracellular vesicles using single RNA tracing. *J. Extracell. Vesicles* **11**, e12178 (2022).
9. Sun, M. *et al.* Potency Assay Development for CAP-1002: An Allogeneic Cell Therapy in Phase 3 Clinical Trial for DMD.

10. Lewis, M. I. *et al.* The ALPHA phase 1 study: pulmonary ArteriaL hypertension treated with CardiosPHere-Derived allogeneic stem cells. *eBioMedicine* **100**, 104900 (2024).
11. Kogan, P.-S. *et al.* Uncovering the molecular identity of cardiosphere-derived cells (CDCs) by single-cell RNA sequencing. *Basic Res. Cardiol.* **117**, 11 (2022).
12. Crisóstomo, V. *et al.* The epicardial delivery of cardiosphere derived cells or their extracellular vesicles is safe but of limited value in experimental infarction. *Sci. Rep.* **11**, 22155 (2021).
13. Kasai-Brunswick, T. H. *et al.* Cardiosphere-derived cells do not improve cardiac function in rats with cardiac failure. *Stem Cell Res. Ther.* **8**, 36 (2017).
14. Qi, T., McGrath, K., Ranganathan, R., Dotti, G. & Cao, Y. Cellular kinetics: A clinical and computational review of CAR-T cell pharmacology. *Adv. Drug Deliv. Rev.* **188**, 114421 (2022).
15. Smyth, T. *et al.* Biodistribution and delivery efficiency of unmodified tumor-derived exosomes. *J. Controlled Release* **199**, 145–155 (2015).
16. Morishita, M., Takahashi, Y., Nishikawa, M. & Takakura, Y. Pharmacokinetics of Exosomes—An Important Factor for Elucidating the Biological Roles of Exosomes and for the Development of Exosome-Based Therapeutics. *J. Pharm. Sci.* **106**, 2265–2269 (2017).
17. Bonios, M. *et al.* Cardiac Resynchronization by Cardiosphere-Derived Stem Cell Transplantation in an Experimental Model of Myocardial Infarction. *J. Am. Soc. Echocardiogr.* **24**, 808–814 (2011).
18. Chiu, Y., Cai, W., Shih, Y. V., Lian, I. & Lo, Y. A Single-Cell Assay for Time Lapse Studies of Exosome Secretion and Cell Behaviors. *Small* **12**, 3658–3666 (2016).
19. Kalluri, R. & LeBleu, V. S. The biology **,** function **,** and biomedical applications of exosomes. *Science* **367**, eaau6977 (2020).
20. Aminzadeh, M. A. *et al.* Exosome-Mediated Benefits of Cell Therapy in Mouse and Human Models of Duchenne Muscular Dystrophy. *Stem Cell Rep.* **10**, 942–955 (2018).
21. Rogers, R. G. *et al.* Disease-modifying bioactivity of intravenous cardiosphere-derived cells and exosomes in mdx mice. *JCI Insight* **4**, e125754 (2019).
22. Rogers, R. G. *et al.* Long-term preservation of muscle function and structure by repeated administration of cardiosphere-derived cells in mdx mice. *Stem Cell Rep.* **20**, 102468 (2025).

23. Chun, J. L., O'Brien, R., Song, M. H., Wondrasch, B. F. & Berry, S. E. Injection of Vessel-Derived Stem Cells Prevents Dilated Cardiomyopathy and Promotes Angiogenesis and Endogenous Cardiac Stem Cell Proliferation in *mdx/utrn* −/− but Not Aged *mdx* Mouse Models for Duchenne Muscular Dystrophy. *Stem Cells Transl. Med.* **2**, 68–80 (2013).

24. Birnkrant, D. J. *et al.* Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol.* **17**, 251–267 (2018).

25. Birnkrant, D. J. *et al.* Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol.* **17**, 347–361 (2018).

26. Birnkrant, D. J. *et al.* Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *Lancet Neurol.* **17**, 445–455 (2018).

27. Feingold, B. *et al.* Management of Cardiac Involvement Associated With Neuromuscular Diseases: A Scientific Statement From the American Heart Association. *Circulation* **136**, (2017).

28. on behalf of the ANSN *et al.* Adult North Star Network (ANSN): Consensus Guideline For The Standard Of Care Of Adults With Duchenne Muscular Dystrophy. *J. Neuromuscul. Dis.* **8**, 899–926 (2021).

29. Esteso, P., Auerbach, S. & Hayes, E. Cardiac treatment for Duchenne muscular dystrophy: consensus recommendations from the ACTION muscular dystrophy committee. *Cardiol. Young*.

30. Adorisio, R. *et al.* Duchenne Dilated Cardiomyopathy: Cardiac Management from Prevention to Advanced Cardiovascular Therapies. *J. Clin. Med.* **9**, 3186 (2020).

31. Kisel, J. *et al.* Cardioprotective medication in Duchenne muscular dystrophy: a single-centre cohort study. *J. Thorac. Dis.* **15**, 812–819 (2023).

32. Soslow, J. H., Usoro, E., Wang, L. & Parra, D. A. Evaluation of tricuspid annular plane systolic excursion measured with cardiac MRI in children with tetralogy of Fallot. *Cardiol. Young* **26**, 718–724 (2016).

33. Forbes, S. C. *et al.* Skeletal Muscles of Ambulant Children with Duchenne Muscular Dystrophy: Validation of Multicenter Study of Evaluation with MR Imaging and MR Spectroscopy. *Radiology* **269**, 198–207 (2013).

34. Li, Y. *et al.* A Novel In Vitro Potency Assay Demonstrating the Anti-Fibrotic Mechanism of Action of CDCs in Deramiocel. *Biomedicines* **13**, 2652 (2025).