Capricor Therapeutics Report

How does Duchenne's work?

- 1 in 3,500 to 5,000 live male births
- occurs because Dystrophin, a cytoskeletal protein essential for maintaining muscle fiber integrity during contraction and relaxation is totally absent or deformed in some way that impairs function.

structural failure in muscles: without dystrophin, muscle cells become fragile, leading to injury, inflammation, and replacement of muscles with scar tissue or fat

The DMD gene spans approximately 2.2mb on Xp21.2 and is split across 79 exons. Its primary transcript encodes Dystrophin; without it, muscle cells become fragile and eventually decay into scar tissue and fat. This protein is also present in the brain, playing a key role in cognition, working memory, and verbal IQ.

Because of the gene's high expression in muscles and its large size, DMD is very prone to mutations—1/3 of DMD cases arise from de novo mutations, occurring during gametogenesis or early embryonic development rather than being inherited. The inheritance pattern is X-linked recessive, meaning males with a pathogenic DMD allele will be affected, while most females don't experience symptoms. Somewhere between 2.5-10% of female carriers show mild symptoms (muscle cramps, elevated creatine kinase), but less than 1% can be classified as true DMD. The most common cause among these 1% is skewed X-inactivation, where the X chromosome carrying the normal DMD allele is inactivated across most cells.

Depending on the parameters of the mutation, a person could end up with Becker muscular dystrophy (a less severe form of DMD where the body produces smaller, less functional dystrophin). The most commonly observed mutation is one where exons between 45-55 or 3-20 are deleted; in this case, the outcome is frame-dependent (in-frame vs out-of-frame). Even though exon 45-55 deletions are common, they're often better tolerated because they remove part of the central rod domain ( ) which are structurally repetitive. As long as the deletion is in-frame, the patient will usually end up with Becker's. Deletions in the 3-20 range include part of the actin-binding domain, which is essential for function. Even an in-frame deletion here leads to a markedly more severe disease. Any other form of mutation (indel, duplication, nonsense) results in Duchenne's a majority of the time.

Pathophysiology

The dystrophin-glycoprotein complex (DGC) is a structural bridge that anchors the internal cytoskeleton of muscle cells to the surrounding extracellular matrix (ECM) via the sarcolemma (the muscle cell membrane). This anchoring stabilizes the muscle cell during contraction-relaxation cycles, which generate mechanical stress. Dystrophin is the most important part; it connects F-actin (cortical actin cytoskeleton) to the DGC (specifically β-dystroglycan). Without dystrophin, the DGC becomes unstable or nonfunctional, and the sarcolemma is prone to damage during muscle activity.

Dystrophin is a rod-shaped protein with 4 major structural domains:

1. N-terminal actin-binding domain (ABD1)—this binds to F-actin (the internal cytoskeleton). If this is damaged or nonexistent, there's no connection to actin (no anchor) and every contraction incurs cell damage.
2. Central rod domain—the long central part built from spectrin-like repeats (structural items that provide flexibility). Some deletions here (exons 45-55) can be tolerated, as only the structure of the protein is mildly impacted. This is essentially BMD.
3. Cysteine-rich domain—this binds to β-dystroglycan, anchoring the DGC to the membrane. If this domain is corrupted or missing, the DGC fails to assemble correctly, leading to severe DMD.
4. C-terminal domain—the tail end of dystrophin. This domain is responsible for the signaling duties within the DGC. Without it, muscle function is impacted at a regulatory level rather than a structural level.

Due to damaged or absent dystrophin, every muscle contraction causes micro-ruptures in the sarcolemma. These tears allow extracellular calcium into the cytosol abnormally. The main entry routes include:

- TRPV2: a stretch activated cation channel. It becomes abnormally upregulated and inserted into the sarcolemma in dystrophic muscle, contributing significantly to calcium overload after mechanical damage.
- SOCE (store-operated calcium entry): Normally, when a muscle contracts, calcium stored in the sarcoplasmic reticulum (SR) is released into the cytosol and binds to troponin, initiating contraction. After contraction, calcium is pumped back into the SR by SERCA (sarco/endoplasmic reticulum Ca2+-ATPase) pumps. When SR calcium falls below a threshold, Orai1 channels on the sarcolemma are activated, allowing more calcium to enter the cell. In dystrophic muscle, there's a constant calcium leak into the cytosol from the micro ruptures. SERCA pumps, already under stress, become overwhelmed. Calcium is not cleared efficiently and SR stores remain depleted, leading to chronic SOCE activation.

Excess calcium in the cytosol activates calpains, a family of calcium-dependent proteases (enzymes that break down other proteins by hydrolyzing peptide bonds). These enzymes degrade myofibrillar proteins—actin, myosin, titin, as well as structural and regulatory proteins in the cytoskeleton and sarcolemma. This is the start of cellular autolysis (destruction of cells by their own enzymes).

Mitochondria inside the cell try to buffer the excess calcium entering the cell by opening the mPTP (mitochondrial permeability transition pore), a high-conductance channel in the inner mitochondrial membrane. If left open too long, ATP production is halted, the mitochondria swells, membrane potential drops, and ROS (reactive oxygen species) are released—primarily from electron transport chain complexes I and II, and NOX2 (NADPH oxidase 2). ROS such as H2O2 oxidize proteins, lipids, and DNA, damaging the cell further.

Muscle injury releases DAMPs (damage-associated molecular patterns), which are bits of DNA, ATP, and protein that normally stay inside cells. When these leak, the immune system flags them as danger signals. Toll-like receptors (TLRs) detect these DAMPs, and P2RX7 responds to extracellular ATP. These receptors sit on resident immune cells (like macrophages), activating them. Immune cells flood in, and M1 macrophages (pro-inflammatory) secrete destructive cytokines (TNF-alpha, IL-6), and T-cells amplify the response further. The regenerative environment becomes pro-inflammatory and pro-fibrotic, meaning the muscle can never be rebuilt; it just accumulates more damage and scarring. Due to the constant repair signals, mTOR is overactive, which inhibits the cell's ability to remove damaged organelles and proteins. The other mechanism that rebuilds muscle cells, satellite cells under the basal laminate (muscle stem cells) struggle to keep up with the constant injury and repair demands inflicted by the above processes; they divide too often and without organization, which drains the stem cell pool and leads to exhaustion.

DMD also causes significant disruptions to key signaling molecules, which impairs blood flow, growth, and repair.

a. nNOS (neuronal nitric oxide synthase)
   In a healthy muscle, nNOS is anchored to the membrane by dystrophin; its main function is to make NO, which dilates blood vessels during exercise. In DMD, nNOS is not at the membrane and blood vessels can't dilate, depriving the muscle of oxygen.

b. Fibrosis-promoting pathways
   Wnt signaling normally promotes controlled regeneration, but in DMD, it can be activated permanently, leading to fibroblast expansion and ECM remodeling. Myostatin, a negative regulator of muscle mass is often upregulated, suppressing regeneration.

The absence of Dystrophin causes the muscle cell to lose its structural anchor and its ability to regulate and repair itself. The result is a cascading failure.

How is the treatment intended to work?

There is essentially only one way to fully "cure" DMD, and that involves modifying the Xp21.2 gene and hoping that the protein expresses properly across the body. This has to be done at a very low age, and comes with its own risks and pitfalls. The other option is to build treatments that extend the life of patients with DMD—the most effective way to do this is to design an intervention that slows a downstream process resulting from lack of Dystrophin. CAP-1002

consists of cardiosphere-derived cells (CDCs), which are a heterogeneous population of stromal cells isolated from donor human heart tissue inserted via IV into the patient (at a dose of 150 million cells) every 3 months. Stromal cells are a stem-like cell that secretes useful molecules. It's okay to inject because it doesn't provoke a strong immune reaction due to their low expression of MHC class I and no expression of MHC class II, the proteins that normally trigger immune rejection.

These cells are made by mincing heart tissue into small pieces, culturing it so that cells migrate out, and then expanding the 3d clusters into 2d layers of adherent CDC cells. They're similar to mesenchymal stromal cells (MSCs such as CD105, CD90, CD73) but differ because of their cardiac origin and some low level progenitor markers like C-kit.

Mechanism of Action:
Cap-1002 is delivered via IV, directly into the bloodstream at doses of about 150 million cells every 3 months. This allows the cells to reach both cardiac and skeletal muscle all around the body. The cells injected disappear within days to weeks, (only 1% remains in host tissue), but their exosomes have longer term effects that alter some of the chain reaction that we described earlier. Exosomes in CDCs contain a few important compounds:

- tetraspanins (cd63, 81, 9) — exosome surface proteins
- miRNAs (miR-146a, 29, 210) — short regulatory RNAs that silence target genes
- proteins like growth factors (vegf, igf-1), anti-inflammatory mediators
- lipids

The release of these compounds reduces the adverse effects of the typical Duchenne pipeline at various points:

a. **Anti-inflammation**
   This intervention occurs at the immune activation phase, where the body's immune system begins attacking the muscle cells due to DNA, ATP, and internal proteins that shouldn't be outside cells. Activation of TLRs and P2RX7 brings in macrophages, immune cells that digest pathogens or debris, and T-cells, which coordinate immune responses. M1 macrophages are a subtype that promote inflammation by releasing cytokines (TNF-alpha, IL-1beta, IL-6). miR-146a inside the exosomes supresses IRAK1 and TRAF6, which are adapter proteins inside immune cells that transmit signals from TLRs to NF-kB, a master switch that turns on pro-inflammatory genes, including TNF-alpha, IL-6, and IL-1beta. By inhibiting this pathway, cytokine production is reduced, macrophages switch from M1 (pro-inflammatory) to M2 (anti-inflammatory), promoting tissue repair. The result is that the body's immune response to the damaged cells is stifled, giving the muscle a higher chance of repairing.
b. **Anti-fibrotic effects**
   In the normal DMD cascade, dead muscle is replaced by fibrosis—non-contractile scar tissue made of collagen, the main protein in connective tissue. This is driven by TNF-beta (transforming growth factor beta), a signaling protein that tells fibroblasts (collagen building cells) to become myofibroblasts, a more active scar-producing cell (activating the SMAD2/3

pathway). CDC exomes carry miR-29, a microRNA that silences genes encoding collagen, and decorin, a natural inhibitor of TGF-B. These two mechanims reduce collagen gene expression and fibroblast to myofibroblast conversion, slowing the rate at which dead muscle is replaced by scar.

c. **Pro-regenerative**
   Satellite cells, which sit under the basal lamina, divide to make new muscle fibers and fuse into existing fibers to repair them. In DMD, divide too often due to constant injuries. mTOR (a growth signaling pathway) is overactive, which interferes with autophagy. CAP-1002 carries signals that support regeneration:
   - IGF-1—insulin like growth factor 1, a protein that promotes muscle growth and satellite cell activation.
   - miR-206, a microRNA that helps satellite cells toward forming new muscle
   - VEGF (vascular endothelial growth factor) and miR-210, which increase angiogenesis (new blood vessel formation), improving oxygen and nutrient delivery
   The result is that muscle regeneration is temporarily improved. This doesn't fix the stem cell exhaustion problem long term, but it slows it down and makes each injury less destructive.

d. **Cardioprotection**
   Dystrophin is also missing from the cardiac muscle. In the heart, CAP-1002 exosomes activate PI3K/Akt, a survival pathway that protects cardiomyocytes from apoptosis. They also reduce ROS via upregulation of SOD2 (superoxide dismutase 2), an antioxidant enzyme. Additionally, through the same mechanism mentioned earlier, fibrosis is suppressed and vascularization is increased. The result is that the structural and functional decay of the heart is slowed, not stopped.

All of the above interventions happen quite late into the disease progression; the muscle still tears due to lack of dystrophin, the micro ruptures let in excess calcium, the mitochondria malfunctions, and ROS are released. CAP-1002 intervenes at the inflammation and fibrosis stages and supports regeneration. The drug does not correct the underlying cause of DMD but modifies the disease environment in a way that reduces downstream effects and delays total muscle decay by a few years when administered early enough. Some of the most destructive processes that happen in DMD are not prevented, including calcium overload, mitochondrial dysfunction, and vascular compromise (due to nNOS loss).

Clear downsides of this treatment:

1. Transience
   The effects of the dose only last weeks to a few months. CDC cells don't engraft and their exosomes are cleared quickly. A patient would require dosing for life, likely every 3 months; if the dosing stops, the disease progression quickly reverts back to normal.
2. Does not restore dystrophin
   The drug doesn't fix the genetic cause of DMD, nor does it help build muscle. The structural anchor between the cytoskeleton and the membrane remains broken. Sarcolemmal tearing, calcium overload, and mitochondrial stress continue, and muscle will still degenerate, just more slowly. The drug works best with other approaches (e.g., exon-skipping, gene therapy) that address the dystrophin deficiency directly.

3. Immune reactions
   Even though the cdc cells are allogeneic and hypoimmunogenic, they're still recognized as foreign. A handful of patients experience mild infusion reactions (rash, fever, chills), and in some cases anti-HLA antibodies can develop. Although no sustained immune rejection was reported, this raises long term concerns about patients who may develop neutralizing antibodies to exosomes or cdc-derived factors, reducing efficacy.
4. Logistical/Clinical burden
   Since the drug is delivered via IV infusion, a patient would need to go to a clinic every 3 months for another dose. For many patients (especially late-stage), this is inconvenient and extremely difficult physically.
5. Scalability and manufacturing limits
   CDC production depends on human donor heart tissue, which is a finite resource. Even with expansion, each lot has variable potency. Capricor has to find a way to ensure that the batch-to-batch variation between samples is low, and that each sample meets purity, identity, and potency per FDA standards. The drug also needs cryopreservation, which means they need to figure out cold-chain logistics as well. This is a very difficult drug to mass produce at scale.

Clinical trials and prior data

There are a few important trials that we need to evaluate to predict Capricor's P3 results, set to release around August 31 (Q3). First, we need to investigate the origins of the drug, what it was initially used for, and how they transitioned CAP-1002 from a cardiomyopathy drug to a DMD drug. CAP-1002 doesn't really cure or help DMD specifically; it was initially intended to help patients with heart infarctions. This is what the first two trials, Allstar and Dynamic, were aimed at. The drug has not changed since 2012; the only thing that has changed is the delivery method and the dosage.

Timeline:
2012: Allstar phase 1/2 (next phase cancelled due to poor data)
2014: Dynamic phase 1/2 (next phase cancelled because of pivot to Duchenne's)
2015: Hope-Duchenne phase 1/2
2018: A Study of CAP-1002 in Ambulatory and Non-Ambulatory Patients With Duchenne Muscular Dystrophy (HOPE-2 Phase 2)—focused on upper limb function
2020: Open-label extension of 2018 study to study long-term impacts and safety of CAP-1002, ended in 2022.
2022: Hope-Duchenne phase 3 (the most important readout for the company—this is the binary event)

The primary endpoint for HOPE-3 is **change from baseline in Performance of the Upper Limb (PUL) v2.0 score**. The PUL score was changed extensively from version 1.2 (measured in trials before HOPE-3) to v2. Structural differences:

	PUL v 1.2	PUL v 2.0
Scored items	21	22
Per-item scale	0-1, 0-2, 0-4, 0-5	0-1 or 0-2
Maximum score	74	42
Items dropped	Shoulder flex, elbow timed lift, reach across table, fine pinch	—
Psychometrics	Ceiling in ambulant boys, some mis-fit items	Better Rasch fit, PSI 0.95, lower floor/ceiling, MDC ≈ 3 pts

Overall, PUL 2.0 shows tighter item fit, markedly lower floor/ceiling effects, and higher sensitivity to 12 month decline than version 1.2.

It is possible to accurately map PUL 1.2 scores to PUL 2.0 scores, using a machine learning model trained to fit 540 paired assessments: R^2 = 0.98, RMSE = 1.76 points. Best fit linear component: PUL 2.0 = 0.57 * PUL 1.2 - 0.1. See the nmd-journal article for the full paper. We'll use this model to help predict the phase 3 endpoint, in the case that no raw data is provided for PUL2.0 endpoints.

Natural PUL 2.0 rate of decline:
To understand how much this drug actually improves upper limb function measured by PUL 2.0, we need to look at how much the score declines naturally among ambulatory and non-ambulatory patients under standard of care (usually glucocorticoids).

- Ambulatory DMD patients - source
  Mean PUL 2.0 decline of -0.45 points at 12 months and -2.07 points over 24 months (-1.04 points/year)
- Non-ambulatory DMD patients
  In the same study, non-ambulant boys declined by -2.17 points at 12 months and -4.36 points over 24 months (-2.18 points per year)

HOPE-Duchenne

This study CAP-1002 in Duchenne patients, specifically those with cardiomyopathy. HOPE-Duchenne (halt cardiomyopathy progression) was a randomized, open-label study that enrolled 25 patients (1:1 usual care/CAP-1002). Patients were administered a one time dose of 75M cells—25M in three coronary arteries supplying the three major cardiac territories of the left ventricle of the heart (anterior, lateral, inferior/posterior). The primary endpoints in this study are mostly safety related, and focus on the effects on the heart rather than the skeletal system.

You can view the trial at clinicaltrials.gov and get the data here.

(Primary) Number of participants with Treatment-emergent adverse events and serious adverse events up to 12 months post infusion:

12 usual care and 13 CAP-1002 patients were analyzed for this endpoint. Overall, safety during this trial was good. Transient atrial fibrillation occurred in 39% of CAP-1002 patients (vs 8% controls), all asymptomatic and self-resolving during infusion. No deaths, discontinuations, or persistent issues; mild/moderate TEAEs were comparable between arms.

(Exploratory) Change from baseline in performance of the upper limb (PUL) overall score (excluding and including shoulder) at baseline, month 6 and 12:
The PUL score assesses upper limb function in DMD and similar neuromuscular conditions. The score is based on function in three areas: shoulder, elbow, and hand/fingers. These tasks usually assess reaching and lifting abilities, like bringing hand to mouth, lifting a light object, picking up coins, using a zipper, opening a container, etc. Some subjectivity remains in judgement, especially around effort, quality of movement, or borderline performance. Excluding the shoulder, the maximum possible score is 58.

The shoulder score is often excluded from analysis because non-ambulant DMD patients usually score 0, whereas ambulant boys score near the top. Including the shoulder the final score can mask meaningful changes in the elbow and hand domains. Removing it is an attempt to reduce the bias inflicted by ambulant patients.

Excluding shoulder

Month 6	Usual Care	CAP-1002
Number analyzed	11	12
* Mean (standard deviation)	-1.8 (4.38)	-0.3 (2.90)
Month 12		
Number analyzed	9	12
* Mean (standard deviation)	-1.2 (2.64)	1.3 (6.12)

Including shoulder

Month 6	Usual Care	CAP-1002
Number analyzed	6	3
* Mean (standard deviation)	0.3 (2.16)	-3.7 (4.04)
Month 12		
Number analyzed	9	12
* Mean (standard deviation)	-1.8 (3.60)	-4.0 (0)

Excluding the shoulder, the data suggests a potential benefit of CAP-1002, with a 1.3 point improvement at 12 months compared to a decline in the usual care group. However, it's important to recognize that a 1 point change on a 58 point scale is only a 2.2% shift, an effect size that is below the threshold for clinical significance. The high standard deviation also suggests that individual responses varied substantially, and the average improvement could be influenced by outliers. The findings are directionally positive, but inconclusive with such small n and no statistical power.

Including shoulder scores may amplify apparent declines due to early loss of function in that domain, making exclusion more appropriate for detecting treatment signals.

Percent change from baseline in PEF at month 6 and 12:
The PEF is a participant's maximum speed of exhalation (in liters per second), as measured with a peak flow meter. To some extent, this measures lung recoil pressure and respiratory muscle strength. All changes recorded within this endpoint are within 0.1 liters per second, which is clinically negligible.

The next endpoint, percent predicted PEF adjusts raw PEF in L/s based on age, sec, height, and race so that the data is normalized and accurately compares to a healthy person in that

demographic. Here, both groups decline as the disease progresses, but the CAP-1002 group declines slightly more at both 6 and 12 months.

CAP-1002 resulted in no meaningful improvement to PEF, often underperforming usual care.

Percent change from baseline in LVEF at month 6 and 12:
LVEF (left ventricular ejection fraction) is the percentage of blood ejected from the left ventricle with each contraction. LVEF is a strong predictor of mortality in heart failure and post-MI, making it one of more important endpoints measured in this study. The results indicate that CAP-1002 has almost no benefit over usual care (see endpoint 16 and 17 on clinicaltrials.gov). In fact, LVEF in the CAP-1002 group is much worse at the 12 month mark compared to the usual care group: -0.88% (5.58) vs 1.88 (8.83).

Pediatric Quality of Life Inventory total summary score, at month 6 and 12:
The DMD module of this quiz contains 4 domains: daily activities, treatment barriers, worry, and communication. Items are reverse-scored; 0 is the best quality of life and 100 is the worst. The difference between a usual care patient and a CAP-1002 patient at 12 months is around 15, which is a massive gap. The high SD is not as much of a problem here, because this is by definition a noisy, subjective score. Usual care participants felt much better, on average, than CAP-1002 patients. Some of this difference could be attributed to the fact that controls did not go through the same invasive procedure that the treatment group did.

Percent change from baseline in LV Late Gadolinium Enhancement at month 6 and 12:
LGE detects fibrotic or scarred myocardium on cardiac MRI. The volume of LGE is a direct index of irreversible cardiac injury; decreasing this value is biologically impressive and rarely seen. At both times, CAP-1002 shows numerical reduction in scar volume, while usual care worsens or stays the same. The difference at month 12 is a little less than 1.5 grams, and the SD is reasonable. The only small catch is that chronic corticosteroids (prednisone, deflazacort) are standard of care in DMD; these are known to slow skeletal muscle decline, reduce cardiomyocyte inflammation, and possibly limit cardiac fibrosis. Any scar regression or attenuation could plausibly be a shared background effect of steroids, not the result of CAP-1002. The effect of CAP-1002 is modest at best, and not supported by LVEF improvement and other clinical endpoints such as QoL and 6MWT. There might still be a small difference between CAP-1002 and usual care, but it's difficult to make that case when none of the other endpoints line up.

Key limitations pointed out in the pubmed report:

1. The treatment group underwent a procedurally intensive cardiac catheterization, while controls did not. This creates performance and expectation bias, particularly for subjective endpoints like PUL and PedsQL.
2. The sample size (n=25) is inadequate for detecting anything but very large effects, especially across many endpoints. Any statistically significant differences may be false positives, while true but modest effects could be missed.

3. LGE limitations in DMD: The technique compares signal intensity against “normal” myocardium, but in DMD, there is no such thing as truly normal myocardium, especially in non-ambulatory patients. The best mechanistic signal in the trial is measured using an imperfect tool.
4. A subset of CAP-1002 patients were on steroids <2 years, where muscle gains are more likely. This creates confounding in interpreting functional improvements (PUL) attributable to CAP-1002. It is impossible to isolate the effect of the treatment from ongoing steroid benefit.
5. 93% of patients in the CAP-1002 group had exon deletions, making the cohort genetically narrow. The findings of this study can’t be generalized to all DMD genotypes.
6. No multiple testing correction. Additionally, the cohort was mostly non-ambulant (92% in treatment arm), which limits applicability to earlier disease.
7. The primary positive result (8 of 9 PUL responders vs 0/5, p=0.007) was post-hoc, unadjusted, excluded missing data, and did not adjust for baseline imbalances.
8. In DMD patients, scoliosis is common and progressive. Ignoring this variable introduces unmeasured confounding in several key endpoints.

The authors end the paper by concluding that repeated administration by IV (every 3 months, in the HOPE-2 trial) might lead to better efficacy in a future trial.

A Study of CAP-1002 in Ambulatory and Non-Ambulatory Patients With Duchenne Muscular Dystrophy (HOPE-2)

clinicaltrial.gov trial registration.
the lancet paper, with supplemental data, p-values and more.

Key changes between this trial and the last include:
- Change from intracoronary infusion to IV
- Increased dosage to 150M cells every 3 months instead of a one-time dose at start of trial
- 8 CAP-1002, 12 placebo (still not big enough to draw conclusions from)
- Quadruple blind
- All ambulatory patients, compared to the 3:1 split in the last trial.

Another major change is that they switched from raw data to least squares mean percentile ranks for all of the endpoints (except two discussed below). In the last trial, we got raw data for each endpoint (exact PUL scores, LVEF changes in percentage points, etc); and this was very straightforward to interpret. In this trial, all we have is percentile rank of percent change. This is calculated as follows:

For each participant, calculate the change in an endpoint from baseline at each post-baseline time point (6, 12 months). Pool all these change values across all participants (all groups) and all relevant time points. Assign a percentile rank (0-100) to each individual change value based on its position relative to the entire pooled set of changes. The highest change gets rank 100, median gets 50, and worst gets 0. Then, these ranks are analyzed using a repeated mixed-effects model or ANCOVA (analysis of covariance), to account for time, group, and covariates

(e.g. baseline LVEF). This yields least squares means (LSM), which are adjusted averages of the ranks for each group at each time point, along with standard errors (SE). This method of representing results highlights relative performance between patients in a trial, but doesn't reveal if the differences are clinically meaningful. The ranks could differ hugely even if the actual changes are tiny.

The only raw data published by Capricor for this study are mid-level PUL1.2 and LVEF.

PUL scores:
The raw data from this endpoint shows that the treatment group had a 0.1 point change in mid-level arm function (PUL1.2), while the placebo group declined by 2.5 points (+2.6 effect size on a 12 point scale). This is clinically significant (p = 0.014); however, the 95% confidence interval is extremely wide (7.9 to 64.5), which suggests that the benefit of the drug was unevenly spread amongst the participants and some subgroups responded to the treatment more.

No raw data was published for the P3 primary endpoint (PUL2.0 upper limb function), but we can make a couple inferences from the available information:

Version	Mean Percentile Rank Difference	95% Confidence Interval	p-value
PUL 1.2	27.4	-6.8 to 61.6	0.11
PUL 2.0	8.6	-14.0 to 31.2	0.44

Neither score is statistically significant, but the effect is clearly diluted in PUL 2.0 (70% lower percentile rank estimate). The observed benefit in PUL 1.2 did not carry over as much to PUL 2.0.

The total PUL1.2 and PUL2.0 scores did measurably improve (p values under 0.05 and around 29 percentile points better), but again, it's difficult to figure out if this difference is meaningful because we don't have raw values for these targets.

Based on the above, meeting the phase 3 primary endpoint (mean change from baseline in PUL2.0 upper limb function at 12 months) is highly unlikely:
- Mid-level PUL 1.2 showed a statistically significant difference
- High level PUL 2.0 showed a weak, non-significant effect
- Total PUL 2.0 score showed a statistically significant improvement, but no raw score change was disclosed, which obscures the true magnitude of the change.

Additionally, the observed benefit in PUL 1.2 came from only 8 treated patients, and the confidence interval (7.9 to 64.5) was extremely wide, signaling heterogeneous responses. Any true effect of CAP-1002 might not be consistently detectable in a broader population. HOPE-3 includes 58 patients, which addresses the main sample size limitation, but the primary endpoint has shifted to one where past trials have shown showed weaker, non-significant results. If the

PUL 2.0 score behaves as it did in this trial, the P3 trial will require a larger effect size, less variance, or both to hit statistical significance.

LVEF and other cardiac data (secondary endpoint for P3):
The CAP-1002 group showed a 4% improvement in LVEF at the 12 month mark (p = 0.0022); the placebo group went down by 3.9%, while the treatment group remained stable at +0.1%. Although an absolute change of >5% is typically the threshold for clinical relevance in cardiology, in DMD stabilization of EF is itself clinically meaningful. Natural history data shows a 2-3% annual EF decline even with standard care. CAP-1002 seems to prevent that drop. That said, this outcome doesn't necessarily reflect functional gain—the treatment group remained essentially flat. It may not yield perceptible improvement in QoL or functional status in 12 months, as seen by the PUL results.

CAP-1002 also produced a consistent benefit in LV remodeling: reductions in ESV, EDVi, and a composite improvement in global cardiac measures. A parallel decrease in CK-MB/total CK ratio supports a biological effect on cardiomyocyte stress or injury. However, regional measures of systolic thickening and circumferential strain did not improve.

Overall, the evidence points to CAP-1002 having a stabilizing role in DMD cardiomyopathy, with statistical robustness but a modest absolute effect size. The clinical impact within one year remains limited in magnitude.

HOPE-2 Open Label Extension

The single arm, open label extension started in 2018 after the completion of HOPE-2, so that the long-term efficacy and safety of the drug could be studied more. This data is materially useless in predicting the results of HOPE-3, for the following reasons:

1. Open label extension; everyone receives CAP-1002. You can't separate the effect of the drug from expectation or regression to mean
2. 6 prior-active + 7 prior-placebo all endured a 7 to 9 month gap without treatment before the OLE started.
3. Only 12 patients treated through Month 36.
4. Hope-3 is powered to detect a ~2-point difference in PUL 2.0 score, the observed effect here — -1.5 (prior-active, n=6) vs -1.9 (prior-placebo, n = 7) is an order of magnitude smaller than
5. Beyond this company slide, there is not much additional information about the HOPE-2 OLE.

These limitations mean that the OLE can support long-term safety, but not much else.

Putting this all together for phase 3

Prior HOPE trials have never shown a statistically significant benefit on the conservative PUL v2.0 endpoint (HOPE-1 and HOPE-2), and the modest mid-level PUL v1.2 signal in HOPE-2 (n=8 treated) came with wide inter-patient variability (CI 7.9–64.5 percentile), making a repeat signal in a larger, more heterogeneous cohort unlikely. Even with 58 patients, unless the

treatment effect size meaningfully increases or variability contracts, HOPE-3 is unlikely to hit statistical significance on PUL v2.0. The FDA's prior Complete Response Letter for CAP-1002 in DMD further underscores that only a clear, statistically significant PUL v2.0 result could clear the regulatory bar.

CAP-1002's consistent LVEF preservation in HOPE-2 (+4% delta vs placebo, p = 0.0022), along with favorable LV remodeling and CK-MB reductions, confirms biological activity—but a cardiac-only label, absent skeletal muscle benefit, weakens patient-perceived value and commercial potential.

With no historical precedent for a PUL v2.0 hit, high inter-patient variability, prior regulatory rebuff, and mounting legal distractions (both in expense and management focus), the odds strongly favor HOPE-3 missing its 12-month primary endpoint.