Repeated intravenous cardiosphere-derived cell therapy in late-stage Duchenne muscular dystrophy (HOPE-2): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

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Summary

Background Cardiosphere-derived cells (CDCs) ameliorate skeletal and cardiac muscle deterioration in experimental models of Duchenne muscular dystrophy. The HOPE-2 trial examined the safety and efficacy of sequential intravenous infusions of human allogeneic CDCs in late-stage Duchenne muscular dystrophy.

Methods In this multicentre, randomised, double-blind, placebo-controlled, phase 2 trial, patients with Duchenne muscular dystrophy, aged 10 years or older with moderate upper limb impairment, were enrolled at seven centres in the USA. Patients were randomly assigned (1:1) using stratified permuted blocks to receive CAP-1002 ($1·5\times10^8$ CDCs) or placebo intravenously every 3 months for a total of four infusions. Clinicians, caregivers, patients, and clinical operations personnel were fully masked to treatment groups. The primary outcome was the change in mid-level elbow Performance of Upper Limb version 1.2 (PUL 1.2) score at 12 months, assessed in the intention-to-treat population. Safety was assessed in all individuals who received an investigational product. This trial is registered with ClinicalTrials.gov, NCT03406780.

Findings Between March 1, 2018, and March 31, 2020, 26 male patients with Duchenne muscular dystrophy were enrolled, of whom eight were randomly assigned to the CAP-1002 group and 12 to the placebo group (six were not randomised due to screening failure). In patients who had a post-treatment PUL 1.2 assessment (eight in the CAP-1002 group and 11 in the placebo group), the mean 12-month change from baseline in mid-level elbow PUL1.2 favoured CAP-1002 over placebo (percentile difference 36·2, 95% CI 12·7–59·7; difference of 2·6 points; p=0·014). Infusion-related hypersensitivity reactions without long-term sequelae were observed in three patients, with one patient discontinuing therapy due to a severe allergic reaction. No other major adverse reactions were noted, and no deaths occurred.

Interpretation CAP-1002 cell therapy appears to be safe and effective in reducing deterioration of upper limb function in patients with late-stage Duchenne muscular dystrophy. Various measures of cardiac function and structure were also improved in the CAP-1002 group compared with the placebo group. Longer-term extension studies are needed to confirm the therapeutic durability and safety of CAP-1002 beyond 12 months for the treatment of skeletal myopathy and cardiomyopathy in Duchenne muscular dystrophy.

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*Study group members are listed at the end of the Article and in the appendix (pp 3–4)

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Introduction

Duchenne muscular dystrophy is a severe, progressive, X-linked disease affecting both skeletal and cardiac muscle with severely reduced life expectancy.[1–3] Patients with Duchenne muscular dystrophy develop progressive quadriparesis, restrictive lung disease, and ever-worsening cardiomyopathy; together, these factors ultimately lead to death, typically in the second to fourth decade.[3,4] More than 80% of patients with Duchenne muscular dystrophy are non-ambulatory after the first decade, and this proportion is increasing.[5] Few trials of Duchenne muscular dystrophy therapeutics have targeted non-ambulatory patients, who now outnumber ambulatory patients.[5,6]

Muscle breakdown in Duchenne muscular dystrophy triggers inflammation and maladaptive immune responses, which further limit intrinsic muscle repair capability.[7] Cardiosphere-derived cells (CDCs) are a type of stromal or progenitor cell that has been shown in preclinical[8,9] and clinical[10–12] studies to exert immunomodulatory, antifibrotic, and regenerative actions in dystrophinopathy and heart failure (appendix pp 4–12). CDCs act by secreting extracellular vesicles known as exosomes, which target macrophages and alter their expression profile so that they adopt a healing, rather than a pro-inflammatory, phenotype.[13] Exosomes secreted by CDCs also reprogramme fibroblasts, rendering them antifibrotic.[14] In the *mdx* mouse model of Duchenne

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See Online for appendix

Research in context

Evidence before this study

Preclinical work showed that allogeneic cardiosphere-derived cells (CDCs) exhibit immunomodulatory, antifibrotic, and regenerative properties, conferring disease-modifying bioactivity in models of Duchenne muscular dystrophy. We searched PubMed for clinical trials of cell therapies for ambulatory and non-ambulatory patients with Duchenne muscular dystrophy published between Jan 1, 2010, and Oct 26, 2021. Search terms included Duchenne muscular dystrophy, cell therapy, cardiosphere-derived cell, stem cell, clinical trial, cardiomyopathy, performance of upper limb, ambulatory, and non-ambulatory. The search yielded only the phase 1 HOPE trial, in which CAP-1002 (the clinical formulation of allogeneic CDCs) delivered to the heart via coronary artery catheterisation met safety criteria and improved various exploratory endpoints related to cardiac and skeletal muscle function.

Added value of this study

HOPE-2 is the first trial of intravenous CAP-1002 for any indication and the first trial with repeat sequential dosing of cells for a genetic illness. Our study is the first double-blind, randomised, placebo-controlled trial of any form of cell therapy in Duchenne muscular dystrophy, and the first placebo-controlled clinical trial in ambulatory or non-ambulatory patients with Duchenne muscular dystrophy to use the Performance of Upper Limb measure as a prespecified primary efficacy endpoint. Compared with the placebo group, patients randomly assigned to CAP-1002 showed stabilisation of upper limb function, as well as improvements in cardiac function and structure, at month 12 (after four doses of CAP-1002). CAP-1002 was well tolerated in severely affected patients with Duchenne muscular dystrophy, with the exception of hypersensitivity reactions. Implementation of a pretreatment procedure with glucocorticoids, an H1 blocker, and an H2 blocker succeeded in preventing serious allergic reactions.

Implications of all the available evidence

The cell therapy CAP-1002 has shown safety and promising bioactivity in patients with late-stage Duchenne muscular dystrophy. The degree of efficacy shown by CAP-1002 in this exploratory study was clinically meaningful, motivating a larger, long-term study to confirm the potential of CAP-1002 to benefit non-ambulatory patients with Duchenne muscular dystrophy.

muscular dystrophy, CDCs reverse the dystrophic phenotype and improve ambulatory capacity and survival by reducing pro-inflammatory cytokines, and altering expression of genes related to oxidative stress, inflammation, mitochondrial integrity, and muscle regeneration.[8,9]

CAP-1002, the clinical formulation of human allogeneic CDCs, is a therapeutic candidate for Duchenne muscular dystrophy. Although findings from preclinical studies suggest that CAP-1002 might work at all stages of Duchenne muscular dystrophy, clinical development efforts have focused on non-ambulant patients, who have limited treatment options and significant unmet needs. In the phase 1 HOPE (Halt cardiomyopathy progression in Duchenne) clinical study, CAP-1002 showed an acceptable level of safety and appeared to preserve upper limb and cardiac function in 13 patients with Duchenne muscular dystrophy after one-time infusion into the coronary arteries.[11] The main objectives of the present HOPE-2 trial were to assess the long-term safety and efficacy of repeated intravenous infusions of CAP-1002 for the treatment of Duchenne muscular dystrophy. The change in delivery route, and multi-dose regimen, were both motivated by preclinical findings in *mdx* mice showing equivalent benefits of intracoronary and intravenous CDCs,[9] and sustained functional improvements with sequential dosing.[8] The efficacy outcomes of HOPE-2 included upper limb function using the Performance of Upper Limb (PUL) motor function scale for Duchenne muscular dystrophy,[15,16] heart function using cardiac MRI imaging, spirometry measures of respiratory function, and circulating biomarkers.

Methods

Study design

HOPE-2 was a randomised, multicentre, double-blind, placebo-controlled, phase 2 clinical trial to assess the safety and efficacy of intravenous infusions of CAP-1002 for the treatment of Duchenne muscular dystrophy. All infusions were conducted between March, 2018, and March, 2020, in an outpatient setting at one of seven investigative sites in the USA (appendix p 3). The protocol was reviewed and approved by each of the investigative sites' institutional review boards.

Capricor Therapeutics (Beverly Hills, CA, USA) provided the active drug and matched placebo. An independent data and safety monitoring board reviewed unblinded safety and efficacy data throughout the trial. Statistical analyses were performed by Pentara and an independent statistical consultant. The study protocol is provided in the appendix (pp 55–171).

Participants

We enrolled late ambulatory (with 10 m walk times of >10 s) and non-ambulatory male patients with genetically confirmed Duchenne muscular dystrophy. Eligible patients were aged 10 years or older, with a PUL entry item score of 2–5 (figure 1) delineating loss of full overhead reach but retained hand-to-mouth function, and previous treatment with a glucocorticoid for at least 12 months (with stable dosing for at least 6 months before randomisation). Full inclusion and exclusion criteria are provided in the protocol (appendix pp 55–171). Patients or caregivers gave written informed consent

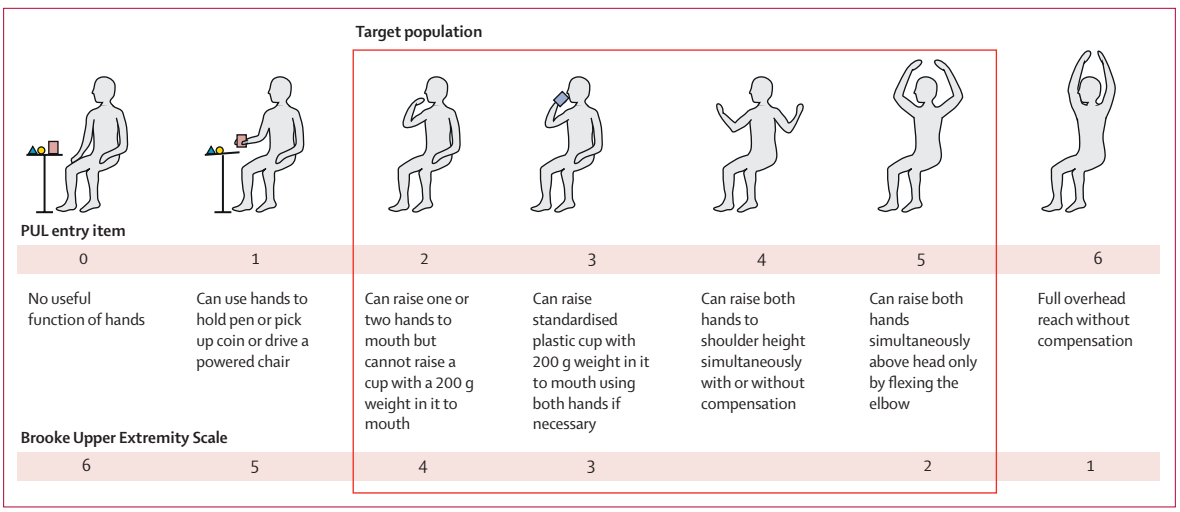


Figure 1: **PUL entry items**
Brooke Upper Extremity Scale values are also shown for comparison. PUL=Performance of Upper Limb.

before enrolling, with children providing assent as appropriate.

Randomisation and masking

Approximately 7 days before the first infusion, patients were randomly assigned at a 1:1 ratio to either CAP-1002 or placebo using stratified permuted blocks via an interactive web-based response system. Randomisation was stratified by site and PUL entry item score. High-level unblinded results were publicly announced by the trial sponsor after an interim analysis for futility. Clinicians, caregivers, patients, and clinical operations personnel remained fully masked before, during, and after the interim analysis.

Procedures

Human allogeneic CDC manufacturing has been described previously.[11] Briefly, two human donor hearts were obtained from an organ procurement organisation, myocardial tissue was cultured to create CDCs, and 12 lots of CDCs were formulated as CAP-1002 and cryopreserved. Identity and purity were confirmed by high (99·6% plus or minus 0·2%) CD105 and low (0·4% plus or minus 0·3%) CD45 expression.[9–12] Viability and safety testing (viral, microbial, and additional purity) were also assessed as product release criteria. CAP-1002 ($1·5\times10^8$ CDCs) and placebo (the same formulation minus CDCs) frozen concentrates were supplied in a total volume of 20 mL of cryogenic cell preservation solution. The investigational product was administered intravenously once every 3 months for a total of four infusions. All patients were followed up until 12 months after the first infusion. The fourth and last infusion was performed 3 months before the 12-month final assessment (ie, 9 months post randomisation).

To minimise the risk of potential severe allergic reactions, such as anaphylaxis, a pretreatment regimen was implemented, which included the administration of: higher-dose oral glucocorticoids than patients were usually taking at baseline starting 12–14 h, and again 2–3 h, before investigational product infusion; an H1 blocker (either diphenhydramine or cetirizine) 1 h before infusion; and an H2 blocker (intravenous famotidine) 1 h before infusion. These precautions were added to the protocol with an amendment on Jan 17, 2019, after one patient experienced an investigational product-related severe allergic reaction.

Outcomes

Upper limb function was assessed with both the PUL 1.2 instrument, used previously in the phase 1 HOPE trial, and the newly validated PUL 2.0 instrument (appendix pp 12–13, 42–44).[15,16] The primary efficacy outcome was change from baseline to the 12-month timepoint in the mid-level elbow dimension of PUL 1.2. The secondary efficacy outcomes were change from baseline in the mid-level elbow dimension of PUL 1.2 at months 3, 6, and 9, and regional systolic left ventricular wall thickening as assessed by cardiac MRI at months 6 and 12. Exploratory outcomes in the study included change from baseline to the 12-month timepoint in PUL 2.0, change from baseline at each assessment timepoint in individual dimensions (high-level shoulder; mid-level elbow and distal-level wrist and finger combined; and distal-level wrist and finger) of PUL 1.2 and PUL 2.0, cardiac structure and function measurements by cardiac MRI, pulmonary function tests, Duchenne muscular dystrophy-specific upper limb patient-reported outcome measure (DMD-UL-PROM),[17] creatine kinase (CK), CK-MB isoenzyme biomarkers of muscle damage, and a 46-cytokine ELISA panel. Primary safety outcomes included the incidence of the following from baseline to 12 months: acute respiratory decompensation within 2 h after investigational product administration, hypersensitivity reaction, all-cause mortality, serious adverse events, treatment-emergent adverse events related to

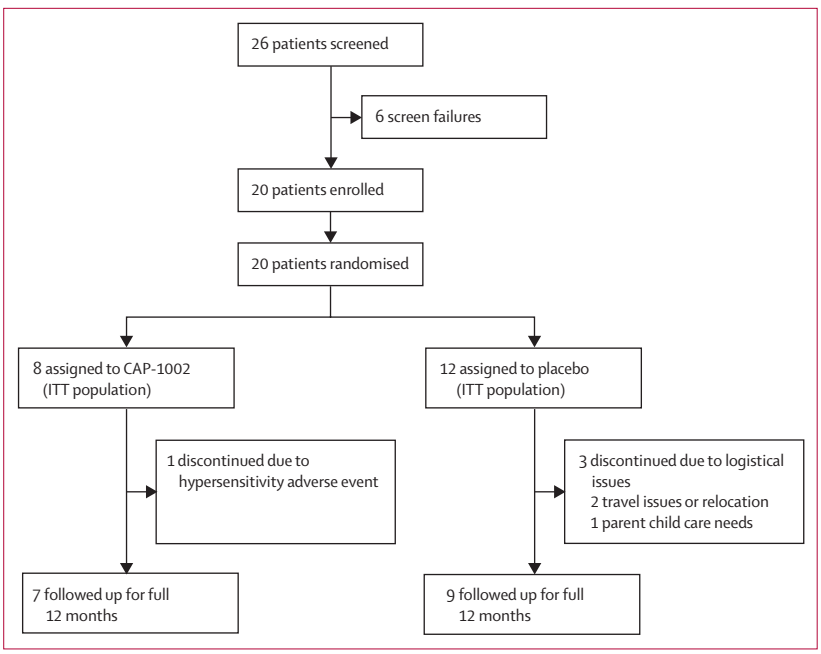


Figure 2: **Trial profile**
ITT=intention-to-treat.

investigational product or administration procedure, and immune sensitisation syndrome.

Statistical analysis

The original sample size of the study was set up to have 80% power to detect a treatment effect of between 1·1 points and 1·3 points on the primary efficacy outcome at a two-sided significance level (α) of 0·05. The original study hypothesis was that there would be a difference between the CAP-1002 and placebo groups of greater than a 1-point change from baseline at the 12-month timepoint in functional capacity as assessed by the mid-level elbow dimension of PUL 1.2. The original study protocol included targeted enrolment of 84 patients to ensure 76 evaluable patients. All statistical tests were two-sided and p values of 0·05 or less were considered statistically significant. The primary efficacy outcome was the only outcome prespecified for formal statistical testing at the conclusion of the study, so other reported p values are considered nominal values unadjusted for multiple testing. Secondary and exploratory outcomes were evaluated in a similar manner to the primary outcome. The safety population was defined as all individuals who received an investigational product. The intention-to-treat population, in which all efficacy outcomes were evaluated, was defined as all individuals who were randomised.

A parametric linear mixed model repeated measures (MMRM) was the prespecified analysis originally performed for all primary, secondary, and exploratory endpoints of the study. A blinded 6-month interim analysis was prespecified after 20 patients were enrolled for futility, because this was the first trial to evaluate repeated intravenous administration of CAP-1002. Due to funding constraints, the trial sponsor elected to pause enrolment in the trial before the interim analysis for futility. Based on the interim analysis and review by the data safety monitoring board, which supported lack of concerning safety signals and lack of futility, the sponsor elected to amend the protocol to reduce enrolment to the 20 already randomised patients. The decision was made to not enrol the full 84-patient cohort due to important input from the US Food and Drug Administration, which recommended transitioning as quickly as possible to a phase 3 trial that would be powered based on the forthcoming 12-month HOPE-2 trial data. All HOPE-2 patients were offered treatment beyond 12 months in an open-label extension protocol (ClinicalTrials.gov, NCT04428476).

Because of the smaller sample size, model residuals were inspected and found to fail the normality assumptions for a parametric MMRM (appendix p 14). Therefore, HOPE-2 data were fitted using a non-parametric version of the prespecified model with change from baseline and baseline values converted to a percentile rank over all timepoints and at baseline (appendix pp 15–16). For a given outcome, this is generated by calculating the percentile rank of each change-from-baseline value relative to all observed change-from-baseline values for the same outcome (across all patients and all post-baseline observation times). The percentile ranked change from baseline was treated as the dependent variable in the regression. This modelling approach was used for primary, secondary, and exploratory endpoints. For PUL and cardiac MRI outcomes, a global statistical test[18] was calculated as the averaged percentile ranked change from baseline. Analyses were performed with SAS software, version 9.4. This trial is registered with ClinicalTrials.gov, NCT03406780.

Role of the funding source

Capricor Therapeutics was involved in the trial design. The funder had no role in data collection, data analysis, or data interpretation. RRS, DDA, SR, PW, and LM from Capricor Therapeutics were coauthors of the report.

Results

Between March 1, 2018, and March 31, 2020, 26 male patients with Duchenne muscular dystrophy were enrolled in the trial. Of these, eight patients were randomly assigned to the CAP-1002 group, 12 to the placebo group, and six were not randomised due to screening failure (figure 2). One patient randomly assigned to CAP-1002 received a partial infusion at month 3 (second infusion) due to a severe hypersensitivity reaction and discontinued further infusions, as specified in the protocol. Three patients randomly assigned to placebo chose to discontinue: two after two infusions and one after a single infusion. Demographic and baseline

	CAP-1002 group (n=8)	Placebo group (n=12)
Male sex	8 (100%)	12 (100%)
Age, years		
Mean (SD)	14 (3·2)	14 (2·9)
Range	10–21	10–19
<15	5 (63%)	6 (50%)
≥15	3 (38%)	6 (50%)
Race		
American Indian or Alaska Native	0	1 (8%)
Asian	1 (13%)	3 (25%)
White	7 (88%)	8 (67%)
Ethnicity		
Not Hispanic or Latino	6 (75%)	12 (100%)
Hispanic or Latino	2 (25%)	0
Body-mass index, kg/m²	23 (5)	22 (5)
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%)

Data are n (%) or mean (SD) unless otherwise indicated. PUL=Performance of Upper Limb.

Table 1: **Demographics and baseline characteristics of randomised patients**

characteristics were generally similar between treatment groups (table 1). All participants except two in the placebo group had at least one post-baseline visit, resulting in a statistical model with ten individuals in the placebo group and eight individuals in the CAP-1002 group. The two patients who dropped out in the placebo group did not show unusual values in the baseline distribution of the primary outcome.

The results of the MMRM analysis for the prespecified primary endpoint, PUL 1.2 mid-level dimension, in patients who had a post-treatment assessment (eight in the CAP-1002 group and 11 in the placebo group) are shown in figure 3A. The model showed a mean 12-month change from baseline in mid-level PUL 1.2, favouring CAP-1002 over placebo (percentile difference 36·2, 95% CI 7·9–64·5; difference of 2·6 points; p=0·014). This finding represents a clinically significant 71% slowing of loss of function with CAP-1002. To interpret the percentile ranked changes in figure 3A and assess clinical meaningfulness, values were matched to the rank-generating data (appendix p 46). The full curve (created using interpolation) indicates that the change in the primary endpoint at 12 months for the CAP-1002 group was –0·8 points (65·5 percentile, 95% CI 43·2–87·9) and for the placebo group was –3·4 points (29·3 percentile, 10·5–48·2), corresponding to a treatment difference of 2·6 points (percentile difference 36·2, 95% CI 7·9–64·5). A cumulative distribution curve for treatment impact is included in the appendix (p 25).

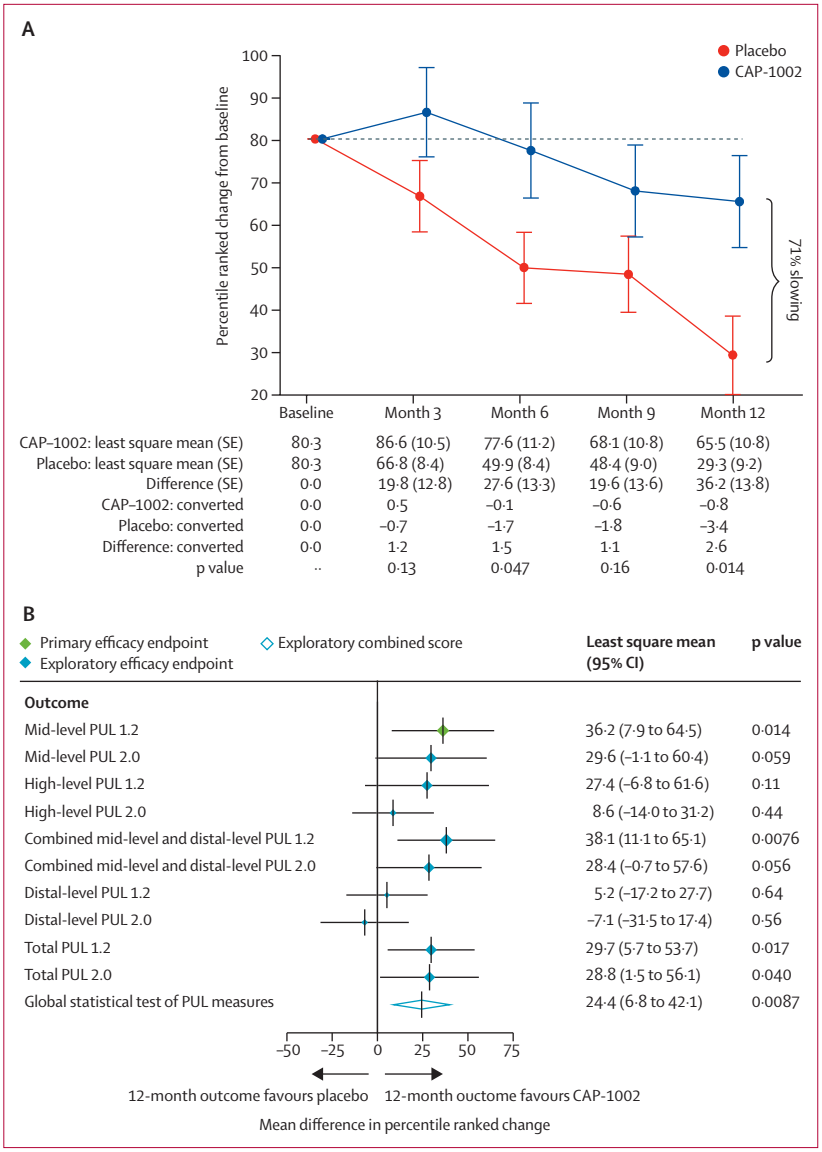


Figure 3: **PUL outcomes**

(A) PUL 1.2 mid-level dimension percentile ranked change. Least square mean percentile ranked change from baseline was plotted over time with SE bars. The table at the bottom of panel A shows least square means and SEs from the model as well as mean changes and differences converted back to the PUL 1.2 scale. Percentage slowing is calculated as (placebo–treatment)/placebo. (B) Forest plot of PUL measures at 12 months. Diamond markers represent mean differences of percentile ranked change, with the line widths representing 95% CIs. The size of diamond markers is scaled to the size of effect only as a visual guide. Global statistical test is an averaged percentile ranked change from baseline over all PUL measures. PUL=Performance of Upper Limb.

The secondary endpoint of 6-month change in mid-level PUL 1.2 was significantly different between groups, favouring CAP-1002 (percentile difference 27·6, 95% CI 0·39 to 54·9; difference of 1·5 points; p=0·047). At 3 months and 9 months, changes also favoured CAP-1002 and were clinically meaningful but were not statistically significant; at 3 months, the difference was 1·2 points (percentile difference 19·8, –6·5 to 46·1) and at 9 months, the difference was 1·5 points (percentile difference 19·6, –8·2 to 47·4; figure 3A). The secondary outcomes of

	CAP-1002 (n=8)	Placebo (n=12)
Primary safety outcomes*		
Acute respiratory decomposition within 2 h after investigational product administration	0	0
Hypersensitivity reaction	3 (38%); 5	0
All-cause mortality	0	0
Any serious adverse event	0	0
Treatment-emergent adverse events related to investigational product or administration procedure	3 (38%); 4	2 (17%); 3
Immune sensitisation syndrome	0	0
Treatment-emergent adverse events related to investigational product or administration procedure†		
Hypersensitivity	1 (13%)	0
Dizziness	1 (13%)	0
Dysgeusia	1 (13%)	2 (17%)
Oropharyngeal pain	1 (13%)	0
Flushing	0	1 (8%)

*Data are number of patients with one or more event (% of patients); number of events. †Data are number of patients with one or more event (% of patients).

Table 2: **Primary safety outcomes and adverse events in the safety population**

systolic left ventricular wall thickening (septal, lateral, inferior, and anterior) by cardiac MRI did not statistically favour CAP-1002 over placebo.

With regard to primary safety outcomes, no patients developed acute respiratory decompensation or immune sensitisation syndrome, and no patients died during the trial (table 2). The treatment was generally well tolerated. Among a total of 69 intravenous infusions of CAP-1002 or placebo over the 12-month duration of the study, seven treatment-emergent adverse events were related to investigational product or administration procedure (table 2). Five hypersensitivity reactions were reported among three (38%) individuals in the CAP-1002 group (appendix p 45). One individual in the CAP-1002 group experienced an acute allergic reaction during his second intravenous CAP-1002 administration (before the implementation of the pretreatment regimen), and the patient was administered intramuscular epinephrine. The event was considered serious, required overnight hospitalisation for observation, and qualified as a suspected unexpected serious adverse reaction. The protocol did not allow further infusions if there was history of a serious allergic reaction to investigational product. After implementation of the pretreatment regimen, 42 infusions of CAP-1002 or placebo occurred; among these, only one hypersensitivity treatment-emergent adverse event, which did not require epinephrine or prolonged monitoring, was reported.

Exploratory PUL 1.2 and PUL 2.0 dimensions at month 12, including total, shoulder, mid-level and distal-level combined, and distal-level, are summarised in figure 3B. The combined mid-level and distal-level PUL 1.2, total PUL 1.2, and total PUL 2.0 measures all favoured the treated group by a statistically significant and clinically meaningful degree, with similar magnitude differences to the primary endpoint. The shoulder-level and distal-level PUL 1.2 and PUL 2.0 measures were not significantly different between the CAP-1002 and placebo groups. Both the PUL 1.2 and PUL 2.0 total dimension scores showed progressive divergence between the CAP-1002 and placebo groups over time (appendix pp 27–28), and both measures showed statistically and clinically significant effects at 12 months (total PUL 1.2: percentile difference 29·7, 5·7–53·7, difference of 3·2 points, p=0·017; total PUL 2.0: percentile difference 28·8, 1·5–56·1, difference of 1·8 points, p=0·040).

Cardiac MRI assessments showed improvements in heart function and structure with CAP-1002 treatment. Left ventricular ejection fraction (LVEF), a global measure of cardiac pump function, decreased significantly in the placebo group over time, but improved slightly in ranked change in the CAP-1002 group, with a statistically significant difference in percentile ranks of 45·7 (95% CI 19·1 to 72·2; figure 4A). The CAP-1002 group had a mean increase in LVEF by 0·1 percentage points (54·5 percentile, 95% CI 35·2 to 73·8), whereas the placebo group had a mean decrease in LVEF by 3·9 percentage points (8·9 percentile, –10·7 to 28·5), giving an effect size of 4·0 percentage points, corresponding to 7% of the baseline LVEF of 54% (SD 5·6). Many of the exploratory cardiac MRI structure endpoints showed improvement in the CAP-1002 group compared with placebo (figure 4B). In particular, indexed left ventricular end systolic and end diastolic volumes were reduced; when elevated, these parameters signal progression of the underlying cardiomyopathy.[19]

No statistically significant treatment effects were identified in pulmonary function endpoints (appendix pp 18, 34), with the exception of percent predicted peak expiratory flow rate, which was improved with CAP-1002. DMD-UL-PROM measures correlated with PUL measures, but changes with CAP-1002 versus placebo were not statistically significant (appendix pp 18, 36).

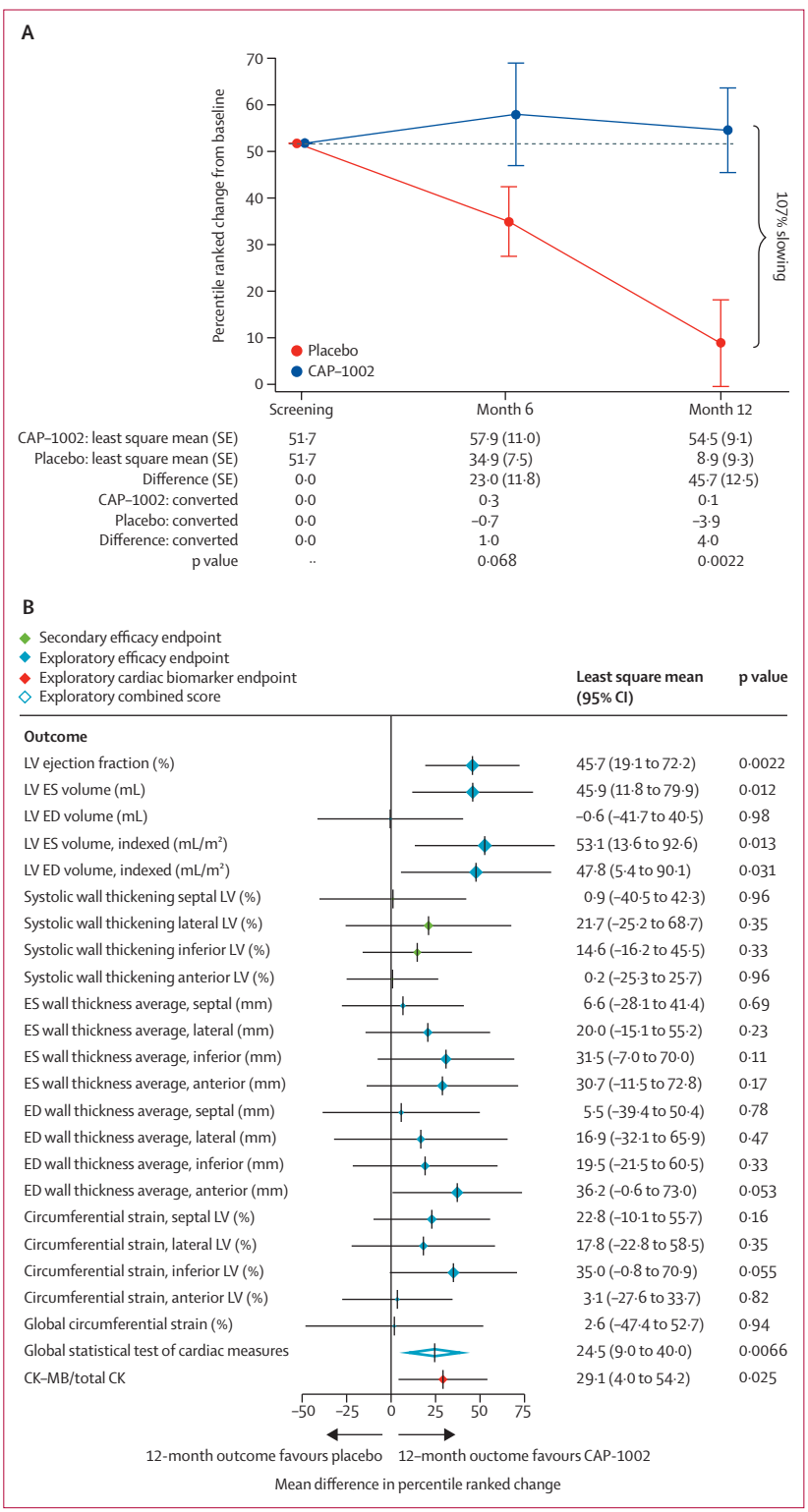
Patients in the CAP-1002 group showed a marked decrease in CK-MB as a proportion of total CK over the course of the study, indicative of reduced cardiac muscle damage.[11] The proportion of CK-MB isozyme at month 12 in the placebo group was increased compared with the CAP-1002 group (figure 4B; percentile difference 29·1, 95% CI 4·0–54·2, p=0·025; appendix p 33).

In a limited exploratory analysis searching for relevant disease-responsive serum biomarkers, a 46-cytokine ELISA panel was run on plasma samples at baseline and at 3 months and 6 months after the first infusion (appendix p 37). Network analyses were used to link changes in concentration of these cytokines, as induced by CAP-1002. Inflammatory and immune pathways were profoundly altered. IFNγ and IL-5, both involved in

activating immune cells, were enhanced at 3 months but inhibited at 6 months, indicating dynamic regulation of these pathways.

Discussion

HOPE-2 is the first therapeutic trial in Duchenne muscular dystrophy to show stabilisation of upper limb function and improved cardiac structure and function relative to placebo. CAP-1002 is distinctive in that it addresses patients with Duchenne muscular dystrophy with the greatest unmet needs, targeting both the skeletal myopathy (manifested here as upper limb functional impairment) and cardiomyopathy, without restriction as to the precise underlying genetic mutation. The ability of CAP-1002 to slow disease progression in Duchenne muscular dystrophy lies in the immunomodulatory, anti-inflammatory, and anti-fibrotic actions of CDCs, which are mediated by secreted exosomes laden with bioactive cargo. Among the cargo elements known to be bioactive in CDC exosomes are microRNAs (specifically, miR-146a and miR-181b) and Y RNA fragments.[10,20,21] Collectively, these non-coding RNA species alter gene expression in macrophages and other target cells, dialling down generalised inflammation and stimulating tissue regeneration in Duchenne muscular dystrophy (and in a variety of other inflammatory diseases).[10] This mechanism of action, which is consistent with the changes observed here in circulating inflammatory biomarkers, contrasts with that of exon-skipping oligonucleotides and gene therapy approaches, which aim to restore dystrophin expression. CAP-1002 slowed the decline in mid-level PUL 1.2 at 12 months, the prespecified primary endpoint and a subscale of the novel PUL 1.2 and PUL 2.0 instruments.[15,16] The observed treatment effect of 2·6 points (percentile difference 36·2, 95% CI 4·9–65·4) in mid-level elbow PUL 1.2 represents major preservation of upper limb function. This patient population is entirely dependent on the upper limbs for mobility, feeding, and self-care. A 1-point change in mid-level PUL 1.2 was felt to be clinically meaningful for the original statistical powering of the study because it translates to loss of one critical activity requiring elbow muscle function. For example, it might represent loss of the ability to bring the hands to the mouth or table, to stack, lift, or move objects on a table, or to remove the lid from a container. In non-ambulant patients dependent on upper limb function, such seemingly small declines signal major deterioration. The ability of CAP-1002 to prevent or delay such deterioration would be expected to



	Screening	Month 6	Month 12
CAP–1002: least square mean (SE)	51·7	57·9 (11·0)	54·5 (9·1)
Placebo: least square mean (SE)	51·7	34·9 (7·5)	8·9 (9·3)
Difference (SE)	0·0	23·0 (11·8)	45·7 (12·5)
CAP–1002: converted	0·0	0·3	0·1
Placebo: converted	0·0	–0·7	–3·9
Difference: converted	0·0	1·0	4·0
p value	..	0·068	0·0022

Figure 4: **Cardiac MRI outcomes**

(A) Left ventricular ejection fraction. Least square mean percentile ranked change from baseline is plotted over time with SE bars. The table at the bottom of panel A shows least square means and SEs from the model, as well as mean changes and differences converted back to percentages. Percentage slowing is calculated as (placebo–treatment)/placebo. (B) Forest plot of cardiac measures at 12 months. Diamond markers represent mean difference of percentile ranked change, with line widths representing 95% CIs. The size of diamond markers is scaled to the size of effect only as a visual guide. Global statistical test is an averaged percentile ranked change from baseline over all measures shown above the dashed line. CK=creatinine kinase. ED=end diastolic. ES=end systolic. LV=left ventricular.

translate to prolonged independence of patients with Duchenne muscular dystrophy. The ability to bring the hand to the mouth is vital for self-feeding, and preservation of distal hand function is required for functions such as computer access and driving of a power wheelchair.

In terms of cardiomyopathy, disease-modifying bioactivity of CDCs was shown by improvements in LVEF, a commonly used measure of global heart function, and reversal of left ventricular chamber dilatation, a pathological process whereby the heart enlarges during worsening heart failure.[22] Indexed left ventricular end systolic and end diastolic volumes improved, representing reversal of imaging biomarkers known to be prognostically negative in Duchenne cardiomyopathy.[19] These cardiac MRI findings support the reversal of adverse remodelling in the CAP-1002 group, in contrast to the typical progressive dilatation evident in the placebo group.[23] Partial reversal of the underlying cardiomyopathy was also observed preclinically with intravenous allogeneic CDCs.[9] The cardiac MRI findings are corroborated by reduced circulating levels of CK-MB, a biomarker for cardiac muscle injury.[24] The earlier HOPE trial, which compared open-label intracoronary delivery of single doses of CAP-1002 to standard of care in a similar patient population, also identified improvements in cardiac structure (in that case, left ventricular scar content) as well as PUL 1.2.[11] HOPE-2 differs from HOPE not only in its double-blind, placebo-controlled design but also in the delivery route (intravenous versus intracoronary, which rationalises the lack of arrhythmias as a complication in HOPE-2) and in the use of repeat dosing. Nevertheless, the two trials are mutually reinforcing in terms of showing, in a total of 45 randomised patients followed up to 1 year, disease-modifying bioactivity of CAP-1002 on both the skeletal myopathy and the cardiomyopathy of Duchenne muscular dystrophy.

The absence of a statistically or clinically significant impact of CAP-1002 on pulmonary function measures was not surprising. Confounding factors in non-ambulant patients with Duchenne muscular dystrophy, such as skeletal deformities (eg, scoliosis), inaccurate height estimation, body habitus, and postural instability, make pulmonary function challenging to assess in patients who have transitioned to a wheelchair. A natural history study of pulmonary function in Duchenne muscular dystrophy concluded that a trial using percent predicted forced vital capacity or percent predicted peak expiratory flow rate as a primary endpoint would require a sample size in excess of 100 subjects to be adequately powered.[25]

CAP-1002 was generally well tolerated in severely affected patients with Duchenne muscular dystrophy, with the exception of hypersensitivity reactions. Implementation of the pretreatment procedure mid-study succeeded in preventing further serious allergic reactions. HOPE-2 generated long-term (12-month) safety data, with a total of 69 infusions of up to 150 million CDCs administered up to four times in most patients. Previous studies using single doses of CAP-1002 identified few serious adverse events or treatment-emergent adverse events.[11,12,26,27] Forthcoming data from an ongoing open-label extension study (NCT04428476) and the anticipated phase 3 pivotal trial (NCT05126758) will be critical in determining the true risk of hypersensitivity reactions and the degree to which they could be prevented by pretreatment with corticosteroids and H2 blockers. Although allogeneic CDCs are well tolerated without hypersensitivity reactions when given in single doses,[11,12,26] repeat doses of CDCs have not been tested previously, which would recruit adaptive immunity not just innate immunity. In any case, the benefits of CAP-1002 appear to outweigh the risks associated with repeated administration of this cell-based regenerative medicine.

Approved exon skipping therapies for exons 45, 51, and 53 currently target 30% of all patients with Duchenne muscular dystrophy, and none have been shown to preserve upper limb function in non-ambulatory patients with Duchenne muscular dystrophy. Although adeno-associated virus (AAV)-mediated gene therapy offers hope for patients with Duchenne muscular dystrophy, a limitation is that previous infection with wild-type AAV is very common; as many as 60% of individuals might have antibodies that neutralise AAV transduction.[28] In addition, considerable regional variability exists in the prevalence of neutralising antibodies to AAV serotypes, and there is substantial cross-reactivity among the AAV serotypes.[28,29] Furthermore, the durability of the effect of gene therapy has not been determined. Repeat dosing using plasma exchange or pheresis strategies is a theoretical possibility to allow repeat dosing, but this approach has not been tested clinically. To date, non-ambulatory patients with Duchenne muscular dystrophy have been excluded from trials of dystrophin-restoring strategies, based on the rationale that they may be too far progressed to benefit. CAP-1002 has no such presumptive limitations; in fact, its complementary mechanism of action renders it not just an alternative, but also possibly an adjunct to genetic interventions.

This study is limited with regard to the small sample size and the 12-month study duration, which precluded the enrolment of early non-ambulatory patients with PUL entry scores of 6 (full overhead reach), who show less deterioration in upper limb function over 1 year. Such patients would potentially benefit from CAP-1002, but a longer duration trial would be necessary to show the benefits of disease stabilisation. Patients with PUL entry scores of 0 or 1 were not included in the trial due to concerns of limited upper limb muscle substrate for the demonstration of treatment effects and having a floor effect on this test measure. Larger numbers of patients would be required to distinguish potential benefits of CAP-1002 on respiratory function, which is much more variable in the advanced Duchenne

muscular dystrophy population than either PUL or cardiac MRI parameters.[25] In addition, cardiac scarring was not assessed by cardiac MRI, as has been done in previous studies of CAP-1002,[11,12] because gadolinium was not administered. Although heart failure is only one cause of mortality in Duchenne muscular dystrophy, it is sufficiently impactful that attenuation of cardiomyopathy progression could logically be predicted to improve survival; this conjecture has been untestable until now given the paucity of agents that alter the course of Duchenne muscular dystrophy cardiomyopathy. Nevertheless, larger, longer studies will be required to determine whether preservation of heart structure and function by CAP-1002 could delay progression to symptomatic heart failure, and, in so doing, prolong the lifespan of patients with Duchenne muscular dystrophy.[30]

In conclusion, CAP-1002 cell therapy appears to be safe and effective in attenuating deterioration of upper limb and cardiac function in late-stage Duchenne muscular dystrophy. Because other therapies that target skeletal muscle have not been shown to be effective in the cardiomyopathy associated with Duchenne muscular dystrophy, a therapy that stabilises or reverses cardiac deterioration while improving upper limb function would be unique in its ability to address, synergistically, the large burden of disease seen in non-ambulatory patients with Duchenne muscular dystrophy. Longer-term extension studies are needed to confirm the therapeutic durability and safety of CAP-1002 beyond 12 months for the treatment of skeletal myopathy and cardiomyopathy in this patient population. In addition, new placebo-controlled trials will be needed to assess the benefit and risks of CAP-1002 in younger, ambulatory patients with Duchenne muscular dystrophy.

HOPE-2 Study Group members

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Contributors

CMM served as national principal investigator for the study, contributed to study design, contributed to study enrolment, analysed and interpreted data, and drafted the manuscript. EM contributed to the study design, analysed and interpreted data, and critically revised the manuscript for intellectual content. SH and NH analysed and interpreted data, and critically revised the manuscript for intellectual content. RRS critically revised the manuscript for intellectual content. ME contributed to the study design and analysed and interpreted data. RSF contributed to study design and study enrolment, analysed and interpreted data, and critically revised the manuscript for intellectual content. CT, JJ, MMH, and ASV contributed to study enrolment and critically revised the manuscript for intellectual content. MDT critically revised the manuscript for intellectual content. KNH performed blinded evaluation of cardiac MRI, analysed and interpreted data, and critically revised the manuscript for intellectual content. OHM and EKH contributed to study design, analysed and interpreted data, and critically revised the manuscript for intellectual content. PF contributed to study design and critically revised the manuscript for intellectual content. DDA contributed to study design. SR and PW contributed to study design and reviewed the manuscript. LM contributed to study design, analysed and interpreted data, and critically revised the manuscript for intellectual content. CMM, EM, SH, NH, and LM (Capricor Therapeutics) had access to the raw data and verified the data and all analyses. All authors participated in the preparation, review, and critical revision of the report, which has been approved by each author. CMM was responsible for submission of the manuscript. All authors vouch for the completeness and accuracy of the data, for the full reporting of adverse events, and for the fidelity of the trial to the protocol.

Declaration of interests

CMM has acted as a consultant on clinical trials of Duchenne muscular dystrophy for Astellas, Avidity Biosciences, Capricor Therapeutics, Catabasis, Edgewise Therapeutics, Entrada Therapeutics, Epirium Bio (formerly Cardero Therapeutics), FibroGen, Italfarmaco, Pfizer, PTC Therapeutics, Roche, Santhera Pharmaceuticals, and Sarepta Therapeutics; he reports honoraria for presentations from PTC Therapeutics, Sarepta Therapeutics, Solid Biosciences, Santhera Pharmaceuticals, Capricor Therapeutics, and Catabasis; he has received compensation for participation in advisory boards from PTC Therapeutics, Sarepta Therapeutics, Avidity Biosciences, Edgewise Therapeutics, and Santhera Pharmaceuticals; he has received research support for clinical trials from Capricor Therapeutics, Catabasis, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics; and reports grants from the US Department of Defense, US National Institutes of Health (NIH), Parent Project Muscular Dystrophy, and the National Institute on Disability, Independent Living and Rehabilitation Research. EM owns founder's equity in Capricor Therapeutics. SH received payments to her employer (Pentara Corporation) for consulting services from Capricor Therapeutics and Fulcrum Therapeutics. NH received payments to his employer (Pentara Corporation) for consulting services. SH and NH received support for the current study, including payments to their employer (Pentara Corporation), for special expertise and knowledge in the field of clinical trial analysis services (including study design, statistical analysis plan creation, data management and case report form design, SDTM/ADaM conversion, TLF, and statistical reporting), as well as statistical consulting and SAS programing. ME is a paid employee of Atom International, and has served as a consultant for Solid Biosciences, Sarepta Therapeutics, Santhera Pharmaceuticals, Roche, PTC Therapeutics, Pfizer, NS Pharma, Genethon, Fibrogen, Catabasis, and Capricor Tharapeutics. RSF has participated (2016–21) as an investigator in clinical trials sponsored by AveXis/Novartis Gene Therapies, Biogen, Catabasis, Cytokinetics, Ionis, Muscular Dystrophy Association, NIH, Lilly, ReveraGen, Roche, Sarepta, Scholar Rock, and Summit; he has received honoraria for participating in symposia and on advisory boards for these same pharmaceutical companies; he serves without compensation as an adviser to the n-Lorem and EveryLife Foundations; his institution receives funding from Biogen for the coordination of a US registry for spinal muscular atrophy, iSMAC; and he receives licensing fees from the Children's Hospital of Philadelphia and publishing royalty fees from Elsevier. CT has participated as an investigator in clinical trials and clinical studies sponsored by AveXis/Novartis Gene Therapies, Bristol Myers Squibb, Catabasis, Capricor Therapeutics, Fibrogen, Muscular Dystrophy Association, NIH, Pfizer, PTC Therapeutics, Roche, Sarepta, Santhera Pharmaceuticals, and Summit. MMH has received research funding for participating in clinical trials from Capricor Therapeutics, Sarepta Therapeutics, PTC Therapeutics, Mallinckrodt Pharmaceuticals, and Wave Life Sciences; he has received a non-restricted educational grant from Sarepta Therapeutics, infrastructure clinical grants from the Muscular Dystrophy Association and Parent Project Muscular Dystrophy, and research grants from CureSMA; he has received honorarium for advisory boards and consulting from Biogen, Avexis/Novartis Gene Therapies, Sarepta Therapeutics, and PTC Therapeutics; he actively consults for Emerging Therapy Solutions; and he serves without compensation on DuchenneXchange and as a board member for Three Gaits and as an adviser for Hopeful Together. KNH has served as a

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Data sharing

The sponsor will make available to academic researchers who provide a methodologically sound proposal individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices). Data will be made available to academic researchers who provide a methodologically sound proposal to achieve specific study aims, as determined by the study sponsor, beginning 12 months and ending 36 months after publication. Proposals should be directed to lmarban@capricor.com; to gain access, data requestors will need to sign a data access agreement.

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