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ORIGINAL RESEARCH

Caregiver Global Impression Observations from EMBARK: A Phase 3 Study Evaluating Delandistrogene Moxeparvovec in Ambulatory Patients with Duchenne Muscular Dystrophy

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ABSTRACT

***Introduction*:** Duchenne muscular dystrophy (DMD) is a rare, progressive, debilitating neuromuscular disease. The early childhood onset and debilitating nature of the disease necessitate decades of caretaking for most patients. Caregivers have a critical role in evaluating patients' physical functioning and/or response to treatment. Using DMD-specific caregiver-reported scales, the impact of delandistrogene moxeparvovec gene therapy on caregivers' perceived change in patient disease status or severity was evaluated using the Caregiver Global Impression of Change and Severity (CaGI-C and CaGI-S, respectively).

***Methods*:** In the Phase 3 randomized, double-blind, placebo-controlled trial (EMBARK; NCT05096221), the CaGI-C at week 52 and change from baseline to week 52 in CaGI-S were evaluated in a post hoc analysis. The CaGI-C assesses caregivers' impressions of change in DMD symptoms, physical ability, ability to perform daily activities, and overall health. The CaGI-S evaluates current severity of DMD symptoms, physical ability, ability to perform activities of daily living, and overall health. Data were evaluated using multi-domain responder index (MDRI) and ordinal regression analyses.

***Results*:** MDRI analyses across all four CaGI-C items yielded a treatment difference of 1.7 (95% confidence interval [CI]: 0.90–2.5) favoring delandistrogene moxeparvovec; a treatment difference of 1.1 (95% CI 0.30–1.9) was observed for the CaGI-S favoring delandistrogene moxeparvovec. After adjusting for age,

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ordinal regression analysis showed a nominally significant increase in the odds of achieving a better rating for delandistrogene moxeparvovec-treated patients on all four CaGI-C items (≥3.8-fold increase). After adjusting for baseline severity and age, ordinal regression analysis showed a nominally significant increase in the odds of improvement on all four CaGI-S items (≥2.2-fold increase).

Conclusion: These exploratory findings captured by caregiver-reported outcomes add to the totality of evidence that supports the clinical benefits of delandistrogene moxeparvovec for patients with DMD.

Trial Registration Number: ClinicalTrials.gov identifier, NCT05096221.

Keywords: Caregiver; Delandistrogene moxeparvovec; Duchenne muscular dystrophy; Gene therapy; Global Impressions scale

Key Summary Points

Why carry out this study?

Caregivers play a critical role in evaluating patients' physical functioning and/or response to treatment in both clinical trial and real-world settings

This analysis evaluated the impact of delandistrogene moxeparvovec, an approved gene transfer therapy for Duchenne muscular dystrophy (DMD), on caregivers' perceived severity and change in patient disease status using Global Impression scales included in part 1 of the pivotal Phase 3 randomized, double-blind, placebo-controlled trial (EMBARK; NCT05096221) assessing safety and efficacy in ambulatory patients with DMD aged ≥4 to <8 years

What was learned from the study?

Caregivers of delandistrogene moxeparvovec-treated patients reported improvements in perceived change in patient disease status or severity compared to placebo-treated patients

These exploratory findings captured by caregiver-reported outcomes add to the totality of evidence supporting the clinical benefits of delandistrogene moxeparvovec

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare, progressive, debilitating neuromuscular disease resulting from pathogenic variants in the *DMD* gene, leading to the absence of functional dystrophin protein that gives rise to progressive muscle weakness and functional decline [1]. DMD primarily affects young males and is usually diagnosed in early childhood (4–5 years of age) [2, 3]. Over time, progressive loss of lower and upper extremity functioning results in loss of independent ambulation, loss of upper limb functioning, serious orthopedic deformities, respiratory and cardiac complications, and, ultimately, premature death [2–5].

Ambulation and transfer ability is lost in the early 2nd decade in most patients, and independent feeding requiring hand-to-mouth function is typically lost in the late teens [6]. Owing to the early onset and complexity of symptoms, including increasing physical disability [1] coupled frequently with cognitive and behavioral challenges [7], individuals with DMD require a lifetime of caretaking that increases as DMD progresses [8]. As such, caregivers play a crucial role in evaluating and relaying information about patients' health, including their clinical status and functional ability as well as the impact of treatment. Caregivers of patients with DMD also face challenges that can impact their mental and physical health and health-related quality of life [9, 10]. Caregiver input is therefore critical in defining patient-centered treatment goals as well as prioritizing those symptoms most likely to impact patient quality of life [11, 12].

The Global Impression (GI) scales are commonly used in clinical research to provide an overall impression of a patient's current severity or change in their condition. The most common GIs used in clinical trials consist of the two main rating scales: GI of Severity and GI of Change,

reported directly by clinicians (CGI), patients, or caregivers. For younger populations, caregiver global impressions (CaGI) are frequently employed to evaluate illness severity and overall changes in patients' condition over time [13]. These instruments have been particularly useful in rare diseases that are heterogenous, affect multiple organ systems, have complex symptomatology, or lack validated disease-specific outcome measures [14–16]. Rett syndrome, Prader-Willi syndrome, Angelman's syndrome, and Schizoaffective disorder [17, 18] are just some examples showcasing the use of GI scales in combination with disease-specific measures to gain deeper understanding of an individual's progress and response to therapy. Recently, the regulatory importance of CaGI scales in DMD has been identified [19].

Delandistrogene moxeparvovec, a single-administration recombinant adeno-associated virus rhesus isolate serotype 74 (rAAVrh74) vector-based gene transfer therapy for DMD, has been approved in the US and in other select countries [20–29]. The objective of the present analysis was to use GI scales to evaluate the impact of delandistrogene moxeparvovec on caregivers' perceived severity and change in patient disease status as part of the ongoing pivotal Phase 3 randomized, double-blind, placebo-controlled trial (EMBARK; NCT05096221) assessing safety and efficacy in patients with DMD aged ≥ 4 to < 8 years. By using GI scales, caregivers were able to evaluate aspects of patients' health that were most impacted when assessing the benefit of treatment. Main study findings from EMBARK Part 1 (52 weeks) were that the trial did not meet its primary endpoint as there was no statistically significant difference in North Star Ambulatory Assessment (NSAA) scores between the delandistrogene moxeparvovec and placebo cohorts at week 52 ($p = 0.244$) [30]. Nominally significant differences favoring delandistrogene moxeparvovec were observed in key pre-specified secondary clinical endpoints, including time to rise-from-floor (TTR; nominal $p = 0.0025$) and 10 m walk/run test (10MWR; nominal $p = 0.0048$) [30]. Analysis of CaGI scales provided an opportunity for a further exploration of a treatment response by allowing each caregiver to make their own determination of the overall impact of delandistrogene moxeparvovec on the DMD patient under their care.

METHODS

Study Design

EMBARK is a crossover study consisting of Part 1 (52 weeks completed) and Part 2 (52 weeks) followed by a 5-year follow-up period. In Part 1, patients were randomized (1:1) to receive either a single intravenous infusion of delandistrogene moxeparvovec (1.33×10^{14} vg/kg) or placebo (0.9% sodium chloride solution) through a peripheral limb vein and stratified by age group (≥ 4 to < 6 years or ≥ 6 to < 8 years) at randomization and NSAA total score (≤ 22 or > 22) at screening. In Part 2, those who received delandistrogene moxeparvovec in Part 1 will receive placebo and patients who received placebo in Part 1 will be treated with delandistrogene moxeparvovec. Patients, caregivers, investigators, and study site staff were all blinded to treatment.

Patients maintained a stable daily dose of oral corticosteroids for at least 12 weeks before the initial screening visit, with the dose remaining constant throughout the study, except for weight-based adjustments. The day before the infusion (SRP-9001 or placebo), subjects began an additional glucocorticoid (prednisone equivalent) for immunosuppression alongside their baseline corticosteroids for DMD. This regimen continued for the first 60 days post-infusion, with earlier tapering allowed for adverse events with Medical Monitor approval. For more details on the steroid dosing, please refer to the supplemental material of the primary EMBARK paper [30].

The primary endpoint was change from baseline to week 52 in NSAA total score. Three prespecified key secondary endpoints (in rank order) were delandistrogene moxeparvovec micro-dystrophin expression level at week 12 (Western blot) and change from baseline to week 52 in TTR and 10MWR. Safety was also evaluated. These pre-specified clinical endpoints and safety data are reported elsewhere [30].

EMBARK, including the present analysis, was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Trial protocol and all amendments were approved by an institutional review board and ethics committee at each site. The full list of institutional review boards and ethics committees is available in the Supplementary Information. Informed consent, including consent to publish, was obtained from parent(s)/legal guardian(s), and patients' assent was obtained when indicated.

CaGI of Severity and Change Scales

The CaGI scales created for DMD consist of two assessments: CaGI of Change (CaGI-C) and the CaGI of Severity (CaGI-S) [31]. During EMBARK, caregivers (defined as the primary caregivers, which, in most cases, referred to the parents) were limited to one per trial participant, and the same caregiver was required to complete both GI scales at baseline and week 52 post treatment.

The CaGI-C was the first scale developed, drawing on insights from concept elicitation interviews with both caregivers and individuals affected by DMD [31]. During cognitive debriefing (CD) interviews, caregivers evaluated the draft CaGI-C items to confirm their relevance and clarity. Suggestions gathered from the CD were then integrated into the final version of the CaGI-C measure. Further details regarding the development of the CaGI-C have been previously published [31]. The CaGI-S measure expanded on the domains and items from the CaGI-C, adapting existing items to reflect the nuances of disease severity from the perspective of DMD caregivers. The CaGI-S subsequently underwent pilot testing with DMD patient community to confirm its content validity in assessing severity of the condition.

In this study, caregivers rated change from baseline to week 52 on a subset of CaGI-C items, including DMD symptoms, physical ability, ability to perform daily activities, and overall health. These items were rated on a 7-point categorical response, ranging from 'very much worse' to 'very much improved.' A fifth item asked about whether these changes were considered meaningful, with a binary yes/no response (not included in the analysis). Each response option and CaGI-C scoring is described in the supplemental methods.

The CaGI-S was administered at baseline and week 52 for caregivers to rate the current severity of patients' DMD symptoms, physical ability, ability to perform activities of daily living (ADLs), and overall health. All items were rated using 5-level categorical response options: very mild impact/impairment (1), mild impact/impairment (2), moderate impact/impairment (3), severe impact/impairment (4), and very severe impact/impairment (5), with lower values indicating less severity. Each response option and CaGI-S scoring is described in the supplemental methods.

While this analysis was not pre-specified in the EMBARK statistical analysis plan (SAP), the CaGI-C and CaGI-S scales were implemented and collected alongside other measures in both Part 1 and Part 2 of the trial. Therefore, while these scales were part of the parent protocol, their analysis was not pre-specified in the main study SAP, making it a post hoc analysis.

Statistical Analysis

A multifaceted approach was employed to analyze caregiver GI scale items, which included the following: stacked bar visualization, composite analysis of CaGI-C and CaGI-S scales, covariate-adjusted ordinal regression analysis, and subgroup analyses.

Stacked Bar Visualization

Initially, stacked bars were constructed to visually represent the distribution of severity and change responses reported by caregivers. This method provided an initial overview of the perceived impact and changes experienced by care recipients and a visual comparison across treatment groups without adjusting for chance imbalances in baseline covariates.

Responses on CaGI-C items were categorized as improvement (combining minimally improved, much improved, or very much improved responses), no change (i.e., no change

response), and worsening (combining minimally worse, much worse, and very much worse categories) from baseline to the end of Part 1 (week 52). The proportion of patients in each category for each item was visualized in a stacked bar chart by treatment group.

Change from baseline scores on all four CaGI-S items had a potential range of − 4 to 4 with lower (negative) scores indicating improvement in severity over 52 weeks. For CaGI-S visualizations, the changes in severity scores were categorized as: improvement (any change from baseline score at week 52 of − 1 or less), no change (change from baseline score at week 52 of 0), and worsening (change from baseline score at week 52 of + 1 or more). The proportion of patients in each category for each item was visualized in a stacked bar chart by treatment group.

Patients with missing data were excluded from the stacked bar chart visualizations.

Composite Analysis of CaGI-C and CaGI-S Scale Items

Subsequently, a multi-domain responder index (MDRI) analysis was carried out for each patient to integrate responses across all four items and test for treatment differences in CaGI-C and CaGI-S [32]. The following responder scores were defined for each patient for each item: + 1 for any level of improvement, 0 for no change, and − 1 for any level of worsening. The MDRI for each patient was then constructed as the sum of responder scores across the four items for CaGI-C and CaGI-S. Differences across treatment groups in this MDRI were tested using an independent samples *t*-test for CaGI-C and CaGI-S separately. The resulting difference, 95% confidence interval (CI), and nominal *p*-value are reported.

This analysis combined caregiver feedback from all dimensions into a single index to generate an understanding of the overall impact of the intervention on the patient. Patients with missing data were excluded from this composite analysis.

Covariate-Adjusted Ordinal Regression Analysis

Lastly, the responses at week 52 to each of the four questions on CaGI-C were analyzed using an ordinal logistic regression adjusting for the following baseline covariates: age group (4–5 years or 6–7 years) and treatment (delandistrogene moxeparvovec or placebo). Similarly, the change from baseline to week 52 in the responses to each of the four questions on CaGI-S was analyzed using an ordinal logistic regression adjusting for the following baseline covariates: age group (4–5 years or 6–7 years), baseline severity level (response on the 5-point Likert scale), and treatment (delandistrogene moxeparvovec or placebo).

An ordinal regression analysis is well suited for analyzing an ordinal response scale with more than two response options, like the CaGI scales. Unlike a linear regression analysis, it does not require the responses to be normally distributed and does not consider the differences between any two consecutive levels across the scale to be equally meaningful. It is also preferable to analyzing the data as a binary response by dichotomizing the response variable as such a transformation leads to loss of power and statistical inefficiency. Finally, the analysis yields an interpretable treatment effect measure in the form of the relative change in the odds of a desirable change in responses.

Since the primary endpoint did not meet statistical significance in the EMBARK study, and because the study did not include a provision for correcting for multiplicity beyond the planned hierarchical testing procedure, treatment effect estimates for both CaGI-C and CaGI-S are reported as odds ratios (ORs) and corresponding 95% CIs, along with associated nominal *p*-values. The proportional odds assumption for all ordinal regression models was tested using a score test (SAS 9.4), and any violation, as indicated by a p-value <0.05, was reported. Patients with missing data at baseline (CaGI-S only as CaGI-C was not collected at baseline) or follow-up (CaGI-C or CaGI-S) were not included in the analysis.

Subgroup Analyses

The covariate-adjusted ordinal regression analysis of change from baseline to week 52 in CaGI-S responses was carried out separately in patients in the following age groups: 4–5 years and 6–7 years. For the age subgroup analyses, the only covariate other than treatment included in the analysis was baseline severity. This covariate applies specifically to the CaGI-S scale, which was collected at baseline. For the CaGI-C scale, the only relevant covariate was age group, as CaGI-C was not collected at baseline. Consequently, performing a covariate-adjusted analysis by age subgroup in CaGI-C would not provide additional value. The analyses of responses at week 52 to CaGI-C questions and the change from baseline at week 52 in responses to CaGI-S were also repeated in the subset of patients without a documented adverse event (AE) of nausea or vomiting within the first 2 weeks of treatment initiation as a sensitivity analysis to assess the likelihood that the findings could be attributed to potential unblinding of caregivers.

For all subgroup analyses, treatment effect estimates, in terms of ORs and corresponding 95% CIs, are reported. The proportional odds assumption for all ordinal regression models was tested using a score test (SAS 9.4), and any violation, as indicated by a p-value <0.05, was reported. Patients with missing data at baseline or follow-up were not included in the analysis.

Sensitivity Analysis (Adjusted Ordinal Regression Analysis with Multiple Imputation of Missing Data)

Missing data were multiply imputed under a missing at random (MAR) assumption before carrying out the ordinal regression analysis described above. Imputations were carried out using a fully conditional specification model in SAS 9.4 where variables are imputed sequentially in a pre-specified order conditional on all other variables. For the imputation of CaGI-S change from baseline scores at week 52, variables in the imputation model included change from baseline scores at week 24, baseline severity level, and age group. In a sequential manner, missing baseline severity level values were imputed first conditional on age group and treatment. Next, missing change from baseline scores at week 24 were imputed given age group, treatment, and baseline severity level. Finally, the change from baseline scores at week 52 were imputed conditional on change from baseline scores at week 24, baseline response, age group, and treatment. The ordinal regression analysis model detailed above was applied to each of the 50 imputed datasets. The results from these datasets were combined using Rubin's rules and PROC MIANALYZE in SAS. Analysis of CaGI-C responses with multiple imputation of missing data was done similarly but using only baseline age group and treatment as covariates in the imputation model.

RESULTS

Baseline and demographic data from the EMBARK study have been previously described [30]. Steroid regimens between the groups were similar throughout the study, including 12 weeks before screening, during the screening period, and throughout Part 1 (please refer to the Supplemental Table 1 of the primary EMBARK paper for more details on the steroid dosing) [30]. The distribution of responses to CaGI-C items at week 52 and the change from baseline to week 52 in CaGI-S items are displayed in Tables 1 and 2, respectively. Stacked bar charts showing the proportion of patients who improved, had no change, or worsened by treatment group for each CaGI-C and CaGI-S item are also shown in Fig. 1A and B, respectively. A notable difference was observed in the proportion of caregivers indicating improvement or worsening between the two treatment arms, with greater proportions of improvement and lower proportions of worsening reported for delandistrogene moxeparvovec-treated patients on both scales (Fig. 1A and B).

The MDRI analysis of CaGI-C responses across all four items yielded a treatment difference of 1.7 (95% CI 0.90–2.5, $p < 0.0001$) favoring treatment. Thus, on average, delandistrogene moxeparvovec-treated patients performed better

Table 1 Treatment group counts and percentages for CAGI-C responses (mITT population; Part 1, post hoc all patients)

	All patients	Missing response	Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	Very much worse
CaGI-C1: Changes in symptoms, *n* (%)									
All patients	125 (100)	6 (5)	16 (13)	29 (23)	32 (26)	31 (25)	10 (8)	1 (1)	0 (0)
Delandistrogene moxeparvovec	63 (100)	5 (8)	11 (7)	19 (30)	18 (29)	7 (11)	3 (5)	0 (0)	0 (0)
Placebo	62 (100)	1 (2)	5 (8)	10 (16)	14 (23)	24 (39)	7 11)	1 (2)	0 (0)
CaGI-C2: Changes in physical ability, *n* (%)									
All patients	125 (100)	5 (4)	10 (15)	29 (23)	35 (28)	23 (18)	12 (10)	2 (2)	0 (0)
Delandistrogene moxeparvovec	63 (100)	4 (6)	14 (22)	19 (30)	18 (29)	6 (10)	2 3)	0 (0)	0 (0)
Placebo	62 (100)	1 (2)	5 (8)	10 (16)	17 (27)	17 (27)	10 16)	2 (3)	0 (0)
CaGI-C3: Changes in activities ability, *n* (%)									
All patients	125 (100)	5 (4)	15 (12)	23 (18)	40 (32)	36 (29)	6 5)	0 (0)	0 (0)
Delandistrogene moxeparvovec	63 (100)	4 (6)	11 (17)	17 (27)	18 (29)	13 (21)	0 0)	0 (0)	0 (0)
Placebo	62 (100)	1 (2)	4 (6)	6 (10)	22 (35)	23 (37)	6 (10)	0 (0)	0 (0)
CaGI-C4A: Changes in overall health, *n* (%)									
All patients	125 (100)	5 (4)	15 (12)	29 (23)	32 (26)	34 (27)	9 (7)	1 (1)	0 (0)
Delandistrogene moxeparvovec	63 (100)	4 (6)	10 (16)	21 (33)	15 (24)	11 (17)	2 (3)	0 (0)	0 (0)
Placebo	62 (100)	1 (2)	5 (8)	8 (13)	17 (27)	23 (37)	7 (11)	1 (2)	0 (0)

CaGI-C Caregiver Global Impression of Change, *mITT* modified intent-to-treat population

in more than one item compared to placebo-treated patients. MDRI analyses of the change from baseline in CaGI-S responses across all four items also yielded a treatment difference of 1.1 (95% CI 0.30–1.9, $p=0.0062$), indicating that, on average, delandistrogene moxeparvovec-treated patients performed better in approximately one item compared to placebo-treated patients.

After adjusting for age group, ordinal regression analysis of CaGI-C responses showed an increase in the odds of achieving a better rating for delandistrogene moxeparvovec-treated patients on all four items (Fig. 2): DMD symptoms (OR [95% CI]: 4.0 [2.0–8.0], $p<0.0001$), physical ability (OR [95% CI]: 4.9 [2.5–10.0], $p<0.0001$), ADLs (OR [95% CI]: 4.0 [2.0–8.0], $p<0.0001$), and overall health (OR [95% CI]: 3.8 [1.9–7.6], $p=0.0001$). After adjusting for baseline severity level and age group, ordinal regression analysis of change from baseline in CaGI-S items showed an increase in the odds of improvement in severity of at least 1 point on all four items for delandistrogene moxeparvovec-treated patients (Fig. 2): DMD symptoms (OR [95% CI]: 3.9 [1.8–8.8], $p=0.0007$), severity of impairment (OR [95% CI]: 4.4 [2.0–10.2], $p=0.0003$), ADLs (OR [95% CI]: 2.2 [1.0–4.9], $p=0.0404$), and overall health (OR [95% CI]: 3.6 [1.7–8.3], $p=0.0015$).

Subgroup analyses revealed no differences across age subgroups with a numerically favorable increase in the odds of improvement for delandistrogene moxeparvovec-treated patients observed in both age groups as measured by the CaGI-S scale (Fig. 3 and Table S1). Among patients with no nausea or vomiting in the first 2 weeks after treatment initiation, the proportion of responses indicating an improvement (Tables S2 and S3) and the increase in the odds of improvement for those treated with delandistrogene moxeparvovec was similar in magnitude to

Table 2 Treatment group counts and percentages for CaGI-S responses (mITT population; Part 1, post hoc all patients)

			Difference at Week 52 from Week 0								
	All patients	**Missing response**	**− 4**	**− 3**	**− 2**	**− 1**	**0**	**1**	**2**	**3**	**4**
CaGI-S1: Severity of DMD symptoms, *n* (%)											
All patients	125 (100)	14 (11)	0 (0)	0 (0)	2 (2)	32 (26)	57 (46)	17 (14)	3 (2)	0 (0)	0 (0)
Delandistrogene moxeparvovec	63 (100)	10 (16)	0 (0)	0 (0)	0 (0)	21 (33)	26 (41)	6 (10)	0 (0)	0 (0)	0 (0)
Placebo	62 (100)	4 (6)	0 (0)	0 (0)	2 (3)	11 (8)	31 (50)	11 (18)	3 (5)	0 (0)	0 (0)
CaGI-S2: Severity of impairment, *n* (%)											
All patients	125 (100)	14 (11)	0 (0)	0 (0)	4 (3)	32 (26)	60 (48)	13 (10)	2 (2)	0 (0)	0 (0)
Delandistrogene moxeparvovec	63 (100)	10 (16)	0 (0)	0 (0)	2 (3)	20 (32)	29 (46)	2 (3)	0 (0)	0 (0)	0 (0)
Placebo	62 (100)	4 (6)	0 (0)	0 (0)	2 (3)	12 (19)	31 (50)	11 (18)	2 (3)	0 (0)	0 (0)
CaGI-S3: Ability of daily activities, *n* (%)											
All patients	125 (100)	14 (11)	0 (0)	0 (0)	2 (2)	31 (25)	58 (46)	18 (14)	2 (2)	0 (0)	0 (0)
Delandistrogene moxeparvovec	63 (100)	10 (16)	0 (0)	0 (0)	0 (0)	18 (29)	27 (43)	8 (13)	0 (0)	0 (0)	0 (0)
Placebo	62 (100)	4 (6)	0 (0)	0 (0)	2 (3)	13 (21)	31 (50)	10 (16)	2 (3)	0 (0)	0 (0)
CaGI-S6: Severity of overall health, *n* (%)											
All patients	125 (100)	14 (11)	0 (0)	0 (0)	4 (3)	23 (18)	65 (52)	16 (13)	3 (2)	0 (0)	0 (0)
Delandistrogene moxeparvovec	63 (100)	10 (16)	0 (0)	0 (0)	2 (3)	15 (24)	32 (51)	4 (6)	0 (0)	0 (0)	0 (0)
Placebo	62 (100)	4 (6)	0 (0)	0 (0)	2 (3)	8 (13)	33 (53)	12 (19)	3 (5)	0 (0)	0 (0)

CaGI-S Caregiver Global Impression of Severity, *mITT* modified intention-to-treat population

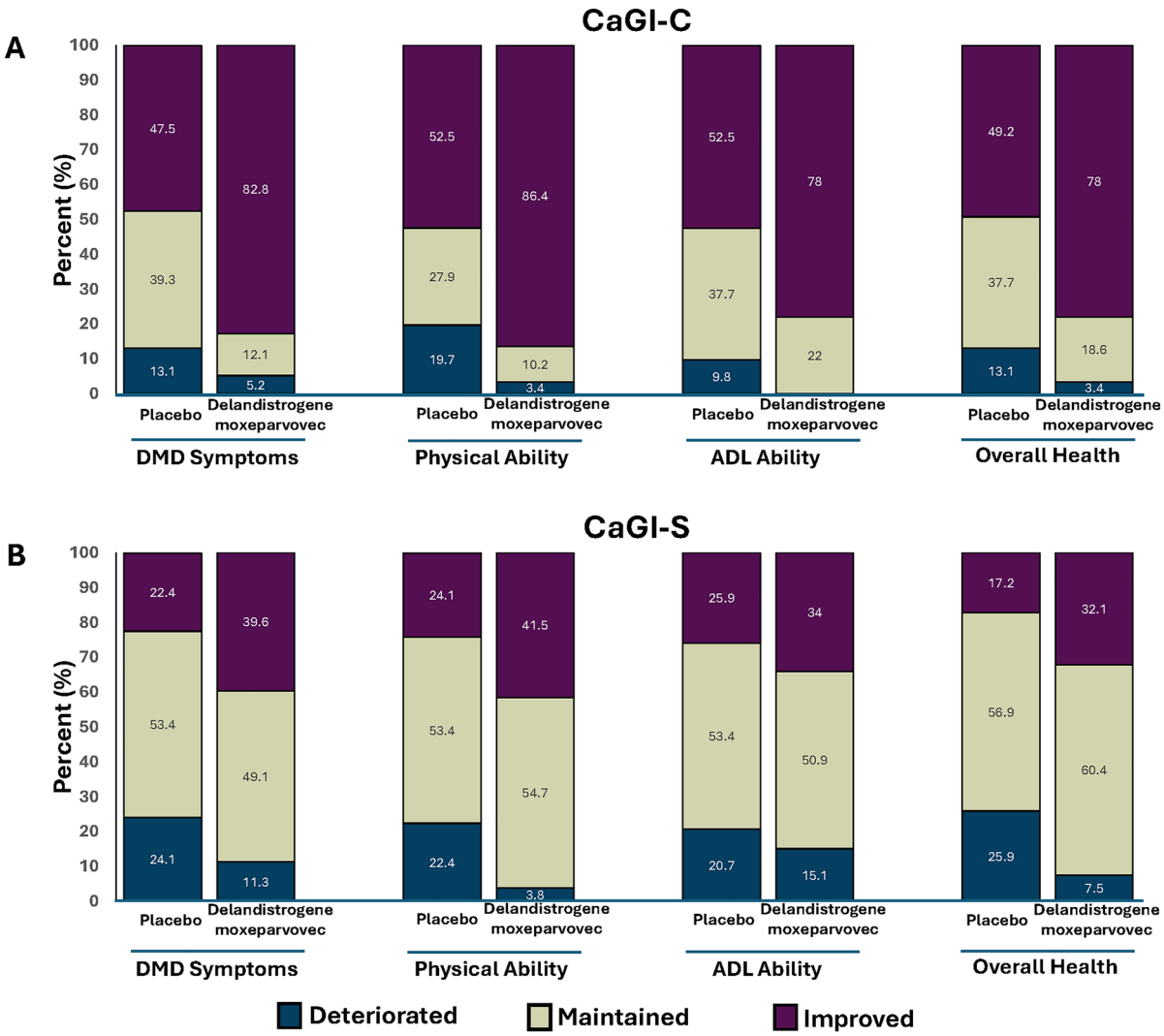

Fig. 1 Stacked bar chart by CaGI question, showing the proportion of patients who improved, maintained, and deteriorated by treatment group. **A** CaGI-C and **B** CaGI-S. Only patients with a valid response at week 52 were included: **A** $N = 119$, **B** $N = 111$. Patients with missing responses were excluded. *ADL* activities of daily living, *CaGI-C* Caregiver Global Impression of Change, *CaGI-S* Caregiver Global Impression of Severity

what was seen when including all patients in the analysis. Specifically, the increases in the odds of achieving a better rating on CaGI-C items for delandistrogene moxeparvovec-treated patients with no nausea or vomiting in the first 2 weeks were as follows: DMD symptoms (OR [95% CI]: 3.1 [1.2–8.2]), physical ability (OR [95% CI]: 3.8 [1.5–10.2]), ADLs (OR [95% CI]: 4.5 [1.7–12.3]), and overall health (OR [95% CI]: 3.1 [1.2–8.3]). In addition, the following increase in the odds of improvement in severity for delandistrogene moxeparvovec-treated patients with no nausea or vomiting in the first 2 weeks were noted: DMD symptoms (OR [95% CI]: 4.0 [1.4–11.6]), severity of impairment (OR [95% CI]: 3.0 [1.1–8.5]), ADLs (OR [95% CI]: 2.1 [0.8–6.0]). The data for the subgroup comparison on the CaGI-S overall health item were found to violate the proportional odds assumption. Owing to the small sample size, the analysis could not be repeated in the subgroup of patients who experienced nausea or vomiting in the first 2 weeks after treatment initiation.

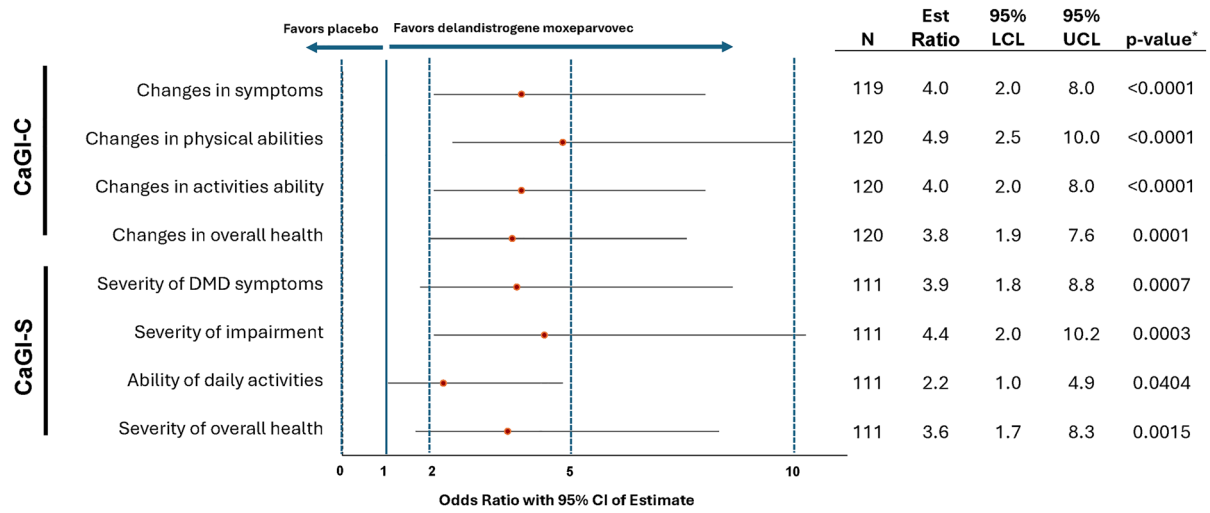

Fig. 2 Ordinal regression analysis showing the odds ratios of achieving a better rating in CaGI response. Only patients with a valid response at week 52 were included. *All *p*-values are nominal

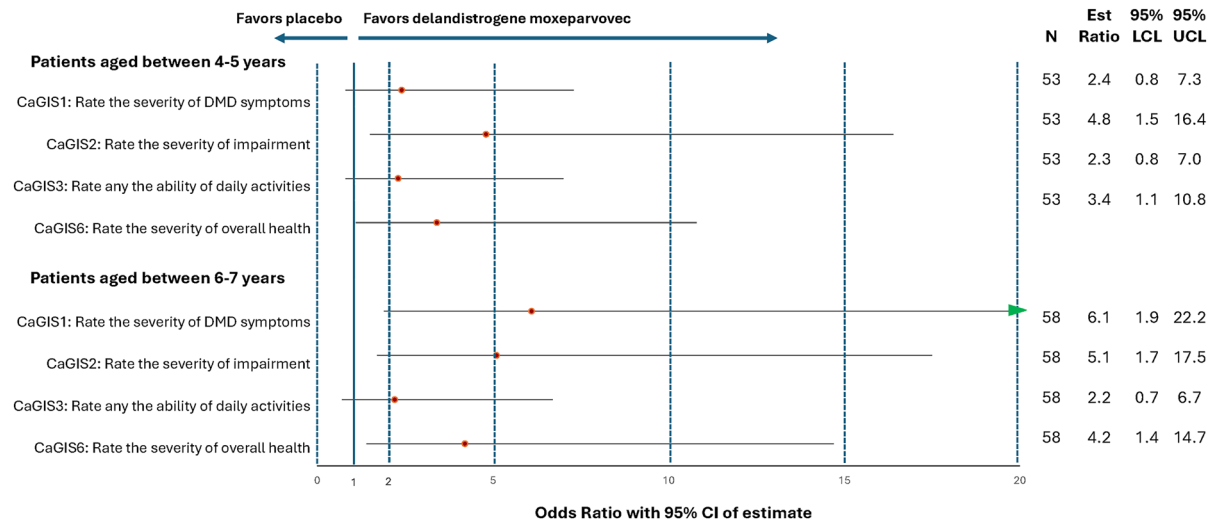

Fig. 3 Subgroup analysis of the proportion of improvers in the CaGI-S by age. Changes in CaGI-S by age group (4–5 years and 6–7 years). Only patients with a valid response at week 52 were included. *CaGI-S* Caregiver Global Impression of Severity

Sensitivity analysis where missing data were imputed was consistent with findings conducted on the main sample (i.e., where no imputation was performed); delandistrogene moxeparvovec-treated patients performed better compared to placebo-treated patients in both the CaGI-C and CaGI-S scales (Tables S4).

DISCUSSION

Using a range of analytical approaches, from a simple visualization to adjusted ordinal regression, our findings suggest that caregivers observed improvements in patients

randomized to delandistrogene moxeparvovec compared to those randomized to placebo, as reflected in both CaGI-C and CaGI-S items. Notably, in the overall population, caregivers of delandistrogene moxeparvovec-treated patients reported nominally significant increases in the odds of improvement across all CaGI-C and CaGI-S items. This is the first time such outcomes have been evaluated in a DMD clinical trial.

MDRI analysis provided a comprehensive evaluation of treatment impact by aggregating multiple domains affected in DMD (i.e., symptoms, physical ability, ADLs and overall health), all of which do not manifest equally across patients [31]. This analysis integrated various aspects of DMD severity and health status into a combined responder endpoint, addressing the multidimensional nature of DMD [18]. Analysis of CaGI-C and CaGI-S responses using MDRI showed a treatment difference in favor of delandistrogene moxeparvovec. Therefore, on average, caregivers of delandistrogene moxeparvovec-treated patients reported improvements compared with those receiving placebo on one or more global item(s). To further evaluate caregiver responses, ordinal regression models specifically designed for analyzing ordinal data were leveraged. Following adjustment for age alone or age and baseline severity, ordinal regression analysis of CaGI-C and CaGI-S responses indicated a nominally statistically significant increase in the likelihood of achieving a better rating in patients receiving delandistrogene moxeparvovec compared to placebo across all four items. The adjustment for age and baseline severity was important with regard to the ability of the gene therapy to demonstrate perceived meaningful change across all ages studied and broad ranges of severity. Nominally significant odds ratios, coupled with increased likelihood of achieving a better rating demonstrated robust association between treatment with delandistrogene moxeparvovec and patients' well-being. Caregivers were more inclined to report improvement on the CaGI-C scale compared to the CaGI-S. One explanation for this could be that the CaGI-C is more sensitive to change, detecting smaller differences than shifts between severity groupings on the CaGI-S; however, we cannot rule out recall bias as a potential explanation for differences between the measures.

These results added to the totality of evidence that delandistrogene moxeparvovec provides clinically meaningful benefits to patients, as captured by caregiver-reported outcomes. Subgroup analysis demonstrated that it was unlikely that these findings could be attributed to potential unblinding of caregivers by the readily apparent AEs, which is important as early nausea and vomiting may be present in a significant percentage of patients treated with delandistrogene moxeparvovec. The inclusion of GI scales along with the functional assessments in EMBARK enhances understanding of the impact of gene therapy on patient-relevant outcomes. The importance of the benefits observed on functional assessments in patients treated with delandistrogene moxeparvovec was supported by nominally significant improvements on both caregiver GI scales (change and severity) compared to placebo. The convergence of various types of data, including objective and subjective outcomes, reinforces the totality of delandistrogene moxeparvovec treatment impact.

This study had several limitations. For example, caregiver demographic data were not collected, which may result in a limited understanding of the context in which caregiving occurs. Factors, such as age, gender, socioeconomic status, and cultural background, may influence caregiving experiences and outcomes. In addition, the GI scales utilized in this analysis were not prespecified endpoints due to their recent application in DMD. The CaGI-C and CaGI-S were initially integrated as anchor measures to aid in interpreting the observed changes in clinical assessments of function, such as NSAA and timed function tests, and patient-reported outcomes. While GI scales aim to provide a holistic view of treatment experience, their reliance on subjective input may introduce variability in precision and specificity, especially given the 52-week recall period for the CaGI-C, which may give rise to the potential for recall bias. Moreover, global assessments may lack specificity needed to identify precise changes or functional improvements that occurred, making it challenging to attribute treatment effects to specific symptoms or impacts. However, the

potential lack of precision in the concepts considered by respondents has been identified as beneficial, particularly in the context of rare, heterogenous diseases characterized by a constellation of symptoms and a limited number of validated, disease-specific outcomes measures [14–16]. Therefore, although GI scales may lack specificity, this inherent flexibility can yield valuable insights not captured by narrowly defined measures. Furthermore, given that the primary endpoint did not reach statistical significance [30] and no adjustment for multiplicity was conducted in the present analyses, the reported *p*-values can only be considered nominally significant. Although EMBARK was a blinded trial, other common treatment-related AEs may have inferred treatment allocation, which in turn may have potentially impacted caregiver evaluations. However, subgroup analysis related to nausea/vomiting indicated that caregiver responses were unlikely to be influenced by the knowledge of being randomized to an active treatment. Finally, patients with DMD participating in clinical trials have reported better overall and emotional quality of life compared to those not involved in clinical trials [33]; therefore, participation in the EMBARK study may have had positive effects on quality of life and psychosocial outcomes.

CONCLUSIONS

GIs of Change and Severity, in combination with specific functional assessments in EMBARK, provided a comprehensive characterization of the impact of delandistrogene moxeparvovec on patient-relevant outcomes. These exploratory findings captured by caregiver-reported outcomes add to the totality of evidence that support the clinical benefits of delandistrogene moxeparvovec in patients with DMD.

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Data Availability. Qualified researchers may request access to the data that support the findings of this study from Sarepta Therapeutics, Inc., by contacting medinfo@sarepta.com.

Declarations

Conflict of Interest. Jacob S. Elkins, Sai Dharmarajan, Katherine Gooch, Ivana Audhya: Employees of Sarepta Therapeutics, Inc., and may hold stock/options in the company. Teofil

Ciobanu: Employee of F. Hoffmann-La Roche Ltd. Claire J. Lansdall: Employee of F. Hoffmann-La Roche Ltd. and shareholder of F. Hoffmann-La Roche Ltd. Alexander P. Murphy: Employee of Roche Products UK and may hold shares in F. Hoffmann-La Roche Ltd. Fiona McDougall: Employee of Genentech, Inc.and shareholder of F. Hoffmann-La Roche Ltd. Craig M. McDonald: Reports grants from Capricor Therapeutics, Catabasis, Edgewise Therapeutics, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics; and has a consultancy/advisory role with Biomarin, Capricor Therapeutics, Catalyst, Edgewise Therapeutics, Italfarmaco, PTC Therapeutics, F. Hoffmann-La Roche Ltd, Santhera Pharmaceuticals and Sarepta Therapeutics. He has received honoraria from PTC Therapeutics and Sarepta Therapeutics. Eugenio M. Mercuri: Reports receiving fees from AveXis, Biogen, and F. Hoffmann-La Roche Ltd.

Ethical Approval. EMBARK was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Trial protocol and all amendments were approved by an institutional review board and ethics committee at each site. The full list of institutional review boards and ethics committees is available in the Supplementary Information. Informed consent, including consent to publish, was obtained from parent(s)/legal guardian(s), and patients' assent was obtained when indicated.

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