Impact of Delandistrogene Moxeparvovec Treatment Delays for Ambulatory Patients With Duchenne Muscular Dystrophy

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Background

- Duchenne muscular dystrophy (DMD) is a rare, progressive, and ultimately fatal neuromuscular disease characterized by widespread, irreversible muscle damage and weakness leading to loss of ambulation (LOA) and upper-limb function, pulmonary insufficiency, cardiomyopathy, and early mortality[1]
- Delandistrogene moxeparvovec is a gene transfer therapy that is approved in the US to treat ambulatory patients ≥4 years old with DMD[2]
- Three-year efficacy outcomes from patients treated with delandistrogene moxeparvovec in the phase 3 EMBARK study (NCT05096221) demonstrated clinically meaningful functional benefits compared with a matched external control cohort[3]
- Given the progressive nature of muscle damage in DMD,[1] delayed (versus immediate) administration of delandistrogene moxeparvovec may result in worse functional outcomes, irreversible loss of muscle, and increasing physical limitations
- The magnitude of this impact is unknown, and evidence-based modeling approaches may provide an opportunity to quantify this impact at a population level
- It is important to understand how treatment administration delays, regardless of the reason, affect functional outcomes in these patients, to highlight the impact of timely intervention and help inform treatment decision-making

Objective

- To model the impact of delandistrogene moxeparvovec treatment delay versus standard of care (SoC) alone or immediate treatment (no delay) on DMD clinical outcomes

Methods

Study design and population

- This study employed a population-based model that simulated multiple outcomes across a prevalent, eligible DMD population of ambulatory patients (≥4 years old with a range of baseline ages)
  - A large sample size of 100,000 hypothetical patients was used to ensure stability of the results
- The baseline age distribution of the synthetic DMD population was estimated based on DMD mortality, diagnosis, and loss of ambulation rates by age, assuming a birth prevalence of 1:5050 live male births and the underlying US male population[4-9]

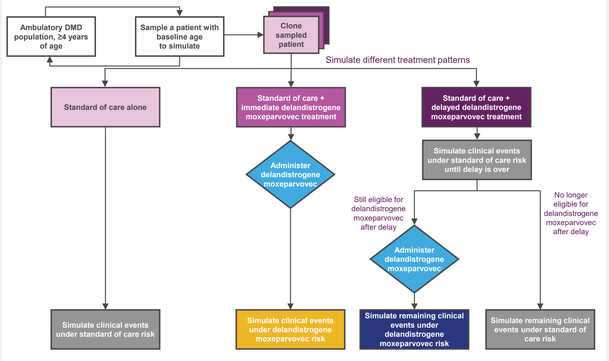
Clinical outcomes

- The 5-year cumulative incidence of the following clinical outcomes were assessed: loss of ability to rise from floor (RFF), LOA, and loss of overhead reach to the scalp or higher, even with compensatory movements (Brooke score ≥3)

Exposure variables

- Each patient was simulated under multiple treatment scenarios (**Figure 1**):
  - SoC alone (corticosteroids and/or medical management)
  - SoC + delandistrogene moxeparvovec treatment administered at baseline
  - SoC + delandistrogene moxeparvovec treatment administered after a delay period of 0.5, 1.0, 1.5, or 2.0 years, assuming eligibility
- Given delandistrogene moxeparvovec's indication, patients who lost eligibility for treatment (ie, lost ambulation) during the delay did not receive delandistrogene moxeparvovec in the model

Figure 1 *Example Modeling Framework of Patient-Level Simulation*



DMD, Duchenne muscular dystrophy.

Risk of progression estimation under SoC alone

- Non-fatal outcome data from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study was used to calculate the risk of progression under SoC alone[10]
- For each outcome, a Kaplan-Meier curve was fit to the most appropriate parametric function for the purpose of modeling

Treatment effect

- Delandistrogene moxeparvovec was simulated to slow DMD progression based on hazard ratios (HRs) by age from EMBARK Year 3 data on RFF loss (HR=0.212) and RFF loss <5 seconds (HR=0.359)
  - Only the HR for RFF loss was used to simulate RFF loss
  - Both HRs were used to simulate LOA and Brooke score ≥3, accounting for outcome uncertainty when extrapolating to other clinical milestones. Treatment benefit scenario 1 used the HR for RFF loss, and treatment benefit scenario 2 used the HR for RFF loss <5 seconds
- Treatment benefit was assumed to be immediate at delandistrogene moxeparvovec treatment infusion

Statistical analysis

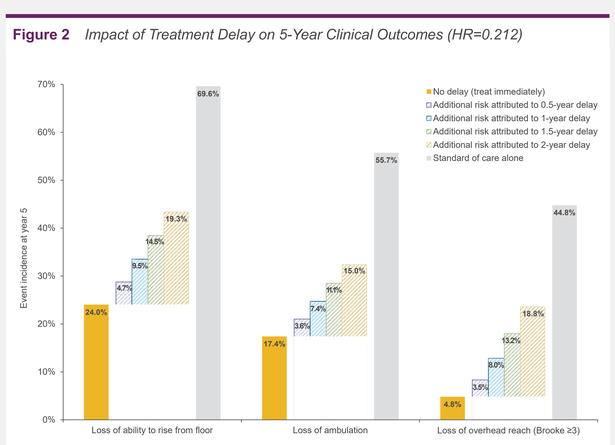
- A Kaplan-Meier analysis was conducted to assess cumulative event incidence at 1, 2, 3, 4, and 5 years for each treatment scenario

Results

Impact of delandistrogene moxeparvovec treatment delay on clinical outcomes over 5 years (treatment benefit scenario 1)

- Applying an HR of 0.212 from EMBARK Year 3 data on RFF loss, immediate delandistrogene moxeparvovec treatment reduced the incidence of all loss of function events versus SoC alone at 5 years post baseline (**Figure 2**)
  - Delaying treatment for up to 2.0 years increased the incidence of loss-of-function events versus immediate treatment, but even delayed treatment improved clinical outcomes compared with SoC
- At Year 5, RFF loss incidence was 69.6% with SoC alone, 24.0% with no treatment delay, and 28.8-43.4% with 0.5-2.0–year delays (**Table 1**)
- LOA incidence was 55.7% with SoC alone, 17.4% with no treatment delay, and 21.0-32.4% with 0.5-2.0–year delays at Year 5 (**Table 2**)
- Loss of overhead reach (Brooke score ≥3) incidence was 44.8% with SoC alone, 4.8% with no treatment delay, and 8.3-23.6% with 0.5-2.0–year delays at Year 5 (**Table 3**)

Figure 2 *Impact of Treatment Delay on 5-Year Clinical Outcomes (HR=0.212)*



HR, hazard ratio.

Table 1 *Cumulative Incidence of Loss of Ability to RFF (HR=0.212)*

	Year 1	Year 2	Year 3	Year 4	Year 5
Standard of care alone	17.0%	32.5%	46.9%	59.3%	69.6%
No delay (treat immediately)	4.0%	8.5%	13.4%	18.6%	24.0%
0.5-year treatment delay	10.5%	14.6%	19.0%	23.9%	28.8%
1.0-year treatment delay	– [a]	20.7%	24.7%	29.1%	33.5%
1.5-year treatment delay	– [a]	26.7%	30.3%	34.3%	38.5%
2.0-year treatment delay	– [a]	– [a]	35.9%	39.5%	43.4%

[a]Same as standard of care, by definition.
HR, hazard ratio; RFF, rise from floor.

Table 2 *Cumulative Incidence of LOA (HR=0.212)*

	Year 1	Year 2	Year 3	Year 4	Year 5
Standard of care alone	11.9%	23.6%	35.0%	45.8%	55.7%
No delay (treat immediately)	2.7%	5.8%	9.4%	13.3%	17.4%
0.5-year treatment delay	7.2%	10.2%	13.5%	17.1%	21.0%
1.0-year treatment delay	– [a]	14.5%	17.6%	21.1%	24.7%
1.5-year treatment delay	– [a]	19.0%	21.9%	25.1%	28.5%
2.0-year treatment delay	– [a]	– [a]	26.2%	29.1%	32.4%

[a]Same as standard of care, by definition.
HR, hazard ratio; LOA, loss of ambulation.

Table 3 *Cumulative Incidence of Loss of Overhead Reach (HR=0.212)*

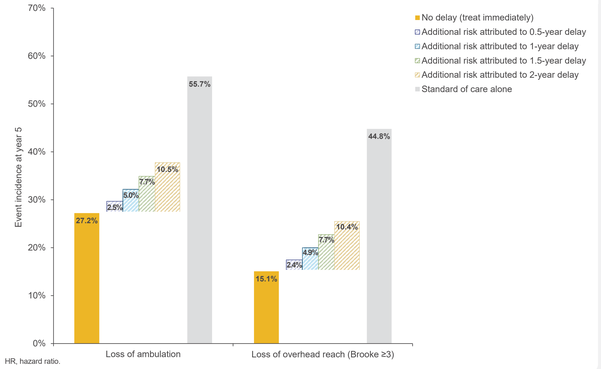
	Year 1	Year 2	Year 3	Year 4	Year 5
Standard of care alone	0.3%	10.4%	22.3%	33.8%	44.8%
No delay (treat immediately)	<0.1%	<0.1%	0.2%	1.2%	4.8%
0.5-year treatment delay	0.2%	5.7%	5.7%	6.3%	8.3%
1.0-year treatment delay	– [a]	10.1%	11.7%	11.9%	12.9%
1.5-year treatment delay	– [a]	10.4%	17.5%	17.6%	18.0%
2.0-year treatment delay	– [a]	– [a]	22.0%	23.5%	23.6%

[a]Same as standard of care, by definition.
HR, hazard ratio.

Impact of delandistrogene moxeparvovec treatment delay on clinical outcomes over 5 years (treatment benefit scenario 2)

- Similar trends for LOA and loss of overhead reach (Brooke score ≥3) were seen under the second treatment benefit scenario that applied an HR of 0.359 from EMBARK Year 3 data on RFF loss <5 seconds (**Figure 3**)
- At Year 5, LOA incidence was 55.7% with SoC alone, 27.2% with no treatment delay, and 29.7-37.8% with 0.5-2.0–year delays (**Table 4**)
- Loss of overhead reach (Brooke score ≥3) incidence was 44.8% with SoC alone, 15.1% with no treatment delay, and 17.5-25.5% with 0.5-2.0–year delays at Year 5 (**Table 5**)

Figure 3 *Impact of Treatment Delay on 5-Year Clinical Outcomes (HR=0.359)*



HR, hazard ratio.

Table 4 *Cumulative Incidence of LOA (HR=0.359)*

	Year 1	Year 2	Year 3	Year 4	Year 5
Standard of care alone	11.9%	23.6%	35.0%	45.8%	55.7%
No delay (treat immediately)	4.5%	9.7%	15.2%	21.1%	27.2%
0.5-year treatment delay	8.1%	13.0%	18.2%	23.9%	29.7%
1.0-year treatment delay	– [a]	16.4%	21.4%	26.6%	32.2%
1.5-year treatment delay	– [a]	20.0%	24.6%	29.6%	34.9%
2.0-year treatment delay	– [a]	– [a]	28.0%	32.7%	37.8%

[a]Same as standard of care, by definition.
HR, hazard ratio; LOA, loss of ambulation.

Table 5 *Cumulative Incidence of Loss of Overhead Reach (HR=0.359)*

	Year 1	Year 2	Year 3	Year 4	Year 5
Standard of care alone	0.3%	10.4%	22.3%	33.8%	44.8%
No delay (treat immediately)	<0.1%	0.1%	2.1%	8.4%	15.1%
0.5-year treatment delay	0.2%	5.7%	6.2%	11.1%	17.5%
1.0-year treatment delay	– [a]	10.2%	11.8%	13.9%	20.0%
1.5-year treatment delay	– [a]	10.4%	17.5%	18.0%	22.7%
2.0-year treatment delay	– [a]	– [a]	22.0%	23.5%	25.5%

[a]Same as standard of care, by definition.
HR, hazard ratio.

Limitations

- Treatment benefit (expressed as an HR) from delandistrogene moxeparvovec was assumed to be immediate and equal for all patients regardless of age or functional ability at treatment administration, though it is possible that patients outside of the EMBARK criteria would experience different relative outcomes
- Treatment benefit was based on HRs for loss of ability to rise from floor <5 seconds and loss of ability to rise from floor, and was extrapolated to other clinical events in the absence of robust data for those later milestones to date
- This study does not account for patients who already received delandistrogene moxeparvovec, which may affect the age distribution of patients who are eligible for treatment at baseline

Conclusions

- Modeling clinical outcomes by extrapolating data from clinical trials is particularly valuable for transformative therapies in rare diseases because additional clinically relevant outcomes often occur after the completion of clinical trials
- This study provides insight into the potential impact of delandistrogene moxeparvovec treatment delay on patient outcomes from a population perspective
  - Highlighting the importance of timely treatment, a delandistrogene moxeparvovec administration delay as short as 6 months resulted in worse clinical outcomes compared with immediate administration
  - Nonetheless, outcomes were better for patients treated with delandistrogene moxeparvovec at any time than those under SoC alone, predicting positive impacts of treatment regardless of timing
- This analysis estimates the consequences of delandistrogene moxeparvovec treatment delays and provides insights into the potential clinical significance of timely treatment

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