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Impact of Eteplirsen Treatment Initiation Delays on Loss of Ambulation Incidence among Ambulatory Patients with Duchenne Muscular Dystrophy

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Background

- Duchenne muscular dystrophy (DMD) is a rare and progressive neuromuscular disease that leads to widespread, irreversible muscle damage, weakness, and loss of ambulation (LOA) and upper limb function, followed by pulmonary insufficiency, cardiomyopathy, and early mortality[1]
- LOA typically manifests in early adolescence and is associated with reduced health-related quality of life and increased costs of disease management[1]
- Before LOA, patients go through an early ambulatory phase (infancy/early childhood), characterized by motor delays and gait abnormalities, and a late ambulatory phase (late childhood/adolescence), characterized by increasing fatigue and muscle weakness, and occasional use of walking aids[1,2]
- Eteplirsen is an FDA-approved phosphorodiamidate morpholino oligomer (PMO) for the treatment of DMD in patients with a confirmed mutation in the *DMD* gene that is amenable to exon 51 skipping[3]
- Clinical study and real-world evidence data have shown that treatment with eteplirsen results in delayed LOA versus external controls[4-9]
- Given the progressive, unrelenting nature of muscle damage in DMD,[1] it is important to understand how treatment initiation delays, regardless of the reason, impact functional outcomes
- It is hypothesized that delayed access to this treatment will result in worse outcomes than if treatment were administered immediately, though the degree to which a delay in treatment initiation impacts future outcomes in the near term is unclear

Objectives

- The primary objective of this study was to assess the impact of eteplirsen treatment initiation delay on LOA for diagnosed, prevalent ambulatory patients with DMD
- The secondary objective was to assess the impact of eteplirsen treatment initiation delay on LOA for a cohort of diagnosed, prevalent late ambulatory patients

Methods

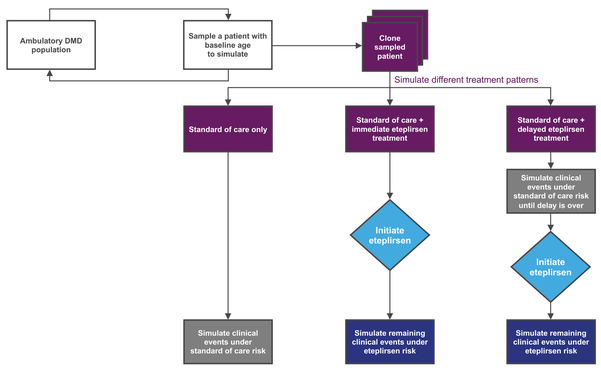
Study design and population

- This was a patient-level discrete event simulation with a large sample size (N=100,000 hypothetical patients) to ensure stability of the results
- Two diagnosed ambulatory exon 51 skip-amenable DMD prevalent populations were assessed: all ambulatory patients and a subpopulation composed of late ambulatory patients only
  - Late ambulatory patients were defined as those with a time to rise from supine ≥5 seconds, as this milestone is associated with progressive mobility decline[10,11]
- The baseline age distribution of the synthetic DMD populations was estimated based on DMD mortality rates by age, DMD diagnosis rates by age, and DMD ambulatory status by age[10,12-15]
- The baseline age distribution of late ambulatory patients was further estimated based on the risk of reaching a time to rise from supine ≥5 seconds by age[10]

Exposure variables

- Multiple treatment scenarios were simulated for each patient (**Figure 1**):
  - Standard of care (SoC) only (corticosteroids and medical management)
  - SoC + eteplirsen treatment initiated at baseline
  - SoC + eteplirsen treatment initiated after a delay period of 0.5, 1.0, 1.5, or 2.0 years

Figure 1 *Example modeling framework of patient-level simulation*



DMD, Duchenne muscular dystrophy.

LOA risk estimations under SoC only

- The risk of LOA under SoC only was calculated based on patients with exon 51 skip-amenable DMD in the Cooperative International Neuromuscular Research Group (CINRG) registry[16] who had been on corticosteroid treatment for DMD for at least 1 year
  - Risk of transition to the late ambulatory phase (loss of time to rise from supine <5 seconds) for exon 51 skip-amenable patients on corticosteroid treatment for at least 1 year was unavailable due to lack of sufficient sample size; thus, risk by age was taken from a previously published Kaplan-Meier analysis (from McDonald et al.[10]) for corticosteroid-treated patients regardless of exon skip amenability
- Kaplan-Meier data were fit to the most appropriate parametric functions for the sake of modeling

Treatment effect

- A 0.38 hazard ratio (estimated from previous real-world evidence of eteplirsen versus external controls[9]) was applied at eteplirsen treatment initiation to estimate eteplirsen-treated risk for LOA over time
- Treatment benefit was assumed to be immediate at eteplirsen initiation

Statistical analysis

- Cumulative LOA incidence via Kaplan-Meier analysis was conducted at 1, 2, 3, 4, and 5 years for each of the treatment scenarios

Results

Cumulative incidence of LOA in all ambulatory patients: SoC only versus immediate eteplirsen treatment

- Immediate eteplirsen treatment reduced cumulative LOA incidence versus SoC only for all ambulatory patients over 5 years (**Table 1**)
- SoC treatment alone led to a 29.2% LOA incidence by Year 3, compared to 13.5% in the immediate eteplirsen treatment scenario
  - This represents an absolute risk reduction of 15.7% for LOA by Year 3
- By Year 5, LOA incidence was 47.8% under SoC only, and 24.8% with immediate eteplirsen treatment—an absolute risk reduction of 23.0%

Table 1 *Cumulative incidence of LOA for an ambulatory population*

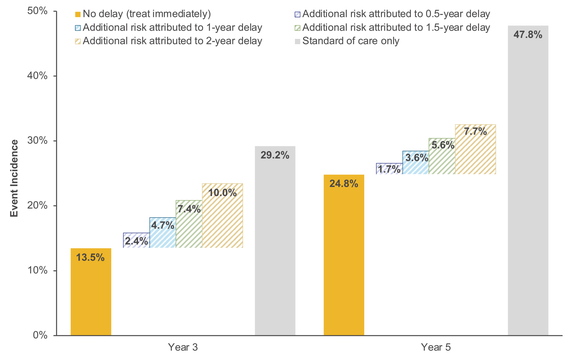
	Year 1	Year 2	Year 3	Year 4	Year 5
Standard of care only	9.8%	19.7%	29.2%	38.6%	47.8%
No delay (treat with eteplirsen immediately)	3.9%	8.4%	13.5%	19.0%	24.8%
0.5-year eteplirsen treatment delay	6.7%	11.0%	15.8%	21.0%	26.6%
1.0-year eteplirsen treatment delay	– [a]	13.7%	18.2%	23.2%	28.4%
1.5-year eteplirsen treatment delay	– [a]	16.5%	20.8%	25.4%	30.4%
2.0-year eteplirsen treatment delay	– [a]	– [a]	23.4%	27.8%	32.5%

Numbers in the table are rounded to the nearest tenths place; absolute risk reductions were calculated using unrounded numbers.
[a]Same as standard of care, by definition.
LOA, loss of ambulation.

Impact of eteplirsen treatment initiation delays on LOA in all ambulatory patients

- Delayed initiation of eteplirsen treatment increased incidence of LOA for all ambulatory patients over 5 years (versus immediate treatment; **Figure 2**)
- At Year 3, a 0.5-year delay in eteplirsen treatment initiation increased absolute risk of LOA by 2.4% compared to immediate treatment (15.8% versus 13.5%), while a 2.0-year delay increased absolute risk by 10.0% (23.4% versus 13.5%)
- By Year 5, an eteplirsen treatment initiation delay of 0.5 years increased absolute risk of LOA by 1.7% compared to immediate treatment (26.6% versus 24.8%), and treatment delay of 2.0 years increased absolute risk by 7.7% (32.5% versus 24.8%)

Figure 2 *Impact of eteplirsen treatment initiation delay on LOA for an ambulatory population*



LOA, loss of ambulation.

Cumulative incidence of LOA in late ambulatory patients: SoC only versus immediate eteplirsen treatment

- Immediate eteplirsen treatment reduced cumulative LOA incidence versus SoC only for late ambulatory patients over 5 years (**Table 2**)
- At Year 3, 84.9% of late ambulatory patients who received SoC only experienced LOA compared to 40.9% of late ambulatory patients who received immediate eteplirsen treatment, corresponding to an absolute risk reduction of 44.0%
- By Year 5, LOA incidence for late ambulatory patients was 99.4% with SoC only versus 69.4% with immediate eteplirsen—an absolute risk reduction of 30.0%

Table 2 *Cumulative incidence of LOA for a late ambulatory population*

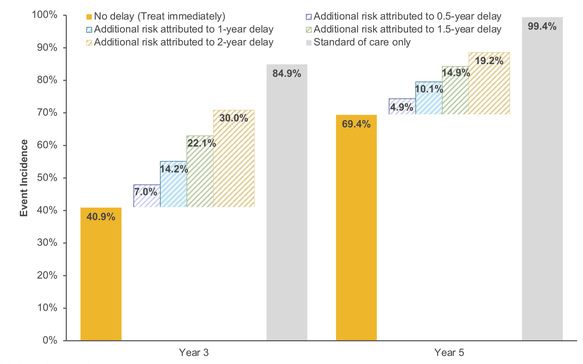
	Year 1	Year 2	Year 3	Year 4	Year 5
Standard of care only	30.0%	59.8%	84.9%	96.4%	99.4%
No delay (treat with eteplirsen immediately)	11.9%	25.7%	40.9%	56.0%	69.4%
0.5-year eteplirsen treatment delay	20.5%	33.5%	47.9%	62.1%	74.3%
1.0-year eteplirsen treatment delay	– [a]	41.8%	55.1%	68.5%	79.5%
1.5-year eteplirsen treatment delay	– [a]	50.5%	63.0%	74.8%	84.3%
2.0-year eteplirsen treatment delay	– [a]	– [a]	70.9%	81.0%	88.6%

Numbers in the table are rounded to the nearest tenths place; absolute risk reductions were calculated using unrounded numbers.
[a]Same as standard of care, by definition.
LOA, loss of ambulation.

Impact of eteplirsen treatment initiation delays on LOA in late ambulatory patients

- Late ambulatory patients also benefitted from immediate versus delayed eteplirsen treatment (**Figure 3**)
- At Year 3, a 0.5-year delay in eteplirsen treatment initiation increased absolute risk of LOA in late ambulatory patients by 7.0% compared to immediate treatment (47.9% versus 40.9%), while a 2.0-year delay increased absolute risk by 30.0% (70.9% versus 40.9%)
- By Year 5, an eteplirsen treatment initiation delay of 0.5 years increased absolute risk of LOA by 4.9% compared to immediate treatment (74.3% versus 69.4%), and treatment delay of 2.0 years increased absolute risk by 19.2% (88.6% versus 69.4%)

Figure 3 *Impact of eteplirsen treatment initiation delay on LOA for a late ambulatory population*



LOA, loss of ambulation.

Limitations

- Eteplirsen treatment benefit with respect to LOA (hazard ratio = 0.38) was assumed for all patients regardless of age or functional ability at eteplirsen initiation, though it is possible that earlier treatment initiation could result in better relative outcomes
- Eteplirsen treatment benefit was assumed to be immediate and did not change with increased eteplirsen exposure
- This study describes LOA incidence for an eteplirsen-naïve ambulatory population, though not all eligible patients in the real world are still treatment-naïve

Conclusions

- Extrapolating evidence from real-world studies, this model suggests that eteplirsen reduces the cumulative LOA incidence versus SoC alone regardless of the timing of initiation
- Delays in initiation of eteplirsen treatment for an ambulatory, eteplirsen-naive DMD population led to a higher incidence of LOA within 5 years than if treatment were initiated immediately
  - Even a 6-month delay in eteplirsen treatment initiation increased the cumulative LOA incidence within 5 years versus immediate treatment, and this impact worsened with longer delays
- This modeled analysis suggests the importance of early treatment with eteplirsen

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