EE241

Modeling the Lifetime Benefits of Eteplirsen in Patients with Duchenne Muscular Dystrophy

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Background

- Duchenne muscular dystrophy (DMD) is a rare, progressive, neuromuscular disease caused by mutations in the *DMD* gene that lead to progressive muscle weakness, loss of ambulation (LOA), loss of upper body function, respiratory insufficiency, and ultimately premature death[1,2]
- The average age at diagnosis is approximately 5 years,[3] after toddlers develop suggestive signs and symptoms such as weakness, clumsiness, a Gowers' sign, toe walking, and difficulty climbing stairs[1]
- 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[4]
- Previous studies have demonstrated clinically meaningful improvements in patients treated with eteplirsen, including delayed LOA[5-7] and prolonged survival compared to external controls[8]
- The mean age of eteplirsen treatment initiation across these studies has ranged from 8.7 to 11.9 years[5-8]
- The lifetime effects of earlier eteplirsen treatment initiation (ie, closer to the mean age of diagnosis) on delaying DMD progression have not yet been assessed

Objectives

- To model the lifetime benefits of eteplirsen for a 5-year-old early ambulatory (EA) cohort of patients with DMD amenable to exon 51 skipping using a partitioned survival model and real-world treatment evidence to date

Methods

Study design

- A partitioned survival model of DMD health states over a lifetime horizon was developed based on clinical feedback and a previously reported lifetime DMD model[9] (**Figure 1**)
- Patients started in the EA state and progressed sequentially through the health states until they reached DMD-related mortality; patients could also die from all-cause mortality while in any health state
  - Transition from EA to late ambulatory (LA) was defined by loss of ability to stand from supine in <5 seconds, as this is associated with progressive mobility decline[10,11]
  - Transition from LA to early non-ambulatory (ENA) was signified by LOA, defined as patient-reported continuous wheelchair use verified by the inability to walk 10 meters unassisted
  - Transition from ENA to late non-ambulatory (LNA) was defined by progression to a Brooke score >4 (signifying a loss of unweighted hand-to-mouth function)
    - A Brooke score >4 is associated with a percent predicted forced vital capacity <50%,[12] which is deemed to be a threshold whereby non-invasive nocturnal ventilation should be initiated[13]

Figure 1 *Partitioned survival modeling framework*

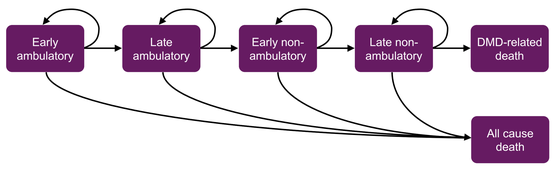


Figure adapted from Klimchak AC, et al. *J Mark Access Health Policy.* 2023;11(1):2216518 under CC BY-NC 4.0.[9]

- The model was run for a homogeneous cohort starting at age 5 in the EA state, assessing standard of care (SoC) only (corticosteroids and medical management) versus eteplirsen + SoC initiated at model entry

Outcomes

- The model was used to calculate:
  - Ambulatory years gained
  - Life years gained
  - Equal value of life years gained
- Results were undiscounted in the base case and discounted annually at 1.5% and at 3.0% in scenario analyses

Risks

- The risk of progression under SoC was age-specific and aligned with the previously published lifetime DMD model with one exception:[9]
  - The risk of LOA was re-calculated specific to corticosteroid-treated exon 51 skip-amenable patients based on data available from the Cooperative International Neuromuscular Research Group registry[10]
  - Risks specific to corticosteroid-treated exon 51 skip-amenable patients were not available for any other transitions due to lack of sufficient sample size
- The risk of DMD-related death was age-specific and estimated based on previously published results[14-16]
- The risk of mortality for the general male population was age-specific and estimated using US Centers for Disease Control and Prevention life tables[17]
- Data were fit to the most appropriate parametric functions for the sake of modeling

Treatment effect

- A 0.38 hazard ratio (HR) was applied to the SoC risks to estimate eteplirsen-treated + SoC risk by age for all non-fatal transitions
  - This HR was calculated for LOA in a recent analysis comparing eteplirsen-treated patients in the EVOLVE study with external controls[7]
  - The transitions from EA to LA and ENA to LNA utilized this HR due to a lack of real-world or clinical trial data on the efficacy of eteplirsen for these specific transitions
- A 0.303 HR was applied to estimate eteplirsen-treated risk by age for mortality
  - This HR was based on a target trial emulation of pooled PMO data (56% of patients were treated with eteplirsen), comparing patients treated with both a PMO plus corticosteroids to those treated only with corticosteroids[18]

Utility

- Utility values were based on Health Utility Index-2 for US patients with DMD (**Table 1**)

Table 1 *Patient utility by health state[19,20]*

	Utility (median)
Early ambulatory	0.96
Late ambulatory	0.67
Early non-ambulatory	0.51
Late non-ambulatory	0.35

Sensitivity analyses

- Sensitivity analyses were conducted to assess the impact of the following model inputs on results (**Table 2**):
  - Treatment efficacy (HR) for non-fatal transitions
  - Treatment efficacy (HR) for mortality
  - Risk of progression under SoC

Table 2 *Sensitivity analysis inputs*

Scenario	Input	Source
Impact of eteplirsen efficacy on non-fatal transitions	HR = 0.18 HR = 0.80	95% confidence interval limits of the EVOLVE comparative analysis of LOA[7]
Impact of eteplirsen efficacy on mortality	HR = 0.34	HR from a survival study of eteplirsen[8]
	HR = 0.373 HR = 0.397 HR = 0.477	HRs estimated via different numbers of pooled trials in the target trial emulation analysis (54, 60, and 66 pooled trials, respectively)[18]
Impact of risk of progression under SoC	Risk of LOA for corticosteroid-treated patients, but not specific to exon 51 skip amenability	Risk aligned with the previously published lifetime DMD model[9]
	Risk of progression for non-fatal events not exclusive to corticosteroid-treated patients	Risk based on the breakdown of corticosteroid and non-corticosteroid treated patients in the CINRG database

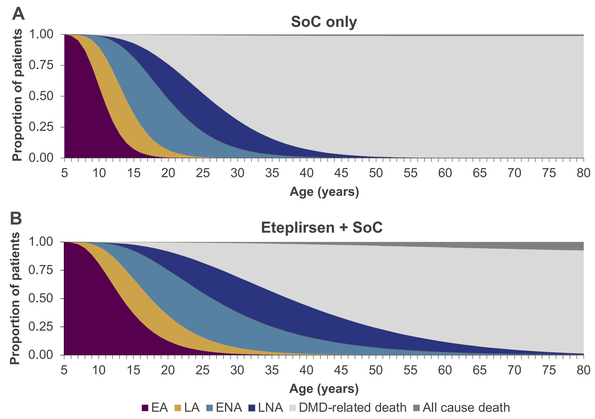
CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; HR, hazard ratio; LOA, loss of ambulation; SoC, standard of care.

Results

Modeled risk of progression

- The proportion of patients remaining in each DMD health state was calculated for both treatment arms (**Figure 2**)
  - Survival curves extended over shorter periods of time for the SoC only group (**Figure 2A**) than for the eteplirsen + SoC group (**Figure 2B**), reflecting a slower disease progression with eteplirsen treatment

Figure 2 *Partitioned survival curves*



Curves depicting proportion of patients across DMD health states by age for (A) the SoC only cohort and (B) eteplirsen + SoC cohort. DMD, Duchenne muscular dystrophy; EA, early ambulatory; ENA, early non-ambulatory; LA, late ambulatory; LNA, late non-ambulatory; SoC, standard of care.

Modeled lifetime effects of eteplirsen

- In the base case model, 5-year-old EA patients treated with eteplirsen + SoC remained in ambulatory health states for 13.77 years versus 9.12 years for SoC alone, representing 4.65 ambulatory years gained (**Table 3**)
- Treatment with eteplirsen also led to a gain of 13.28 life years and 13.99 equal value of life years versus SoC only

Table 3 *Base case and discounted scenario analyses results*

	SoC only	Eteplirsen + SoC	Incremental
Ambulatory years			
Undiscounted	9.12	13.77	4.65
1.5% annual discount	8.51	12.27	3.76
3% annual discount	7.97	11.05	3.08
Life years			
Undiscounted	21.39	34.67	13.28
1.5% annual discount	18.06	26.20	8.14
3% annual discount	15.52	20.73	5.21
Equal value of life years			
Undiscounted	13.12	27.11	13.99
1.5% annual discount	11.50	20.59	9.10
3% annual discount	10.22	16.43	6.21

SoC, standard of care.

Sensitivity analyses

- Sensitivity analyses for the undiscounted scenario are presented in **Table 4**
- Ambulatory years gained were most sensitive to the treatment benefit (HR) for non-fatal transitions, life years gained were most sensitive to the treatment benefit (HR) for mortality, and equal value of life years gained was sensitive to both HRs
- Varying the risk of progression under SoC had a modest impact on ambulatory years gained and equal value of life years gained

Table 4 *Sensitivity analyses for the undiscounted scenario*

	Ambulatory years gained	Life years gained	Equal value of life years gained
Base Case	4.65	13.28	13.99
Impact of eteplirsen efficacy on non-fatal transitions			
HR = 0.18	11.47	13.28	16.38
HR = 0.80	0.82	13.28	11.84
Impact of eteplirsen efficacy on mortality			
HR = 0.34	4.65	11.67	12.62
HR = 0.373	4.65	10.42	11.56
HR = 0.397	4.65	9.61	10.87
HR = 0.477	4.65	7.34	8.93
Impact of risk of progression under SoC			
Risk of LOA not specific to exon 51 skip amenability	5.94	13.28	14.19
Risk of non-fatal events transitions not exclusive to corticosteroid-treated patients	4.24	13.28	14.17

HR, hazard ratio; LOA, loss of ambulation; SoC, standard of care.

Limitations

- The transitions from EA to LA and from ENA to LNA utilized the LOA HR (HR = 0.38)[7] due to a lack of clinical trial or real-world data on the efficacy of eteplirsen for these specific transitions
- The treatment mortality benefit (HR = 0.303) was based on an analysis that pooled 3 different PMOs together: eteplirsen (56%), casimersen (33%), and golodirsen (11%)[18]
- All risks except risk of LOA (signifying progression from LA to ENA) were not specific to exon 51 skip-amenable patients

Conclusions

- These results provide an estimate of potential lifetime benefits for patients who initiate eteplirsen treatment at an early age
- The model complements the totality of RWE for eteplirsen and suggests that early treatment initiation yields gains in ambulatory years, life years, and equal value of life years

Acknowledgments & Disclosures

Acknowledgments: This study was funded by Sarepta Therapeutics, Inc. Medical writing and editorial support were provided by Bettina Voelcker, PhD, an employee from the Publications and Medical Affairs Division of Omnicom Health Medical Communications, in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022) and was funded by Sarepta Therapeutics, Inc.

Disclosures: All authors are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company.

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