Progressive Disease Milestones and Survival in Duchenne Muscular Dystrophy (DMD): A Model-Based Synthesis for Extrapolating Lifetime Treatment Effects from Clinical Trial Results

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Objective

- To develop a model-based framework to project plausible gene therapy effects on long-term disease milestones in DMD, including mortality, based on 1-year outcomes from clinical trials and longer-term natural history (NH) data.

Conclusions

- Lifetime effects of novel therapies for DMD will ultimately be determined based on real-world evidence over several decades.
- In the near-term, the projection approach presented here, which incorporates natural history data and published evidence, provides plausible extrapolations based on straightforward and transparent assumptions, and can complement and supplement the lifetime projections used in health economic evaluations.

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Background

- Randomized controlled trials of gene therapies (GTx) in Duchenne muscular dystrophy (DMD) have studied effects on ambulatory function limited to one year using the North Star Ambulatory Assessment (NSAA).
- The projected lifetime effects of these therapies on overall survival will need to be considered in health economic evaluations.

Methods

MODEL DEVELOPMENT (**FIGURE 1**)

- A quantitative NH model of progressive milestones (see Bushby and Connor 2011 for disease progressive milestones) was developed to link 1-year changes in NSAA total score to mortality through the following associations:
  1. Baseline age and NSAA total score
  2. Age at loss of ambulation (LoA)
  3. Age at loss of pulmonary function (i.e., start of mechanical ventilation)
  4. Age at death
- Ages at which milestones typically occur were calibrated based on analyses of patient-level natural history data and published data extracted from a targeted literature review:

Analyses of natural history data

- Median age at LoA and median time from LoA to the start of ventilation was estimated through Kaplan-Meier (KM) analysis of the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG) database
- CINRG data includes 440 boys with DMD. On average, patients had 8.1 visits and a typical follow-up period of 4.7 years.
- For database analysis, patients were required to have evidence of motor or pulmonary function to conduct a KM analysis of the time to LoA and the time from LoA to ventilation, respectively.

Targeted literature review

- Median ages at LoA, start of ventilation, and death were extracted from a targeted literature review.
- Median times between events were computed.

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Disclosures:

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Results

AGE AT LOA, START OF VENTILATION, AND DEATH (**TABLE 1**)

- The typical ages for LoA and start of ventilation were consistent across sources. Median age of death, however, ranged from 27 to 36.2 years.

Table 1. Summary of DMD progression milestone ages derived from the literature and natural history data

Reference	Median Age of LoA	Median Age of Ventilation	Median Age of Death
Zambon et al. 2022	11.7	-	-
CINRG [McDonald et al. 2013]	11.0	20.4	-
Rall et al. 2012	-	20.0	27.0
Kieny et al. 2012	-	20.1[b]; 21.7[c]	36.2
Kohler et al. 2008	9.4 (SD 2.4)[a]	19.8 (SD 3.9)[a]	35.0

[a] Estimate was reported as the mean value.
[b] Median age was reported for non-invasive ventilation.
[c] Median age was reported for tracheotomy ventilation.

MODEL SCENARIOS

- Based on the modeling framework (**Figure 1**), three scenarios were developed to characterize possible lifetime disease trajectories.
  - *Natural history:* DMD natural history progression for patients under a steroid-treated standard of care based on literature and natural history data.
  - *Persistent slowing scenario:* An assumed treatment effect is modeled as slowing the rate of disease progression by a constant degree that persists across all disease stages.
  - *Fixed-shift scenario:* The treatment effect is modeled as shifting the age at LoA after which disease progression proceeds to mortality at a rate consistent with natural history, so that all subsequent disease milestones are delayed by the same number of years as was LoA.

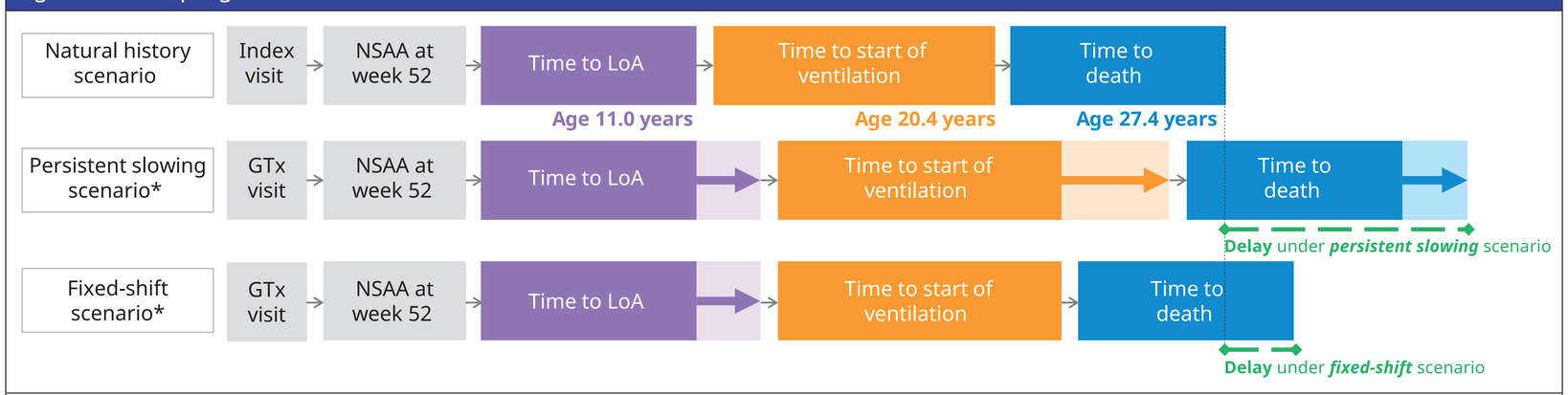
Figure 1. Modeling framework

Scenarios	Modeled stages in DMD disease progression from changes in NSAA total score to death			
	52-week change in NSAA total score	NSAA and Age of LoA	Years from LoA to ventilation	Years from ventilation to death
Natural History	Phase 3 clinical trial placebo arm	Literature review; assessed in database analyses as well	Database analyses corroborated by literature: Median time from LoA to ventilation	Literature review: Extract median time from ventilation to death and/or median age at death
Treatment Effect	Phase 3 clinical trial (treatment)	Extrapolated from clinical trial effect on NSAA total score*	Persistent slowing scenario: Treatment effect on rate of disease progression during the clinical trial is applied throughout the disease course.	
			Fixed-shift scenario: No further treatment effect on disease progression after shift observed in time to LoA.	

* The approach, to be developed as part of this study, will allow translation of the 52-week treatment effects on NSAA total score into effects on time to LoA regardless of whether both the treatment and control groups are improving or declining on average for the NSAA total score. If the control group is declining while the treatment group is improving, additional assumptions may be required.

- The NH scenario would project the median age of LoA at 11.0 years and median time from LoA to first use of mechanical ventilation at 9.4 years, consistent with published estimates:
  - A literature review yielded a median time of 7.0 years from ventilation to death (**Table 1**).
  - The model-based median age at death was 27.4 years, consistent with published medians of 27.0-36.2 years (**Table 1**).
- The two treatment scenarios project a plausible range of potential GTx impacts on the disease course (**Figure 2**).

Figure 2. DMD progression under three scenarios



* Numeric projections will become available once trial results are published.

Limitations

- Any extrapolation of lifetime treatment effects relies on biological and quantitative assumptions.
- Extrapolations cannot substitute for empirical evidence of long-term treatment effects.