Poster # P.67

Development and Evaluation of a Time to Event Endpoint for Clinical Trials in Duchenne Muscular Distrophy (DMD)

Craig M. McDonald[1], Francesco Muntoni[2], Jessica R. Marden[3], Nathalie Goemans[4], Andres Gomez-Lievano[3], Adina Zhang[3], Susan J. Ward[5], James Signorovitch[3,5]

[1] University of California Davis, Sacramento, California [2] University College London, London, UK [3] Analysis Group, Inc., Boston, Massachusetts
[4] University of Leuven, Leuven, Belgium [5] Collaborative Trajectory Analysis Project, Cambridge, Massachusetts

Background

- Therapeutics under development for DMD aim to slow or reverse disease progression which, for full regulatory approval, is ideally measured in a randomized controlled trial.
- The use of placebo controls for DMD clinical trials presents practical and ethical challenges that are heighted due to the rarity of the disease and the growing number of approved and investigational treatment options.
- The number of patients assigned to placebo — and their durations of placebo exposure — should be minimized while remaining sufficient to measure drug efficacy and safety.
- To this end, we explored the potential for ***event-driven trials*** in DMD.

Event driven trials

- The primary outcome is the time from baseline to a clinically meaningful progression endpoint.
- The trial ends after a pre-determined number of patients has reached this endpoint.
- When individual patients receiving placebo reach the endpoint, they may cross-over to receive active therapy before the end of the trial.
- In this way, placebo exposure is individualized to each patient and the total amount of disease progression occurring on placebo is limited to that which is necessary to assess drug effects. Individuals progressing faster will receive a shorter duration of placebo exposure compared to those progressing more slowly.

Study Objectives

1. Characterize an endpoint representing meaningful disease progression in ambulatory DMD in terms of time-to-event, stability, and prognostic meaning
2. Assess power and sample size requirements for potential event-driven clinical trials in DMD

Methods

Data sources

Placebo arm data from phase 3 clinical trials:

- The PTC Therapeutics phase 3 trial of ataluren (Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy [ACT DMD]; NCT01826487)
- The Eli Lilly phase 3 trial of tadalafil (NCT01865084)
- The GlaxoSmithKline phase 3 trial of drisapersen (DEMAND III; NCT01254019; provided by CureDuchenne)

Real-world/natural history data sources:

- Universitaire Ziekenhuizen Leuven (provided by the Leuven Neuromuscular Reference Center in Leuven, Belgium)
- BioMarin natural history study (PRO-DMD-01; NCT01753804; provided by CureDuchenne)
- North Star Clinical Network (NSUK; http://www.northstardmd.com)
- iMDEX/French Muscular Dystrophy Association (iMDEX; NCT02780492)

Patients

- Ambulatory DMD patients aged 6 to 18, and likely to have declining ambulatory function, were identified as those with rise from floor times greater than or equal to 5 seconds and North Star Ambulatory Assessment (NSAA) total scores greater than or equal to 12 points
- Prior use of steroids for at least 6 months was required
- Baseline and follow-up data for the NSAA total score and items scores were required
- For each patient, the **baseline visit** was defined as the first visit to satisfy these inclusion criteria

Outcomes

- Progression endpoint: loss of ≥3 NSAA total score points since baseline at the patient level, which has been previously identified as the minimal detectable decline[3]
  - Additional progression endpoints were also explored as sensitivity analyses:
    - Loss of 2 NSAA total score points
    - Loss of 2 NSAA item functions
- Disease milestones for assessing the prognostic meaning of the progression endpoint:
  - Loss of ambulation (LoA) defined as 6MWD = 0 or NSAA walk item = 0 or recorded inability to walk
  - Approaching LoA (aLoA) defined as 10MWR > 10s, which has been associated with LoA within the next 2 years
- Stability of the progression endpoint: regain of the baseline NSAA total score or better after reaching the progression endpoint

Statistical Analyses

- Kaplan-Meier (KM) analyses were conducted to assess time from baseline to the progression endpoint
- To assess the prognostic significance of progression, associations with subsequent times to LoA and ALoA were estimated using landmark Kaplan-Meier analyses
- To assess the stability of the progression endpoint, time from progression to regain of baseline NSAA score or better was described using Kaplan-Meier analyses
- Sample size and trial duration requirements were computed to assess the suitability of progression for use as an endpoint in event-driven clinical trials, assuming scenarios with different treatment effect sizes

Results

Baseline characteristics

- Analyses were based on N=619 patients from the pooled placebo arms and RWD/NHD sources
- At baseline, mean age was 9.3 years (range: 6-18yrs), average age at diagnosis of DMD was 4.5 (range: 0-11.7yrs), mean NSAA total score was 22 (range:12-34); 62.7% were receiving prednisone, 40% deflazacort, and 18.6% had missing steroid information or were not on steroids (**Table 1**)

Time-to-event analyses

- Median time to the progression endpoint was 11 months (95% CI: 9-12), based on Kaplan-Meier analyses (**Figure 1**)
  - Median times to progression for the sensitivity endpoints (loss of 2 points & loss of 2 item functions) were ~7 months and ~13 months, respectively
- A progression event during the first year after baseline was associated with significantly shorter subsequent time to LoA and aLoA, with hazard ratios of 2.5 and 1.5 ($p<0.05$), respectively, based on landmark analyses (**Figure 2**)
- Among the patients who progressed, approximately 10% regained their baseline level of function within a year, and 13% after two years

Table 1. Baseline Characteristics

	Total N = 619
Patient Characteristics (Mean ± SD)	
Age (years)	9.3 ± 2.1
Age at DMD diagnosis (years)	4.5 ± 2.2
Height (cm)	125.3 ± 9.9
Weight (kg)	30.6 ± 10.0
BMI (kg/m2)	19.3 ± 4.2
Steroid Information	
Steroid use, n (%)	
Deflazacort	187 (40.0%)
Prednisone	317 (62.7%)
Not on steroids/Missing	115 (18.6%)
Steroid duration, Mean ± SD	34.0 ± 23.6
Daily steroids	308 (64.8%)
Ambulatory Function (Mean ± SD)	
NSAA total score	26.9 ± 4.4
Timed 10-meter walk/run (seconds)	5.3 ± 2.2
6MWD (meters)	397.6 ± 62.0
Timed rise from supine (seconds)	3.6 ± 0.9
Timed 4-stair climb	2.7 ± 1.0
FVC %-predicted	93.1 ± 20.4

Sample size requirements for trials

A hypothetical, well-powered, randomized, event-driven trial enrolling 160 DMD patients (1:1 TX to PBO ratio) over a period of 9 months would require an expected duration of 10, 14, or 25 months to detect treatment effects delaying the progression endpoint by 13.0, 8.4 or 5.4 months, respectively (**Table 2**)

Table 2. Expected trial durations and sample size requirements for event-driven clinical trials using ≥3 point decline in NSAA as a progression endpoint, based on target treatment effect size

Target Treatment effect size: Median delay in progression (months)	Number of patients[1]		
	N = 120	N = 160	N = 200
	Expected trial duration (months)		
13.0 (HR = 0.4)	12	10	9
8.4 (HR = 0.5)	18	14	12
5.4 (HR = 0.6)	46	25	19

Notes:
[1] Total number of patients across the treatment and placebo arms with equal allocation two both groups.
[2] Accrual/enrollment time = 9 months; confidence level (alpha) = 5%; power = 80%; withdrawal/attrition rate = 10%; 1:1 treatment-to-control ratio; placebo incidence rate = 8.25 per 10 person-years (= median time to progression of 10 months).
[3] The 9-month accrual/enrollment time are included in the expected trial durations.
[4] Calculations were based on Schoenfeld's formula.

Figure 1. Time to progression for three progression endpoints

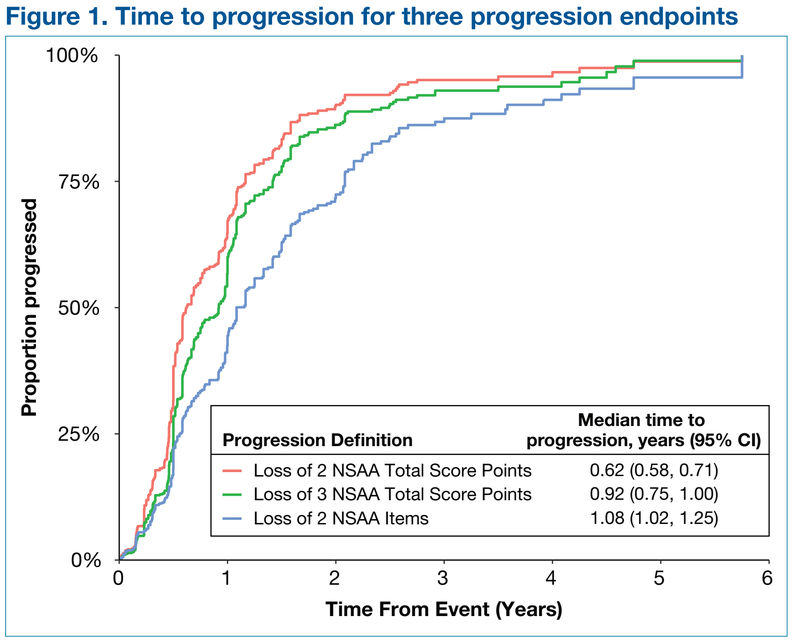
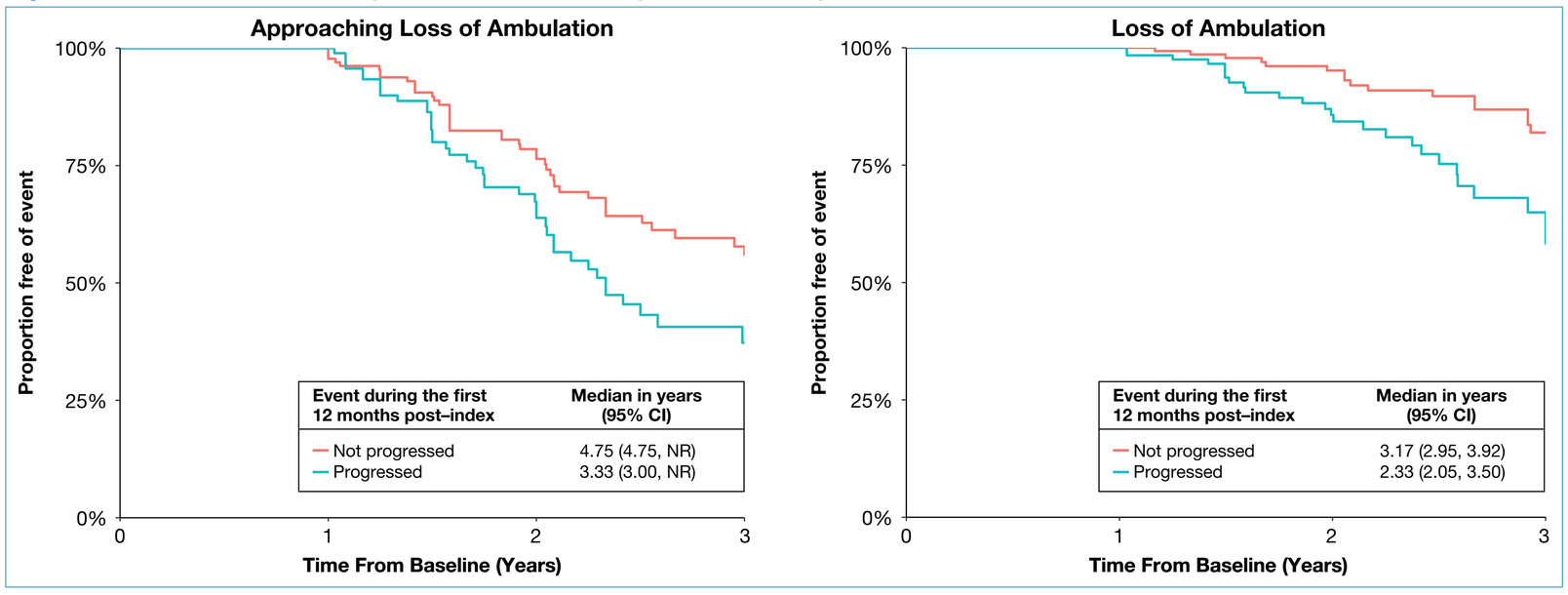


Figure 2. Decline in NSAA of ≥3 points over 12 months predicts subsequent accelerated aLoA and LOA



Notes:
[1] Approaching Loss of Ambulation (ALoA) was defined as the first visit with 10MWR > 10 seconds.
[2] Loss of Ambulation (LoA) was defined as the first visit where at least one of the following was true: 6MWD = 0, NSAA walk item score = 0, or recorded inability to walk 10 meters. If there was a conflict between any of these measures, the visit was classified as ambulatory.

Limitations

- Event-driven trials in DMD would need to consider the reliability of performance-based endpoints that can impact access to active therapy
- The clinical meaningfulness of a 3 or more point decline in NSAA total score would benefit from additional substantiation
- The variability in the definition of LoA across data sources may have contributed some noise to the landmark analyses, but we do not expect it to be related to whether patients progressed

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Conclusions

- A progression endpoint in DMD defined as loss of ≥3 NSAA total score points exhibits a favorable combination of event rate, prognostic validity, and stability for event driven clinical trials
- The power and sample size needed for event-driven trials is favorable, but needs to be compared to that of traditional approaches looking at mean changes from baseline in NSAA to fully assess the suitability of event driven-trials in DMD

References

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Disclosures

- This study was conducted within the collaborative Trajectory Analysis Project (cTAP), a precompetitive coalition of academic clinicians, drug developers, and patient foundations formed in 2015 to overcome the challenges of high variation in clinical trials in DMD. cTAP has received sponsorship from Astellas (Mitobridge), Avidity Biosciences, BioMarin Pharmaceutical, Bristol Meyers Squibb, Catabasis, Daiichi Sankyo, Edgewise Therapeutics, Entrada Therapeutics, FibroGen, Italfarmaco SpA, Marathon Pharmaceuticals, NS Pharma, Pfizer, PTC Therapeutics, Roche, Sarepta Therapeutics, Shire, Solid Biosciences, Summit Therapeutics, Ultragenyx, Vertex Pharmaceuticals, Parent Project Muscular Dystrophy, Charley's Fund, and CureDuchenne, a founding patient advocacy partner and provider of initial seed funding to cTAP.
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