Can natural history controls be used for functional outcomes in Duchenne muscular dystrophy (DMD) drug trials? Assessing the consistency of 48-week changes in six-minute walk distance (6MWD) between multiple natural history data sources and clinical trial placebo arms.

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Background: Using patients from natural history (NH) cohorts to supplement, or replace, placebo arms in clinical trials of new DMD treatments is a high priority for DMD patients and families, and could also allow for smaller and faster clinical trials. However, an important concern with the use of NH controls is that functional outcomes could be biased by differences in patient motivation, supportive care or assessment procedures between clinical trial and NH settings. The potential for such differences has been noted by regulatory agencies and may be particularly pertinent for functional outcomes such as six minute walk distance (6MWD). To empirically assess this potential for bias we conducted a multi-sponsor, multi-institution, multi-registry collaboration enabled by the Trajectory Analysis Project (cTAP) to systematically compare 48-week changes in 6MWD between clinical trial placebo arms and NH data sources.

Methods: Participating collaborators included UZ Leuven, Fondazione Telethon, CINRG, ImagingDMD, and the PRO-DMD-01 study provided by CureDuchenne, altogether providing data from 420 NH patients. Five placebo arms yielding a total of 375 patients and employing four sets of I/E criteria were identified: tadalafil phase 3, ataluren phases 2b and 3, drisapersen phase 2 trials (pooled), and drisapersen phase 3. The key inclusion/exclusion (I/E) criteria for each trial were applied to each NH data source to create cohorts of NH patients meeting the same criteria as required by the trials. Average 48-week change in 6MWD was then compared between patients in trial placebo arms and patients in these harmonized NH cohorts.

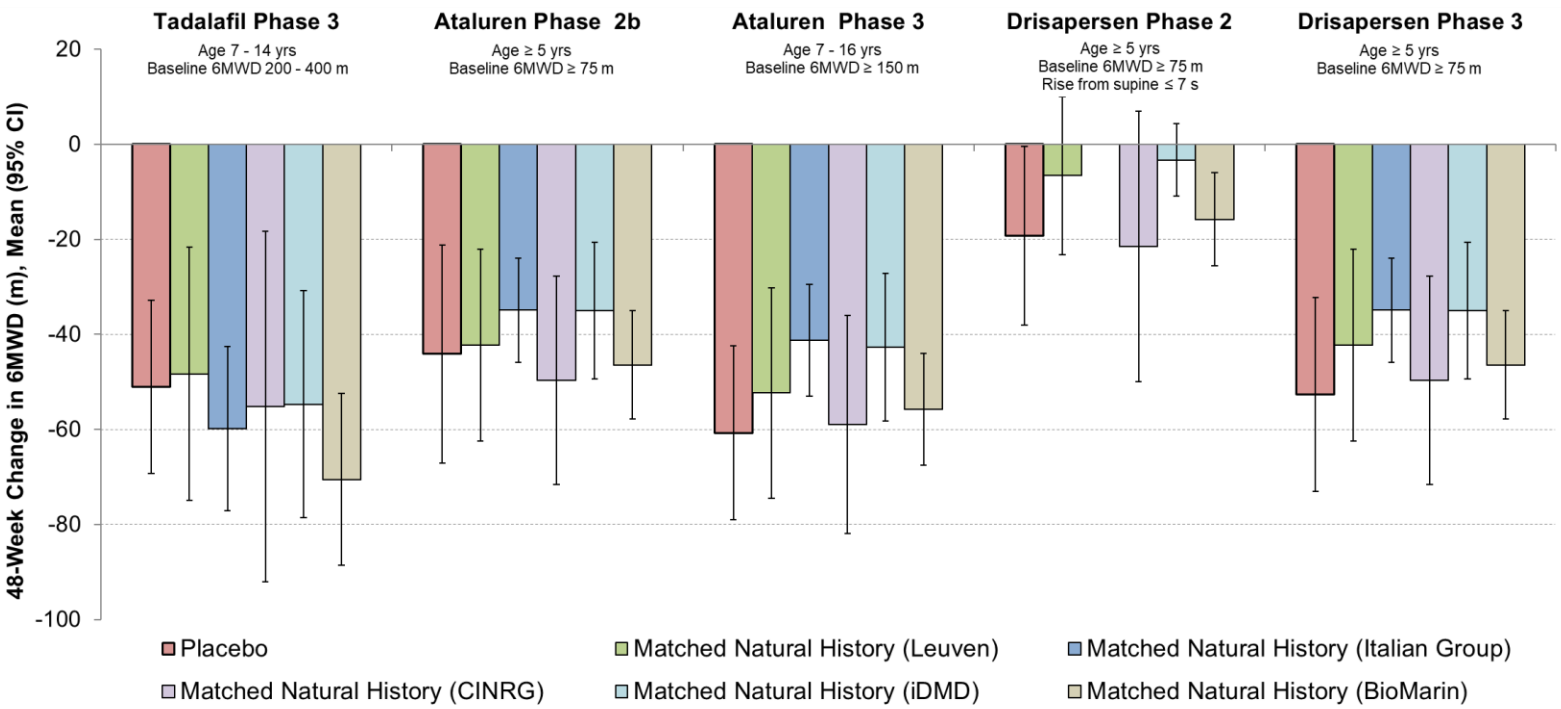
Results: Differences in average 48-week change in 6MWD between trial placebo arms and harmonized NH cohorts ranged from -19.4 meters (indicating smaller declines in NH than in trial placebo arms) to 19.5 meters (indicating larger declines in NH than in trial placebo arms). Average declines in 6MWD in NH cohorts were smaller than in trials in 17 comparisons, and larger than in trials in 7 comparisons. None of the differences observed between trial placebo arms and NH cohorts were statistically significant.

Conclusion: These results indicate strong consistency between average 48-week changes in 6MWD in trial placebo arms and NH cohorts that were subject to equivalent inclusion/exclusion criteria. This lack of evidence of systematic bias is encouraging for the potential use of NH controls in DMD trials. Ongoing cTAP research is further evaluating consistency between NH and trials after adjusting for multiple baseline prognostic factors that may differ between NH and trials, and also assessing the consistency of other functional outcomes.

Table 1. 48-Week Change in 6MWD Comparing Natural History Cohorts with Clinical Trial Placebo Arms

Placebo Arm	Inclusion/Exclusion Criteria			48-Week Change in 6MWD (m) Mean ± SE					
	Age (yrs)	6MWD (m)	Rise from supine (s)	Placebo	Leuven	Italian Group	CINRG	iDMD	BioMarin
A. Tadalafil Phase 3	7-14	200-400	-	-51.0 ± 9.3	-48.3 ± 13.6	-59.8 ± 8.8	-55.2 ± 18.8	-54.7 ± 12.2	-70.5 ± 9.2
B. Ataluren Phase 2b	≥5	≥75	-	-44.1 ± 11.7	-42.2 ± 10.3	-34.9 ± 5.6	-49.7 ± 11.2	-35.0 ± 7.3	-46.4 ± 5.8
C. Ataluren Phase 3	7-16	≥150	-	-60.7 ± 9.3	-52.3 ± 11.3	-41.3 ± 6.0	-59.0 ± 11.7	-42.7 ± 7.9	-55.8 ± 6.0
D. Drisapersen Phase 2	≥5	≥75	≤7	-19.3 ± 9.6	-6.6 ± 8.5		-21.5 ± 14.5	-3.3 ± 3.9	-15.8 ± 5.0
E. Drisapersen Phase 3	≥5	≥75	-	-52.6 ± 10.4	-42.2 ± 10.3	-34.9 ± 5.6	-49.7 ± 11.2	-35.0 ± 7.3	-46.4 ± 5.8

Figure 1. 48-Week Change in 6MWD Comparing Natural History Cohorts with Clinical Trial Placebo Arms


Tadalafil Phase 3
Age 7 - 14 yrs
Baseline 6MWD 200 - 400 m
Ataluren Phase 2b
Age ≥ 5 yrs
Baseline 6MWD ≥ 75 m
Ataluren Phase 3
Age 7 - 16 yrs
Baseline 6MWD ≥ 150 m
Drisapersen Phase 2
Age ≥ 5 yrs
Baseline 6MWD ≥ 75 m
Rise from supine ≤ 7 s
Drisapersen Phase 3
Age ≥ 5 yrs
Baseline 6MWD ≥ 75 m
48-Week Change in 6MWD (m), Mean (95% CI)
20
0
-20
-40
-60
-80
-100
Placebo
Matched Natural History (Leuven)
Matched Natural History (Italian Group)
Matched Natural History (CINRG)
Matched Natural History (iDMD)
Matched Natural History (BioMarin)