Poster # P.65

Consistency of Changes in %-Predicted Forced Vital Capacity Between Real-World Data and Trial Placebo Arms in Ambulatory Duchenne Muscular Dystrophy

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Introduction

- Use of real-world and natural history data (RWD/NHD) as external controls for pulmonary outcomes is of interest for drug development in ambulatory Duchenne muscular dystrophy (DMD)
- However, concerns about bias due to differences in patient characteristics and clinical protocols across RWD/NHD and clinical trial settings can be raised for pulmonary outcomes such as forced vital capacity - % predicted (FVC%p)
- FVC%p is a commonly assessed secondary or exploratory endpoint in trials in ambulatory DMD
- While previous research has demonstrated consistency in changes in ambulatory outcomes[1,2] between RWD/NHD and clinical trial placebo arms, similar assessments of consistency of change have not been done for FVC%p
- In this study, we assess suitability of external controls for change in FVC%p in the setting of ambulatory DMD

Objective

- To assess differences in 48-week changes in FVC%p among between RWD/NHD sources and clinical trial placebo arms in ambulatory boys with DMD

Methods

Data sources

Table 1: Data sources

RWD/NHD	Description (data collection period)
Leuven	Curated real-world data from routine clinical practice at the pediatric neurology clinic at the Leuven Neuromuscular Reference Center in Leuven, Belgium (2001-2016)
PRO-DMD-01	A prospective, natural history study of DMD conducted in 16 tertiary care centers worldwide (2012-2016)
North Star UK	Natural history data from a registry of 20+ clinical centers in the North Star Clinical Network in the United Kingdom (2005-2016)
CCHMC	Curated clinical data from electronic health records of boys receiving care at the Comprehensive Neuromuscular Center at Cincinnati Children's Hospital Medical Center (CCHMC) (2004-2016)
Trial placebo arms	**Description (data collection period)**
Tadalafil DMD trial	Placebo arm data from Eli Lilly's phase 3 trial of tadalafil in DMD (2013-2015)
DEMAND III	Placebo arm data from BioMarin's phase 3 trial of drisapersen in DMD (2011-2013)
Drisapersen 117	Placebo arm data from BioMarin's phase 2 trial of drisapersen in DMD (2010-2012)

Note: CCHMC data was only used in sensitivity analyses

Outcome

- FVC is a global assessment of lung volume, reflecting function of inspiratory and expiratory muscles[3]
- To account for increases in FVC with growth, FVC%p - which reflects patients' pulmonary function relative to predicted FVC values calculated based on height, race, age and sex – was used
- Predicted FVC values were based on established reference equations (NHANES III or GLI).[4,5]
- This analysis focused on 48-week changes in FVC%p (ΔFVC%p)

Sample selection

- All pairs of patient visits (i.e., follow-up intervals) meeting the following inclusion criteria were included in the analysis:
  - Age 5 years and older at baseline visit
  - On glucocorticosteroid treatment at baseline visit
  - FVC%p> 50% at baseline visit
  - Follow-up FVC%p available approximately ~48-weeks after baseline (9-13 months, inclusive)
- Patients with missing data on FVC%p or baseline covariates used in adjusted models were excluded
- Patients in the RWD/NHD sources could have multiple ~48-week intervals meeting these criteria; all eligible intervals that did not overlap in terms of follow-up time were included in the analysis

Statistical analysis

- Mean ΔFVC%p was compared between pooled RWD/NHD sources and the pooled placebo trial arms, with and without statistical adjustment using multivariable linear regression models
- Three models were fit, adjusting for different sets of covariates:
  - Base model: Unadjusted
  - Intermediate model: Adjusted for age, steroid type, baseline FVC%p,
  - Full model: Adjusted for age, steroid type, baseline FVC%p, height, weight, body mass index, North Star Ambulatory Assessment total score, and velocities for the rise from floor and 10-meter walk/run tests
- Generalized estimating equation models were used to account for the use of multiple ~48-week intervals for patients in the RWD/NHD sources
- In a sensitivity analysis, the analysis was repeated replacing the North Star UK data with the data from CCHMC, as these two sources differed with respect to availability of adjustment factors.
  - In this sensitivity analysis, adjustment in the full model was made for age, baseline FVC-% predicted, steroid type, height, weight, body mass index, North Star Ambulatory Assessment total score, and 4-stair climb velocity

Results

Baseline characteristics

- The primary analysis included 409 intervals (263 patients) from the pooled RWD/NHD sources and 161 intervals (161 patients) from the pooled placebo arms
- Baseline patient characteristics were comparable between pooled RWD/NHD and trial placebo arms, but patients in RWD/NHD were slightly older and had lower baseline FVC%p on average (**Table 2**)

Table 2: Baseline characteristics

	Pooled RWD/NHD N = 409	Pooled trial placebo N = 161
Number of patients	263	161
Age (years)	9.50 ± 2.62	8.81 ± 1.93
Steroid type		
Prednisone	184 (45%)	88 (55%)
Deflazacort	225 (55%)	73 (45%)
FVC%p	97.2 ± 18.4	103.6 ± 23.1
FVC (liters)	1.65 ± 0.52	1.64 ± 0.46
NSAA total score	23.12 ± 7.33	22.45 ± 6.61
10-meter walk/run (10MWR) velocity (m/s)	1.84 ± 0.59	1.71 ± 0.50
Rise from supine velocity (1/s)	0.19 ± 0.12	0.17 ± 0.18
Height (cm)	124.33 ± 11.40	123.64 ± 9.68
Weight (kg)	30.91 ± 10.56	29.27 ± 9.40

Notes: N is the number of non-overlapping intervals. Numbers in table reflect Mean ± SD or N (%).

Comparing ΔFVCp between RWD/NHD sources and placebo arms

- ΔFVC%p in the RWD/NHD reflected smaller mean declines (-0.4 vs -3.4 percentage points) and were less variable (standard deviation of 17.5 vs 23.0 percentage points) than in the placebo arms (**Figures 1A and 1B**)
- Difference in mean ΔFVC%p in RWD/NHD relative to placebo arms was 2.9 percentage points (95% confidence interval [CI]: -1.0%, 6.7%; p=0.14) in unadjusted analyses. After adjusting for baseline characteristics, the difference in mean ΔFVC%p decreased to -0.1 percentage points (95% CI: -3.6, 3.5; p=0.97) (**Figure 2**)
  - Some differences were observed across individual data sources after adjustment for baseline characteristics, with mean ΔFVC%p differing in North Star UK compared to other RWD/NHD sources (**Figure 3**)
- In sensitivity analyses, mean ΔFVC%p between RWD/NHD and placebo arms were similarly not significant before (-3.3 percentage points (95% CI: -6.9, 0.3; p=0.07)], or after adjustment for all patient characteristics [-2.1 percentage points (95% CI: -5.8, 1.5; p=0.26)]

Figure 1. Mean ΔFVC%p in a) pooled and b) individual RWD/NHD sources and placebo arms

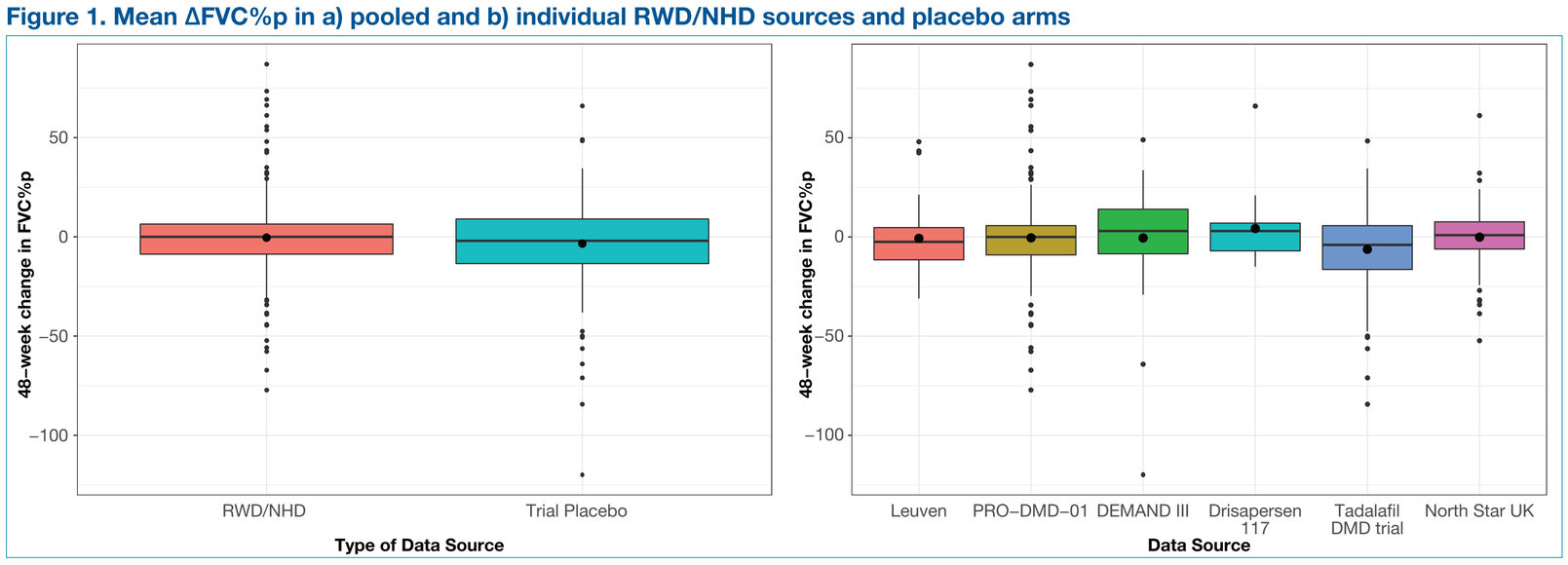
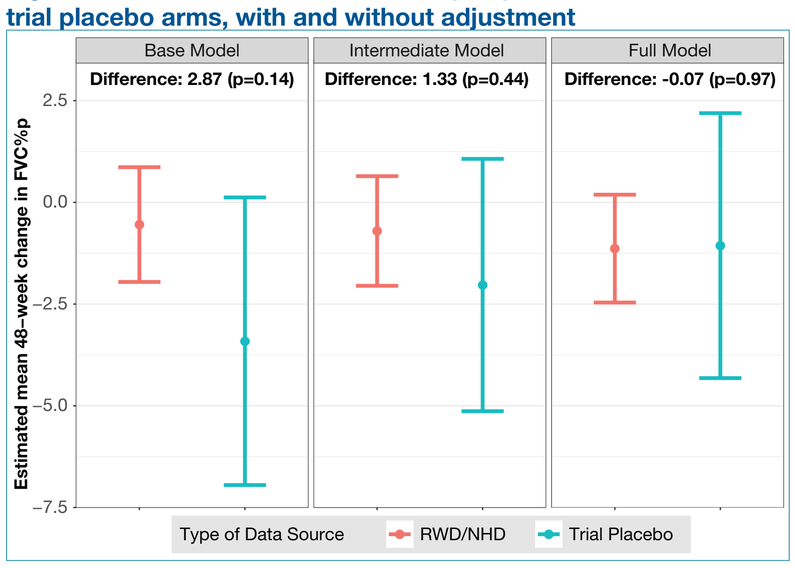
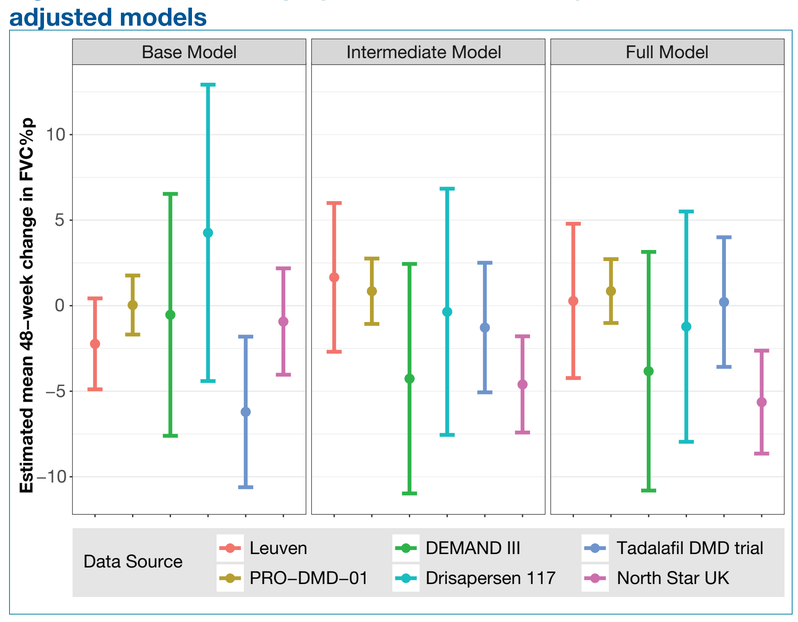


Figure 2. Differences in mean ΔFVC%p in pooled RWD/NHD and trial placebo arms, with and without adjustment



Note: Base model is unadjusted. Intermediate model adjusts for age, baseline FVC%p, and steroid type. Full model adjusts for age, baseline FVC%p, steroid type. height, weight, body mass index, NSAA total score, 10MWR velocity, and rise from supine velocity.

Figure 3. Mean ΔFVC%p by data source in unadjusted and adjusted models



Limitations

- This study focused on 48-week changes in FVC%p in ambulatory boys who had FVC%p of 50% or higher at baseline. Consistency of change in FVC%p in settings in which greater pulmonary declines would be expected will need to be evaluated separately (e.g., in ambulatory boys who are older and/or already have <50% FVC%p at baseline; over time frames longer than 48 weeks; and in non-ambulatory boys)
- Prognostic factors considered for adjustment were limited to those available across data sources. Other unavailable predictors (e.g., other markers of pulmonary function) may add more prognostic value and allow for further adjustment of baseline differences between data sources
- While changes in FVC%p between pooled placebo and pooled RWD/NHD sources were similar, small differences were noted across individual sources, even after adjustment for baseline characteristics. This may be due to differences across data sources in unadjusted patient characteristics, reference equations for predicted FVC, or factors related to the conduct or availability of FVC data in ambulatory boys in RWD/NHD settings. Standardization of these factors across sources may further improve consistency.

Conclusions

- Mean 48-week changes in FVC%p in ambulatory boys was consistent between trial placebo arms and RWD/NHD sources in this analysis of ambulatory boys. These findings are encouraging for use of external controls for FVC%p outcomes in this population.
- Additional research is needed to assess consistency of FVC%p over longer-time frames, and among older and non-ambulatory boys with lower levels of pulmonary function.

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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cTAP COLLABORATIVE TRAJECTORY ANALYSIS PROJECT

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