M161

Delayed Pulmonary Progression in Golodirsen-Treated Patients With Duchenne Muscular Dystrophy vs Mutation-Matched External Controls

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Introduction

- Duchenne muscular dystrophy (DMD) is a rare, fatal, genetic disease caused by a lack of dystrophin protein, which leads to progressive and irreversible muscle damage from birth[1]
- Pulmonary decline in DMD leads to the irreversible disease milestone of pulmonary insufficiency, which affects patients' quality of life, increasing the risk of hospitalization, morbidity, and mortality[2–5]
- Studies have established a linear decline in pulmonary function of ~5 percentage points between 10 and 18 years[6,7]
- Golodirsen is FDA approved for the treatment of DMD in boys with mutations amenable to exon 53 skipping and has been shown in Study 4053-101 (NCT02310906) to have functional benefits in a declining population of patients with DMD vs mutation-matched external controls (ECs)[6,8]

Objective

To compare longitudinal trajectories of percent predicted forced vital capacity (FVC%p) and projected time to cough-assist and nighttime ventilation in patients with DMD receiving golodirsen vs mutation-matched EC patients

Methods

Data sources

- Golodirsen-treated patients were from Study 4053-101 who continued into the open-label 3-year Study 4045-302 (NCT03532542) and were required to have at least 2 FVC%p assessments at age ≥10 years during the study period
- EC patients were from the Cooperative International Neuromuscular Research Group (CINRG) (NCT00468832),[9] PRO-DMD-01 (NCT01753804),[10] and Study 4658-301 (NCT02255552),[11] and were required to have confirmed mutations amenable to exon 53 skipping and at least 1 FVC%p assessment between the ages of 10 and 12 years followed by at least 1 additional valid FVC%p assessment

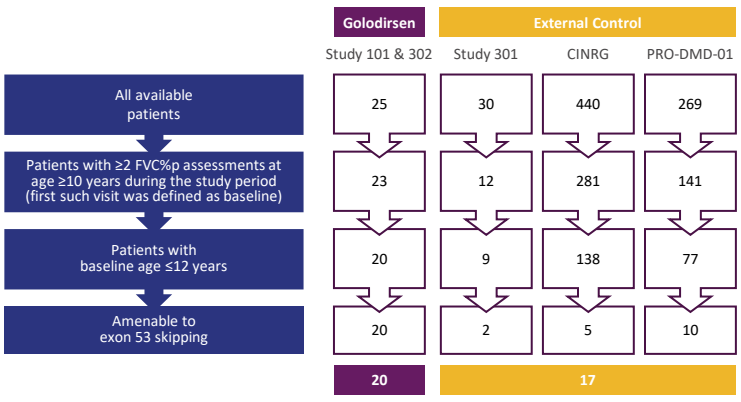
Statistical analyses

- A mixed-effects model for repeated measures was used to evaluate the impact of golodirsen on the decline in FVC%p
- The model was fit with FVC%p as the response variable and with treatment group (golodirsen vs EC), age (at visit), and the interaction between treatment group and age as the fixed effects and the patient-level random effects
- Models with and without adjusting for baseline FVC%p and age were estimated, and measures of model fit (ie, the Akaike information criterion [AIC] and Bayesian information criterion [BIC]) were assessed
- Average annual rate of FVC%p decline was predicted using a linear extrapolation of the model-estimated decline in FVC%p from the average FVC%p values observed in patients between ages 10 and 18 years
- Time to cough-assist (recommended FVC%p ≤60) and nighttime ventilation (recommended FVC%p ≤50) was predicted using a linear extrapolation of the model-estimated decline in FVC%p (from average FVC%p readings observed)

Results

- A total of 37 patients met the inclusion criteria (**F1**)
- At baseline, golodirsen-treated (n=20) and mutation-matched EC (n=17) patients were well-balanced for age and FVC%p
- Golodirsen-treated patients had a longer average follow-up duration (mean [SD], 3.6 [1.8] years) than the mutation-matched EC patients (2.4 [1.3] years) (**T1**)

F1 *Pulmonary Analysis Population Selection Flowchart*



CINRG=Cooperative International Neuromuscular Research Group; FVC%p=percent predicted forced vital capacity.

T1 *Summary of Patient Characteristics*

	Total N=37	Golodirsen N=20 (A)	EC N=17 (B)	Mean Difference (B) – (A)	*P*-value[a]
Baseline age, years					
Mean ± SD	10.4 ± 0.4	10.3 ± 0.3	10.4 ± 0.4	0.1 ± 0.1	0.34
Median	10.3	10.3	10.3		
Range	(10.0, 11.5)	(10.0, 11.2)	(10.0, 11.5)		
Missing, n (%)	0/37 (0.0)	0/20 (0.0)	0/17 (0.0)		
Baseline FVC					
Mean ± SD	1.7 ± 0.4	1.7 ± 0.3	1.8 ± 0.5	0.1 ± 0.1	0.45
Median	1.7	1.7	1.8		
Range	(0.9, 3.2)	(0.9, 2.8)	(1.3, 3.2)		
Missing, n (%)	0/37 (0.0)	0/20 (0.0)	0/17 (0.0)		
Baseline FVC%p					
Mean ± SD	89.5 ± 17.9	89.5 ± 15.3	89.4 ± 21.0	0.0 ± 6.2	1.00
Median	88.0	89.2	87.0		
Range	(51.4, 136.0)	(51.4, 132.2)	(57.0, 136.0)		
Missing, n (%)	0/37 (0.0)	0/20 (0.0)	0/17 (0.0)		
Length of follow-up, years					
Mean ± SD	3.1 ± 1.7	3.6 ± 1.8	2.4 ± 1.3	-1.2 ± 0.5	<0.05
Median	2.4	3.2	2.1		
Range	(0.9, 7.1)	(0.9, 7.1)	(0.9, 6.0)		
Missing, n (%)	0/37 (0.0)	0/20 (0.0)	0/17 (0.0)		

[a]*P*-values from 2 sample t-tests comparing golodirsen-treated and EC groups are reported.
EC=external control; FVC=forced vital capacity; FVC%p=percent predicted forced vital capacity.

Golodirsen attenuates the rate of FVC%p decline:

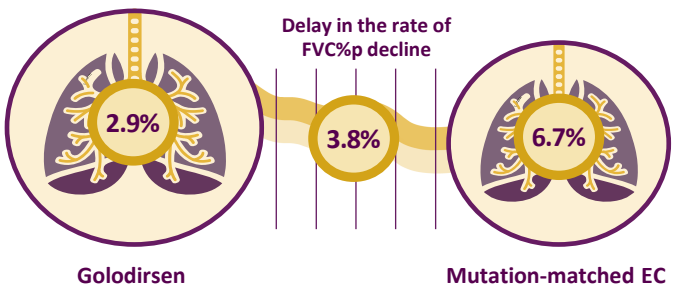
- Results from the adjusted model for baseline age and baseline FVC%p indicated an attenuation of 3.8 percentage points in the annual rate of FVC%p decline for golodirsen-treated patients vs mutation-matched EC patients (2.9% vs 6.7%, respectively; *P*<0.01) (**F2**)
  - A previously published analysis of eteplirsen vs mutation-matched EC patients demonstrated similar rates of FVC%p decline[12]
- The model adjusted for baseline age and FVC%p had the best fit of the 3 models estimated based on lower values of both the AIC and the BIC (**T2**)

T2 *Model-Based Slope Estimates of Decline in FVC%p*

	MMRM		
Characteristic	**Unadjusted**	**Adjusted for Baseline Age**	**Adjusted for Baseline Age and FVC%p**
Constant	155.87*** (13.69)	−7.34 (90.08)	**19.38 (39.08)**
Age	−6.07*** (1.11)	−6.27*** (1.12)	**−6.67*** (1.06)**
Golodirsen	−35.78** (16.16)	−35.96** (16.07)	**−41.14*** (14.44)**
Baseline age	–	15.85* (8.65)	**5.86 (3.88)**
Baseline FVC%p	–	–	**0.92*** (0.08)**
Age × golodirsen	3.22** (1.28)	3.39*** (1.28)	**3.77*** (1.22)**
N observations	244	244	**244**
N patients	37	37	**37**
AIC	1956.4	1949.0	**1894.9**
BIC	1977.4	1973.5	**1922.9**

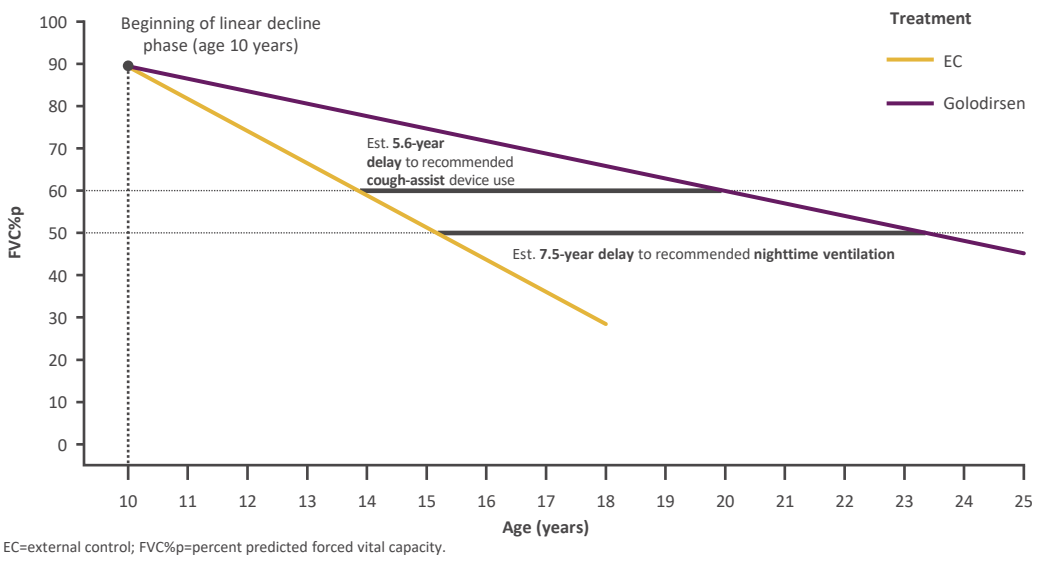
*P<0.1. **P<0.05. ***P<0.01. Data are mean (SE) unless otherwise noted.
AIC=Akaike information criterion; BIC=Bayesian information criterion; FVC%p=percent predicted forced vital capacity; MMRM=mixed-effects model for repeated measures.

F2 *Attenuation of FVC%p Decline in Golodirsen-Treated vs EC Patients*



EC=external control; FVC%p=percent predicted forced vital capacity.

F3 *Model-Estimated Time to Recommended Cough-Assist*



EC=external control; FVC%p=percent predicted forced vital capacity.

Golodirsen delays the time in which patients reach pulmonary milestones (F3):

5.6 The **estimated delay** in time to **reach cough-assist** for golodirsen-treated patients vs mutation-matched EC patients was **5.6 (~14 vs 19) years**

7.5 The **estimated delay** in time to **nighttime ventilation** for golodirsen-treated patients vs mutation-matched EC patients was **7.5 (~16 vs 23) years**

Key Finding

Golodirsen treatment was associated with significant attenuation of pulmonary decline based on FVC%p

Conclusions

This analysis of clinical trial data for golodirsen-treated and mutation-matched EC patients demonstrated that golodirsen was associated with significant attenuation in the rate of decline in FVC%p (2.9% vs 6.7%; *P*<0.01)

- A previously published analysis of eteplirsen vs mutation-matched EC patients demonstrated similar rates of FVC%p decline[12]

Data suggest clinically meaningful delays in reaching the need for recommended cough-assist and nighttime ventilation, implying clinically meaningful delays of 5 years or more in reaching pulmonary milestones

These data provide the longest follow-up of pulmonary benefit in a declining DMD population treated with golodirsen vs EC patients (**see poster M162 for more details**)

Acknowledgments & Disclosures

Acknowledgments
The authors and Sarepta Therapeutics, Inc., thank the patients and their families. Study 3045-302 (NCT02500381) was funded by Sarepta Therapeutics, Inc. Editorial support was provided by Paraskevi Briassouli, PhD, of Eloquent Scientific Solutions and was funded by Sarepta Therapeutics, Inc.

Disclosures
JI: Employee of Sarepta Therapeutics, Inc., and may own stock/options in the company. **ET**, **YL**, **FW**, **ND**: Employees of Analysis Group, Inc., which received payment from Sarepta Therapeutics, Inc., for participation in this research. **LS**, **MG**: Received speaker honoraria from and have research collaborations with Sarepta Therapeutics, Inc. **AMS**: Has research collaborations with Sarepta Therapeutics, Inc. **VS**: Participated in advisory boards, received speaker honoraria, and has a research collaboration with Sarepta Therapeutics, Inc. **EM**: Received consultant fees from Sarepta Therapeutics, Inc. **FM**: Received consultant fees and speaker honoraria from Sarepta Therapeutics, Inc. Previously presented at the 28th International Annual Congress of the World Muscle Society, October 3–7, 2023, Charleston, SC; AMCP Nexus, October 16-19, 2023, Orlando, FL.

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Presented at the 2024 MDA Clinical and Scientific Conference;

March 3–6, 2024; Orlando FL