P149

Presented at the 28th International Annual Congress of the World Muscle Society; October 3–7, 2023; Charleston, SC

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

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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 Duchenne muscular dystrophy (DMD) receiving golodirsen vs mutation-matched external control (EC) patients

Key Findings

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

BACKGROUND

- 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 ECs[6,8]

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)

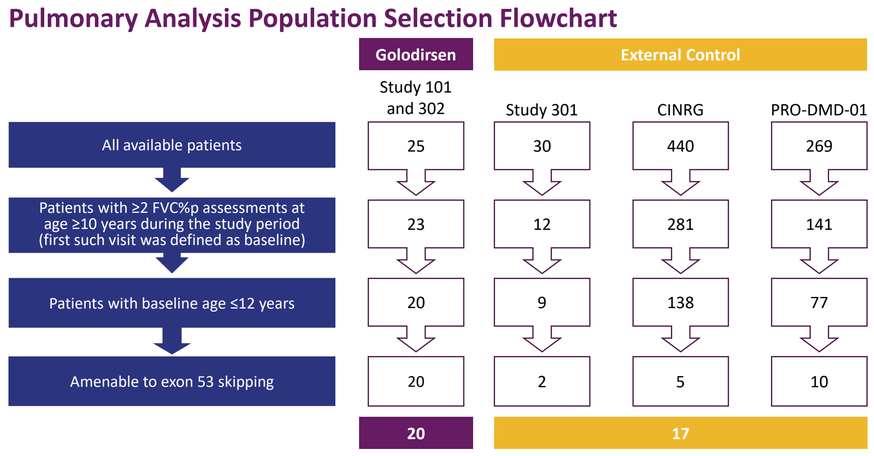
CONCLUSIONS

- 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 P147 for more details)**

RESULTS

- A total of 37 patients met the inclusion criteria
- At baseline, golodirsen-treated (n=20) and mutation-matched EC patients (n=17) 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)

Pulmonary Analysis Population Selection Flowchart



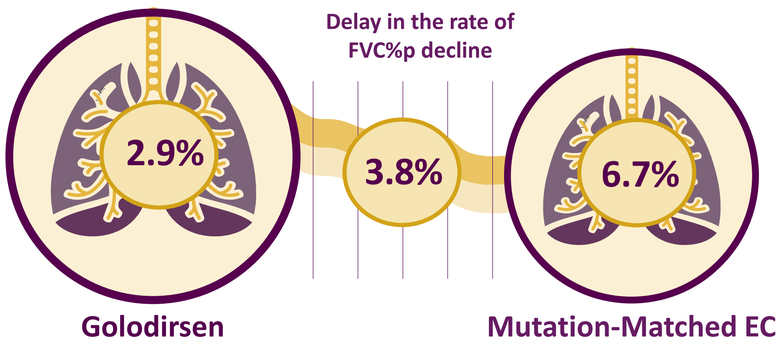
CINRG=Cooperative International Neuromuscular Research Group; FVC%p=percent predicted forced vital capacity.

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 Rate of FVC%p Decline vs EC Patients



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

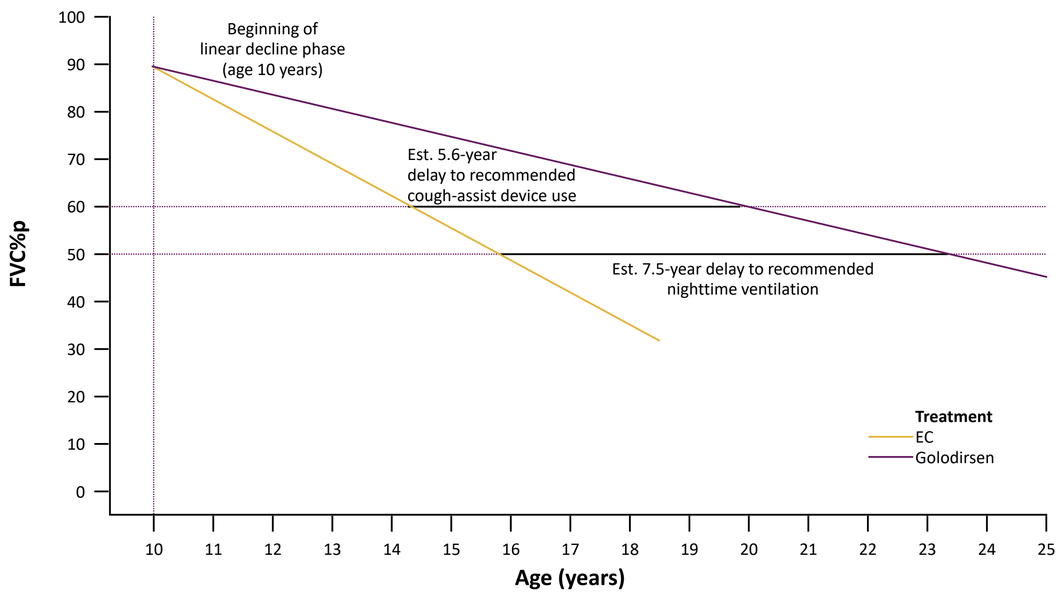
- Results from the adjusted model for baseline age and baseline FVC%p indicated an attenuation of 3.8 percentage points in the annual rate of FVC%p decline for golodirsen-treated patients vs mutation-matched EC patients (2.9% vs 6.7%, respectively; $P<0.01$)
  - A previously published analysis of eteplirsen vs mutation-matched EC patients demonstrated similar rates of FVC%p decline
- 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

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***	-7.34	**19.38**
	(13.69)	(90.08)	**(39.08)**
Age	-6.07***	-6.27***	**-6.67*** **
	(1.11)	(1.12)	**(1.06)**
Golodirsen	-35.78**	-35.96**	**-41.14*** **
	(16.16)	(16.07)	**(14.44)**
Baseline age	-	15.85*	**5.86**
		(8.65)	**(3.88)**
Baseline FVC%p	-	-	**0.92*** **
			(0.08)
Age × golodirsen	3.22**	3.39***	**3.77*** **
	(1.28)	(1.28)	**(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.

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:

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

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ACKNOWLEDGMENTS & DISCLOSURES

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.