DELAYS IN PROGRESSION OF DUCHENNE MUSCULAR DYSTROPHY WITH ETEPLIRSEN: ATTENUATION OF PULMONARY DECLINE AND PROJECTED FREEDOM FROM CONTINUOUS VENTILATION

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Joel Iff,[1] Charles Gerrits,[1] Erica Birk,[2] Edward Tuttle,[2] Yeya Zheng,[2]Erik Henricson,[3] Craig McDonald,[3] and the CINRG DNHS Investigators

Sarepta Therapeutics, Inc., Cambridge, MA; [2]Analysis Group, Menlo Park, CA; [3]UC Davis Medical Center, Sacramento, CA 25th International Annual Congress of the World Muscle Society, September 30th-October 4th 2020

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare, fatal genetic disorder caused by a lack of dystrophin protein which leads to progressive and irreversible muscle damage from birth.[1] Loss of ambulation occurs at approximately 12 years.[2, 3] The median age of death with standard of care is 26–28 years,[4, 5] with the major causes of death being respiratory insufficiency and cardiomyopathy.[1, 4] Studies have established a linear decline in pulmonary function between 10-18 years irrespective of ambulatory status.[5]

Eteplirsen is indicated to treat DMD patients with genetic mutations amenable to exon 51 skipping.[6] Previous analyses have shown that eteplirsen is associated with significant and clinically meaningful delays in time to loss of ambulation[7] and significant attenuation of pulmonary decline,[8] and studies indicate that such delays are associated with delays in other disease milestones.[9-11]

OBJECTIVE

To compare temporal patterns of forced vital capacity % predicted (FVC%p) and projected time to continuous ventilation in DMD patients receiving eteplirsen versus standard of care, via a post-hoc pooled analysis.

METHODS

DATA SOURCES

DMD patients with exon 51 skipping mutations treated with eteplirsen or standard of care were considered for the study

Patients were included if they had glucocorticoid steroid use by visit, at least 1 FVC% predicted value post baseline, and individual observations between ages 10-18

Eteplirsen-treated patients were from study 204 (open label 2-year study, primarily non-ambulatory patients)[8], n=20; and study 301 (ongoing open-label study, primarily ambulatory patients)[12], n=52

Standard of care (SoC) patients were drawn from the Cooperative International Neuromuscular Research Group (CINRG) database (n=20)

Control patients from DEMAND III (48 week randomised placebo-controlled trial, ambulant patients)[13], n=21, were included as a scenario analysis

STATISTICAL ANALYSES

A mixed effects model with repeated measures (MMRM) was used to evaluate the impact of eteplirsen on the decline in FVC%p

The model fit FVC%p as the response variable, treatment group (eteplirsen vs control), age (at visit), and the interaction between treatment group and age as the fixed effects, and patient as random effect

Time to continuous diurnal ventilation (FVC%p <30%) was predicted using a linear extrapolation of the model estimated decline in FVC%p from the average FVC%p readings observed in patients between 10-10.5 years

Delay in time to continuous ventilation was estimated as the difference in years to FVC%p =30% between treatment and control cohorts based on estimated slope from the MMRM model

RESULTS

SAMPLE CHARACTERISTICS

The analysis included 72 eterplirsen-treated patients and 20 standard of care (SOC) patients.

Trial 204 included primarily non-ambulatory patients while trial 301 included only ambulatory patients; CINRG included patients providing data at both phases.

Baseline FVC% was lower in trial 204 because patients were older and had more advanced disease.

	204 Trial	301 Trial*	CINRG	DEMAND
Number of patients	20	52	20	21
Number of obs	117	250	88	86
Baseline Age (mean (SD))	**13.04** (2.28)	**11.04** (1.44)	**11.78** (2.24)	**10.9** (1.34)
Baseline FVC% predicted (mean (SD))**	**65.94** (16.60)	**78.15** (14.40)	**79.60** (13.30)	**95.95** (22.80)

BASE CASE ANALYSIS

Eteplirsen-treated patients experienced a **statistically significant attenuation in the FVC%p decline** compared to SoC patients (annual rate of decline of 3.47% vs. 5.95%, respectively; P<0.01).

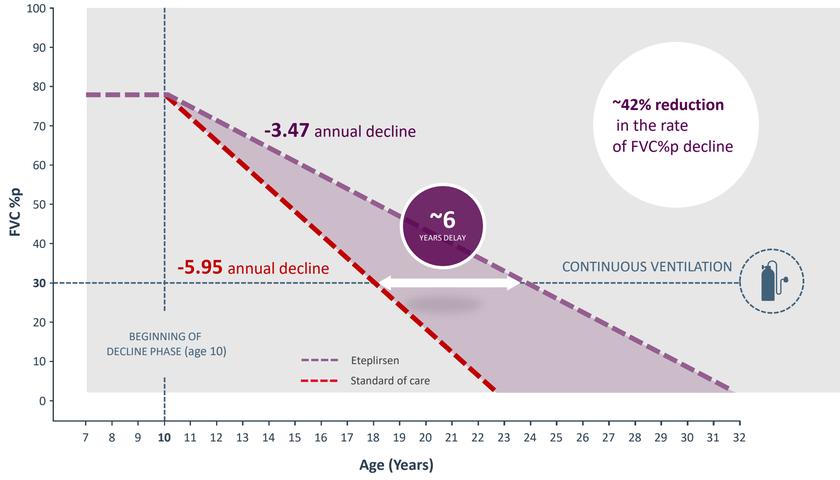
This represents a **42% reduction** in the rate of FVC%p decline for eteplirsen-treated patients versus standard of care.

The estimated rate of pulmonary decline was similar between ambulatory patients (trial 301) non-ambulatory patients (trial 204)

	301 vs CINRG	204 vs CINRG	301 & 204 vs CINRG
Model-based slope estimates of decline in FVC%p*	(Pooled regressions treated vs. controls)		
Epteplirsen-treated	-3.25%	-3.54%	**-3.47%**
Control	-5.88%	-6.05%	**-5.95%**
Average FVC%p value at ~10 years old**	**78.20%**	**75.04%**	**77.58%**
Delay (years) in time to FVC%p =30%* **	**7**	**5**	**6**

*Estimated slopes reflect estimates generated from the MMRM model using a pooled sample of the specified treatment and control cohorts. **Annual declines are assumed to start at 10 years old from the average FVC%p readings observed between 10-10.5 years old for patients who are treated with glucocorticoid steroids in the specified trials ***Delay in time to continuous ventilation is estimated as the difference in years to FVC%p =30% between treatment and control cohorts based on estimated slope

Assuming an average starting FVC%p of ~77.58% at age 10, a decline in FVC%p for eteplirsen corresponds to **a delay of ~6 years** in time to needing continuous ventilation vs. SoC patients



SCENARIO ANALYSIS

Results are robust to the inclusion of control patients in DEMAND III. When pooling data from DEMAND III in the regression, Eteplirsen-treated patients experienced an annual rate of decline of 3.48% vs. 6.07% for SoC patients; P<0.01.

Assuming an average starting FVC%p of ~83.40% at age 10 (reflecting the inclusion of DEMAND III patients), a decline in FVC%p for eteplirsen corresponds to a delay of ~7 years in time to needing continuous ventilation vs. SoC patients

CONCLUSION

Data indicate that eteplirsen is associated with significant attenuation of pulmonary decline based on FVC%p and clinically meaningful projected time to continuous ventilation

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