Combined Prospective and Retrospective Analysis of Duchenne Muscular Dystrophy Patient Outcomes Following 7 Years of Eteplirsen Treatment Compared With Natural History External Control Cohorts

Olga Mitelman,[1] Hoda Z. Abdel-Hamid,[2] Barry J. Byrne,[3] Anne M. Connolly,[4] Peter Heydemann,[5] Crystal Proud,[6] Perry B. Shieh,[7] Kathryn R. Wagner,[8] Ashish Dugar,[1] Sourav Santra,[1] James Signorovitch,[9] Katherine Tsai,[1] Jerry R. Mendell[4]

[1]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [2]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA; [3]University of Florida, Gainesville, FL, USA; [4]Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH, USA; [5]Rush University Medical Center, Chicago, IL, USA; [6]Children's Hospital of The King's Daughters, Norfolk, VA, USA; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [8]Kennedy Krieger Institute, Johns Hopkins School of Medicine, Baltimore, MD, USA; [9]Analysis Group, Inc., Boston, MA, USA

BACKGROUND

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin gene (*DMD*)[1,2]
- Eteplirsen binds to exon 51 of dystrophin pre-mRNA to allow skipping of exon 51, restoring the mRNA reading frame and allowing translation of a truncated dystrophin protein[1,3,4]
- A positive correlation has been observed between exon skipping and dystrophin protein production[5]
- Clinical trials of eteplirsen have confirmed the mechanism of action and demonstrated a significant increase in dystrophin protein accumulation, and indicate that eteplirsen may slow muscle deterioration, prolong ambulation, and preserve pulmonary function in patients with DMD with eligible genetic mutations[3-7]
- The pivotal study of eteplirsen was a 24-week, double-blind, placebo-controlled trial (Study 201; NCT01396239) with a 4-year, open-label extension (Study 202; NCT01540409)[3,4]

OBJECTIVE

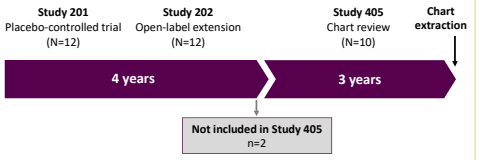
- To describe long-term treatment patterns and clinical outcomes in patients from Study 201/202 who participated in Study 4658-405 (Study 405)

METHODS

Study Design

- Study 405 was a retrospective chart review of participants who completed Study 201/202 (**Figure 1**)
- Study 201 inclusion criteria were:
  - Males >7 to ≤13 years old with a *DMD* mutation amenable to exon 51 skipping
  - Baseline 6-minute walking distance (6MWD) >180 to ≤440 m
  - Stable dose of oral glucocorticoids ≥24 weeks before study entry

Figure 1. Study Design



Study 405 Assessments and Statistical Analyses

- Intent-to-treat analysis was conducted, incorporating all available follow-up
  - Follow-up from all patients who received eteplirsen in Study 201
  - Time to milestone events was measured from eteplirsen initiation (at baseline or following initial placebo in Study 201)
  - Patients in Study 201/202 who did not participate in Study 405 were included but censored at the end of Study 202
- Loss of ambulation (LOA) was defined as 6MWD=0 m in Study 201/202 or 100% wheelchair use in chart review Study 405
  - Comparison cohorts for standard of care (SOC) were exon 51 skipping–amenable patients from the Fondazione Telethon NMD Italian Network Registry[8] (n=8), the Leuven NMRC Registry[9] (n=3), and the placebo arm of the DEMAND III trial[10] (n=60)
- Forced vital capacity (FVC) measurements were collected from charts in Study 405, and percent predicted FVC (FVC%p) was calculated using the Hankinson formula (heights)[11]
  - FVC%p post eteplirsen initiation was analyzed using segmented linear mixed models with repeated measures (MMRM) with age as a covariate
  - Comparison cohort was exon 51 skipping–amenable untreated male patients from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS)
  - Comparisons were conducted using MMRM (response variable: FVC%p; fixed effects: treatment group, age at visit, and treatment group by age interaction; random effect: patient)

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Corresponding author: Olga Mitelman; email: omitelman@sarepta.com

RESULTS

Patients

- Of 12 patients enrolled in Study 201/202, 10 underwent chart review in Study 405
- Study 405 participants had comparable demographics and disease characteristics with the 2 patients whose charts were not available, with the exception of timed rise from floor
  - Median age: 9.5 in Study 405 vs 10.1 years in nonparticipants
  - 6MWT: 356 vs 401 m
  - Timed 10-meter walk/run: 6.2 vs 6.1 s
  - Timed rise from floor: 8.9 vs 4.8 s
- Baseline age and function of eteplirsen-treated patients were similar to those of the SOC controls (**Table 1**)
- Total mean (SD) follow-up time was 7.0 (6.8–7.5) years for patients in Study 405

Table 1. Baseline Characteristics for LOA Analysis

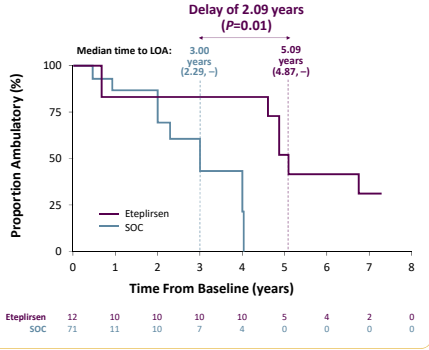
Parameter	Study 201/202/405[a] (n=12)	SOC (n=71)
Age, years		
Mean ± SD	9.48 ± 1.18	8.60 ± 2.09
Median	9.75	8.60
Function, mean ± SD		
6MWD, m	363.17 ± 42.19	350.27 ± 89.42
Timed 10-m walk/run speed, m/s	1.71 ± 0.44	1.57 ± 0.55
Timed rise from floor speed, 1/s	0.18 ± 0.09	0.19 ± 0.25
Steroid type, n (%)		
Deflazacort	8 (66.7)	32 (46.4)
Prednisone	4 (33.3)	37 (53.6)
Total follow-up time, years		
Mean ± SD	5.72 ± 0.90	1.34 ± 1.04
Median	6.06	0.92

[a]Patient characteristics for the eteplirsen-treated group were measured at eteplirsen initiation (at the start of Study 201 or 202).

LOA

- The eteplirsen treatment group had a statistically significant delay in LOA vs the SOC group (**Figure 2**)
  - The median time to LOA in the eteplirsen treatment group (5.09 years [95% CI: 4.87, –]) was 2.09 years longer than in the SOC group (3.00 years [2.29, –]; *P*=0.01)

Figure 2. LOA in Study 201/202/405 Eteplirsen-Treated Patients Compared With External SOC Controls

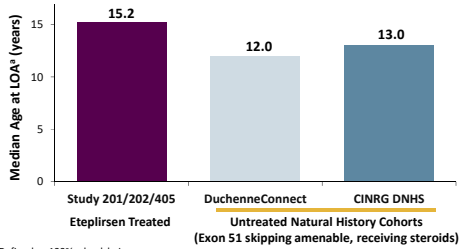


- Median age at LOA for eteplirsen-treated patients in Study 201/202/405 was higher than published data of patients in untreated natural history cohorts (**Figure 3**)[12,13]
  - All patients in Study 405 and the published cohorts were exon 51 skipping amenable and were receiving steroids, and each study used the same definition of LOA (100% wheelchair use)

Pulmonary Function

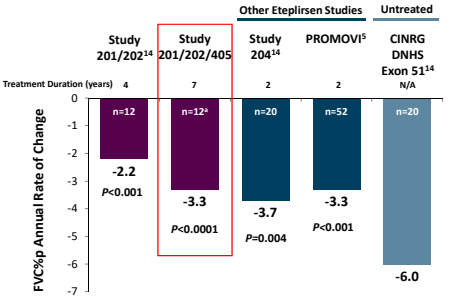
- Eteplirsen-treated patients in Study 405 had a significant, clinically meaningful attenuation of pulmonary decline vs untreated patients in the CINRG DNHS comparison cohort (*P*<0.001; **Figure 4**)
  - Pulmonary function results in patients from Study 405 were similar to those seen in patients from other eteplirsen studies[5,14]

Figure 3. Descriptive Analysis of Age at LOA in Eteplirsen-Treated Patients and Published Natural History Cohort Data[12,13]



[a]Defined as 100% wheelchair use.

Figure 4. Pulmonary Function in Study 405 Compared With the Untreated CINRG DNHS Exon 51 Cohort



[a]Includes observations from 12 patients during Study 201/202 and observations from 10 patients from Study 405. Nominal *P* values vs CINRG DNHS exon 51 patients. Height was measured as standing height in Study 201/202/405 and as ulnar length in Study 204, PROMOVI, and CINRG DNHS.

CONCLUSIONS

- Study 405 contributes to the growing body of evidence for the functional benefits of eteplirsen and provides up to 7 years of follow-up data for patients originally enrolled in Study 201/202
  - This study is the longest follow-up of eteplirsen-treated patients currently available
- Eteplirsen prolonged ambulatory status of treated patients compared with external controls
  - Mean time to LOA was delayed by 2.09 years in the eteplirsen-treated group
  - Median age at LOA was 15.2 years in eteplirsen-treated patients
- Eteplirsen-treated patients demonstrated a significant, clinically meaningful attenuation of pulmonary function decline vs untreated controls
  - Eteplirsen treatment slowed disease progression compared with a matched external control, confirming the findings seen in the first 4 years of treatment

REFERENCES

1. Cirak S, et al. *Lancet*. 2011;378:595-605. **2.** Emery AE, et al. *Duchenne Muscular Dystrophy*. 4th ed. Oxford, UK: Oxford University Press; 2015. **3.** Mendell JR, et al. *Ann Neurol*. 2016;79:257-71. **4.** Mendell JR, et al. *Ann Neurol*. 2013;74:637-47. **5.** McDonald C, et al. MSG 2020. **6.** Kinane TB, et al. *J Neuromuscul Dis*. 2018;5:47-588. **7.** Alfano LN, et al. *Medicine*. 2019; 98:26(e15858). **8.** Ambrosini A, et al. *Orphanet J Rare Dis*. 2018;13:176. **9.** Roy AJ, et al. *Acta Neurol Belgica*. 2014;115:97-104. **10.** Goemans N, et al. *Neuromuscul Disord*. 2018; 28:4-15. **11.** Hankinson JL, et al. *Am J Respir Crit Care Med*. 1999; 159:179-87. **12.** Bello L, et al. *Neurology*. 2016;87:401-9. **13.** Wang RT, et al. *Hum Mutat*. 2018;39:1193-202. **14.** Khan N, et al. *J Neuromuscul Dis*. 2019;6:213-25.

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