Open-Label Evaluation of Eteplirsen in Patients With Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping: PROMOVI Trial

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin gene [1,2]
- Eteplirsen binds to exon 51 of dystrophin pre-mRNA to allow skipping of exon 51, restore the mRNA reading frame, and allow translation of a truncated dystrophin protein[1,3,4]
- 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[3-6]
- Accumulation of natural history studies demonstrates disparate disease trajectories for patients with different mutations; nonmutation-matched comparisons may be inappropriate[7]

OBJECTIVE

- To report results from the Phase 3 PROMOVI study of eteplirsen efficacy/safety in boys with DMD amenable to exon 51 skipping

METHODS

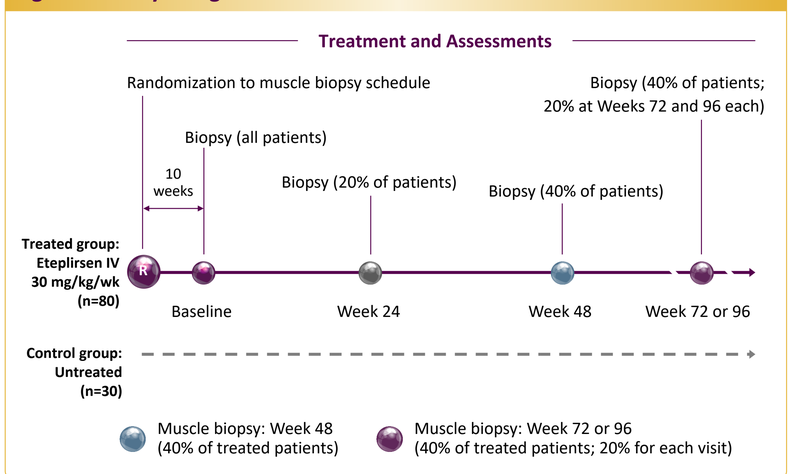
Study Population

- Confirmed DMD, amenable to exon 51 skipping
- 7–16 years of age, inclusive
- Stable oral corticosteroids ≥24 weeks before study
- Stable pulmonary function: forced vital capacity (FVC) ≥50%
- 6-minute walk test (6MWT) distance: ≥300 m

Study Design/Treatment

- The PROMOVI study design is shown in **Figure 1**; treated patients received eteplirsen IV 30 mg/kg/wk for 96 weeks

Figure 1. Study Design



Study Endpoints

- Primary: change from baseline to Week 96 in 6MWT distance
- Additional endpoints, measured from baseline to Week 96:
  - Change in dystrophin protein levels
    - Western blot, immunohistochemistry
  - Exon 51 skipping
    - A quantitative digital droplet PCR assay was used, providing precise and accurate measurements
  - Percent predicted FVC (FVC%p) annual rate of change
- Safety and tolerability

RESULTS

Patient Characteristics

- Patients were enrolled over a 2.5-year period starting October 2014
- A total of 79 patients were enrolled in the eteplirsen-treated group and 30 in the untreated group
  - Baseline characteristics of the eteplirsen-treated group are shown in **Supplementary Table 1**
  - 78 patients received eteplirsen and completed 96 weeks of treatment
  - 13 patients in the untreated group completed the study; only 9 patients completed in the primary efficacy set
- The untreated control arm did not retain sufficient patients; statistically and clinically meaningful comparisons were precluded
  - 50% of patients in the untreated arm withdrew from the study; as their mutations were not amenable to exon 51 skipping, they could not cross over into the treatment arm (**Table 1**)

Table 1. Primary Efficacy Set: Untreated Group

Endpoints	Baseline (n=20)	96 Weeks (n=9)
6MWT distance, m		
Mean (SD)	382.63 (45.69)	252.17 (133.08)
Min, max	301.5, 448.0	0.0, 453.5
FVC%p		
Mean (SD)	96.85 (17.71)	91.90 (14.17)
Min, max	67.54, 125.79	70.50, 113.83

- PROMOVI included a flawed comparison of eteplirsen-treated patients (**Table 2**) to a control arm consisting entirely of patients with mutations not amenable to exon 51 skipping
  - Emerging natural history data demonstrate patients with different mutations have different disease trajectories[7-9]
  - The untreated arm does not provide a relevant comparator group because patient mutations were not equivalent
  - Inadequate choice of control group became clear only after study initiation

Table 2. Primary Efficacy Set: Eteplirsen-Treated Group

Endpoints	Baseline (n=67)	96 Weeks (n=66)
6MWT distance, m		
Mean (SD)	374.64 (44.06)	256.18 (148.71)[a]
Min, max	303.0, 449.5	0.0, 496.0
FVC%p		
Mean (SD)	90.44 (15.95)	87.27 (16.32)
Min, max	50.00, 125.99	56.04, 128.43

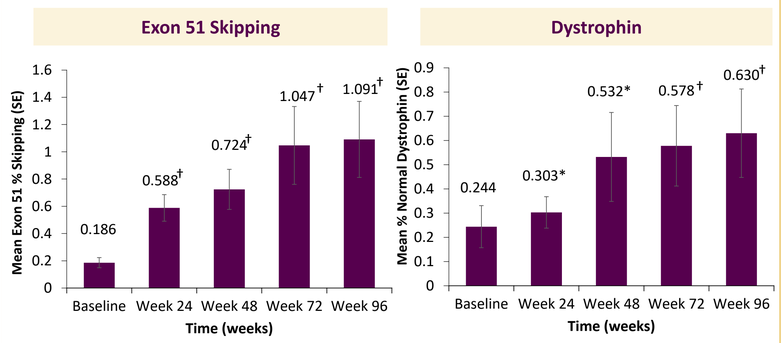
[a]n=65

- Post hoc, matched comparisons were performed
  - For 6MWT, PROMOVI patients were matched to study 201/202 baseline criteria
  - PROMOVI FVC%p data were compared to study 201/202 and the Cooperative International Neuromuscular Research Group (CINRG) exon 51 cohort

Exon 51 Skipping and Dystrophin: PROMOVI Consistent With Study 201/202 and Shows Accumulation Over Time

- Exon 51 skipping and increases in dystrophin were observed following eteplirsen treatment (**Figure 2**)
- Positive correlation was observed between exon 51 skipping vs dystrophin (Pearson coefficient = 0.710 [*P*<0.001]; Spearman coefficient = 0.692 [*P*<0.001])

Figure 2. Exon 51 Skipping and Dystrophin Accumulation in Eteplirsen-Treated Patients



Absolute Difference of Means (Week 96 vs baseline)	Fold Change[a]	*P*-Value[b]
0.956	18.74	<0.001

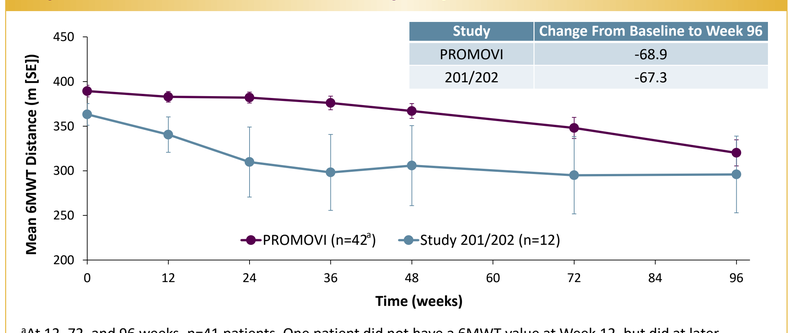
Absolute Difference of Means (Week 96 vs baseline)	Fold Change[a]	*P*-Value[b]
0.516	7.02	<0.001

*P-value <0.05; †P-value <0.001. SE=standard error
[a]Calculated from scatter plot (not shown) of change from baseline dystrophin level vs change from baseline in percent exon 51 skipping. [b]*P* value is based on one-sample permutation t-test.

6MWT at Week 96: PROMOVI Consistent With Study 201/202 in Slowing Disease Progression

- Mean change from baseline in 6MWT in eteplirsen-treated patients was -68.9 m in PROMOVI compared with -67.3 m in patients from study 201/202 (**Figure 3**); baseline characteristics are shown in **Supplementary Table 2**

Figure 3. Mean Change From Baseline to Week 96 in 6MWT in Eteplirsen-Treated Patients From Study 201/202 and PROMOVI



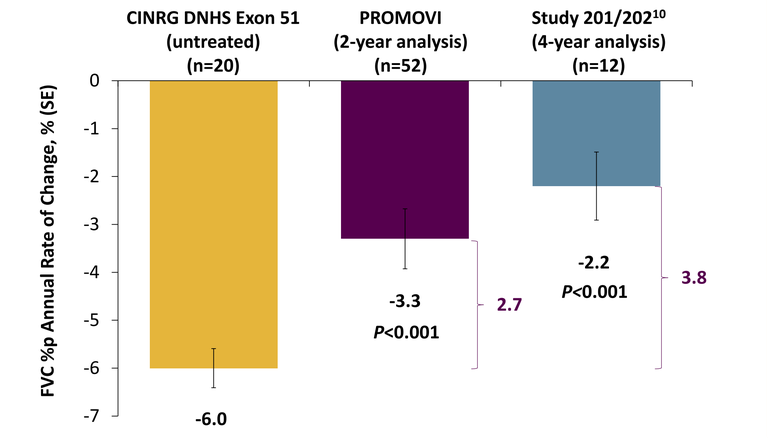
Study	Change From Baseline to Week 96
PROMOVI	-68.9
201/202	-67.3

[a]At 12, 72, and 96 weeks, n=41 patients. One patient did not have a 6MWT value at Week 12, but did at later visits. Another patient withdrew after Week 48. SE=standard error

FVC%p: PROMOVI Consistent With Study 201/202 in Slowing Pulmonary Annual Decline

- Compared with the untreated CINRG exon 51 cohort, eteplirsen-treated patients experienced a significant, clinically meaningful attenuation in pulmonary function decline (*P*<0.001) (**Figure 4**)
  - In PROMOVI, the annual rate of decline in FVC%p was -3.3 based on the use of ulnar calculated height and -3.1 based on standing height
- Baseline characteristics are shown in **Supplementary Table 3**

Figure 4. FVC%p in Eteplirsen-Treated Patients From PROMOVI vs Study 201/202 and Untreated CINRG Exon 51 Cohort (Age 10–18 Years)



Safety: PROMOVI Consistent With Study 201/202

- Adverse events (AEs) reported in PROMOVI reflected those observed in other PMO studies, with no major differences; overall, once-weekly eteplirsen IV appeared to be well tolerated
- The majority of the treatment-emergent AEs (TEAEs) reported were mild or moderate in severity
- No treatment-related discontinuations due to TEAEs
- AEs observed among patients who received eteplirsen and those in the untreated control group were generally consistent with AEs observed in a younger population with DMD and in patients with DMD receiving chronic corticosteroid treatment
  - One treatment-related serious AE of urticaria was observed approximately 15–20 minutes after infusion and resolved approximately 1 hour after an IV steroid and antihistamine were administered; although the patient continued on eteplirsen without subsequent events and without pretreatment with corticosteroids, the event may have been related to drug hypersensitivity
  - Overall, 8 eteplirsen-treated patients (10.1%) experienced renal TEAEs; each as proteinuria, which resolved in all but one individual
  - One infected venous port serious AE was reported as severe and unrelated to treatment

CONCLUSIONS

- PROMOVI, a large, US-based, multi-center study, contributes to the growing body of evidence for eteplirsen and confirms evidence of treatment effect and safety profile seen in study 201/202
- PROMOVI control arm did not retain sufficient patients, precluding statistically and clinically meaningful comparisons
- PROMOVI included a flawed comparison of eteplirsen-treated patients to a mismatched control arm that consisted entirely of patients with mutations not amenable to exon 51 skipping
  - Inadequate choice of control group became clear only after study initiation, as emerging natural history data demonstrate patients with different mutations have different disease trajectories
- Exon skipping increases post treatment demonstrating target engagement, and dystrophin protein accumulated over time
- Matched comparison with previous eteplirsen study 201/202 and natural history data suggest eteplirsen treatment slowed disease progression
- Long-term eteplirsen treatment was shown to have a favorable safety profile, with generally mild-to-moderate AEs and no discontinuations due to safety

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ADDITIONAL BASELINE CHARACTERISTICS

Supplementary Table 1. Baseline Characteristics: Treated Group (Efficacy Set)

Characteristic	Eteplirsen IV 30 mg/kg/wk (N=79)
Age (years), mean ± SD (min, max)	9.1 ± 2.0 (7.0, 16.0)
Standing height (cm), mean ± SD (min, max)	125.5 ± 9.0 (106.0, 148.5)
Time since DMD diagnosis at baseline (months), mean ± SD (min, max)	53.3 ± 33.3 (5.5, 147.1)
Corticosteroid treatment, n (%)	
Deflazacort	22 (27.8)
Prednisone	57 (72.2)
Corticosteroid schedule, n (%)	
Continuous	65 (82.3)
Intermittent	14 (17.7)

Supplementary Table 2. Baseline Characteristics for 6MWT-Matched Comparator Analysis: PROMOVI vs Study 201/202

Characteristic, mean ± SD (min, max)	PROMOVI (n=42)[a]	Study 201/202 (n=12)
Age, years	9.0 ± 2.1 (7.0, 13.0)	9.5 ± 1.2 (7.4, 11.0)
6MWT distance, m	389.3 ± 41.9 (301.0, 450.0)	363.2 ± 42.2 (256.0, 416.0)
NSAA total score	25.0 ± 4.2 (17.0, 31.0)	24.9 ± 4.9 (17.0, 31.0)
10-m run, s	5.2 ± 0.8 (3.8, 7.2)	6.2 ± 1.5 (3.9, 8.7)
Age at start of corticosteroid use, years	5.8 ± 1.9 (1.9, 10.0)	5.1 ± 1.1 (3.4, 6.6)
Duration of corticosteroid use, months	43.0 ± 28.4 (5.7, 120.4)	52.1 ± 24.1 (15.5, 91.7)
Time since DMD diagnosis, months	59.4 ± 33.0 (5.5, 131.2)	58.3 ± 26.0 (18.0, 112.0)

NSAA=North Star Ambulatory Assessment.
[a]Primary efficacy subset for comparison to study 201/202: consists of all treated patients with ≥1 postbaseline assessment who have a baseline 6MWT distance of 300–450 m, inclusive, baseline NSAA score 17–31, and age 7–13 years, inclusive.

Supplementary Table 3. Baseline Characteristics for FVC%p Matched Comparator Analysis: PROMOVI vs CINRG DNHS vs Study 201/202 (10 to <18 Age Group)[a]

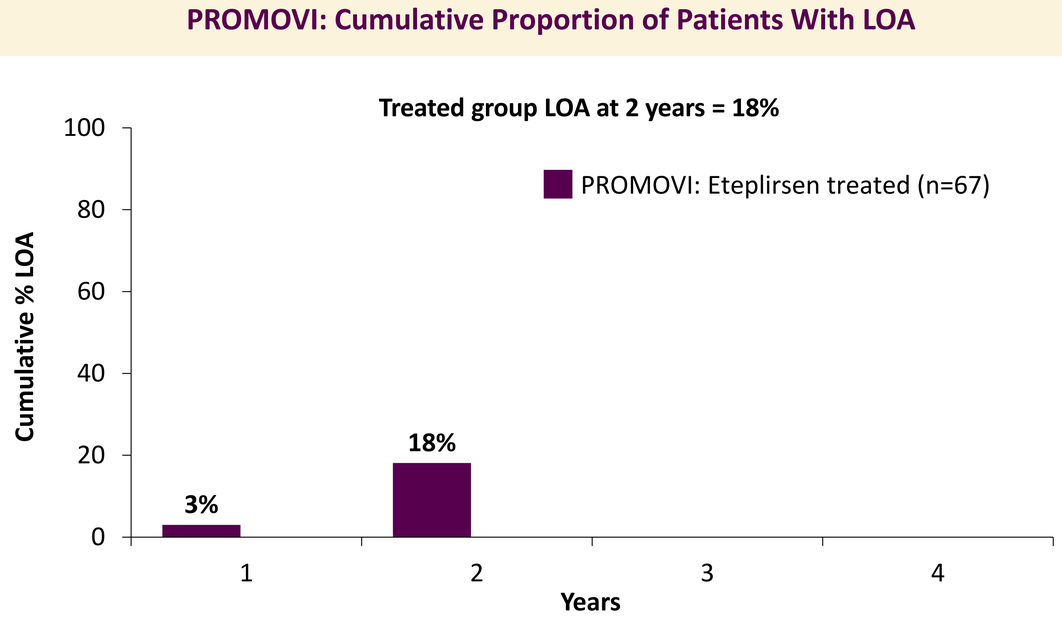
Characteristic, mean ± SD (min, max)	CINRG DNHS Exon 51 (n=20)	PROMOVI (n=52)[a]	Study 201/202 (n=12)
Age at baseline, years	11.8 ± 2.2 (10.0, 17.9)	11.0 ± 1.4 (10.0, 16.3)	10.3 ± 0.3 (10.0, 11.0)
Height at baseline,[b] cm	140.8 ± 12.1 (124.0, 178.1)	138.3 ± 7.7[c] (122.4, 155.2)	126.1 ± 7.6 (116.0, 140.5)
FVC%p at baseline,[b] %	79.6 ± 13.3 (50.0, 106.0)	78.5 ± 14.5[c] (52.6, 127.0)	96.9 ± 14.0 (84.0, 121.0)

[a]The analysis set included all treated patients with assessments in age group 10 to <18 years. [b]PROMOVI and CINRG DNHS used ulnar length calculated height, Study 201/202 used actual standing height. [c]n=51.

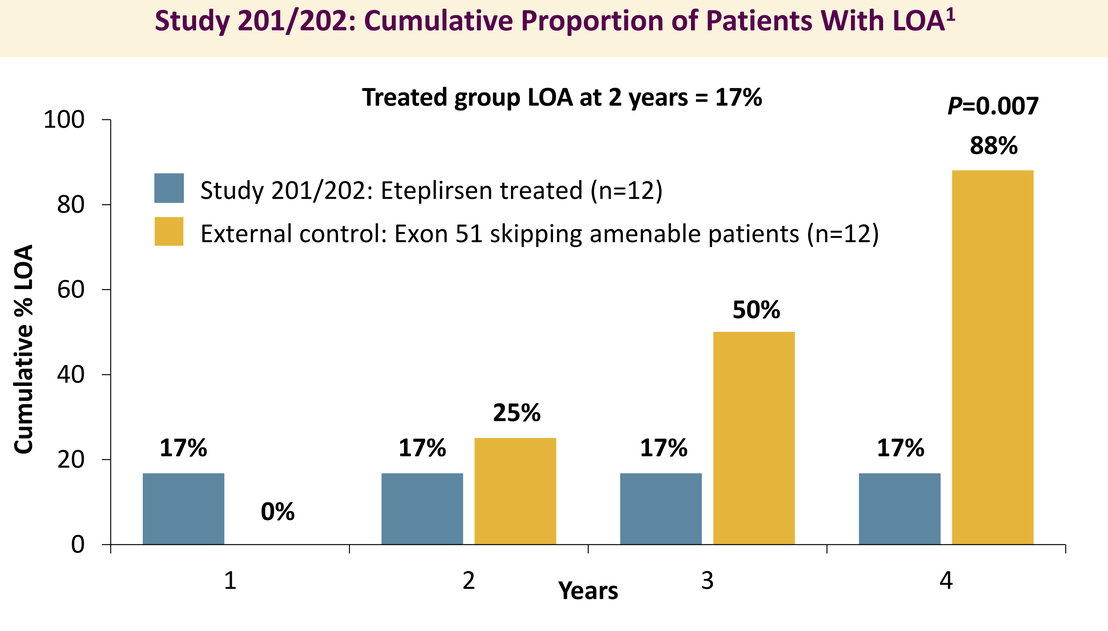
SUPPLEMENTARY RESULTS

Supplementary Figure 1. Loss of Ambulation (LOA) at 2 Years: PROMOVI vs Study 201/202

PROMOVI: Cumulative Proportion of Patients With LOA



Study 201/202: Cumulative Proportion of Patients With LOA[1]



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