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

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on behalf of the PROMOVI Clinical Investigators

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by dystrophin mutations[1]
- 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]
- Clinical trials of eteplirsen have demonstrated a significant increase in dystrophin protein accumulation, and indicate eteplirsen may slow muscle deterioration, prolong ambulation, and preserve pulmonary function in patients with DMD with eligible genetic mutations[2-5]

OBJECTIVE

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

METHODS

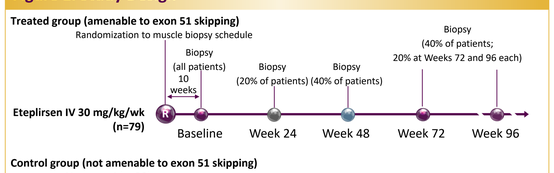
Study Population

- Confirmed DMD, amenable to exon 51 skipping
- 7–16 years of age, inclusive
- Stable dose of 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
  - — 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

Patients

- Patients enrolled over 2.5 years (eteplirsen, n=79; untreated, n=30)
- 13 (43%) patients in the untreated group completed the study; only 9 patients completed in the primary efficacy set
  - — Poor retention precluded meaningful comparisons
  - — Additionally, the intended comparison of eteplirsen-treated patients with a control arm consisting entirely of patients with mutations not amenable to exon 51 skipping was flawed, given that emerging natural history data demonstrate patients with different mutations have different disease trajectories[6-8]
  - — Inadequacy of control group became clear after study initiation

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RESULTS

- 78 of 79 patients who received eteplirsen completed 96 weeks of treatment; baseline characteristics are shown in **Table 1**

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

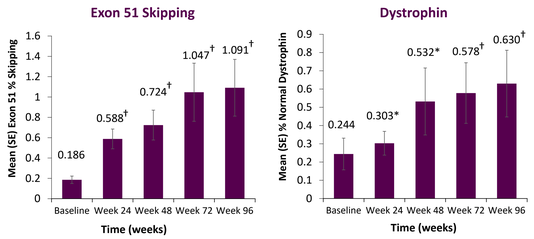
Characteristic	Eteplirsen IV 30 mg/kg/wk (N=79)
Age, years	9.1 ± 2.0 (7.0, 16.0)
Standing height, cm	125.5 ± 9.0 (106.0, 148.5)
Time since DMD diagnosis, months	53.3 ± 33.3 (5.5, 147.1)
Corticosteroid treatment, n (%)	
Deflazacort	22 (27.8)
Prednisone	57 (72.2)
Corticosteroid schedule, n (%)	
Continuous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

Values are mean ± SD (range), unless otherwise noted.

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.
[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.

Efficacy in Eteplirsen-Treated Patients

- Results for the eteplirsen-treated arm are shown in **Table 2**
- Results for the untreated arm are shown in **Supplementary Table 1**

Table 2. Primary Efficacy Set: Eteplirsen-Treated Group

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

Values are mean ± SD (range). [a]n=65

- Post hoc, matched comparisons were performed to evaluate efficacy

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

- For 6MWT, PROMOVI patients were matched to study 201/202 baseline criteria (**Table 3**)
- 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**)
- Loss of ambulation occurred in 18% of PROMOVI patients at Year 2, which was comparable to results from study 201/202 at that time point (17%; **Supplementary Figure 1**)[9]

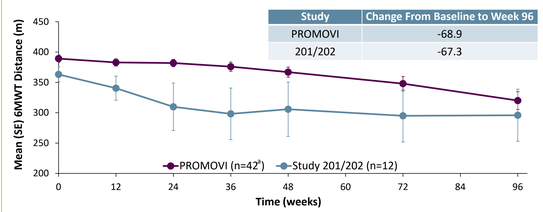
RESULTS

Table 3. Baseline Characteristics for 6MWT Matched Comparator Analysis: PROMOVI vs Study 201/202

Characteristic	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)
Duration of corticosteroid use, months	43.0 ± 28.4 (5.7, 120.4)	52.1 ± 24.1 (15.5, 91.7)

NSAA=North Star Ambulatory Assessment. Values are mean ± SD (range). [a]Primary efficacy subset for comparison with study 201/202, consists of all treated patients with ≥1 postbaseline assessment and baseline 6MWT distance of 300–450 m, inclusive, baseline NSAA score 17–31, and age 7–13 years, inclusive.

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



[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.

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

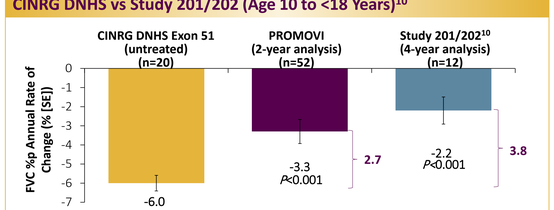
- FVC%p data were compared to study 201/202 and the CINRG DNHS exon 51 cohort, matched for baseline characteristics (**Table 4**)
- Compared with the untreated CINRG DNHS exon 51 cohort, eteplirsen-treated patients experienced a significant, clinically meaningful attenuation in pulmonary function decline (P<0.001; **Figure 4**)
  - — The annual rate of decline in FVC%p was -3.3 based on ulnar calculated height and -3.1 based on standing height

Table 4. Baseline Characteristics for FVC%p Matched Comparator Analysis: PROMOVI vs CINRG DNHS vs Study 201/202 (Age 10 to <18 Years)[a]

Characteristic	CINRG DNHS Exon 51 (n=20)	PROMOVI (n=52)[a]	Study 201/202 (n=12)
Age, 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,[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,[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)

CINRG DNHS=Cooperative International Neuromuscular Research Group Duchenne Natural History Study. Values are mean ± SD (range). [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.

Figure 4. FVC%p in Eteplirsen-Treated Patients From PROMOVI vs CINRG DNHS vs Study 201/202 (Age 10 to <18 Years)[10]



RESULTS

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 was 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, multicenter 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 vs 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 demonstrated patients with different mutations have different disease trajectories[6-8]
- Exon skipping increased 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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SUPPLEMENTARY RESULTS

Untreated Arm Efficacy Results

- The untreated control arm did not retain sufficient patients; statistically and clinically meaningful comparisons with eteplirsen-treated patients 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
  - —Furthermore, accumulation of natural history studies demonstrates disparate disease trajectories for patients with different mutations; non–mutation-matched comparisons may be inappropriate[1]
  - —Results for the untreated arm are shown in **Supplementary Table 1**

Supplementary Table 1. Primary Efficacy Set: Untreated Group

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

Values are mean ± SD (range).

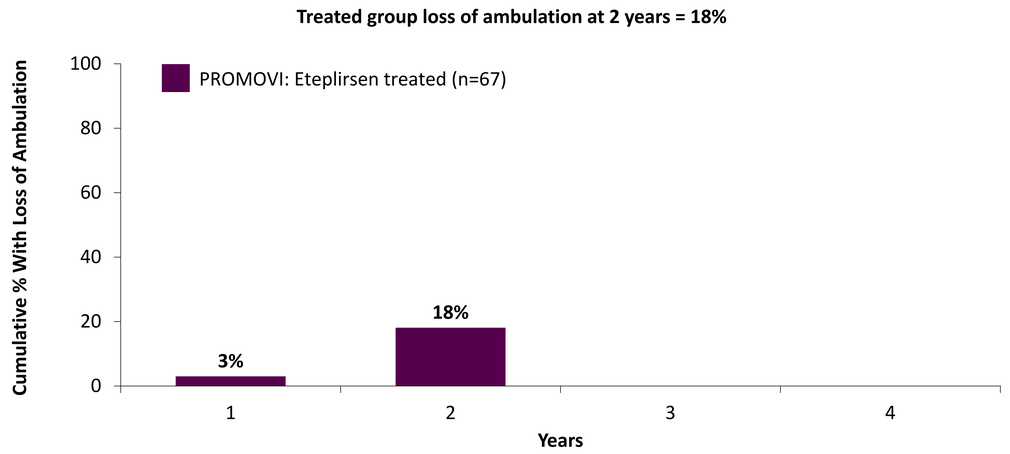
- PROMOVI included a flawed comparison of eteplirsen-treated patients to a control arm consisting entirely of patients with mutations not amenable to exon 51 skipping
  - —Emerging natural history data demonstrate patients with different mutations have different disease trajectories[1-3]
  - —The untreated 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
  - —Efficacy comparisons for eteplirsen-treated patients were instead conducted post hoc using matched, exon 51 skipping–amenable controls

Loss of Ambulation: PROMOVI Consistent With Study 201/202 in Slowing Ambulatory Decline

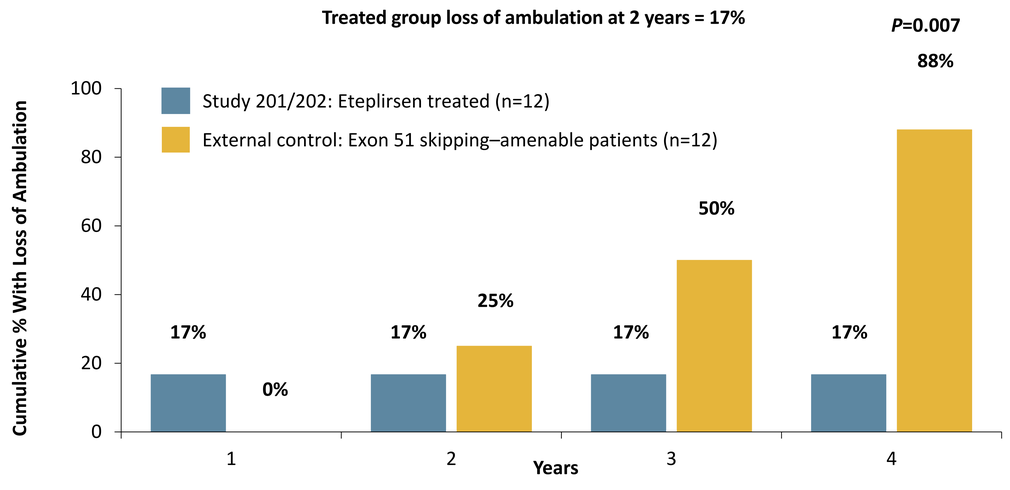
- Loss of ambulation occurred in 18% of PROMOVI patients at Year 2, comparable to results from study 201/202 at that time point (17%; **Supplementary Figure 1**)[4]
- Loss of ambulation after 4 years was significantly lower in study 201/202 compared with an external control cohort of exon 51 skipping–amenable patients from the Leuven Neuromuscular Research Center and the Telethon Foundation DMD Italian Network (17% vs 88%; *P*=0.007)[4]

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

PROMOVI: Cumulative Proportion of Patients With Loss of Ambulation



Study 201/202: Cumulative Proportion of Patients With Loss of Ambulation[4]



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