A Phase IIb Placebo-Controlled Study of the Exon-Skipping Drug Eteplirsen in Subjects with Duchenne Muscular Dystrophy (DMD)

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Background

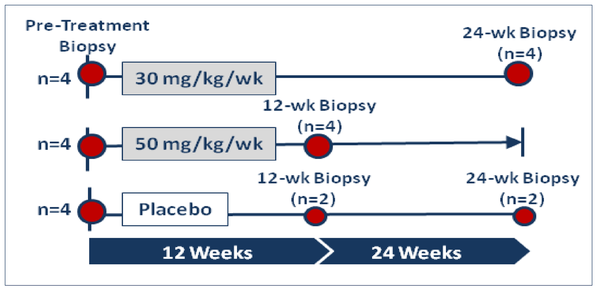
DMD is a devastating, rare childhood disease with no curative therapies currently available. Affected children (1 in 4000 male births)[1] are unable to produce more than 5% of the protein dystrophin, resulting in progressive muscle deterioration and death (on average) in their late twenties. Clinical and pre-clinical investigations have linked dystrophin levels of 10% to 20% of normal with improved muscle function.[2-4] Eteplirsen is AVI BioPharma's lead drug candidate for DMD. Eteplirsen uses AVI's phosphorodiamidate morpholino oligomer (PMO)-based chemistry to skip exon 51 of the dystrophin gene. By skipping exon 51, eteplirsen restores the gene's ability to make a shorter but functional form of dystrophin.

References

1. Mendell JR, et al. ***Ann Neurol*** 2012; 71:304-313
2. Alter, J.. et al ***Nat Med*** 2006; 12(2):175-7
3. Taylor, L. et al ***Neuropathol Appl Neurobiol*** 2012; Epub
4. Sharp, P.S. et al ***Mol Ther*** 2011; 19:165–171
5. Neri, M. et al ***Neuromuscul Disord*** 2007; 17:913–918

Study Design

Primary Endpoint: Increase in dystrophin positive fibers as measured by immunohistochemistry.



Randomized, single-center, double-blind, placebo-controlled Phase IIb study to assess the efficacy and safety of 24 once-weekly I.V. infusions of Eteplirsen.

Patient Characteristics at Baseline

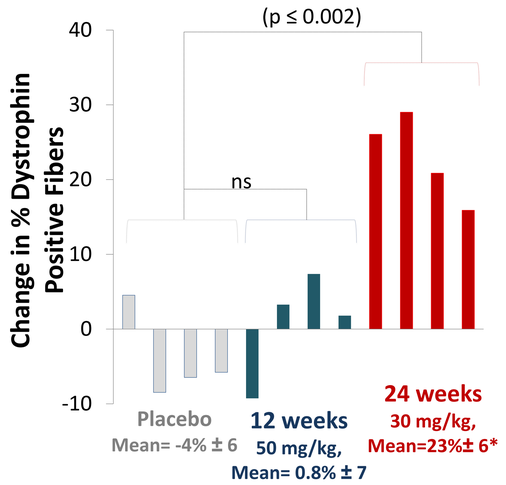
Cohort	N	Age (yrs) mean, median	Weight (kg) mean, median	Height (cm) mean, median	BMI (kg/m²) mean, median	6 MWT (m) mean, median
Placebo	4	8.5, 8.5	31, 32	119, 118	21, 22	380, 366
30 mg/kg	4	9.3, 9.0	35, 37	130, 133	20, 21	347, 351
50 mg/kg	4	8.5, 8.5	29, 27	121, 117	20, 20	385, 383
Total	12	8.8, 9.0	32, 32	124, 118	20, 20	371, 368
(Min, Max)		*(7, 10)*	*(22, 40)*	*(116, 138)*	*(16, 26)*	*(259, 437)*

Key Inclusion Criteria

- Out-of-frame deletion(s) amenable to skipping exon 51
- Between the ages of 7 and 13 years
- Between 200 and 400 meters on 6 MWT at Baseline
- Receiving treatment with oral corticosteroids and have been on a stable dose for at least 24 weeks before study entry

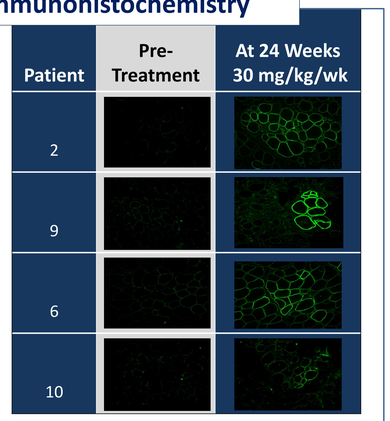
Efficacy

Change in % Dystrophin Positive Fibers



*** 30 mg/kg Eteplirsen x 24 weeks significantly increased dystrophin compared to placebo; (p≤0.002)**

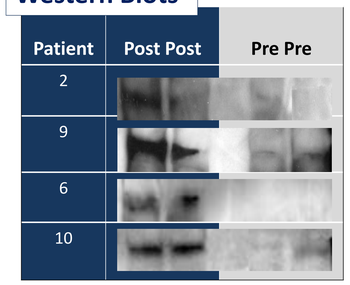
Immunohistochemistry



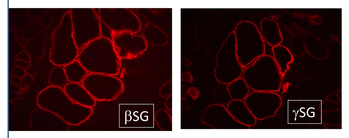
Membrane intensity post treatment mean: 21.2 ± 4.7%

Methodology: Muscle biopsy pre- & post. Two tissue blocks cut and stained with Mandys 106. Quantified in 12 fields photographed at 20X from 3 levels in each block (n =24 fields).

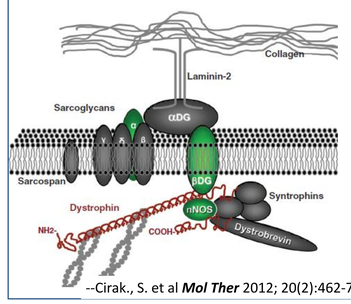
Western Blots



Eteplirsen-Produced Dystrophin Restored the Dystrophin-Associated Glycoprotein Complex

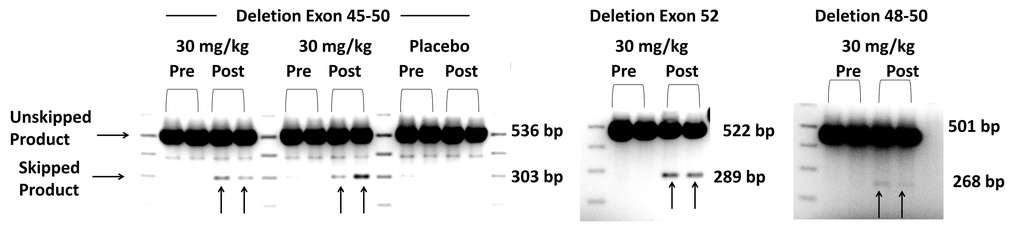


Components of the sarcoglycan complex restored with dystrophin expression induced by eteplirsen (example shown (#6) similar in all cases receiving 30 mg/kg)

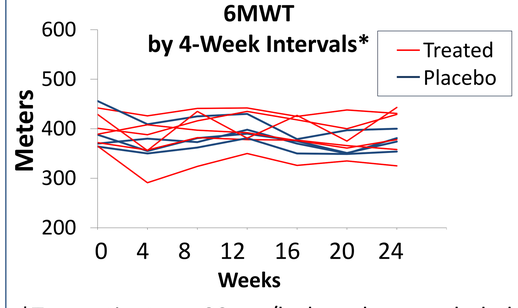


--Cirak., S. et al ***Mol Ther*** 2012; 20(2):462-7

RT-PCR Products of Exon Skipping 51



6-Minute Walk Test (6MWT)*



	6MWT Adjusted Mean Change from Baseline at 24 Wks*
Placebo (N=4)	-21.0 m
Treated (N=6)	-3.2 m
Benefit Over Placebo	***17.8 m***

*Two patients on 30 mg/kg have been excluded from the analysis because they exhibited a rapidly progressive decline on this measure (> 50 meters by week 12). A trend of slower progression was demonstrated in the remaining treated patients, with a benefit over placebo of 17.8 meters.

Safety

Treatment Emergent Adverse Events

Adverse Event	Treated N=8 (%)	Placebo N=4 (%)
Hypokalemia	4 (50.0%)	2 (50.0%)
Procedural pain	4 (50.0%)	3 (75.0%)
Balance disorder	3 (37.5%)	0
Vomiting	3 (37.5%)	0
Cough	2 (25.0%)	2 (50.0%)
Dermatitis Contact	2 (25.0%)	0
Hematoma	2 (25.0%)	1 (25.0%)
Back pain	1 (12.5%)	2 (50.0%)
Fall	1 (12.5%)	1 (25.0%)
Headache	1 (12.5%)	2 (50.0%)
Diarrhoea	1 (12.5%)	1 (25.0%)
Polyuria	1 (12.5%)	0
Nausea	1 (12.5%)	1 (25.0%)*
Rhinitis	1 (12.5%)	1 (25.0%)
Muscle Spasms	1 (12.5%)	0
Musculoskeletal Pain	1 (12.5%)	0
Pyrexia	1 (12.5%)	2 (50.0%)
Proteinuria	0	1 (25.0%)
Abdominal pain	0	2 (50.0%)

- No proteinuria
- No change in blood coagulation profiles
- No evidence of treatment-related inflammatory responses
- No infusion-associated reactions
- No thrombocytopenia
- No change in liver-specific enzymes
- No change in kidney function

No Treatment-Related Adverse Events

Conclusions

- Eteplirsen produced significant levels of dystrophin in DMD patients after 24 weeks of treatment (mean=23% of dystrophin-positive fibers).
- Eteplirsen proved safe at both dose levels (up to 50mg/kg/wk over 28 weeks) with no treatment-related adverse events.
- Eteplirsen's favorable safety profile supports continuing treatment and may enable long-term chronic administration.
- Eteplirsen induced production of dystrophin at consistent levels; The range observed (between 15% to 30% dystrophin-positive fibers) is likely to produce a clinical benefit if maintained over time.