Safety and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping

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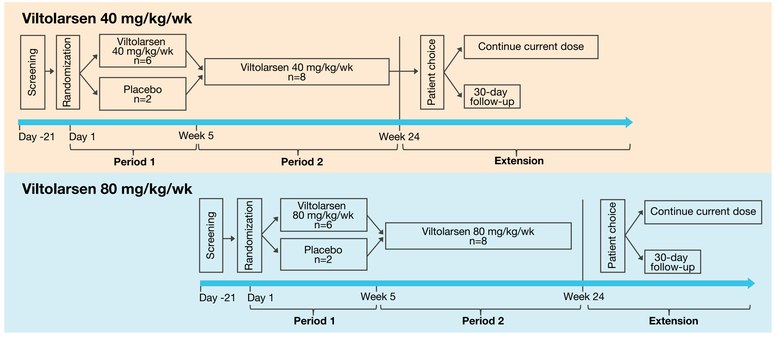
INTRODUCTION

- Duchenne muscular dystrophy (DMD) is a progressive muscle disease caused by one of many types of genetic mutations (deletions, duplications, nonsense) in the dystrophin gene in muscle tissue[1,2]
- Approximately 10% of patients with DMD caused by an out-of-frame deletion are amenable to exon 53 skipping.[2] In these patients, skipping exon 53 is predicted to restore the reading frame (return to in-frame), resulting in production of an internally shortened dystrophin that contains essential functional portions[3,4]
- Viltolarsen is an antisense oligonucleotide designed to skip exon 53 and therefore is effective in patients with deletions such as, but not limited to, 43-52, 45-52, 47-52, 48-52, 49-52, 50-52, or 52 alone.[5] Patients with just the 52 deletion are unique in that they can be brought into frame by skipping exon 53 or 51[2]
- The study presented in this poster was conducted in 16 participants with DMD amenable to exon 53 skipping treatment

METHODS

Figure 1. Study Design



Two groups of participants (Group 1: 40 mg/kg/wk; Group 2: 80 mg/kg/wk) each comprising 8 participants, were treated with weekly infusions of viltolarsen for 20 to 24 weeks (2 participants in each group were to receive placebo treatment for the first 4 weeks before changing over to viltolarsen for the remainder of the study). All participants underwent a pre- and posttreatment skeletal muscle biopsy. At the conclusion of the 24 weeks all participants were offered and accepted treatment in an open-label extension study.

Key Inclusion/Exclusion Criteria

- Confirmed diagnosis of DMD with confirmed mutation that was amenable to exon 53 skipping
- Ambulatory
- Aged 4 to <10 years
- Has been on stable glucocorticoid regimen for at least 3 months and is expected to remain on stable regimen for the remainder of the trial

Endpoints

Primary endpoints consisted of dystrophin levels as measured by Western blot, safety, and tolerability

Secondary endpoints consisted of dystrophin levels as measured by immunofluorescence, exon-skipping efficiency as measured by RT-PCR and functional changes as measured by TTSTAND, TTRW, 6MWT, and TTCLIMB

6MWT, six-minute walk test; RT-PCR, reverse transcription-polymerase chain reaction; TTCLIMB, time to climb; TTRW, time to run/walk 10 meters test; TTSTAND, time to stand from supine.

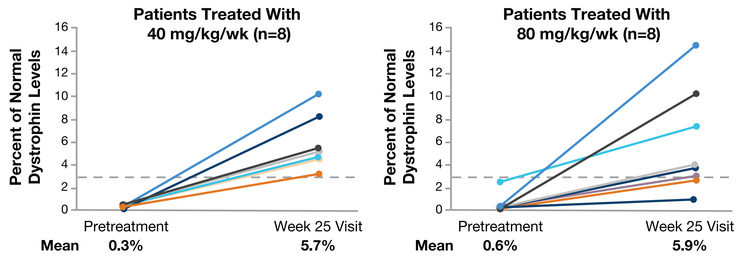
RESULTS

Table 1. Baseline Demographics

Baseline Demographic Characteristics	40 mg/kg/wk (n=8)	80 mg/kg/wk (n=8)	Total (N=16)
Age, y, mean (range)	7.5 (4.3, 9.8)	7.2 (4.8, 9.8)	7.4 (4.3, 9.8)
Weight, kg, mean (range)	23.7 (14.9, 30.4)	22.3 (15.5, 35.4)	23.0 (14.9, 35.4)
Height, cm, mean (range)	114.6 (102.5, 123.4)	112.2 (99.4, 127.1)	113.4 (99.4, 127.1)
BMI, kg/m^2, mean (range)	17.9 (14.2, 20.0)	17.4 (15.4, 21.9)	17.7 (14.2, 21.9)

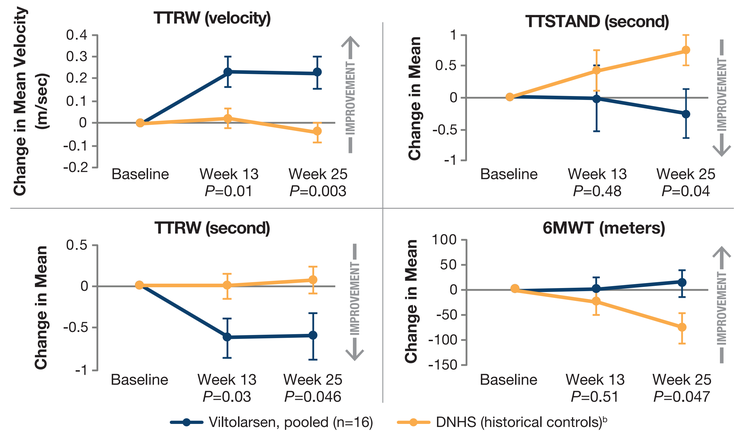
- The majority of patients (15/16) were white with one patient being of Asian race

Figure 2: Evaluation of Dystrophin Induction



- Percentage of normal dystrophin levels was graphed for each participant at baseline and posttreatment at week 25 visit. Dystrophin was measured using Western blot and normalized to myosin heavy chains. The gray dashed line denotes 3% of normal dystrophin levels. Each line indicates a different patient
- At week 25, the change from baseline in mean percentage of normal dystrophin level was statistically significant for viltolarsen 40 mg/kg/wk (P<0.001) and 80 mg/kg/wk (P=0.012), as measured by Western blot

Figure 3. Change in Timed Function Tests[a]



6MWT, six-minute walk test; DNHS, Duchenne Natural History Study; TTRW, time to run/walk 10 meters test; TTSTAND, time to stand from supine.
[a]Direction of arrows indicate improvement in time function tests.
[b]Observed sample size for DNHS was n=69, n=43, and n=46 for TTSTAND; n=69, n=44, and n=46 for TTRW and n=18, n=14, and n=11 for 6MWT at baseline, week 13, and week 25, respectively.

- At week 25, viltolarsen treatment significantly improved performance on the timed motor tests TTSTAND, TTRW, and 6MWT

Table 2. Viltolarsen Safety Profile

AEs, n (%)	Viltolarsen Treatments					
	Grouping A[a]			Grouping B[b]		Total (N=16)
	Placebo (n=5)	40 mg/kg/wk (n=6)	80 mg/kg/wk (n=5)	40 mg/kg/wk (n=8)	80 mg/kg/wk (n=8)	
TEAEs by preferred term (occurring in >1 patient)						
Infections and infestations	1 (20)	0	1 (20)	1 (13)	5 (63)	6 (38)
Nasopharyngitis	1 (20)	0	1 (20)	0	4 (50)	4 (25)
Respiratory, thoracic and mediastinal disorders	0	1 (17)	2 (40)	2 (25)	2 (25)	7 (44)
Cough	0	0	1 (20)	2 (25)	2 (25)	5 (31)
Nasal congestion	0	1 (17)	0	1 (13)	0	2 (13)
Injury, poisoning, and procedural complications	1 (20)	0	1 (20)	2 (25)	1 (13)	4 (25)
Contusion	0	0	1 (20)	0	1 (13)	2 (13)
Musculoskeletal and connective tissue disorder	1 (20)	0	1 (20)	2 (25)	1 (13)	4 (25)
Arthralgia	1 (20)	0	1 (20)	0	0	2 (13)
Gastrointestinal disorders	0	0	0	1 (13)	2 (25)	3 (19)
Diarrhea	0	0	0	1 (13)	1 (13)	2 (13)
Vomiting	0	0	0	0	2 (25)	2 (13)

AE, adverse event; TEAE, treatment-emergent adverse event.
[a]Group A included all AEs that occurred prior to dosing at the week 5 visit (ie, study period 1).
[b]Group B included all AEs that occurred after dosing at week 5 (ie, study period 2).

- No serious AEs, drug-related treatment-emergent AEs, discontinuations due to AEs, or deaths occurred during this study

CONCLUSIONS

- Treatment with viltolarsen in patients with DMD who are amenable to exon 53 skipping resulted in significant increases in dystrophin production
- Timed function tests provided supportive evidence of treatment-related clinical improvement
- AEs were mild to moderate. No serious AEs were reported and there were no discontinuations from the study

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Author Disclosures

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