Pulmonary and motor function in ambulatory and nonambulatory participants with Duchenne muscular dystrophy treated with viltolarsen

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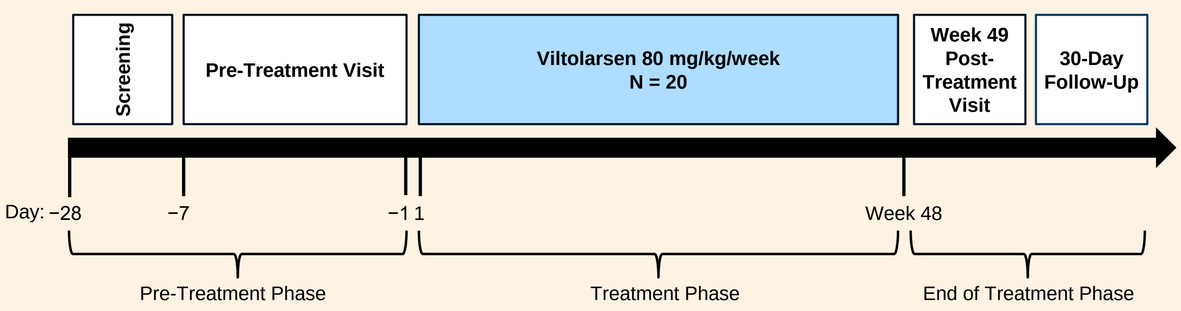
BACKGROUND

- Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by mutations in the dystrophin gene, resulting in loss of functional dystrophin protein[1]
- Pulmonary function of boys with DMD is severely affected as the disease progresses, with the eventual need for assisted ventilation[2]
- Without treatment, boys with DMD lose ambulation and become wheelchair dependent at approximately age 12, and they continue to lose muscle strength with time[3]
- The majority of reported dystrophin gene mutations that cause DMD result in frame shifts[4]
- Exon skipping therapies restore the open reading frame of the dystrophin pre-mRNA, resulting in the production of shortened dystrophin protein containing essential functional portions[3]
- Viltolarsen is an antisense oligonucleotide that received accelerated approval in the US and conditional approval in Japan for the treatment of DMD in patients with dystrophin mutations amenable to exon 53 skipping[5]
- Here we report safety and pulmonary and motor function from the Phase 2 Galactic53 trial of viltolarsen in ambulatory and nonambulatory boys with DMD amenable to exon 53 skipping

METHODS

Figure 1. Galactic53 study design



- Galactic53 was a Phase 2, open-label, multicenter study of viltolarsen administered intravenously 80 mg/kg once weekly in ambulatory and nonambulatory boys with DMD amenable to exon 53 skipping (NCT04956289; **Figure 1**)
- Safety and tolerability were assessed through recording treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Pulmonary function was evaluated using percent predicted forced vital capacity (FVC%p)
- Motor function was measured using the total and midlevel elbow scores from performance of upper limb (PUL) 2.0
- Results from participants treated with viltolarsen were compared to matched controls from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS)[6]
  - Matching criteria included age, ambulatory and steroid status, and FVC testing at baseline and Week 49
- Data analysis by ambulatory status was performed post hoc, and all *P*-values are considered as nominal

RESULTS

- Baseline characteristics were well matched between participants receiving viltolarsen and the CINRG DNHS control group (**Table 1**)
- Consistent with the natural progression of the disease, nonambulatory boys were generally older, larger, and more symptomatic than ambulatory boys

Table 1. Baseline characteristics and demographics of ambulatory and nonambulatory participants

Participant characteristic	Ambulatory		Nonambulatory	
	Viltolarsen 80 mg/kg/wk n = 10	CINRG DNHS control cohort n = 25	Viltolarsen 80 mg/kg/wk n = 10	CINRG DNHS control cohort n = 23
Age, years, mean (SD)	9.8 (1.6)	10.0 (2.3)	15.8 (6.4)	15.6 (3.5)
Range	8–12	8–17	8–26	10–21
Race, n (%)				
Black or African American	0	1 (4)	0	1 (4)
Asian	4 (40)	2 (8)	1 (10)	5 (22)
White	6 (60)	22 (88)	9 (90)	16 (70)
Other	0	0	0	1 (4)
Ethnicity, n (%)				
Not Hispanic or Latino	10 (100)	21 (84)	10 (100)	22 (96)
Baseline steroid type, n (%)				
None	0	0	1 (10)	0
Deflazacort	5 (50)	14 (56)	5 (50)	18 (78)
Prednisone or prednisolone	5 (50)	11 (44)	4 (40)	5 (22)
Weight, kg, mean (SD)	33.1 (10.4)	33.4 (8.8)	49.4 (19.5)	54.3 (21.4)
Height, cm, mean (SD)	127.2 (6.6)	126.6 (10.5)	148.1 (14.5)	150.3 (11.4)
Body mass index, kg/m^2, mean (SD)	20.1 (4.2)	20.6 (3.4)	21.9 (6.2)	23.5 (7.5)
Functional assessments, mean (SD)				
PUL 2.0 total score	38.1 (2.2)	NA[a]	23.5 (9.3)	NA[a]
FVC%p	83.5 (9.3)	85.3 (18.2)	58.8 (14.6)	59.7 (17.2)

One 26-year-old participant treated with viltolarsen reported use of nighttime ventilation prior to study entry. No other participants reported use of nighttime ventilation during the study. Cough assist devices were not used during the study.
[a]Data not collected.
CINRG, Cooperative International Neuromuscular Research Group; DNHS, Duchenne Natural History Study; FVC%p, percent predicted forced vital capacity; NA, not available; PUL, Performance of Upper Limb; SD, standard deviation.

Safety

- In the safety population (N = 20), 19 of 20 (95%) participants reported TEAEs, and 4 events were considered drug-related (**Table 2**)
  - Drug-related TEAEs were hematuria (n = 2), allergic reaction (n = 1), and hypertension (n = 1)
- All TEAEs were mild or moderate in severity and there were no SAEs, discontinuations due to TEAEs, or deaths
- No induction of anti-viltolarsen or anti-dystrophin antibodies was observed in participants receiving viltolarsen

Table 2. Summary of TEAEs in participants receiving viltolarsen

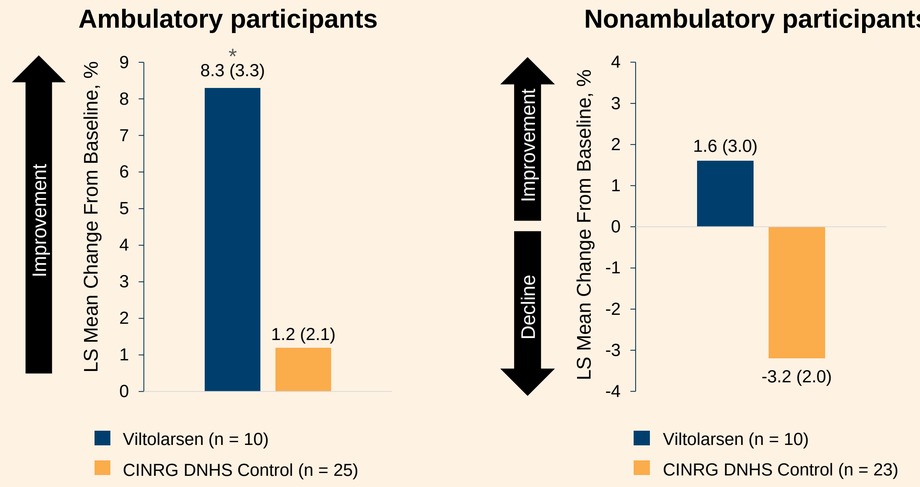
Participants with the following:	Viltolarsen 80 mg/kg/wk N = 20[a]
Any TEAE, n (%)	19 (95)
Any treatment-related TEAE[b], n (%)	4 (20)
Discontinuation due to TEAE, n (%)	0
Any serious treatment-related TEAE, n (%)	0
Death, n (%)	0

[a]Includes both ambulatory and nonambulatory participants.
[b]Hematuria (n = 2), allergic reaction (n = 1), and hypertension (n = 1).
TEAE, treatment-emergent adverse event.

Pulmonary function

- At Week 49, viltolarsen improved the least squares (LS) mean change from baseline in FVC%p for ambulatory and nonambulatory participants (**Figure 2**)
  - For ambulatory participants, 70% (7/10) of participants receiving viltolarsen showed improvement in LS mean change from baseline FVC%p, and the overall change was significant compared with baseline (8.3% improvement, $P = 0.02$)
  - For nonambulatory participants, the LS mean change from baseline FVC%p increased for participants receiving viltolarsen, whereas this value decreased for the control cohort (1.6% vs −3.2%)

Figure 2. LS mean change from baseline in FVC%p at Week 49

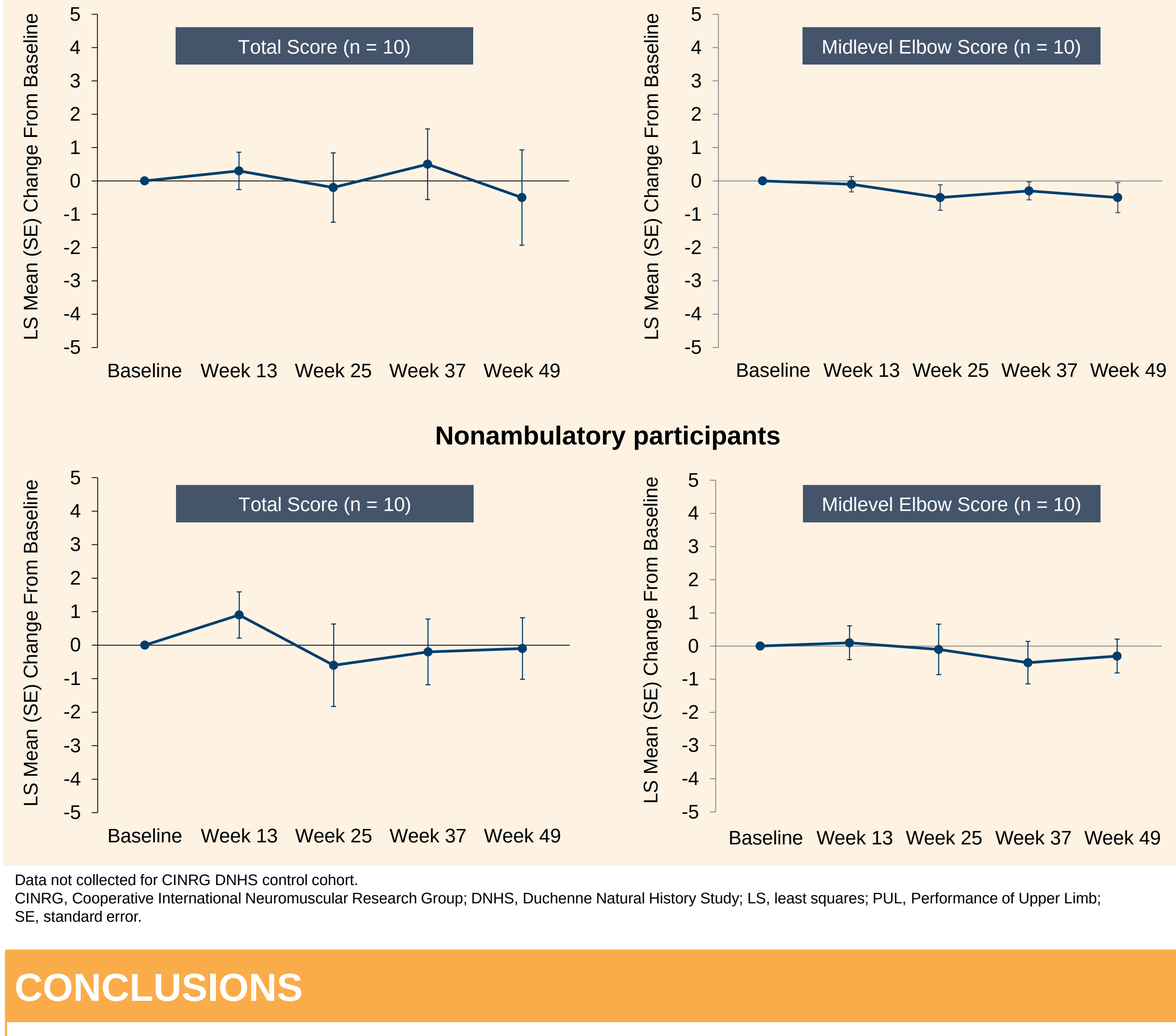


Data presented as LS mean (standard error). All *P*-values are nominal. *P <0.05 vs baseline.
CINRG, Cooperative International Neuromuscular Research Group; DNHS, Duchenne Natural History Study; FVC%p, percent predicted forced vital capacity; LS, least squares.

Motor function

- The total and midlevel elbow scores from PUL 2.0 remained stable over 49 weeks for both ambulatory and nonambulatory participants receiving viltolarsen (**Figure 3**)

Figure 3. LS mean change from baseline in PUL 2.0 scores in participants receiving viltolarsen



Data not collected for CINRG DNHS control cohort.
CINRG, Cooperative International Neuromuscular Research Group; DNHS, Duchenne Natural History Study; LS, least squares; PUL, Performance of Upper Limb; SE, standard error.

CONCLUSIONS

- In Galactic53, viltolarsen was well tolerated, and the safety profile was consistent with previous reports
- This is the first viltolarsen trial to evaluate pulmonary function in male participants with DMD
- Over this 48-week trial, 90% (18/20) of the participants demonstrated stabilization or improvement in FVC%p
- The motor function of participants receiving viltolarsen was stabilized over 49 weeks in both ambulatory and nonambulatory participants
- Viltolarsen can be considered an important part of the treatment strategy for patients with DMD amenable to exon 53 skipping therapy

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DISCLOSURES

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