Viltepso®
(viltolarsen) injection

# A treatment option for people with Duchenne could mean hope to share meaningful moments

**VILTEPSO is for people with Duchenne muscular dystrophy amenable to exon 53 skipping**

## Indication

VILTEPSO is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VILTEPSO. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

## Important Safety Information

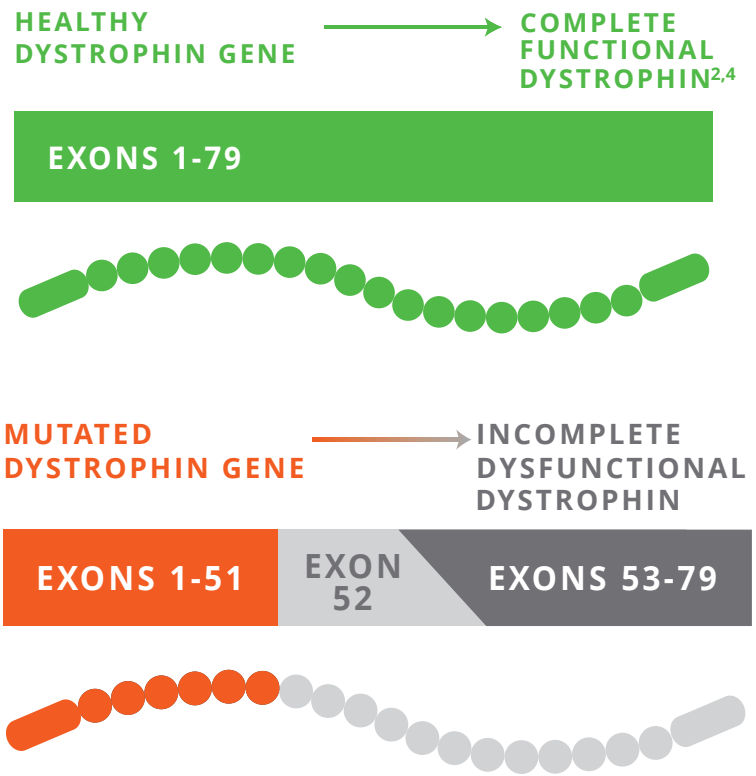
**Warnings and Precautions:** Kidney toxicity was observed in animals who received viltolarsen. Although kidney toxicity was not observed in the clinical studies with VILTEPSO, the clinical experience with VILTEPSO is limited, and kidney toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Kidney function should be monitored in patients taking VILTEPSO. Serum creatinine may not be a reliable measure of kidney function in DMD patients.

**Please see Important Safety Information throughout. For additional information about VILTEPSO, see accompanying full Prescribing Information.**

# Lack of dystrophin causes a progressive loss of muscle strength and motor function[1,2]

DMD is caused by mutations in the dystrophin gene, which leads to a lack of dystrophin production[3]

Patients with DMD experience progressive muscle weakness, with symptom onset as early as 2 years[5]




**EARLY DIAGNOSIS** is instrumental to inform the management of progressive muscle weakness and motor function decline in patients with DMD.[6,7]

## Important Safety Information

**Warnings and Precautions (continued):** Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting VILTEPSO. Consider also measuring glomerular filtration rate before starting VILTEPSO. During treatment, monitor urine dipstick every month, and serum cystatin C and urine protein-to-creatinine ratio every three months.

# VILTEPSO is for DMD patients with a confirmed mutation that is amenable to exon 53 skipping[8]

VILTEPSO is designed to skip **exon 53 of the dystrophin pre-mRNA,*** resulting in the production of a shortened dystrophin protein containing essential functional portions[8]

Exon-skipping is designed to correct an out-of-frame variant and **enables the expression of a shorter dystrophin protein**[10]

VILTEPSO increased dystrophin levels in **100% of patients**† during clinical trials as measured by western blot, the laboratory standard for protein detection[8]

*Inside each muscle cell, DNA provides the genetic information to create dystrophin. The first step in this process is the formation of pre-mRNA from DNA. The pre-mRNA is further processed into mRNA, which is then translated into a protein.[9]

†Mean increase in dystrophin expression to nearly 6% of normal with VILTEPSO (80 mg/kg/wk) vs 0.6% at baseline. Please see the study details listed on page 6.[8]

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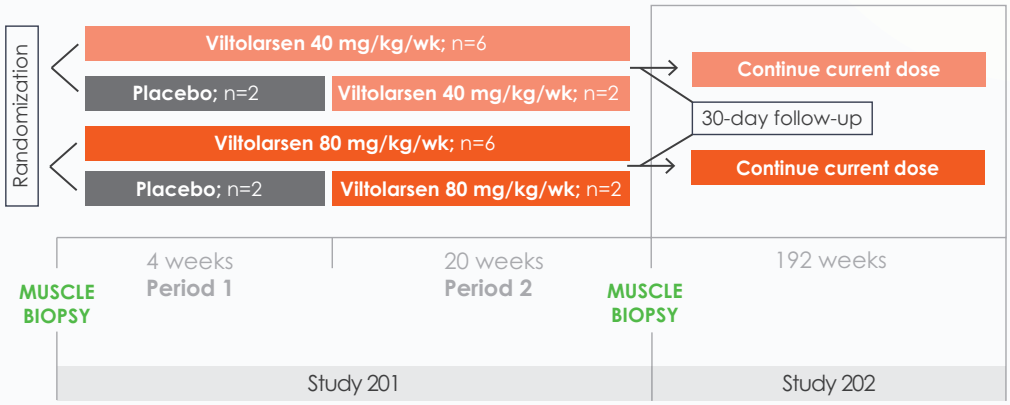
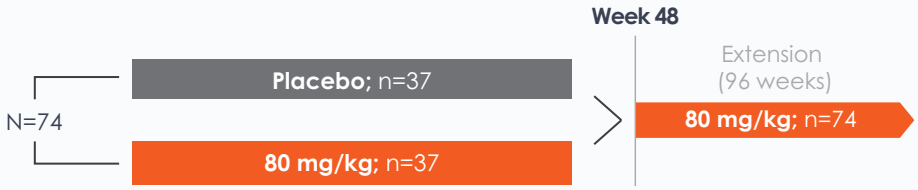
# Ongoing VILTEPSO clinical trial program results[4,8,11-15]

## STUDY 1 (PHASE II) / EXTENSION STUDY (PHASE II)




**80 MG/KG/WK IS THE APPROVED RECOMMENDED DOSE FOR VILTEPSO**

## RACER53 (PHASE III)




## Important Safety Information

**Warnings and Precautions (continued):** Urine should be free of excreted VILTEPSO for monitoring of urine protein. Obtain urine either prior to VILTEPSO infusion, or at least 48 hours after the most recent infusion. Alternatively, use a laboratory test that does not use the reagent pyrogallol red, which has the potential to generate a false positive result due to cross reaction with any VILTEPSO in the urine.

| STUDY ENDPOINTS | DESCRIPTION |
|---|---|
| **STUDY 201 (PHASE II)**<br>**Primary:** Safety, tolerability, dystrophin protein production (western blot)[4]<br>**Secondary:** Other dystrophin measures (RT-PCR, MS, and IFS), timed motor function tests (6MWT, TTCLIMB, TTRW, TTSTAND), and NSAA[4] | A 2-period, randomized, double-blind, placebo-controlled, dose-fining study, with ambulant males aged 4 to <10 years with a confirmed mutation of the DMD gene amenable to exon 53 skipping who were receiving a stable dose of corticosteroids for ≥3 months (N=16).[4,8,11]<br>Patients received a once-weekly infusion of 40 or 80 mg/kg viltolarsen or placebo for a 4-week safety period followed by a 20-week open-label study to assess the efficacy and safety of viltolarsen.[8]<br>After completion of the 24-week study, patients could enroll in up to an 192-week extension study with efficacy assessments conducted every 12 weeks. Patients were required to remain on a stable dose of glucocorticoids for the duration of the study.[13]<br>**216 weeks** |
| **STUDY 202 (PHASE II)**<br>**Primary:** TTSTAND[12]<br>**Secondary:** Safety and motor function tests (TTRW, 6MWT, TTCLIMB, NSAA, QMT)[12] | |
| **STUDY 301 (PHASE III)**<br>**Primary:** TTSTAND[14]<br>**Secondary:** TTRW, TTCLIMB, 6MWT, NSAA, and muscle strength[14] | A global, multicenter, randomized, double-blind, placebo-controlled study in ambulant males aged 4 to <8 years with a confirmed mutation of the DMD gene amenable to exon 53 skipping who were receiving a stable dose of corticosteroids for ≥3 months (N=74)[14,15]<br>**48 weeks**<br>Open-label extension study up to 96 weeks |

IFS=immunofluorescence staining; MS=mass spectrometry; NSAA=North Star Ambulatory Assessment; RT-PCR=reverse transcriptase-polymerase chain reaction; 6MWT=6-minute walk test; TTCLIMB=time to climb 4 stairs; TTRW=time to run/walk 10 meters; TTSTAND=time to stand from supine; QMT=quantitative muscle test (analysis to be conducted at study conclusion).

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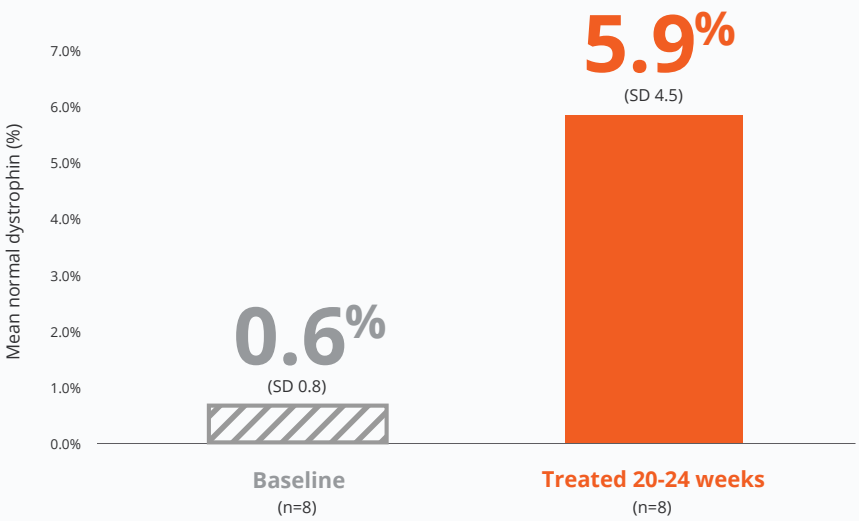
# VILTEPSO provided significant improvements in dystrophin expression[8,11]

**In Study 1, the efficacy of 20-24 weeks of VILTEPSO was evaluated in ambulant males aged 4 to <10 years.[8,11]**

**Study 1:** Mean increase in dystrophin expression to nearly 6% of normal with VILTEPSO (80 mg/kg/wk) vs 0.6% at baseline[8,11]




*P*=0.01 normalized to myosin heavy chain*

- Efficacy was assessed by validated western blot (normalized to myosin heavy chain) based on the change from baseline in dystrophin protein level, measured as percentage of the dystrophin level in healthy subjects at week 25[8]
- Mean change in dystrophin was 5.3% (SD 4.5) of normal levels (p=0.01)[8]
  - Median change from baseline was 3.8%[8]

**P*-value for change from baseline at week 25 was statistically significant[11]

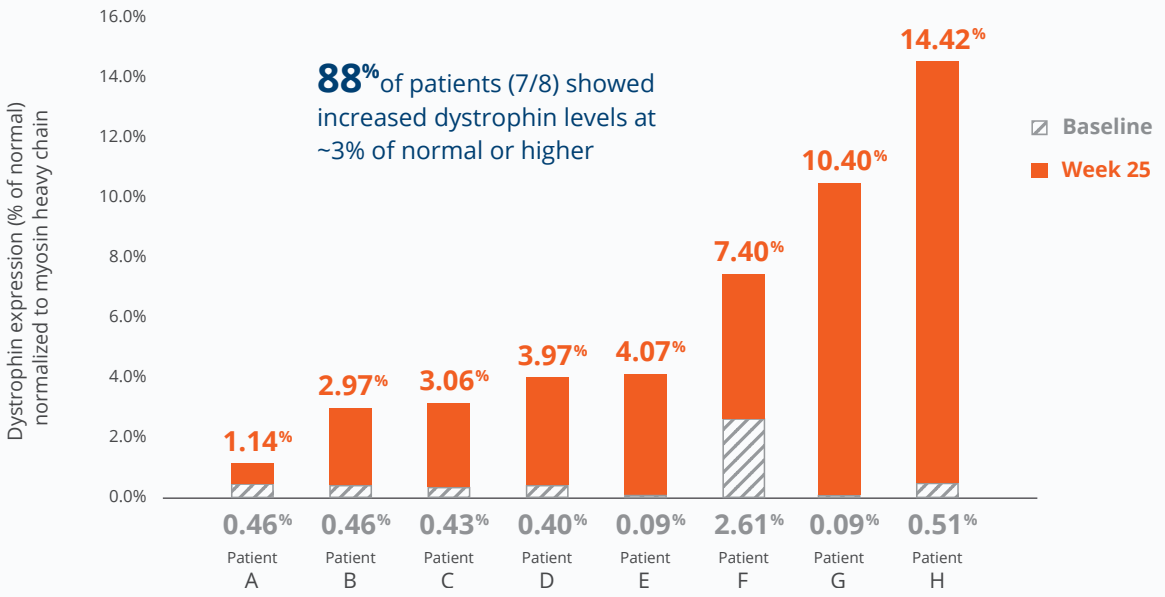
**DYSTROPHIN WHERE IT MATTERS:** Immunofluorescence staining showed VILTEPSO-induced increases in dystrophin levels were correctly localized to the muscle cell membrane, where dystrophin is needed to support muscle health.[8]

## Important Safety Information

**Warnings and Precautions (continued):** If a persistent increase in serum cystatin C or proteinuria is detected, refer to a pediatric nephrologist for further evaluation.
**Adverse Reactions:** The most common adverse reactions include upper respiratory tract infection, injection site reaction, cough, and pyrexia.

# 100% of patients showed an increase in dystrophin levels with VILTEPSO[8]

**Study 1:** Dystrophin levels at 25 weeks vs baseline[8]




- In a clinical study of patients aged 4 to <10 years, **100%** of patients showed an increase in dystrophin levels with VILTEPSO, with a mean increase in dystrophin expression to ~6% of normal vs 0.6% at baseline[8]
- Exon 53 skipping was observed, on average, in **43.9%** of dystrophin mRNA molecules in patients treated with VILTEPSO (80 mg/kg/wk), as measured by RT-PCR[4]
- The statistically significant increase in dystrophin expression was measured by western blot analysis, which is a **validated, highly sensitive,** and **reproducible** methodology[4,8]

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# In the same 24-week study, secondary endpoint results included evidence of dystrophin production and several motor function tests[4]

| Secondary endpoint | Baseline (n=8) | Week 25 VILTEPSO (n=8) |
|---|---|---|
| Exon 53 skipping efficiency assessed by RT-PCR | 0.0% | 43.9%<br>*P*=0.0001 |
| Dystrophin production assessed by MS* | 0.6% | 4.2%<br>*P*=0.03 |
| Dystrophin localization by IFS | 1.8% | 34.8%<br>*P*=0.0026 |

*Mean dystrophin levels as assessed by mass spectrometry (normalized to filamin C) increased from 0.6% (SD 0.2) of normal at baseline to 4.2% (SD 3.7) of normal by week 25, with a mean change in dystrophin of 3.7% (SD 3.8) of normal levels (nominal *P*=0.03, not adjusted for multiple comparisons); the median change from baseline was 1.9%.[8]

**Functional tests were compared to Duchenne natural history data as the control group rather than to placebo. Definitive conclusions should not be drawn. Functional data are not in the US Prescribing Information.**

| Secondary endpoint | DNHS-mean change from baseline at week 25 (n=65)† | VILTEPSO-mean change from baseline at week 25 (n=8) |
|---|---|---|
| **Time to stand** | | |
| velocity (rise/second)‡<br>(seconds)§ | -0.01<br>0.66 | 0.02<br>-0.44 |
| **Time to climb 4 stairs** | | |
| velocity (task/second)<br>(seconds) | 0.01<br>0.15 | 0.00<br>0.00 |
| **Time to run/walk 10 meters** | | |
| velocity (task/second)‡<br>(seconds)§ | -0.04<br>0.08 | 0.24<br>-0.66 |
| **6-minute walk test** ‖ | | |
| meters | -65.3 | 44.0 |
| **North Star Ambulatory Assessment**¶ | -1.1 | 1.1 |

†The control subjects for this trial were matched for age and corticosteroids from the CINRG DNHS registry.
‡Negative velocity means lower rate of velocity; positive velocity means higher rate of velocity.
§Negative time means less time; positive time means more time.
‖Negative number means less distance traveled; positive number means greater distance traveled.
¶Negative number means a lower score relative to baseline; positive number means a higher score relative to baseline.
CINRG=Cooperative International Neuromuscular Research Group; DNHS=Duchenne Natural History Study.

## Important Safety Information

**Warnings and Precautions:** Kidney toxicity was observed in animals who received viltolarsen. Although kidney toxicity was not observed in the clinical studies with VILTEPSO, the clinical experience with VILTEPSO is limited, and kidney toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Kidney function should be monitored in patients taking VILTEPSO. Serum creatinine may not be a reliable measure of kidney function in DMD patients.

# Safety profile evaluated in two 24-week clinical studies[8]

**Adverse reactions reported in ≥10% of DMD patients treated with VILTEPSO 80 mg/kg once weekly[8]**

| Adverse reaction | VILTEPSO (80 mg/kg once weekly) (N=16); n (%) |
|---|---|
| Upper respiratory tract infection* | 10 (63%) |
| Injection site reaction‡ | 4 (25%) |
| Cough | 3 (19%) |
| Pyrexia | 3 (19%) |
| Contusion | 2 (13%) |
| Arthralgia | 2 (13%) |
| Diarrhea | 2 (13%) |
| Vomiting | 2 (13%) |
| Abdominal pain | 2 (13%) |
| Ejection fraction decreased | 2 (13%) |
| Urticaria | 2 (13%) |

*Upper respiratory tract infection includes the following terms: upper respiratory tract infection, nasopharyngitis, and rhinorrhea.

‡Injection site reaction includes the following terms: injection site bruising, injection site erythema, injection site reaction, and injection site swelling.

This profile includes data from a multicenter, parallel-group, open-label, dose-finding study conducted in Japan in ambulant and non-ambulant males aged 5 to <18 years with a confirmed mutation of the DMD gene amenable to exon 53 skipping. Non-ambulant is defined as patients with a 6MWT distance of <75 meters.[8]

No treatment-related SAEs, drug-related TEAEs, discontinuations, or deaths occurred.[11,16]

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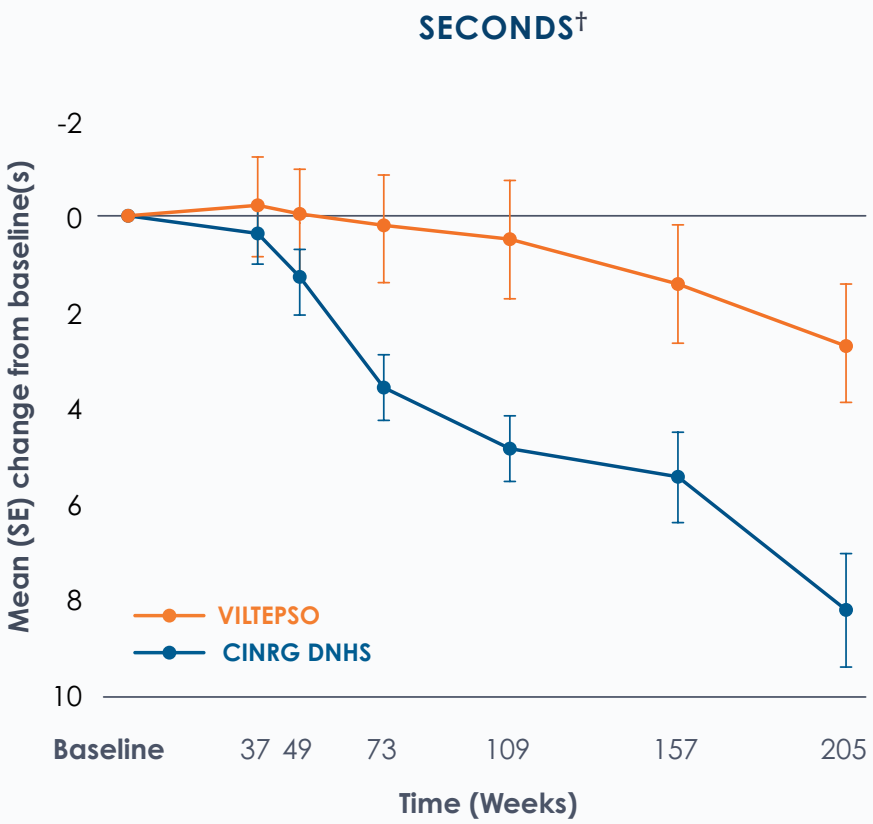
# Open-label, 4-year extension functional assessment data[13]

## Time to stand over 205 weeks*



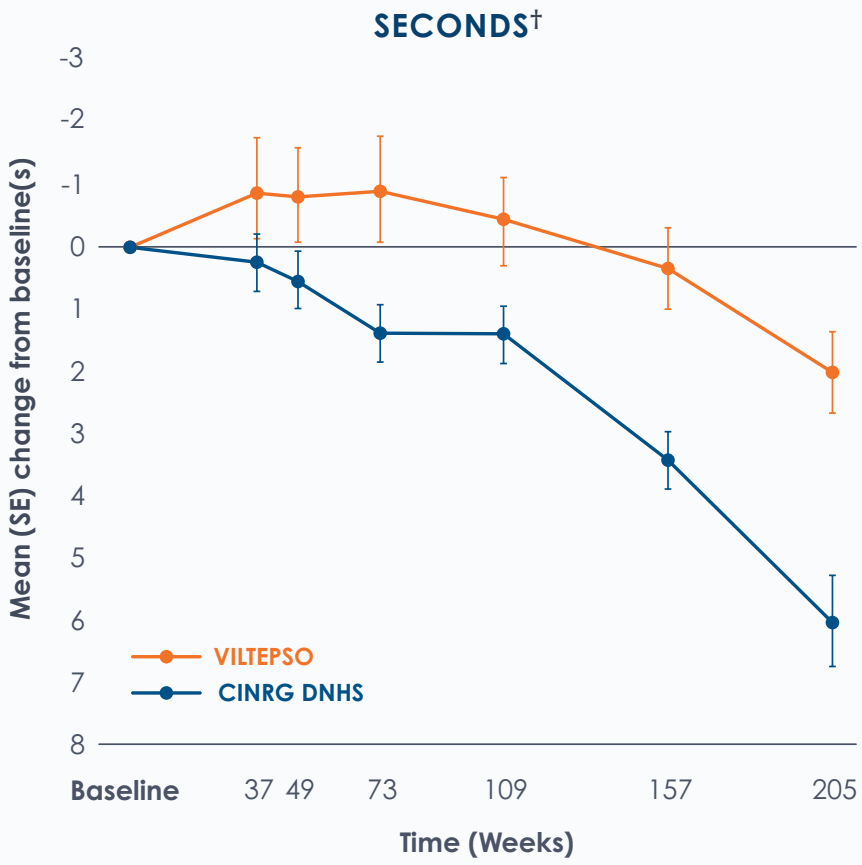

*The control subjects for this trial were matched for age, ambulatory status, corticosteroid use, and geographic location from the CINRG DNHS registry.
†Negative time means less time; positive time means more time.
CINRG=Cooperative International Neuromuscular Research Group; DNHS=Duchenne Natural History Study.

## Important Safety Information

**Warnings and Precautions (continued):** Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting VILTEPSO. Consider also measuring glomerular filtration rate before starting VILTEPSO. During treatment, monitor urine dipstick every month, and serum cystatin C and urine protein-to-creatinine ratio every three months.

**Functional tests were compared to Duchenne natural history data as the control group rather than to placebo. Definitive conclusions should not be drawn. Functional data are not in the US Prescribing Information.**

## Time to run/walk 10 meters over 205 weeks*

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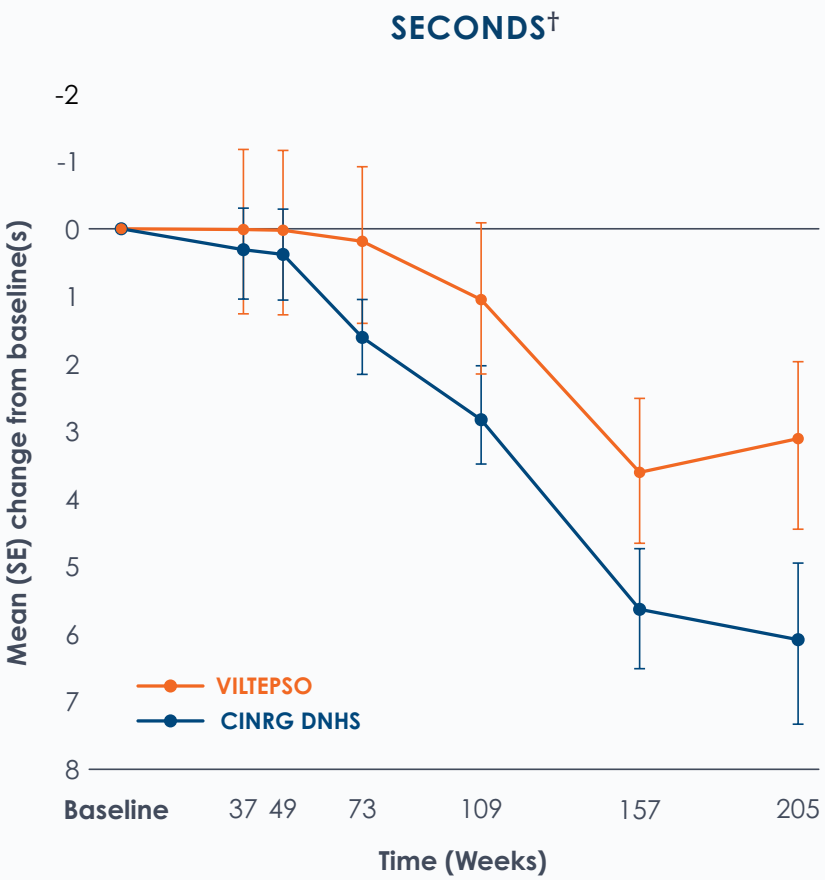
## Time to climb four stairs over 205 weeks*




*The control subjects for this trial were matched for age, ambulatory status, corticosteroid use, and geographic location from the CINRG DNHS registry.
†Negative time means less time; positive time means more time.
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## Important Safety Information

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# Safety assessment for open-label, 4-year extension study data[13]

| | Viltolarsen participants | | |
|---|---|---|---|
| **Participants with:** | **40 mg/kg/wk n=8** | **80 mg/kg/wk n=8** | **Total N=16** |
| **Any TEAE, n (%)** | 8 (100) | 8 (100) | 16 (100) |
| **Any drug-related TEAE, n (%)** | 0 | 1 (13) | 1 (6) |
| **Any serious treatment-related AE, n (%)** | 0 | 0 | 0 |
| **Study drug discontinuation due to TEAE, n (%)** | 0 | 0 | 0 |
| **Death, n (%)** | 0 | 0 | 0 |

AE=adverse event; TEAE=treatment-emergent AE; wk=week.

No patients discontinued the study; no patients died;
3 patients had SAEs, none of which were considered related to study drug

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For the treatment of DMD in patients amenable to exon 53 skipping

## VILTEPSO provided a mean increase in dystrophin to nearly 6% of normal[8]

**100%**
of patients who received VILTEPSO showed an increase in dystrophin levels from baseline[8]

**SAFETY PROFILE**
evaluated in two 24-week clinical studies[8]

Infused over
**1 HOUR**
by a healthcare professional, at home, or at a treatment center[8]

## Important Safety Information

**Warnings and Precautions (continued):** If a persistent increase in serum cystatin C or proteinuria is detected, refer to a pediatric nephrologist for further evaluation.

**Adverse Reactions:** The most common adverse reactions include upper respiratory tract infection, injection site reaction, cough, and pyrexia.

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**References: 1.** Hoffman EP, Brown RH Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell*. 1987;51(6):919-928. doi:10.1016/0092-8674(87)90579-4. **2.** Niks EH, Aartsma-Rus A. Exon skipping: a first in class strategy for Duchenne muscular dystrophy. *Expert Opin Biol Ther.* 2017;17(2):225-236. doi:10.1080/14712598.2017.1271872. **3.** Birnkrant DJ, Bushby K, Bann CM, et al; for the DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018;17(3):251-267. doi:10.1016/S1474-4422(18)30024-3. **4.** Data on file, NS Pharma, Inc. **5.** Blake DJ, Weir A, Newey SE, Davies KE. Function and genetics of dystrophin and dystrophin-related proteins in muscle. *Physiol Rev*. 2002;82(2):291-329. doi:10.1152/physrev.00028.2001. **6.** US Food and Drug Administration. Duchenne muscular dystrophy and related dystrophinopathies: developing drugs for treatment guidance for industry. Accessed May 27, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/duchenne-muscular-dystrophy-and-related-dystrophinopathies-developing-drugs-treatment-guidance. **7.** Institute for Clinical and Economic Review. Deflazacort, eteplirsen, and golodirsen for Duchenne muscular dystrophy: effectiveness and value. Accessed May 27, 2020. https://icer-review.org/wp-content/uploads/2018/12/ICER_DMD_Draft_Scope_011119-1.pdf. **8.** Viltepso [prescribing information]. Paramus, NJ: NS Pharma, Inc.; 2021. **9.** Alberts B, Johnson A, Lewis J, et al. *Molecular Biology of the Cell*. 4th ed. New York: Garland Science; 2002. From RNA to Protein. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26829/. **10.** Watanabe N, Nagata T, Satou Y, et al. NS-065/NCNP-01: an antisense oligonucleotide for potential treatment of exon 53 skipping in Duchenne muscular dystrophy. *Mol Ther Nucleic Acids*. 2018;13:442-449. doi:10.1016/j.omtn.2018.09.017. **11.** Clemens PR, Rao VK, Connolly AM, et al; for the CINRG DNHS Investigators. Safety, tolerability, and efficacy of viltolarsen in boys with Duchenne muscular dystrophy amenable to exon 53 skipping: a phase 2 randomized clinical trial. *JAMA Neurol.* 2020;77(8):982-991. doi:10.1001/jamaneurol.2020.1264. **12.** US National Library of Medicine. Extension study of NS-065/NCNP-01 in boys with Duchenne muscular dystrophy (DMD). ClinicalTrials.gov Identifier: NCT03167255. **13.** Clemens PR, Rao VK, Connolly AM, et al; Efficacy and Safety of Viltolarsen in Boys with Duchenne Muscular Dystrophy: Results From the Phase 2, Open-label, 4-year Extension Study. Poster presented at *World Muscle Society Congress*; October 11-15, 2022; Halifax, Nova Scotia, Canada. **14.** US National Library of Medicine. Study to assess the efficacy and safety of viltolarsen in ambulant boys with DMD (RACER53). ClinicalTrials.gov Identifier: NCT04060199. **15.** US National Library of Medicine. Study to assess the safety and efficacy of viltolarsen in ambulant boys with DMD (RACER53-X). ClinicalTrials.gov Identifier: NCT04768062. **16.** Komaki H, Takeshima Y, Matsumura T, et al. Viltolarsen in Japanese Duchenne muscular dystrophy patients: a phase 1/2 study. *Ann Clin Transl Neurol*. 2020;7(12):2393-2408. doi:10.1002/acn3.51235.

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## DYSTROPHIN WHERE IT MATTERS

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NS Pharma