Viltolarsen for Duchenne Muscular Dystrophy Patients Amenable to Exon 53 Skipping Therapy
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NS Pharma

Paramus, NJ, USA

- Wholly-owned, US subsidiary of Nippon Shinyaku Co., Ltd (Kyoto, Japan) founded in 1919
- Sponsor of the North American Phase 2 trials
- Focus area: Orphan Rare Disease
## Duchenne Muscular Dystrophy Pipeline

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<tr>
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<th>Discovery</th>
<th>Preclinical</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>viltolarsen (NS-065/NCNP-01) (Exon 53 Skipping)</td>
<td></td>
<td></td>
<td>P2(US)</td>
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<td></td>
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<td>P1/2(JPN)</td>
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<tr>
<td>Other Exon Skipping Programs</td>
<td>Discovery/Preclinical</td>
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</table>
Exon Skipping Strategy

Example of a deletion that disrupts the dystrophin mRNA reading frame that is restored to in-frame by exon 53 skipping

Exon 48-52 deletion: disrupts reading frame

Exon 53 skipping by viltolarsen (NS-065/NCNP-01): restores reading frame

Abnormal protein

Partly functional dystrophin protein

viltolarsen (NS-065/NCNP-01)
Overview: How Protein is Made

Step 1: Make the message

Step 2: Trim the message

Step 3: Make the protein

Step 4: Utilize the protein
Exon Skipping Overview

Step 1: Make the message
Step 2: Trim the message
Step 3: Make the protein
Step 4: Utilize the protein
Viltolarsen: Treatment of DMD in Patients Amenable to Exon 53 Skipping

• Currently, there is no cure for DMD\(^1\)

• Most treatments are palliative and do not target the molecular cause of the disease and may lead to adverse side effects
  – Steroids reduce inflammation and are a mainstay of treatment
  – Respiratory care and physical therapy for lung and muscle function, respectively
  – ACE inhibitors and beta blockers to slow the deterioration of cardiac muscle

• An estimated 8% to 10% of patients with DMD would be amenable to exon 53 skipping\(^2\)

• Viltolarsen injection is being studied as a once-weekly, 40-mg/kg or 80-mg/kg, 60-minute intravenous infusion intended for the treatment of DMD in patients amenable to exon 53 skipping of the dystrophin pre-mRNA\(^3\)

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**Duchenne Population Amenable to Exon Skipping\(^2,4\)**

- May not be amenable to exon skipping – \(~20\%\)
- Other exon skips – \(~30\%\)
- Exon 51 – 13%
- Exon 53 – \(~8\%\)
- Exon 45 – 8%
- Exon 44 – 6%
- Exon 50 – 4%
- Exon 52 – 4%
- Exon 43 – 4%
- Exon 55 – 2%
- Exon 8 – 2%

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ACE, angiotensin-converting enzyme; DMD, Duchenne muscular dystrophy; pre-mRNA, pre-messenger ribonucleic acid.

Viltolarsen Regulatory and Clinical Development Program

- November 2016: FDA granted viltolarsen with Fast Track designation\(^1\)
- January 2017: FDA granted viltolarsen with orphan drug designation\(^1\)
- February 2017: FDA granted viltolarsen with rare pediatric disease designation\(^1\)
- September 2019: NS Pharma plans to complete the NDA submission\(^1\)
- A post-approval phase 3 study is currently in development with plans to initiate enrollment in Q4 2019\(^1\)

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Clinical Development Program\(^2\)

**NCNP**: National Center of Neurology and Psychiatry

### Phase 1:
- Investigator-initiated study (Japan)
  - 1.25, 5, 20 mg/kg/wk; 12 weeks

### Phase 2:
- Dose-finding study (Japan)
  - 40, 80 mg/kg/wk; 24 weeks

### Phase 2:
- Dose-finding study (North America)
  - 40, 80 mg/kg/wk; 24 weeks

### Phase 2:
- Extension study (North America)
  - 40, 80 mg/kg/wk; long-term extension
Viltolarsen

**Origin**  
Nippon Shinyaku jointly with National Center of Neurology and Psychiatry (NCNP)

**Mechanism**  
Exon 53 skipping

**Characteristics**

- Antisense oligonucleotide with a morpholino backbone and a neutral charge
- Demonstrated exon 53 skipping activity
- Demonstrated dystrophin production across multiple models
- I.V. administration, once weekly
Phase III Study to Assess the Efficacy and Safety of Viltolarsen in Ambulant Boys With DMD
<table>
<thead>
<tr>
<th>Brief Title</th>
<th>Study to Assess the Efficacy and Safety of Viltolarsen in Ambulant Boys With DMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Official Title</td>
<td>A Phase 3 Randomized, Double-blind, Placebo-controlled, Multi-center Study to Assess the Efficacy and Safety of Viltolarsen in Ambulant Boys With Duchenne Muscular Dystrophy (DMD)</td>
</tr>
<tr>
<td>Summary</td>
<td>The main objective of this study is to evaluate the efficacy of Viltolarsen compared to placebo in Duchenne muscular dystrophy (DMD) patients amenable to exon 53 skipping.</td>
</tr>
<tr>
<td>Enrollment</td>
<td>N=74 (Anticipated)</td>
</tr>
<tr>
<td>Arms</td>
<td>Viltolarsen : Placebo = 1:1</td>
</tr>
<tr>
<td>Dosage</td>
<td>Intravenous (IV) infusion of Viltolarsen (80 mg/kg) or placebo, weekly for up to 48 weeks</td>
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</table>
Study Design

Screening → Pre Treatment Visit → Randomization → Viltolarsen 80 mg/kg/week N = 37 → Week 49 → 30 Day Follow up

Placebo N = 37 → Week 49 → 30 Day Follow up

Day -28 → Day -7 → Day -1 → Day 1 → Week 48

Pre Treatment Phase → Treatment Phase → End of Treatment Phase
### Primary and Secondary Endpoints

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Change in Time to Stand (TTSTAND)</th>
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</table>
| **Secondary Endpoints** | • Change in Time to Run/Walk 10 Meters Test (TTRW)  
• Change in Six-minutes Walk Test (6MWT)  
• Change in North Star Ambulatory Assessment (NSAA)  
• Change in Time to Climb 4 Steps Test (TTCLIMB)  
• Change in Hand-held dynamometer (elbow extension, elbow flexion, knee extension and knee flexion on the dominant side only) |
### Inclusion Criteria

- Male $\geq$ 4 years and < 8 years of age
- Confirmed DMD mutation(s) in the dystrophin gene that is amenable to skipping of exon 53 to restore the dystrophin mRNA reading frame
- Able to walk independently without assistive devices
- TTSTAND $<$ 10 seconds
- Stable dose of glucocorticoid (GC) for at least 3 months prior to study entry and is expected to remain on stable dose of GC treatment for the duration of the study
- Other inclusion criteria may apply

### Exclusion Criteria

- Surgery within the 3 months prior to the first dose of study drug or surgery is planned for anytime during the duration of the study
- Currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to the first dose of study drug or within 5 times the half-life of a medication, whichever is longer
- Previously enrolled in an interventional study of Viltolarsen
- Currently taking any other exon skipping agent or has taken any other exon skipping agent within 3 months prior to the first dose of study drug
- Having taken any gene therapy
- Other exclusion criteria may apply

### Site Locations

Japan, South Korea, Taiwan, Russia, Spain, USA and more
Thank you to all the patients and families in the Duchenne Muscular Dystrophy community who made these studies possible!