NS Pharma and the Viltolarsen Clinical Development Program

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Disclosure

- National Center of Neurology and Psychiatry and Nippon Shinyaku Co., Ltd are co-inventors of viltolarsen (previously NS-065/NCNP-01)
- Ana Christensen is a TRiNDS employee, working for NS Pharma
- This presentation is done on behalf of NS Pharma to provide general information about the studies using materials provided by NS Pharma
NS Pharma and Nippon Shinyaku

**NS Pharma, Inc. (Paramus, NJ, USA)**
- Wholly-owned, US subsidiary of Nippon Shinyaku Co., Ltd. (Kyoto, Japan)
- Sponsor of the North American Phase 2 and 3 trials
- Focus area: orphan rare disease

**Nippon Shinyaku Co., Ltd. (Kyoto, Japan)**
- Parent company of NS Pharma, Inc.
- Founded in 1919
- Four focus areas are: drugs for rare diseases, urological diseases, hematology, and gynecology
Overview of Duchenne Muscular Dystrophy (DMD) and Exon Skipping
Overview: Protein Synthesis

Transcribe the pre-mRNA
Splice the pre-mRNA
Translate the mRNA
Utilize the protein

DMD Is Caused by Mutations to the Dystrophin Gene

- **Mutation (deletion) in DMD gene**
- **DMD genetic deletion transcribed into pre-mRNA**
- **Disruption of reading frame in mRNA**
- **Production of a nonfunctional and unstable dystrophin protein**

**Diagram:**
- **DNA**
- **Exon**
- **Intron**
- **Pre-mRNA**
- **mRNA**
- **Transcription**
- **Splicing**
- **Translation**
- **Exon Deletion**
- **Cell Membrane**
- **Nonfunctional, truncated dystrophin**

“Exon Skipping” as a Strategy for DMD

Deletion in *DMD* gene

Exon neighboring the deleted exon is targeted by an AON, which is complementary to mRNA, and binds to block the exon from the splicing machinery, forcing the exclusion of the targeted exon.

Conversion of an out-of-frame deletion to an in-frame deletion

Production of a truncated but semifunctional dystrophin protein

Viltolarsen: An Investigational Drug Being Studied in Patients With DMD Amenable to Exon 53 Skipping

Viltolarsen is an investigational product that is not approved in the U.S. or globally. Its safety and efficacy has not been established by any health authorities.
Viltolarsen is being studied as a once-weekly intravenous infusion in patients with DMD amenable to exon 53 skipping.1

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

Viltolarsen Regulatory Timeline

October 2016: FDA granted viltolarsen fast-track designation

January 2017: FDA granted viltolarsen with orphan drug designation

January 2017: FDA granted viltolarsen with rare pediatric disease designation

Q3 2019: NS Pharma NDA submission completed

Q3/Q4 2019: Phase 3 study plans to initiate enrollment

2016 2017 2018 2019

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<th>Phase 1: investigator-initiated study (Japan)</th>
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<td>1.25, 5, 20 mg/kg/wk; 12 weeks¹</td>
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<th>Phase 1/2: dose-finding study (Japan)</th>
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<td>40, 80 mg/kg/wk; 24 weeks¹</td>
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<th>Phase 2: dose-finding study (North America)</th>
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<td>40, 80 mg/kg/wk; 24 weeks¹</td>
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<th>Phase 2: extension study (North America)</th>
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<td>40, 80 mg/kg/wk; long-term extension; 144 weeks¹</td>
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<th>Phase 3: efficacy and safety study (North America and Global)</th>
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<td>80 mg/kg/wk; 48 weeks²</td>
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Phase 3 Clinical Trial for Boys with DMD Amenable to Exon 53 Skipping
"Study to Assess the Efficacy and Safety of Viltolarsen in Ambulant Boys
With DMD"
Viltolarsen Phase 3 Study

**Study Design:** Randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of viltolarsen in ambulant boys with DMD amenable to exon 53 skipping.

- **74** Males 4 to <8 years of age with DMD amenable to exon 53 skipping
- **48 weeks** Weekly intravenous infusion of viltolarsen 80mg/kg or placebo (1:1)
Viltolarsen Phase 3: Primary and Secondary Endpoints

• **Primary Clinical Endpoint:** Change in Time to Stand (TTSTAND)

• **Secondary Clinical 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)

• **Safety Assessments:**
  - Adverse events
  - Physical exams, laboratory tests, electrocardiograms (ECGs), and vital signs
Viltolarsen Phase 3: Inclusion Criteria

- Male 4 to <8 years of age
- Confirmed DMD mutation(s) in the dystrophin gene 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
Viltolarsen Phase 3: Exclusion Criteria

- Current or history of chronic systemic fungal or viral infections
- Positive test results for hepatitis B antigen, hepatitis C antibody or human immunodeficiency virus (HIV)
- Acute illness within 4 weeks prior to the first dose of study drug
- Evidence of symptomatic cardiomyopathy (Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary)
- Allergy or hypersensitivity to the study drug or to any of its constituents
- Severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the investigator
- Surgery within 3 months prior to the first dose of study drug or planned surgery during the duration of the study
- Previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow-up will be correctly completed or impair the assessment of study results, in the opinion of the investigator
- Currently taking any investigational drug or has taken any 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 a study with viltolarsen
- Currently taking any exon skipping agent or has taken any exon skipping agent within 3 months prior to the first dose of study drug
- Having taken any gene therapy
- Other exclusion criteria may apply
Viltolarsen Phase 3: Study Design

Additional information on this trial is available at www.clinicaltrials.gov (NCT#04060199).
Thank you to all the patients and their dedicated families and healthcare professionals in the DMD community who make these studies possible!

For patients and families with questions about our clinical studies, please email us at DMDresearch@nspharma.com.