NS-065/NCNP-01
Phase 2 dose finding study

PPMD Annual Connect Conference
July 1, 2017
NS-065/NCNP-01 is currently in development as a treatment for DMD; it is not approved for sale in any country.

This presentation is intended for dissemination and discussion of scientific information only and is not intended as a recruitment tool.

Disclosure information for Session Chairs and Planning Committee members is included in the Disclosure Insert of the program guide. All conflicts of interest have been resolved in accordance with ACCME Standards for Commercial Support℠.

I have no actual or potential conflict of interest in relation to this program/presentation.

Grant/Research Support: NIH, Department of Defense, Sanofi/Genzyme, Amicus, NS Pharma.

Consultant: DSMB member for NIH and Pfizer. Pompe Disease Board of Advisors member for Sanofi/Genzyme.
Overview

- Sponsor and Partners
- NS-065/NCNP-01 (Exon 53 Skipping)
- Clinical Trials
- Latest Update (NS-065/NCNP-01-201)
- Next Steps
Introduction

✓ **NS Pharma, Inc.** (Sponsor) is a wholly-owned, US subsidiary of Nippon Shinyaku Co., Ltd. (Kyoto, Japan)

  - National Center of Neurology and Psychiatry (Tokyo, Japan) is a co-inventor of NS-065/NCNP-01

✓ **PharmaLex Development Services, LLC (PDS)** is a regulatory affairs and drug development consultancy

✓ **CINRG Network** and **TRiNDS**

  ✓ Dr. Paula Clemens is the Phase 2 Study Chair and CINRG Medical Director

  ✓ TRiNDS, overseen by Lauren Morgenroth, is responsible for clinical trial project management with the CINRG clinical sites
Sponsor: Nippon Shinyaku and NS Pharma

Head Office & Discovery Research Labs. in Kyoto

Tajima Shokuhin Kogyo Co., Ltd.

Sioe Pharmaceutical Co., Ltd.

Discovery Research Labs. in Tsukuba

Odashara Central Factory <Japanese GMP, ISO 14001>

NS Pharma Inc.(US)

Beijing Office

London Office
Sponsors and Partners

Study Sponsor

NS Pharma, Inc.

Regulatory/Strategic Consulting

PHARMALEX

Clinical Project Management

TRiNDS

CINRG Clinical Study Sites
# In-house DMD Pipeline

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

- **Other Exon Skipping Programs**
  - 4 programs: Discovery

![Diagram of pipeline](image-url)
NS-065/NCNP-01

- **Antisense oligonucleotide** with a novel *morpholino* backbone and molecule size
- Originated in Nippon Shinyaku jointly with National Center of Neurology and Psychiatry (NCNP)
- **Exon 53 skipping agent** (Mechanism of Action)
- **IV infusion, once weekly**
Mechanism of Action

Dystrophin mRNA

Normal

DMD

DMD + NS-065

Exon 53 skipping

Partly functional protein

Normal

Out of frame

Abnormal

51 52 53 54

51 52 53 54

51 54

51 54

53
NS-065/NCNP-01 is targeted to skip Exon 53

<table>
<thead>
<tr>
<th>Target Exon</th>
<th>Deleted Exon</th>
<th>Patient % out of DMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>29-50, 50, 45-50, 48-50, 49-50, 52, 52-63</td>
<td>13</td>
</tr>
<tr>
<td>53</td>
<td>43-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52</td>
<td>8</td>
</tr>
<tr>
<td>44</td>
<td>35-43, 45, 45-54</td>
<td>6</td>
</tr>
<tr>
<td>43</td>
<td>44, 44-47, 44-48</td>
<td>4</td>
</tr>
<tr>
<td>46</td>
<td>45, 47-54</td>
<td>4</td>
</tr>
<tr>
<td>50</td>
<td>51, 51-53, 51-55</td>
<td>4</td>
</tr>
<tr>
<td>52</td>
<td>51, 53, 53-55</td>
<td>4</td>
</tr>
</tbody>
</table>

Investigator-Initiated Phase 1 Study

Design: Open label, Escalating dose, Safety, PK, Muscle dystrophin

# of patients: 10 DMD boys

Dosing: Once weekly IV infusion for 12 weeks

Study site: NCNP, Tokyo, Japan

Cohort 1
- 1.25 mg/kg IV (n=3) for 12 weeks

Cohort 2
- 5.0 mg/kg IV (n=3) for 12 weeks

Cohort 3
- 20 mg/kg IV (n=4) for 12 weeks
Completed Phase 1 Study

March 23, 2015

- Muscle dystrophin mRNA with amino acid reading frame restored by exon 53 skipping in every dose group
- Restored muscle protein expression detected in the high dose group
- No serious adverse events
- No discontinuation of treatment
- Adverse events of anemia and mild impairment of renal function

For more information:
Clinical Study: NS-065/NCNP-01-201

Current Study in the US

A Phase 2, Dose Finding Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of NS-065/NCNP-01 in Boys with Duchenne Muscular Dystrophy (DMD)
Clinical Sites

For updated information, please visit at ClinicalTrials.gov
Phase 2 design

Star 1st Muscle biopsy

Screening → Randomization

NS-065/NCNP-01
40 or 80mg/kg
N=6

Placebo
N=2

NS-065/NCNP-01
40 or 80mg/kg
N=8

Star 2nd Muscle biopsy

Patient Choice

Continue current dose

30-day Follow-up

Day-21 Day1 Period 1 (4wks) Week5 Period 2 (20wks) Week24 Extension (24wks)

• All patients will receive NS-065/NCNP-01 40 or 80mg/kg
• Muscle biopsy is conducted twice during the study
• 80mg/kg cohort will be initiated after safety of 40mg/kg is confirmed (at week 5)
Study Population

Approximately 16 patients, 8 in each cohort
(4 - <10 years of age)
with DMD amenable to exon 53 skipping
Summary of Inclusion Criteria

✓ Patient has a confirmed DMD mutation(s) in the dystrophin gene that is amenable to skipping of exon 53

✓ Patient is ≥ 4 years and <10 years of age

✓ Patient is able to walk independently without assistive devices

✓ Patient is able to complete strength and function tests

✓ Patient must be on a stable dose of glucocorticoid for at least 3 months prior to study entry
Summary of Exclusion Criteria

- Patient has evidence of symptomatic cardiomyopathy
- Patient has an allergy or hypersensitivity to the study medication
- Patient is taking any other investigational drug currently or within 3 months prior to the start of study treatment
- Patient has had surgery within the 3 months prior to the first anticipated administration of study medication
- Patient has positive test results for HB antigen, HCV antibody or HIV antibody
Study Endpoints

• Primary
  - Safety and tolerability
  - Muscle dystrophin protein (mass spectrometry)
  - Pharmacokinetics

• Secondary
  - Muscle dystrophin mRNA, protein (IHC, WB)
  - Strength, mobility, functional exercise capacity
Safety Data (Cohort 1 preliminary results)

- There are no serious AEs, no AEs leading to discontinuation and no drug-related AEs.
- All AEs are mild in severity.
- DSMB review of the safety data of Cohort 1.
PHASE ½ DOSE FINDING STUDY (JPN)

Design: Phase1/2, Open label, multicenter
Subjects: ≥ 5 years and <18 years of age (including non-ambulant) Amenable to skipping of exon53

Objectives:
- **Primary Endpoint**
  - Efficacy
- **Secondary Endpoint**
  - Safety
  - Pharmacokinetics
Next Steps

➢ Extension Study

  Duration : Additional 24 Weeks
           (Total 48 Weeks)
  Endpoints : Safety, Effects on muscle strength, mobility, and functional exercise capacity
Patient Advocate

For more information,
Please contact to Lauren Morgenroth
(trialinfo@nspharma.com)

or

Visit at ClinicalTrials.gov
(NCT02740972)

http://www.nspharma.com/