A Phase 1/2 Study Of NS-050/NCNP-03, An Investigational Exon 50 Skipping Therapy, In Boys With Duchenne Muscular Dystrophy (Meteor50): Trial Design

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is an X-linked recessive disease caused by dystrophin gene mutations, resulting in loss of functional dystrophin protein[1]
- The majority of reported dystrophin gene mutations that cause DMD result in frame shifts[2]
- 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 (**Figure 1**)[3]
- NS-050/NCNP-03 is an antisense oligonucleotide designed to treat patients with DMD mutations amenable to exon 50 skipping DMD developed by the National Center of Neurology and Psychiatry (NCNP) and Nippon Shinyaku Co., Ltd.
- NS-050/NCNP-03 has shown, even in low concentration, exon 50 skipping activity on cells derived from DMD patients and the restoration of dystrophin protein expression. An exon 50 skipping activity on skeletal muscles of cynomolgus monkeys was also seen on intravenous administration studies
- Here we describe the design of Meteor50, a Phase 1/2 study assessing the safety, tolerability, pharmacodynamics, pharmacokinetics, and efficacy of NS-050/NCNP-03 in ambulant boys with DMD mutations amenable to exon 50 skipping (NCT06053814)

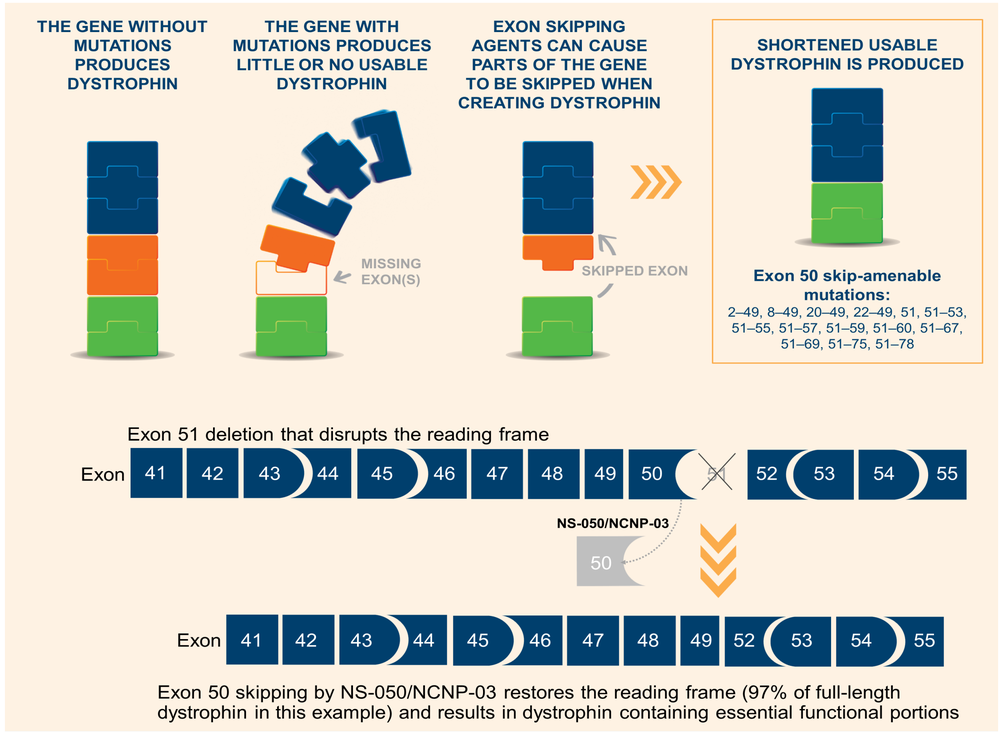

Figure 1. Exon 50 skipping strategy

NS-050/NCNP-03 CLINICAL DEVELOPMENT PROGRAM

PHASE 1/2 (METEOR50) STUDY DESIGN

- This is a planned Phase 1/2, first-in-human, randomized, multicenter, 2-part study of NS-050/NCNP-03 in ambulant boys with DMD amenable to exon 50 skipping
- In Part 1, 9 participants will be randomized 2:1 to receive escalating intravenous (IV) doses of NS-050/NCNP-03 or a matching placebo once weekly for 2 weeks per dose level (**Figure 2**)
- In Part 2, 11 additional participants (N = 20) will receive IV NS-050/NCNP-03 once weekly for 24 weeks at the maximum tolerated dose determined in Part 1
- Muscle biopsy samples will be taken during the Pre-Infusion Visit and at Week 25 of Part 2
- Participants who complete the study will be eligible to enter an open-label extension study under a separate protocol

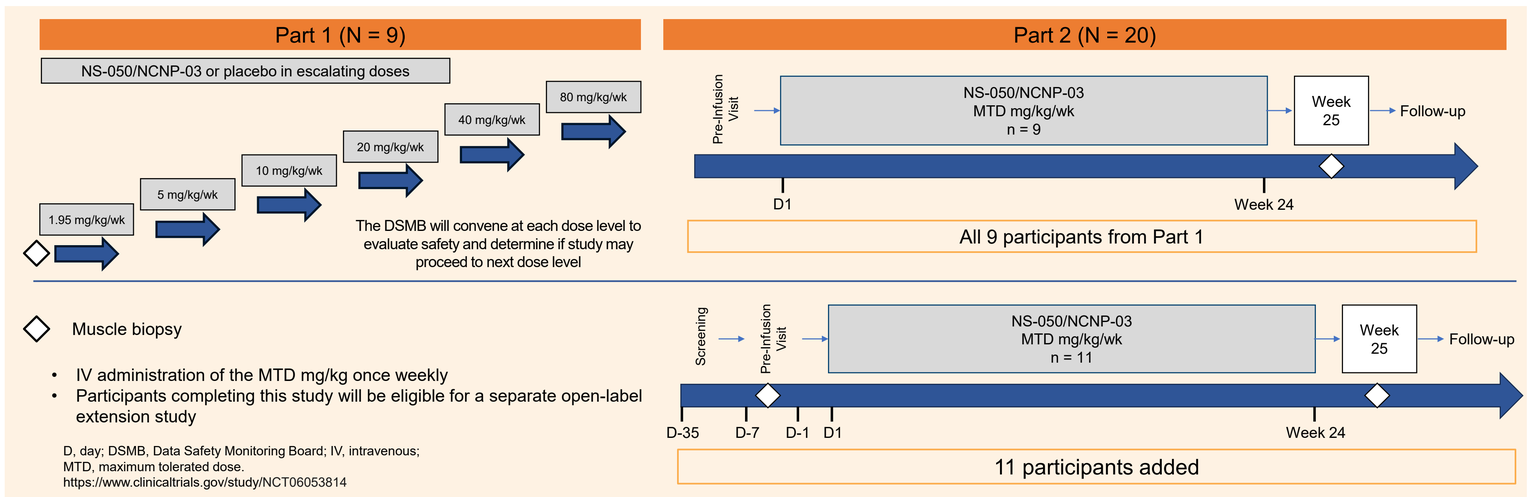

Figure 2. Meteor50 study design

KEY ELIGIBILITY CRITERIA

Key Inclusion criteria

- Male aged ≥4 and <15 years at the time of first infusion of study drug
- Has a confirmed diagnosis of DMD with a mutation(s) amenable to skipping of exon 50 to restore the dystrophin mRNA reading frame
- Able to walk independently without assistive devices
- Able to complete TTSTAND without assistance in <20 seconds
- Must be on a stable dose of glucocorticoid for at least 3 months prior to first dose of study drug and expected to remain on a stable dose for the duration of the study

Key Exclusion criteria

- Evidence of symptomatic cardiomyopathy (New York Heart Association Class III or higher)
- Current or previous treatment with anabolic steroids or products containing resveratrol or adenosine triphosphate or has taken these drugs within 3 months prior to first dose of study drug
- Currently taking another investigational drug or has taken one within 3 months prior to the first dose of study drug
- Had surgery within 3 months prior to the first administration of study drug or has major surgery planned for any time for the duration of the study
- Has taken any gene therapy

STUDY OBJECTIVES

Part 1

- The safety and tolerability of multiple ascending dose (MAD) levels of NS-050/NCNP-03
- The pharmacokinetics (PK) of MAD levels of NS-050/NCNP-03.

Part 2

Primary

- The effects of NS-050/NCNP-03 on the induction of dystrophin protein in skeletal muscle by Western blot

Secondary

- The effects of NS-050/NCNP-03 on the induction of dystrophin messenger ribonucleic acid (mRNA) and protein in skeletal muscle by mass spectrometry and immunofluorescence staining
- Compare the effect of NS-050/NCNP-03 on muscle strength, mobility, and functional exercise capacity vs. a group-matched natural history control group
- The safety and tolerability of NS-050/NCNP-03 after 24 weeks of once-weekly IV treatment

REFERENCES
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COI
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