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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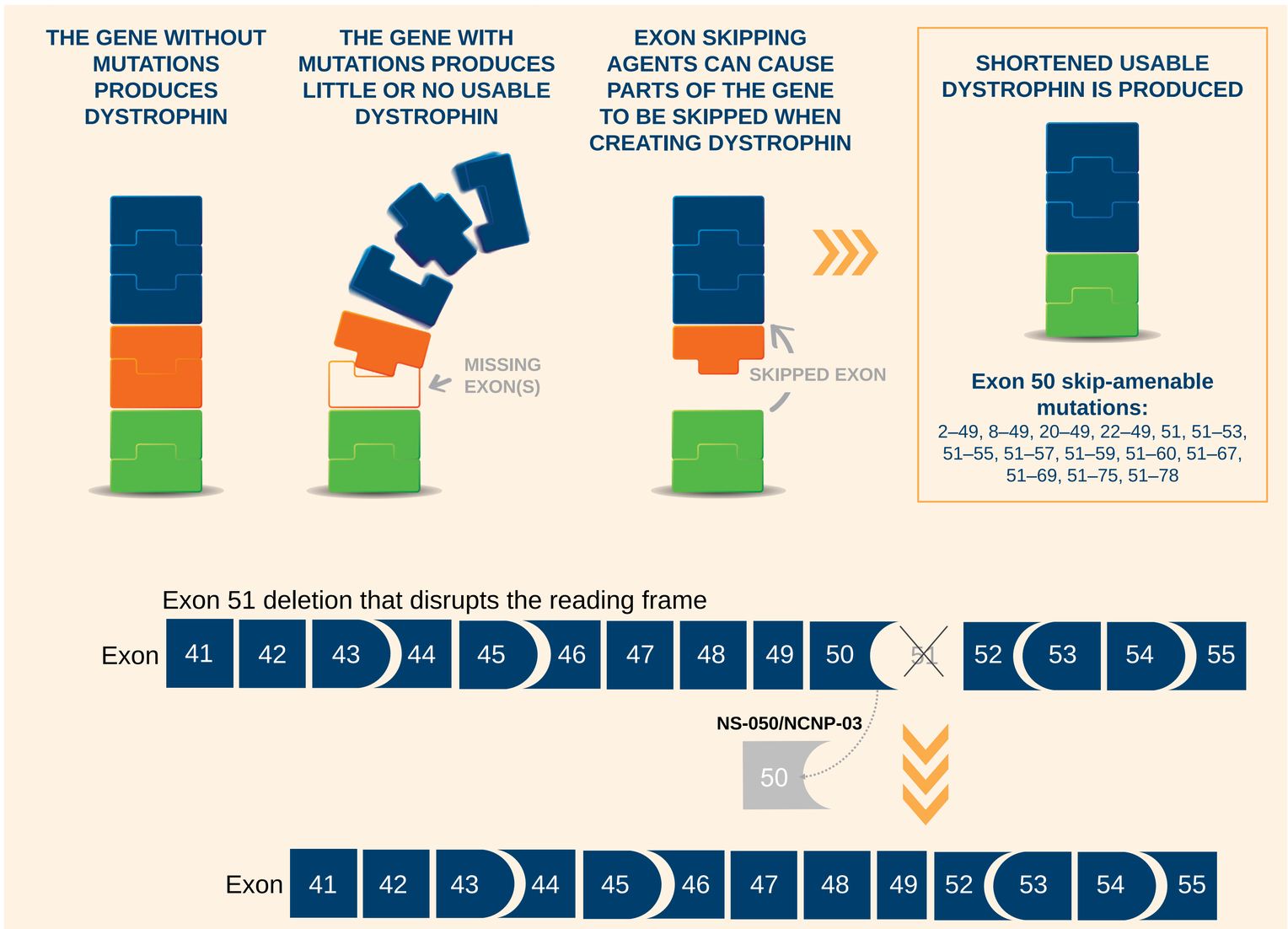
BACKGROUND

- 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
- 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

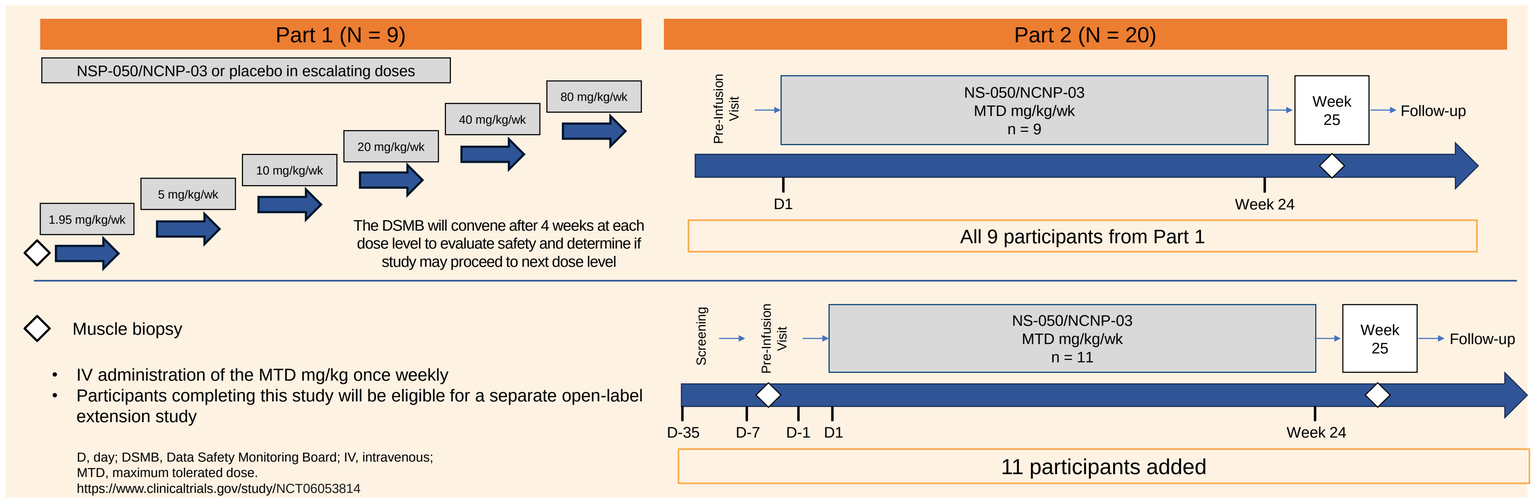


Exon 50 skipping by NS-050/NCNP-03 restores the reading frame (97% of full-length dystrophin in this example) and results in dystrophin containing essential functional portions

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 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



D, day; DSMB, Data Safety Monitoring Board; IV, intravenous; MTD, maximum tolerated dose.
https://www.clinicaltrials.gov/study/NCT06053814

Key eligibility criteria

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 <7 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
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

DMD, Duchenne muscular dystrophy; TTSTAND, time to stand from supine.

STUDY OUTCOMES

Outcomes	Part 1	Part 2
Safety	★	✓
Tolerability	★	✓
Pharmacokinetics	★	
Dystrophin induction in skeletal muscle as measured by validated Western blot		★
Dystrophin mRNA splicing measured by reverse transcriptase polymerase chain reaction		✓
Dystrophin localization by immunofluorescence staining		✓
Dystrophin protein production by mass spectrometry		✓
Motor function assessments: North Star Ambulatory Assessment, time to run/walk 10 m, time to stand from supine, 6-minute walk test, time to climb 4 stairs, quantitative muscle test, grip and pinch strength, Performance of Upper Limb 2.0		✓

★ Primary outcome ✓ Secondary outcome

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