Brogidirsen, an investigational exon 44 skipping agent for the treatment of Duchenne muscular dystrophy: Clinical trial design (Phase 2)

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by mutations in the dystrophin gene, 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[3]
- Brogidirsen (NS-089/NCNP-02) is a novel phosphorodiamidate morpholino oligomer (PMO) that causes exon skipping by utilizing 2 linked sequences targeting 2 separate binding sites within exon 44 (**Figure 1**)
- In a previous Phase 1/2 study (Study ID: NCNP/DMT02; NCT04129294), skeletal muscle dystrophin levels increased significantly after 24 weeks of brogidirsen treatment (mean change from baseline: 13.1%, *P* = 0.031; **Figure 2**)[4]
- Here, we describe the design of a Phase 2 study assessing the safety, tolerability, efficacy, and pharmacokinetics of brogidirsen (NS-089/NCNP-02) for the treatment of DMD (NCT05996003)

Figure 1. Exon skipping with brogidirsen's novel dual binding mechanism of action

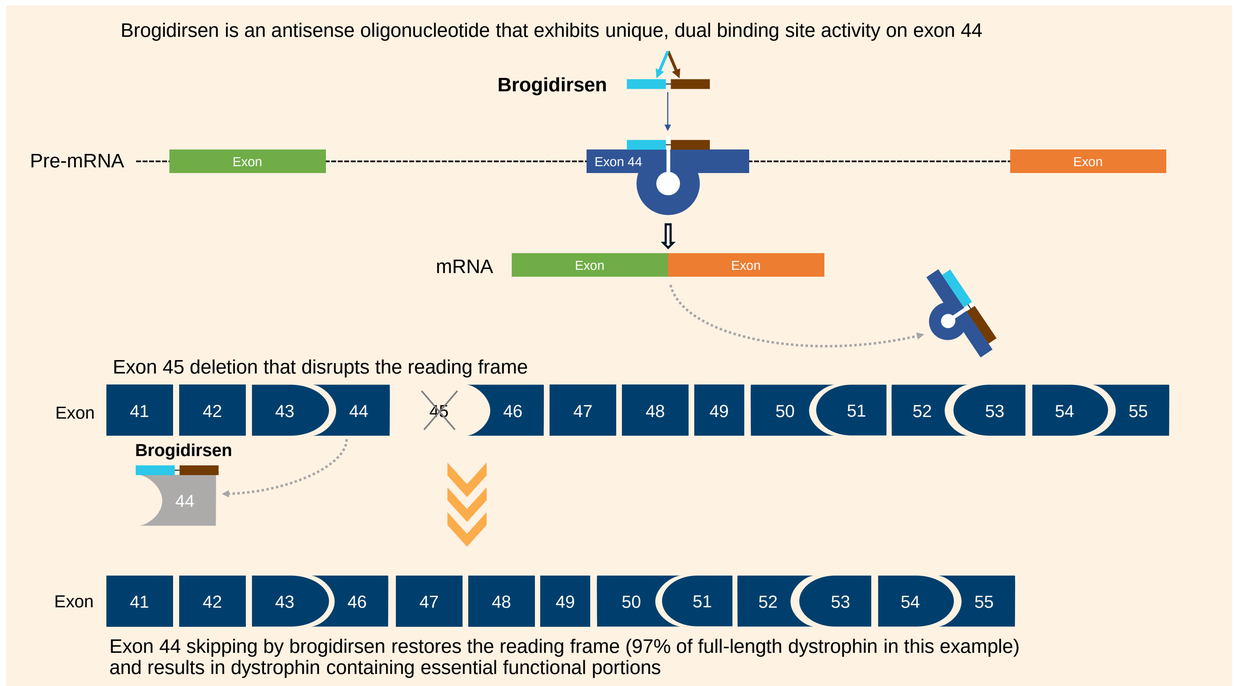
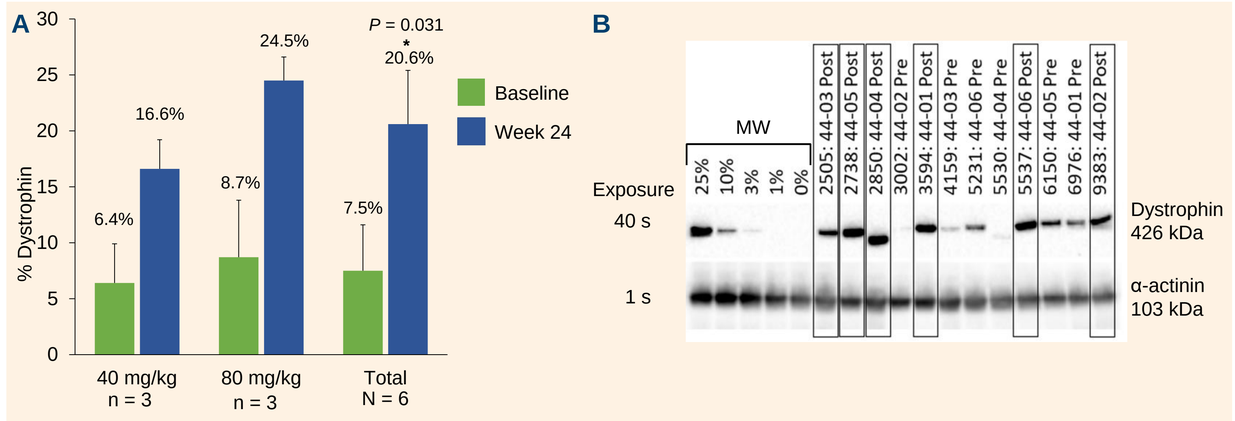


Figure 2. Dystrophin protein induced by brogidirsen treatment at Week 24 in a previous Phase 1/2 trial

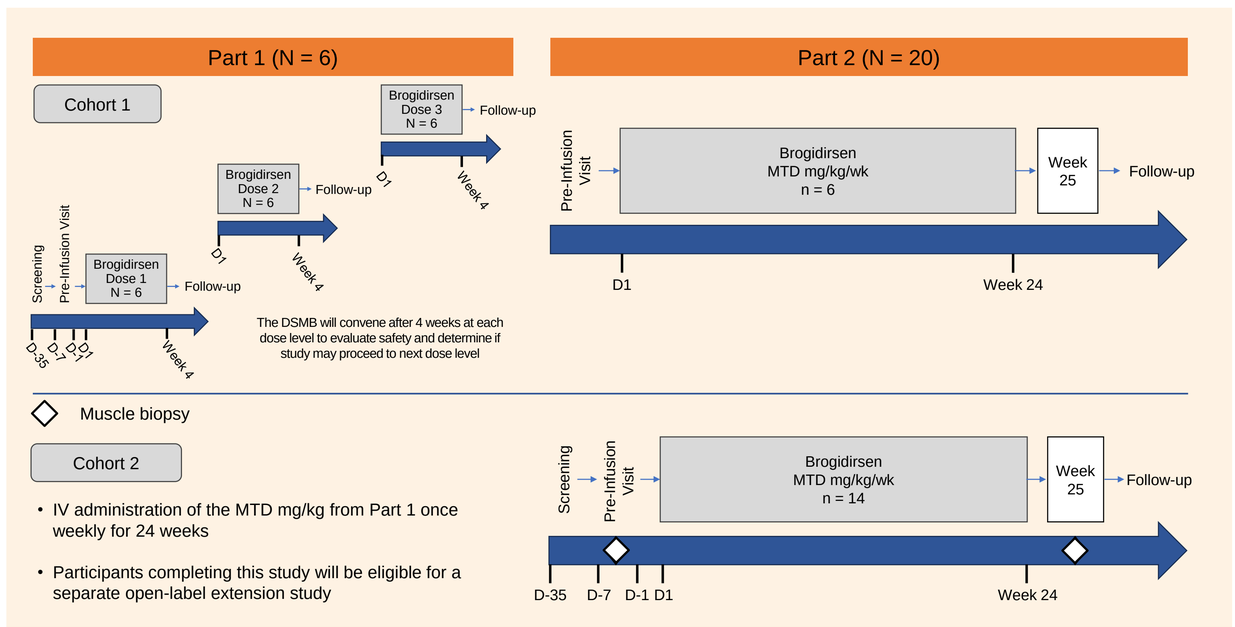


Data previously presented at World Muscle Society Congress 2022.
A: Shown are the mean + standard deviation; *P*-value is of the mean change from baseline and was derived using the Wilcoxon signed-rank test.
B: Dystrophin was normalized to alpha actinin.
Da, Dalton; MW, molecular weight.

STUDY DESIGN

- This is a Phase 2, open-label, multicenter, 2-part study of brogidirsen in ambulatory boys with DMD amenable to exon 44 skipping
- In Part 1, 6 participants will receive ascending intravenous (IV) brogidirsen once weekly for 4 weeks at 3 different dose levels (**Figure 3**)

Figure 3. NS-089/NCNP-02-201 study design



- IV administration of the MTD mg/kg from Part 1 once weekly for 24 weeks
- Participants completing this study will be eligible for a separate open-label extension study

D, day; DSMB, Data Safety Monitoring Board; IV, intravenous; MTD, maximum tolerated dose.

- The Data Safety Monitoring Board will convene after 4 weeks at each dose level to evaluate safety and determine if the study may proceed to next dose level
- In Part 2, 14 additional participants (N = 20) will receive IV brogidirsen once weekly for 24 weeks at the maximum tolerated dose determined in Part 1
- Muscle biopsies will be taken for Cohort 2 in Part 2 at the Pre-Infusion Visit and at Week 25
- Participants who complete the study will have the option to enter an open-label extension study under a separate protocol

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) in the dystrophin gene amenable to exon 44 skipping to restore the dystrophin mRNA reading frame
Able to walk independently without assistive devices
Able to complete the TTSTAND without assistance in <7 seconds
Must be on a stable dose of glucocorticoid for ≥3 months prior to the 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)
Currently taking 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 or has taken any other investigational drug within 3 months prior to the first dose of study drug or within 5× the half-life, whichever is longer
Had major 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 or other exon skipping oligonucleotide

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

STUDY OUTCOMES

Part 1 (US only)	Cohort 1 (n = 6)
Safety	★
Tolerability	★
Pharmacokinetics	★
Part 2 (US and Japan)	**Cohort 1 (n = 6)** / **Cohort 2 (n = 14)**
Safety	★ / ★
Tolerability	★ / ★
Pharmacokinetics	★ / ★
Dystrophin protein induction in bicep muscle as measured by Western blot	/ ★
Dystrophin mRNA splicing measured by reverse transcriptase polymerase chain reaction	/ ✓
Dystrophin localization by immunofluorescence staining	/ ✓
Dystrophin protein induction 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, and Performance of Upper Limb 2.0[a]	✓ / ✓

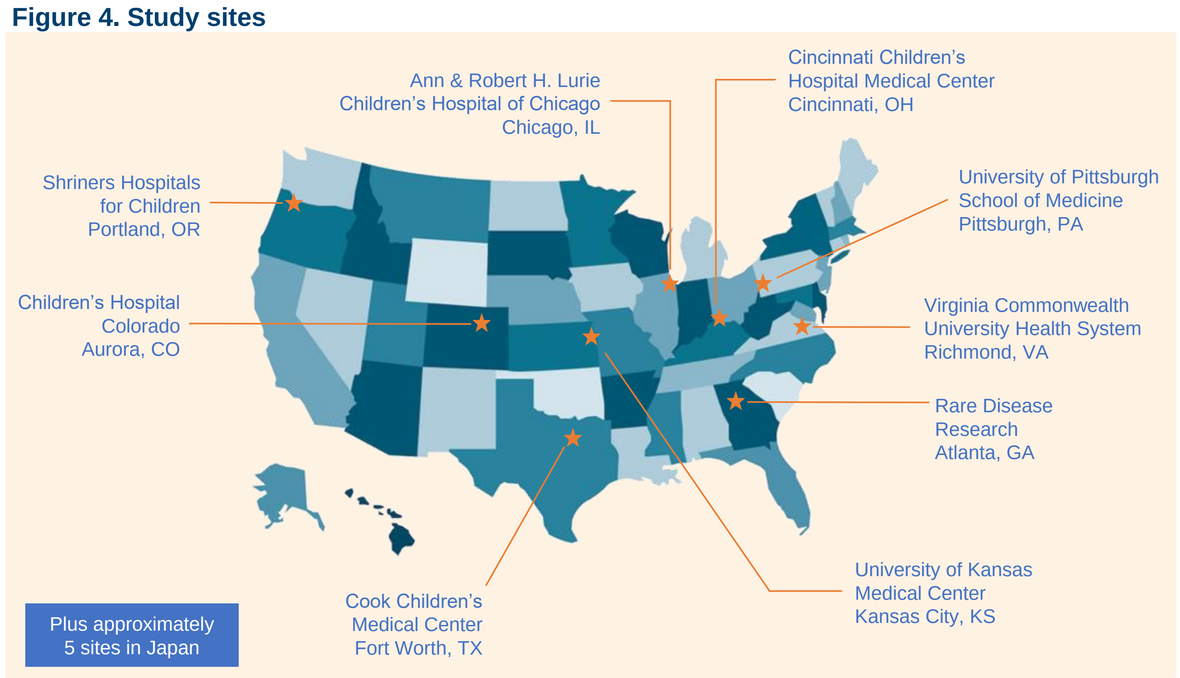
[a]These assessments will be compared against a matched historical control group.

★ Primary outcome ✓ Secondary outcome

STUDY SITES

- Study site details and contact information can be found at ClinicalTrials.gov (**Figure 4**)

Figure 4. Study sites



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