

Brogidirsen 5-Year Safety and Efficacy Outcomes in Duchenne Muscular Dystrophy Patients: Findings From an Ongoing Open-Label Extension Study

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1. Background

- Duchenne muscular dystrophy (DMD) is a progressive genetic muscle disease linked to the X chromosome caused by mutations in the DMD gene which encodes dystrophin, a protein crucial for muscle function.
- Brogidirsen (NS-089/NCNP-02) is a novel phosphorodiamidate morpholino oligomer (PMO) developed by NCNP and Nippon Shinyaku. It induces exon skipping by utilizing 2 linked sequences targeting two separate binding sites within exon 44. This dual-targeting induces efficient exon 44 skipping and restores dystrophin expression in DMD patients with exon deletion(s) amenable to exon 44 skipping.
- Reported Phase 1/2 Study¹ and the Phase 2 Extension Study data up to Week 195² showed no safety or tolerability concerns, dystrophin restoration and motor functional stabilization in DMD patient administered with brogidirsen.

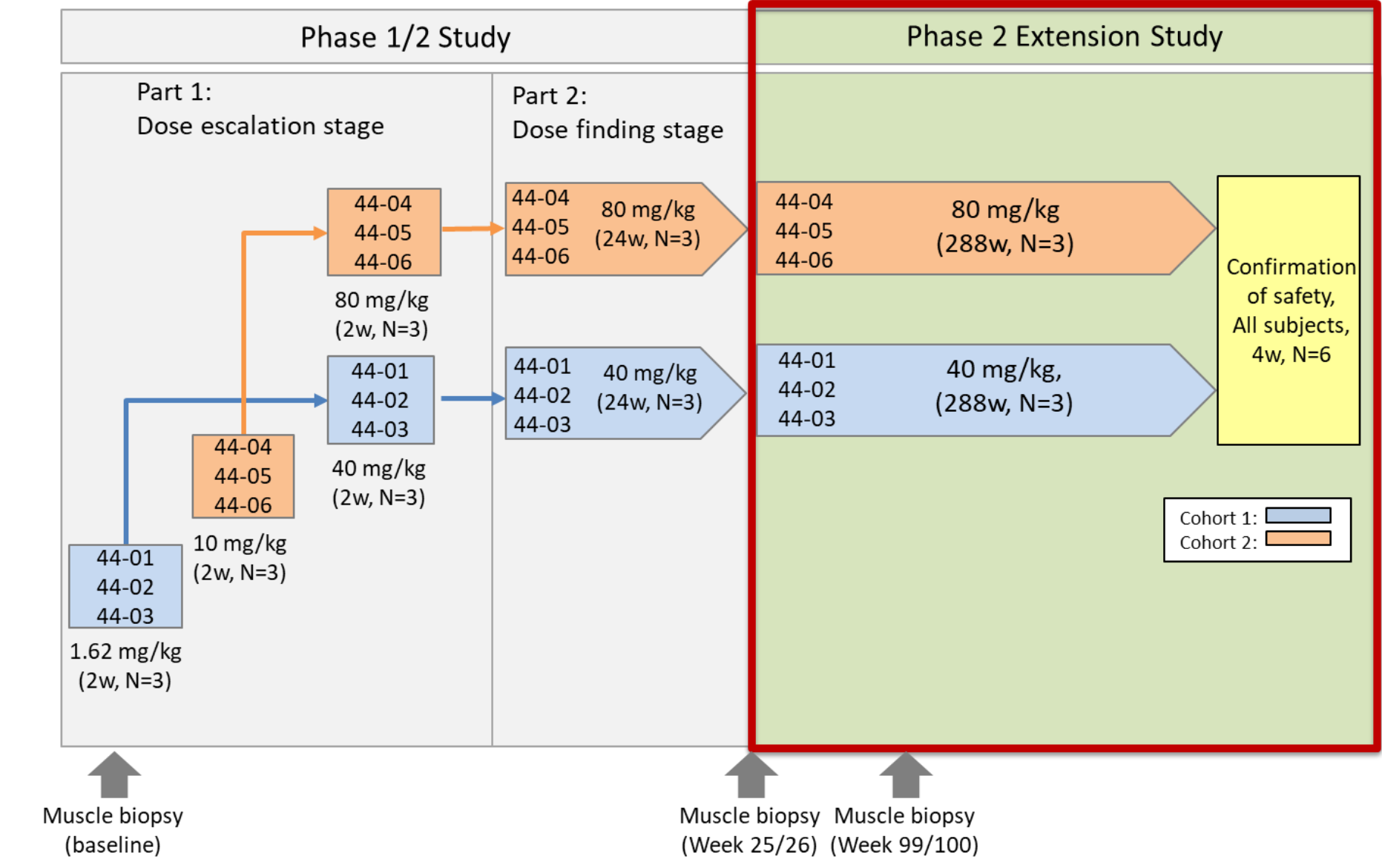
2. Summary of Results

- The Phase 1/2 Study and the Phase 2 Extension Study (up to Week 267) did not reveal any drug-related severe adverse events that interfered with the continuation of the study.
- Motor function was maintained or improved in some participants from the initiation of weekly administration in assessments such as NSAA and PUL 2.0.
- After 5 years of continued treatment, some participants showed favorable TTSTAND and TTRW results, whereas the natural history group declined.

3. Study Design

Phase 1/2 Study (NCNP/DMT02; NCT04129294)

Phase 2 Extension Study (NS089/NCNP02-P2OE; NCT05135663)



4. Participant Characteristics

		40 mg/kg (Cohort 1, N=3)	80 mg/kg (Cohort 2, N=3)	Total (N=6)
Age at Phase 1/2 Study	Mean (SD)	10.0 (4.6)	9.7 (0.6)	9.8 (2.9)
	Range	5-14	9-10	5-14
Age at Phase 2 Extension Study W267 (yrs)	Mean (SD)	15.0 (4.6)	14 (0.0)	14.5 (2.9)
	Range	10-19	14-14	10-19
Mutation (deleted exons)N (%)				
	45	3 (100)	2 (66.7)	5 (83.3)
	45-54	0 (0)	1 (33.3)	1 (16.7)
	Steroid treatment	Yes/No	Yes*	Yes
Dystrophin Expression (Western blot: normalized to α-Actinin (%))**				
Part 1 Pre-treatment	Mean (SD)	6.36 (3.45)	8.68 (5.14)	7.52 (4.12)
W25/26	Mean (SD)	16.63 (2.58)	24.46 (2.08)	20.55 (4.78)
Phase 2 Extension Study W99/100	Mean (SD)	13.18 (11.31) [#]	18.17 (4.10)	16.17 (6.92)
Exon 44 Skipping Efficiency by RT-PCR (molarity (%))**				
Part 1 Pre-treatment	Mean (SD)	11.41 (7.00)	18.42 (11.12)	14.92 (9.16)
W25/26	Mean (SD)	40.97 (10.52)	53.07 (15.94)	47.02 (13.78)
Phase 2 Extension Study W99/100	Mean (SD)	47.84 (1.89) [#]	61.66 (16.55)	56.14 (13.97)

* : 44-02 initiated steroid use during the post-treatment period of the Phase 1/2 Study. ** : Phase 2 Extension Study W99/100 has limited quantitative comparability with the other time points due to separate measurements and different measurement conditions. # : N=2

5. Safety Results

- All adverse events (AEs) observed up to Week 267 were mild or moderate, and most of them resolved within 30 days.
- There was no serious or severe AEs related to brogidirsen, or AEs related to infusion-related reactions such as anaphylaxis, or immune-mediated myositis, or discontinuation observed due to AEs.

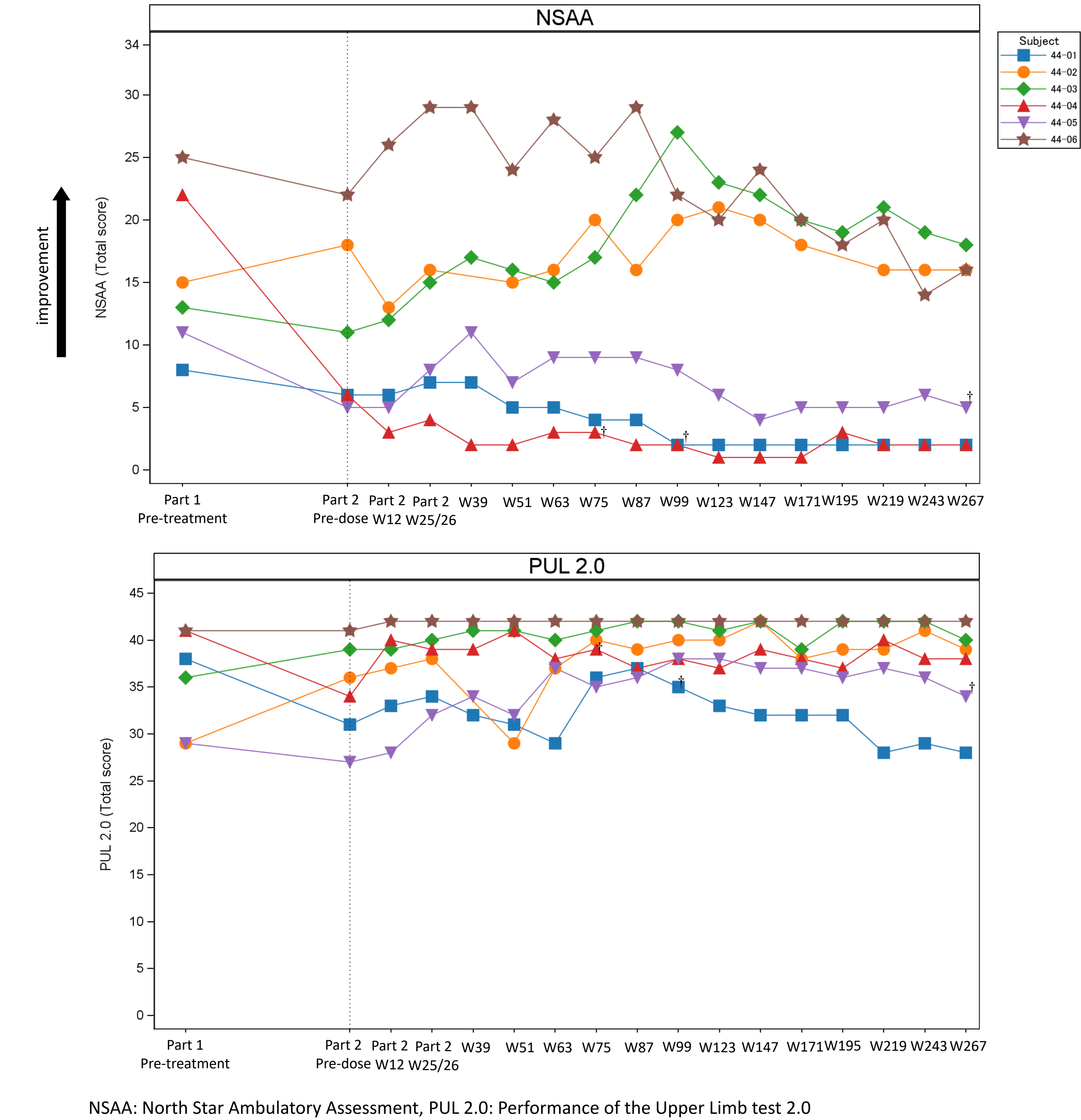
Drug-related AEs reported in ≥2 participants in Phase 2 Extension Study (MedDRA/J ver.24)

AEs	40 mg/kg (N=3)	80 mg/kg (N=3)	Total (N=6)
Beta 2 microglobulin urine increased	3 (100.0)	0 (0.0)	3 (50.0)
Urine albumin/creatinine ratio increased	3 (100.0)	1 (33.3)	4 (66.7)
Cystatin C increased	1 (33.3)	1 (33.3)	2 (33.3)

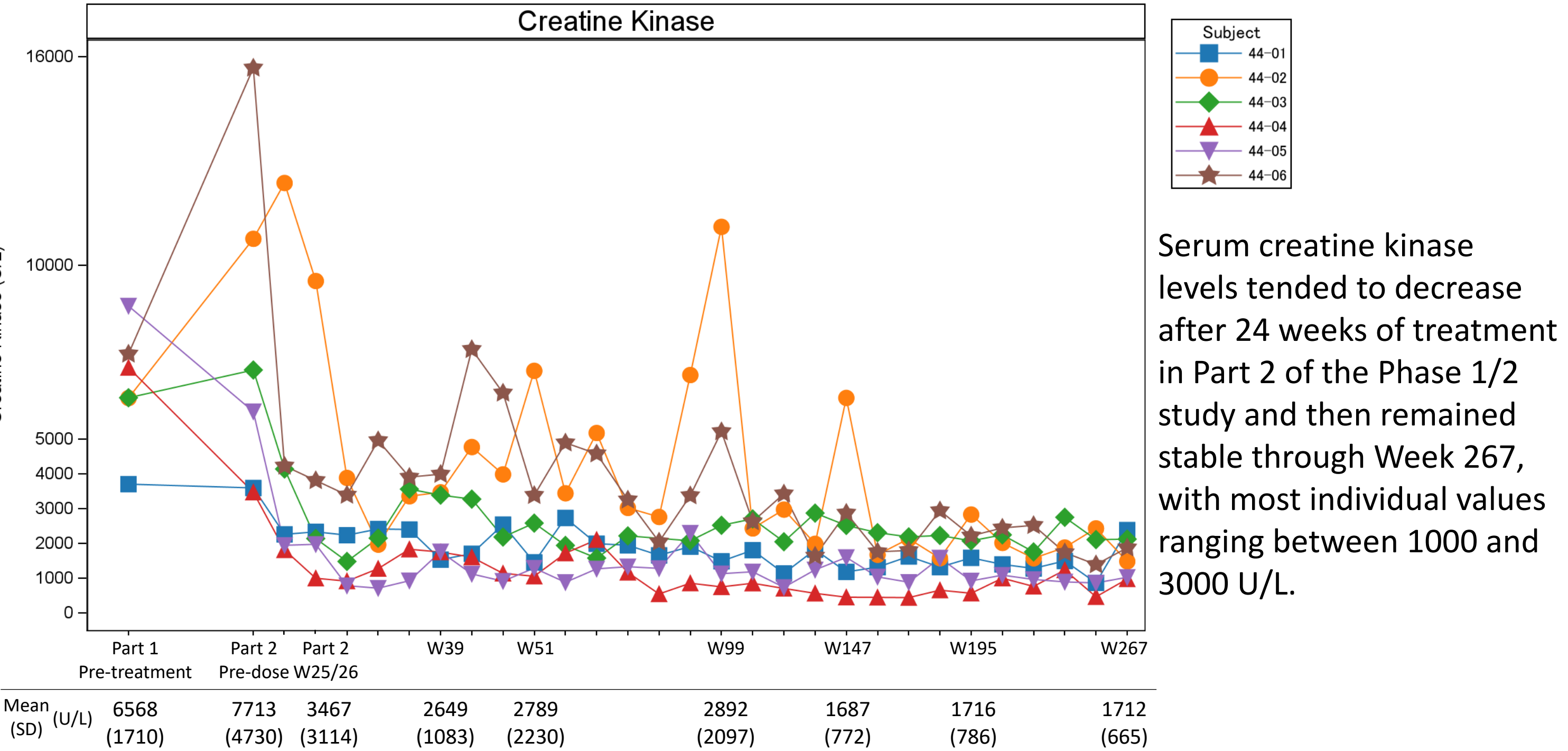
6. Efficacy Results (Motor function Assessment)

- Participant 44-03 showed sustained motor function improvement, with a 7-point increase in NSAA total scores from Part 2 pre-dose to Week 267.
- Participants (44-01, 04, 05) maintained their PUL 2.0 total scores through 5-year study participation despite loss of ambulation (LOA) due to disease progression.

† : All subsequent visits occurred post-LOA. LOA defined as self-reported full-time wheelchair use. Post-LOA visits for participants 44-01, 44-04, and 44-05 were Weeks 99, 75, and 267, respectively.



8. Efficacy Results (Creatine Kinase)



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References ¹: H. Komaki, et al. Cell Reports Medicine, Volume 6, Issue 1, 101901, ²: H. Komaki, et al. 658P Poster presented at World Muscle Society 2025, Vienna, Austria, October. ³: C. M. McDonald, et al. Muscle & Nerve, Volume 48, Issue 1, 32–54, 2013.
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7. Efficacy Results (Motor function Assessment Compared With Natural History)

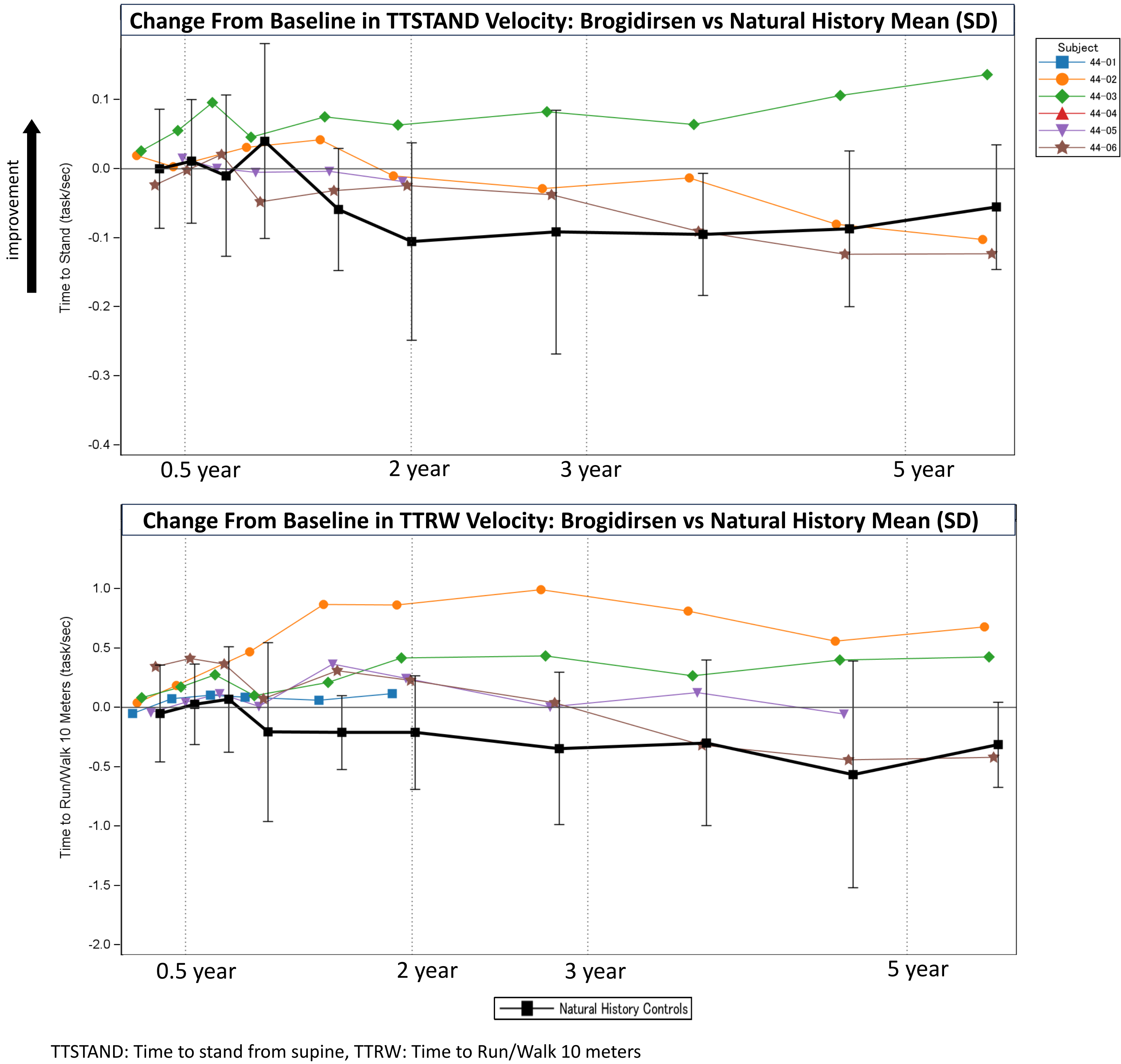
- Brogidirsen-treated participants were compared with natural history data from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS) ³.
- After 5 years of continued treatment, TTSTAND improved from baseline in participant 44-03, and TTRW improved in participants 44-02 and 44-03, whereas the natural history mean declined.

Baseline Characteristics:

Mean (SD)	Brogidirsen (N=6)	CINRG DNHS (N=16)
Age (yrs)	9.8 (2.9)	7.1 (2.1)
TTSTAND(sec)	11.6 (8.0)	3.9 (1.4)
TTRW (sec)	11.3 (4.8)	4.8 (1.8)

CINRG DNHS selection criteria:

- Exon 44 skipping amenable
- Age ≥ 4
- Stable steroid use ≥ 3 months pre-baseline
- TTRW and TTSTAND at baseline and Week 48



9. Discussion

- Long-term Safety & Biological Activity:** Brogidirsen was well-tolerated over 267 weeks with no drug-related serious/severe AEs. Sustained biological activity was confirmed by decreased serum CK, increased dystrophin expression, and exon skipping efficiency. The results up to 267 weeks suggest the potential of brogidirsen to slow the disease progression in patients with DMD who are amenable to exon 44 skipping.
- Clinically Meaningful Motor Function:** Despite baseline imbalances limiting quantitative natural history comparison, 5-year individual trajectories showed functional maintenance/improvement, even though participants were followed from a mean age of 9.8 to 14.5 years during the Extension study, a period typically associated with rapid functional decline in DMD.
 - e.g., Participant 44-03 achieved a 7-point NSAA increase over 267 weeks.
- Preserved Upper Limb Function Post-LOA:** PUL 2.0 scores were maintained even in participants who experienced loss of ambulation (44-01, 04, 05), highlighting comprehensive long-term benefits.
- Limitations & Future Directions:** Limited by the small sample size (N=6) and open-label design, these findings should be considered exploratory. Safety and efficacy are being further evaluated in the ongoing Phase 2 study (NCT05996003).