AAV gene therapy with delandistrogene moxeparvovec in two-year old patients with Duchenne muscular dystrophy: clinical efficacy measured by digital endpoints

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Background

Clinical assessment of the efficacy of AAV microdystrophin gene therapy in very young Duchenne muscular dystrophy patients below the age of 4 years is a challenge. We utilized the regulatory qualified digital endpoint Stride velocity 95th centile (SV95c) measured by the Syde device (SYSNAV Health) to assess the clinical efficacy over 12 months following AAV gene therapy with delandistrogene moxeparvovec in two year old patients with DMD.

Objectives and Methods

Two patients with Duchenne muscular dystrophy (2 years and 2 years 3 months) were treated with delandistrogene moxeparvovec as part of the Sarepta Therapeutics Study SRP-9001-103 (ENDEAVOR; NCT04626674). Under a separate protocol, patients wore the Syde device for two to 4 weeks consecutively prior to treatment and at 3-, 6-, 9- and 12-months post-treatment. External comparator data from the ActiLiège-Next study (NCT05982119), a multicenter natural history study of ankle wearable technology in DMD patients <4 years.

Participant Characteristics

Patient 1

- Exon 44–51 deletion
- Height 88cm, weight 15.4 kg
- 2 years 5 months at AAV infusion
- Treated with prednisone per DMD care standards

Patient 2

- Nonsense mutation c.4375C>T
- Height 85cm, weight 11.2 kg
- 2 years 3 months at AAV infusion
- Treated with prednisone per DMD care standards

Clinical Outcomes

Traditional Functional Clinical Outcome Measures

Patient 1:

- Bayley-4 stable (Sum 11 → 11);
- NSAA improved 16 → 17; timed tests stable (rise 4.5 → 3.2s; 10m 5.6 → 6.3s)

Patient 2:

- Bayley-4 variable (17 → 15);
- NSAA = 16 at 3.5 years; timed tests preserved (rise 3.8s, 10m 5.9s, stairs 4.0s)
- Clinical measures showed preserved function in both patients.

Digital Endpoints

- Both patients had optimal compliance (with exception of month 0)

Patient 1:

- Stride/hour and SV95c remained within Duchenne natural history range

Patient 2:

- Stride/hour and SV95c exceeded natural history, approaching healthy trajectories
- **Stair metrics:** variable, but preserved across both patients

Functional Outcomes Patient 1

Timepoint	Age	NSAA (score/34)	Rise from Floor (s)	10 m Walk/Run (s)	4-Stair Climb (s)	100 m Walk/Run (s)
Week 36	3 yr 1 mo	16	4.47	5.6	5.02	13.06
Week 52	3 yr 5 mo + 26 d	17	3.2	6.28	6.41	13.20

Figure 1. Functional Outcomes for Patient 1 at two time points.
North Star Ambulatory Assessment (NSAA), rise from floor (seconds), 10-meter walk/run (seconds), 4-stair climb (seconds), 100-meter walk/run (seconds). Not recorded prior to age 3 years per protocol.

Functional Outcomes Patient 2

Timepoint	Age	NSAA (score/34)	Rise from Floor (s)	10 m Walk/Run (s)	4-Stair Climb (s)	100 m Walk/Run (s)
Week 52	3 yr 5 mo	16	3.8	5.9	4.0	Not completed (behavioural)

Figure 2. Functional Outcomes for Patient 2 at one time point.
North Star Ambulatory Assessment (NSAA), rise from floor (seconds), 10-meter walk/run (seconds), 4-stair climb (seconds), 100-meter walk/run (seconds). Not recorded prior to age 3 years per protocol.

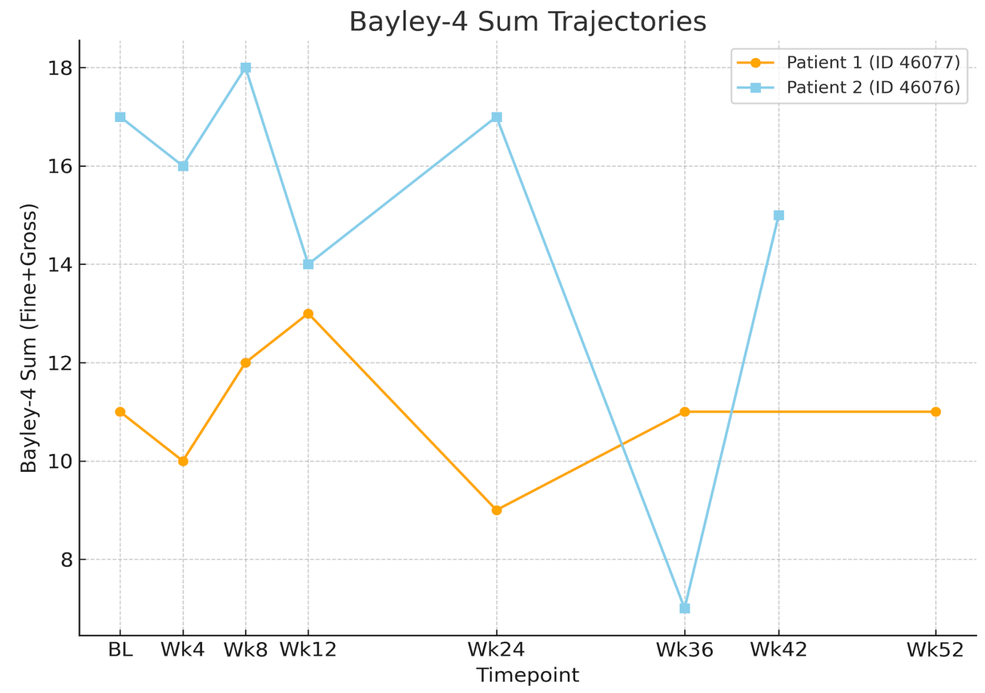

Figure 3: Bayley-4 Fine and Gross Motor Scaled Scores combined (Sum) for Patient 1 and Patient 2 measured longitudinally at baseline (BL), week 4, week 8, week 12, week 24, week 36, week 42, and week 52.

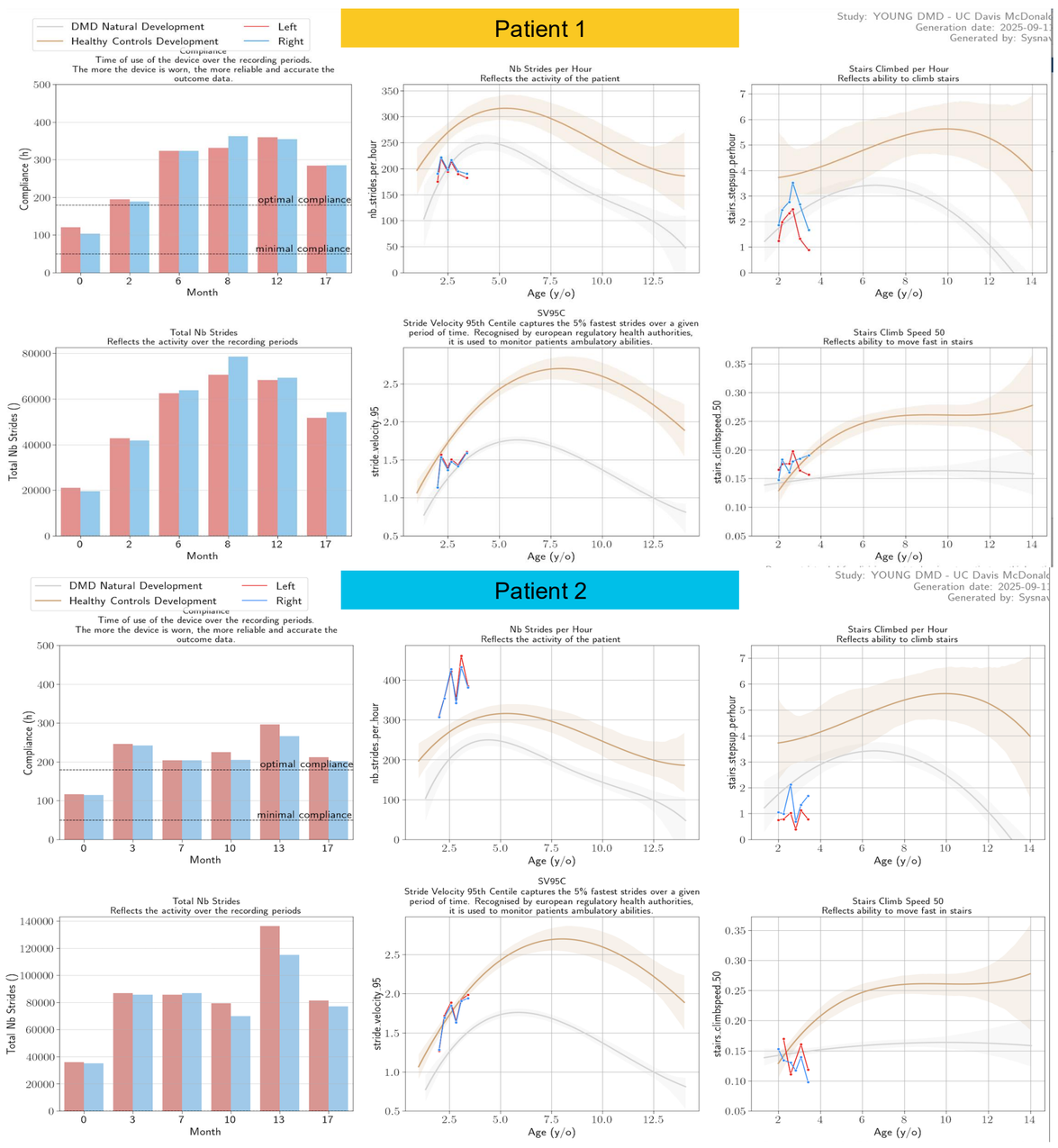

Figure 4: 17 months of bilateral Syde data for Patients 1 and 2 depicting wear time, total steps, SV95c relative to mean for DMD (gray) and typically-developing toddlers (tan), stairs climbed per hour, and 50th percentile stair climb velocity (same groups).

Discussion

- Digital endpoints (SV95c, stride/hour) were feasible in 2-year-old DMD patients and sensitive to mobility changes seen with delandistrogene moxeparvovec gene therapy.
- Patient 1 showed modest, Duchenne-like gains; Patient 2 improved beyond DMD natural history and approached function seen in healthy controls (typically developing children).
- Stair activity was variable and is dependant on home environment. Stair climb speed was more informative (Patient 1 above, Patient 2 within DMD range)
- Traditional scales (Bayley-4, NSAA and timed function tests) confirmed preserved function but were less sensitive to early changes.
- SV95c and stride/hour are more robust than Bayley-4 in toddlers and can detect divergence from DMD natural history earlier after delandistrogene moxeparvovec

Conclusion

- Wearable endpoints are feasible and reliable in DMD patients <3y.
- Patient 1: modest gains within a typical Duchenne muscular dystrophy range.
- Patient 2: improvements beyond DMD natural history similar to healthy controls.
- SV95c and stride/hour are sensitive measures of early efficacy following AAV gene therapy with delandistrogene moxeparvovec in DMD.