Two-year Sevasemten Treatment Outcomes in Becker Muscular Dystrophy Compared to Natural History Controls for the North Star Ambulatory Assessment

Erik H. Niks[1], James Signorovitch[2], Esther J. Schrama[1], Zaida Koeks[1], Jan Verschuuren[1], Mirko Fillbrunn[2], Shuang Wang[2], James MacDougall[3], Joanne Donovan[3]

[1]Leiden University Medical Center, Leiden, Netherlands; [2]Analysis Group, Inc., Boston, MA, USA; [3]Edgewise Therapeutics, Boulder, CO, USA

1. Introduction & Objectives

- Sevasemten is an investigational fast skeletal myosin inhibitor designed to limit muscle damage from functional dystrophin deficits and is being studied for the treatment of muscular dystrophies
- The ARCH study (NCT05160415) is a single-arm, open-label, single-center, Phase 1b trial evaluating sevasemten in 12 male adult patients with Becker muscular dystrophy (BMD)[1]
- To contextualize motor function outcomes for sevasemten-treated patients in ARCH, a predicted control for North Star Ambulatory Assessment (NSAA) outcomes was developed using a validated model of BMD natural history data

2. Methods

Primary outcome

- Changes from baseline in the NSAA total score (ΔNSAA) were studied at months 12, 18, and 24
- The NSAA assesses 17 activities, with patients' performance on each activity graded as 0 (unable to perform the activity independently), 1 (able to perform a modified activity independently), or 2 (able to perform the activity independently without modification). The NSAA total score is the sum of all item scores and ranges from 0 to 34, with a higher score indicating better functional health

Treated patients

- All 12 male subjects (aged 18 to 55 years) were included from ARCH, which required for enrollment a *DMD* gene mutation and a BMD phenotype
- All patients were ambulatory at enrollment, defined as the ability to complete a 100-meter timed walk/run test with or without assistance
- Follow-up data from ARCH extended up to 24 months at the time of this analysis

Predicted controls

- The prediction model used for this study generates slopes for ΔNSAA based on a patient's baseline age, NSAA total score, 10-meter walk/run velocity, rise from supine velocity, and 4-stair climb velocity
  - The model was trained on natural history data from 24 ambulatory adult patients with BMD treated at the Leiden University Medical Center
  - Development and validation of the model is described elsewhere (Niks et al. 2025[2])
- Using this model, mean ΔNSAA up to month 24 was predicted at both the individual and group levels for the ARCH population
  - These predictions represent expected ΔNSAA trajectories for patients in ARCH had they not received sevasemten, adjusted to the observed baseline profile of age and functional measures listed above
- To estimate the sevasemten treatment effect, the group-level mean ΔNSAA was compared between ARCH and the predicted control; statistical comparisons were based on z-tests

3. Results

Baseline characteristics

- At baseline, mean (standard deviation) age was 32.9 (8.0) years and mean NSAA total score was 15.1 (8.4) units (**Table 1**)
- All 12 patients had NSAA assessments available at 12 months, while data were available for 9 patients at both 18 and 24 months

Table 1: Baseline patient characteristics of patients in ARCH

Patient characteristics, mean ± SD	N = 12
Age, years	32.9 ± 8.0
Body mass index, kg/(m²)[a]	25.3 ± 3.2
Height, cm[a]	175.4 ± 6.7
Weight, kg[a]	77.8 ± 10.6
NSAA total score	15.1 ± 8.4
10-meter walk/run velocity, meter/s	1.2 ± 0.5
Rise from supine velocity, 1/s	0.2 ± 0.2
4-stair climb velocity, climb/s	0.2 ± 0.2

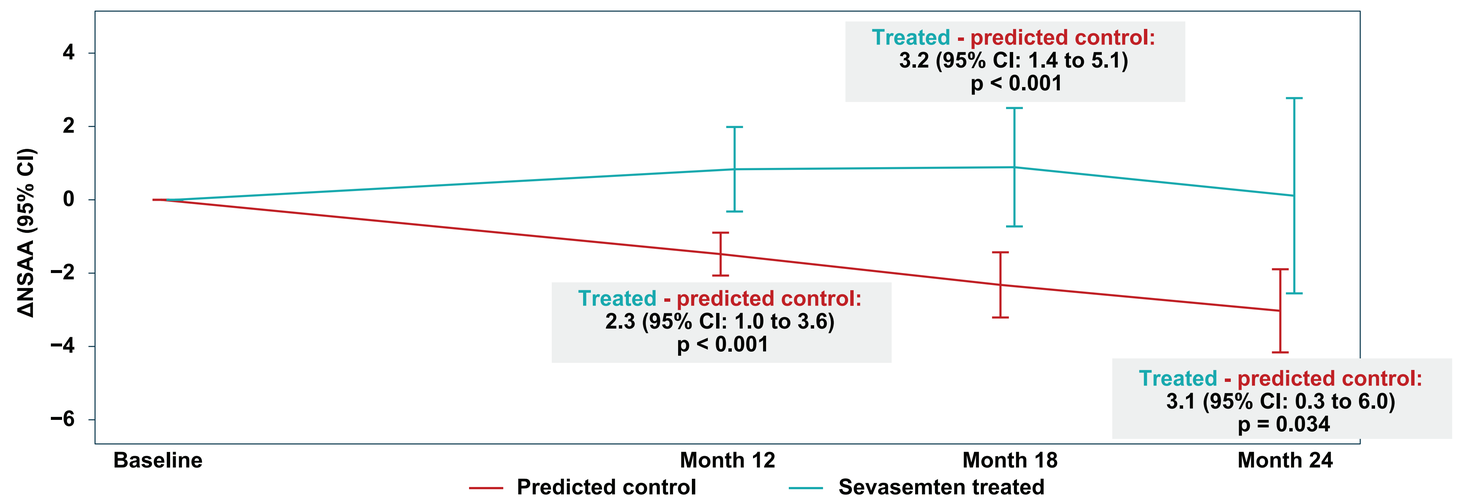
Abbreviations: NSAA, North Star Ambulatory Assessment; SD, standard deviation; s, seconds
Note:
[a] Body mass index, height, and weight were not used in the prediction model.

3. Results (Continued)

NSAA outcomes

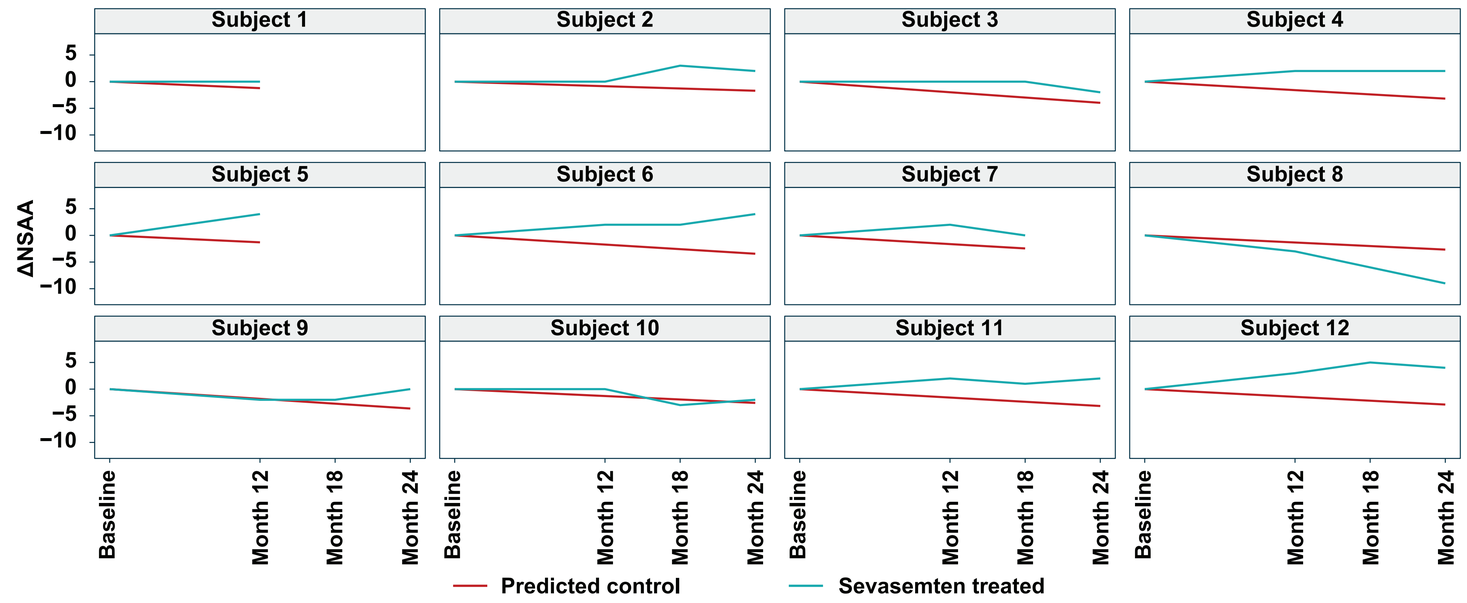
- Among patients treated with sevasemten in ARCH, mean ΔNSAA did not differ significantly from 0 (no change) at month 12 (0.8; 95% confidence interval [CI]: -0.5 to 2.1), month 18 (0.9; 95% CI: -1.0 to 2.8), and month 24 (0.1; 95% CI: -3.0 to 3.2) (**Figure 1**)
- In contrast, among predicted controls, mean ΔNSAA declined significantly over time, decreasing from baseline to month 12 (-1.5; 95% CI: -2.1 to -0.9), month 18 (-2.3; 95% CI: -3.2 to -1.4), and month 24 (-3.0; 95% CI: -4.2 to -1.9) (**Figure 1**)
- Relative to the expected natural history trajectory, sevasemten treatment was associated with significantly greater preservation of NSAA total scores, with differences of 2.3 units at month 12 (95% CI: 1.0 to 3.6; p < 0.001), 3.2 units at month 18 (95% CI: 1.4 to 5.1; p < 0.001), and 3.1 units at month 24 (95% CI: 0.3 to 6.0; p = 0.034) (**Figure 1**)
- Examining individual trajectories, all but one treated patient (subject 8, who had surgery for a torn meniscus at Month 16) exhibited numerically greater preservation of NSAA scores than expected in natural history at the time of their last NSAA assessment (**Figure 2**)

Figure 1: Mean ΔNSAA among sevasemten treated patients and predicted controls



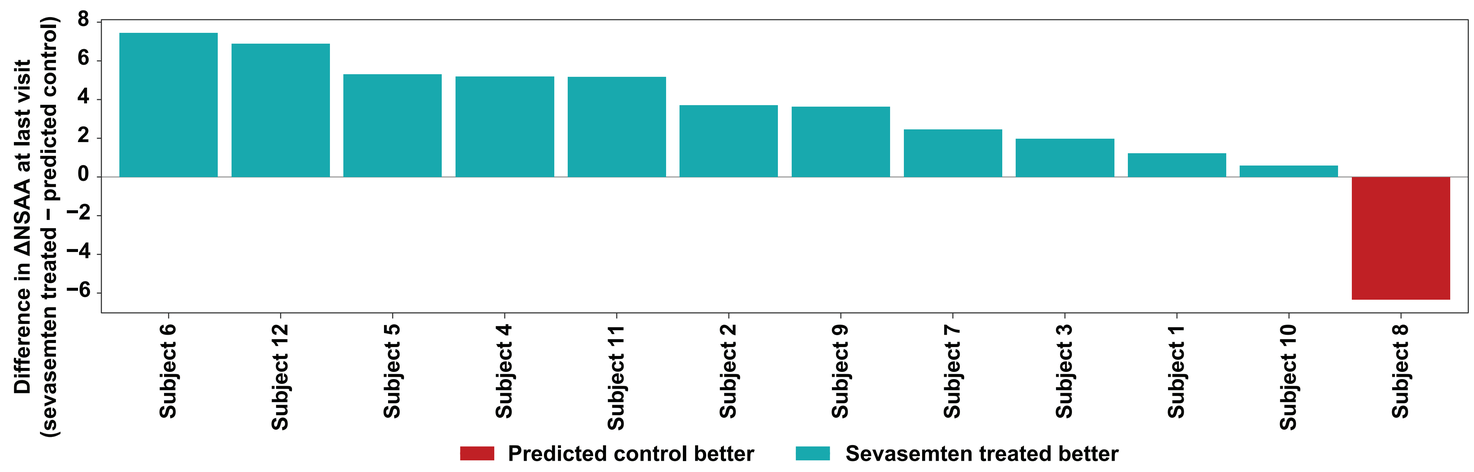
Abbreviations: CI, confidence interval; NSAA, North Star Ambulatory Assessment

Figure 2: Individual trajectories of ΔNSAA (observed and predicted) at months 12, 18, and 24



Abbreviations: NSAA, North Star Ambulatory Assessment

Figure 3: Difference in ΔNSAA at patients' last visits (observed - predicted)



Abbreviations: NSAA, North Star Ambulatory Assessment

4. Limitations

- As in any comparison of non-randomized groups, there is potential for confounding due to unobserved differences that are not accounted for in the prediction model

5. Conclusions

- In this comparison with predicted controls, sevasemten was associated with the preservation of meaningful ambulatory motor function over 24 months
- These findings add to the evidence for sevasemten as a promising investigational therapy for BMD

Disclosures
This study is funded by Edgewise Therapeutics. James MacDougall and Joanne Donovan are employees of and hold shares of Edgewise Therapeutics. James Signorovitch, Mirko Fillbrunn, and Shuang Wang are employees of Analysis Group, Inc. Analysis Group received research funds from Edgewise Therapeutics for the conduct of this study. Erik H. Niks is an ad hoc consultant for Edgewise Therapeutics. Reimbursements are received by LUMC. No personal financial benefits were received. Erik Niks and Esther Schrama are local (sub)investigators in clinical trials sponsored by Edgewise Therapeutics. Zaïda Koeks and Jan Verschuuren report no relevant disclosures.

Acknowledgments
The LUMC natural history study was funded by ZonMw. The authors are grateful to patients for participating in the clinical study. The authors thank Edgewise Therapeutics for contributing the treatment arm data from the ARCH Phase 1b study.

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Presented at the 2025 MDA Clinical & Scientific Conference (March 16-19, 2025) in Dallas, Texas

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