629P

Trajectory of North Star Ambulatory Assessment with Sevasemten Compares Favorably to Natural History Modeling in Becker Muscular Dystrophy

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Introduction

- Sevasemten is an investigational fast skeletal myosin inhibitor designed to protect muscle against contraction-induced damage while preserving function. Sevasemten is currently being studied in Becker and Duchenne muscular dystrophy (BMD and DMD).
- Models to predict disease trajectories provide contextualization for clinical trial outcomes. This is valuable over multi-year periods in BMD for which placebo controls are not feasible.
- **Objective:** To compare a predictive model for North Star Ambulatory Assessment (NSAA) based on natural history to outcomes from two clinical trials evaluating sevasemten in ambulatory adults with BMD[1]

Methods

A predictive model based on BMD natural history data was developed and validated[5]:

1. Input Data Set

- Leiden University Medical Center BMD natural history study
- Participant population: 24 male BMD Data cut-off date: Apr 2024 – Jul 2019
- Median follow-up: 37.2 months (range to 5 years)

2. Predictive Model

- Baseline predictors applied:
  - Age
  - 4-Stair climb velocity
  - 10m walk/run velocity
  - Time to rise from floor
- Marginal R^2
- Validated against mean values from publications

3. Prediction

Predicted, individualized NSAA trajectories for participants

- The prediction model generates the expected change for NSAA based on time and each individual participant's baseline characteristics: age, NSAA total score, 10-meter walk/run (10MWR) velocity, rise from supine (RFS) velocity, and 4-stair climb (4SC) velocity.

Validation

- For external validation, suitable independent datasets identified through targeted literature review.
  - These studies were not used in model training and served solely to assess external validation of model predictions.

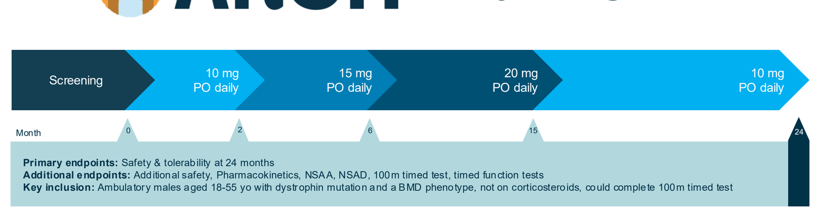
External Validation of Model Predictions

Study	ΔNSAA Time Point	Predicted (95% CI)	Observed (95% CI)
Bello, et al. 2016[3]	12-Months	-0.9 (-1.3, -0.5)	-0.9 (-1.3, -0.5)
De Wel, et al. 2024[4]	9-Months	-0.9 (-1.2, -0.7)	-1.3 (-2.2, -0.4)
	18-Months	-1.9 (-2.4, -1.4)	-2.5 (-3.9, -1.1)
LUMC Data	12-Months	-1.0 (-1.4, -0.7)	-0.9 (-1.6, -0.2)
	24-Months	-2.1 (-2.7, -1.5)	-2.1 (-3.0, -1.2)

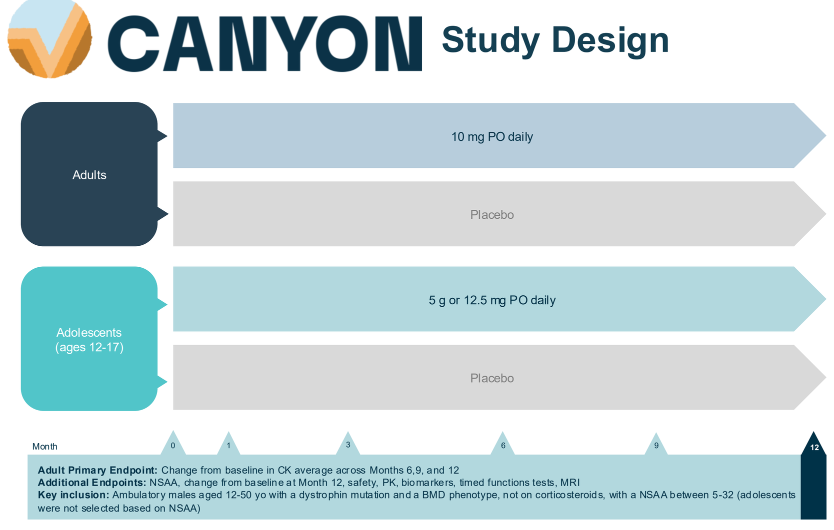
Clinical Trial Comparisons with the Model

- **ARCH (NCT05160415):** Phase 1b clinical trial of sevasemten in ambulatory adults 18 to 55 years old with BMD[1]
  - 12 participants
- **CANYON (NCT05291091):** Phase 2 clinical trial evaluating sevasemten in ambulatory adults age 18 to 50 with NSAA 5-32 with BMD[2]
  - 28 adult participants in sevasemten arm
  - Adolescent participants not included as they were not included in model

ARCH Study Design



CANYON Study Design



- Using the predictive model, mean ΔNSAA up to month 24 for ARCH and up to month 12 for CANYON was predicted.
  - These represent expected ΔNSAA trajectories for participants in ARCH and CANYON 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 CANYON and the predicted trajectories; statistical comparisons were based on z-tests.

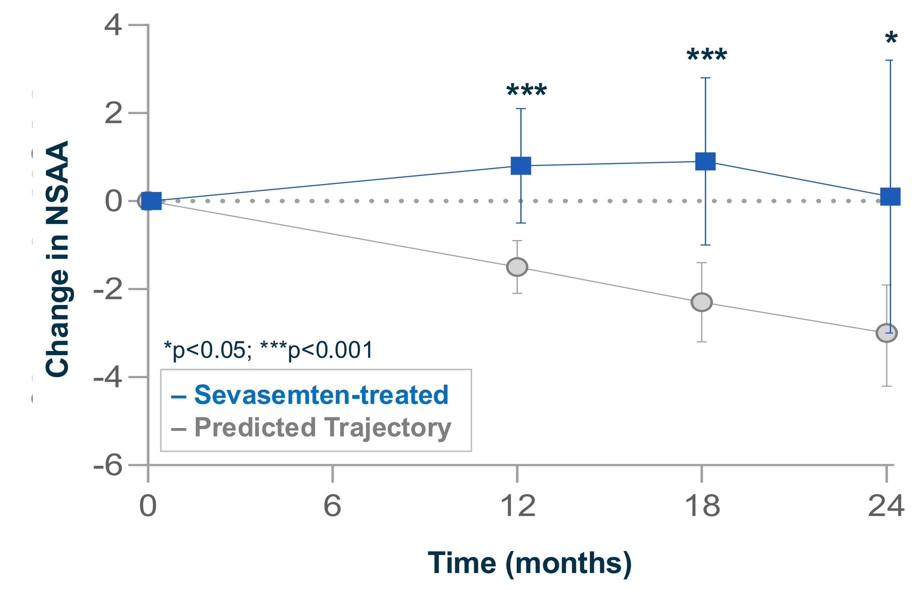
Results

ARCH Sevasemten was associated with significant improvement in NSAA compared to the trajectory predicted for trial participants over 24 months.

Month	Difference in NSAA Total Scores, units (95% CI)	P-value
Month 12	2.3 (1.0 – 3.6)	p<0.001
Month 18	3.2 (1.4 – 5.1)	p<0.001
Month 24	3.1 (0.3 – 6.0)	p<0.05

Examining individual trajectories, all but one treated participant (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.

NSAA Change in Sevasemten-Treated Participants in ARCH Compared with Their Predicted Trajectories

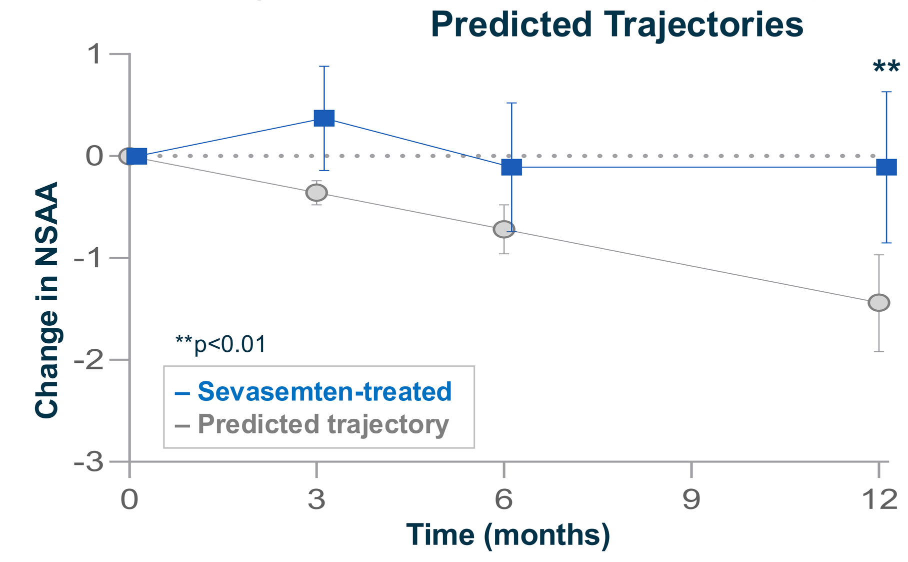


Month 24 Treated – Predicted Trajectory: 3.1 (95% CI: 0.3 to 6.0); p<0.05

CANYON

At 12 months, sevasemten-treated participants in CANYON experienced statistically significant improvement in NSAA vs. their predicted trajectories.

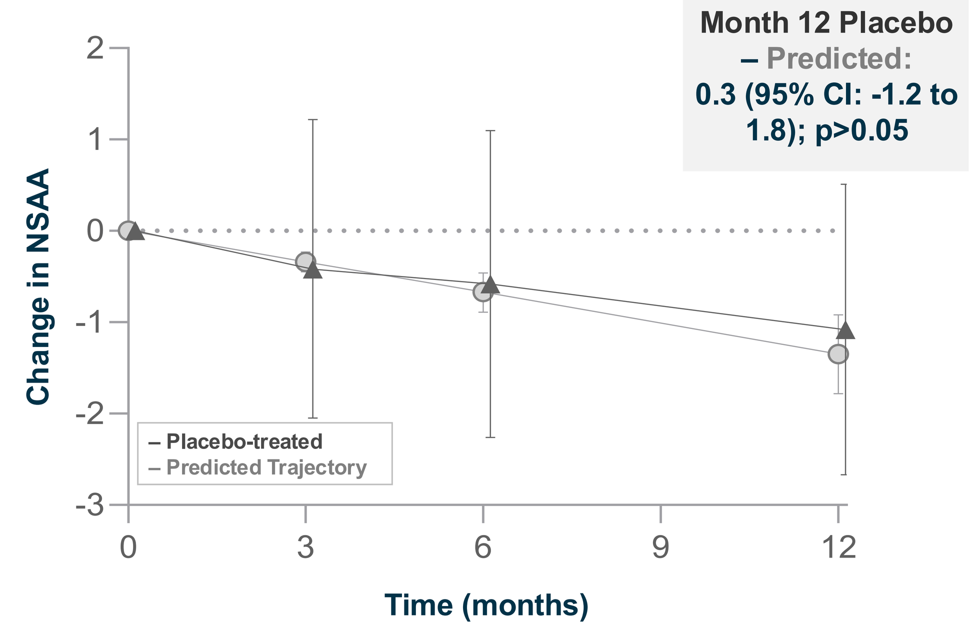
NSAA Change in Sevasemten-Treated participants in CANYON and Predicted Trajectories



Month 12 Treated – Predicted Trajectory : 1.3 (95% CI: 0.5 to 2.2); p<0.01

In the CANYON placebo group, NSAA was predicted to decrease by 1.3 points after 12 months, based on baseline characteristics. The actual decrease in NSAA at Month 12 was 1.1 points.

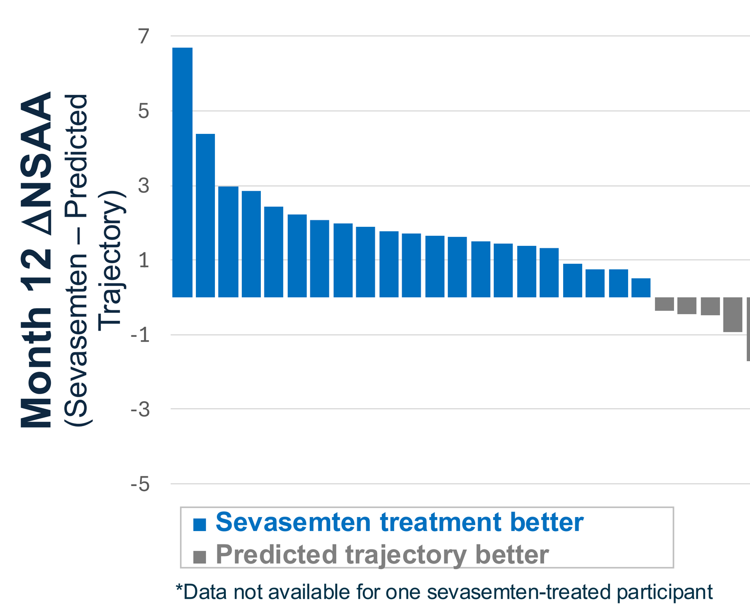
Δ NSAA at Month 12 for Placebo-Treated Participants in CANYON and Predicted Trajectories



Month 12 Placebo – Predicted: 0.3 (95% CI: -1.2 to 1.8); p>0.05

21 of 27 (78%)* of participants in CANYON had increased NSAA scores at Month 12 compared to their predicted natural history trajectories, with a median improvement of 1.5 NSAA points.

Δ NSAA at Month 12 for Sevasemten-Treated Participants in CANYON



*Data not available for one sevasemten-treated participant

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.

Conclusions

- In the ARCH and CANYON trials, **participants on sevasemten had preserved NSAA over 24 and 12 months** respectively, compared to participants' expected trajectories based on their individual baseline characteristics.
- In CANYON, **participants on placebo had declines in NSAA** similar to their expected trajectories.
- These findings strengthen support for sevasemten as a potential treatment for BMD; sevasemten is currently being evaluated GRAND CANYON (NCT05291091), an ongoing pivotal study.

References

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2. GRAND CANYON. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/study/NCT05291091. Accessed 09July2025.
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4. De Wel B, et al. Eur J Neurol. 2024;31(7):e16282.
5. Niks EH, et al. Poster presented at MDA Clinical & Scientific Conference; March 16-19, 2025; Dallas, Texas. #P10.
6. Niks EH, et al. Poster presented at MDA Clinical & Scientific Conference; March 16-19, 2025; Dallas, Texas. #P11.

Disclosures:
Sevasemten is an investigational agent that is not approved for use by any regulatory authority in any territory.
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