In the Global Phase 3 PolarisDMD Trial for Edasalonexent, Standardized Outcome Measure Training Produces Excellent Test-Retest Variability in the North Star Ambulatory Assessment

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Introduction

Overview of the North Star Ambulatory Assessment (NSAA)

NSAA is a validated scale specifically developed to measure physical performance of everyday activities in ambulatory boys with Duchenne

*These are tested individually on the left and right leg
Mazzone 2009, Mayhew 2011, FDA 2018, EMA 2016, Bonikarni 2018.

As Primary Endpoint for Phase 3 PolarisDMD, NSAA Incorporates Measures of Daily Function

Primary endpoint: North Star Ambulatory Assessment

Assessment measures, from most to least difficult

Hop right leg	Climb box step right
Hop left leg	Climb box step left
Stand on heels	Stand on one leg right
Rise from floor	Stand on one leg left
Run	Get to sitting
Jump	Rise from chair
Lift head	Walk
Descend box step right	Stand
Descend box step left	

Secondary Endpoints: Timed Function Tests

10-meter walk/run

4-stair climb

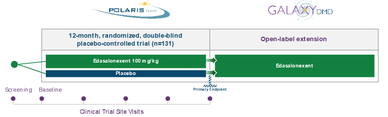
Time to rise from supine

Background and Aims

- **While reproducibility of assessor grading has been demonstrated during the development of the NSAA (Mazzone et al., 2009), test-retest variability of NSAA has not been available in a clinical trial setting for boys as young as 4**
- **The design of the global Phase 3 PolarisDMD trial of edasalonexent allowed an assessment of the variability of repeat NSAA assessments prior to treatment and allowed several questions of importance to clinical trial design to be addressed:**
  - What is the variability for repeat functional assessments within a short time period during which disease progression is not a factor?
  - Is there an age difference for variability of assessments, i.e., are 4-year olds less consistent than older boys?
  - Is there a difference in variability of assessments depending on baseline functional level?
  - In these young boys with limited clinical trial experience, is there a learning effect for any of the functional tests between screening and baseline?
  - How does the variability of NSAA compare to that of the Timed Function Tests in this young population?

Methods

Edasalonexent Phase 3 PolarisDMD Trial Designed for Global Registration



Eligibility:
- All mutations
- Age 4 to 7 (up to 8th birthday); off steroids for ≥6 months
- Able to complete Stand from Supine in <10 seconds at the Screening Visit
- Able to swallow placebo capsules at the Screening Visit

Endpoints measured at Screening and Baseline (Day 1), with Primary Endpoint at 52 Weeks:
- Primary: Change in North Star Ambulatory Assessment (NSAA)
- Key secondary: Velocity of age-appropriate Timed Function Tests
- Additional assessments include growth, cardiac and bone measures

Topline results expected in Q4 2020

The Phase 3 PolarisDMD Clinical Trial Was Conducted Globally

- **131 patients enrolled in 8 countries**
- **Designed the trial with input from advocacy organizations, families, physicians**
  - Understand the burden of clinical trial participation
- **NSAA and additional endpoints are measures that reflect everyday life**
  - Standing up from the ground, walking, climbing stairs

Clinical Evaluators in the Phase 3 PolarisDMD Trial Received Standardized Training to Ensure Reproducibility of NSAA

- **As part of the Phase 3 PolarisDMD trial protocol, Clinical Evaluators received standardized protocol-specific training and reliability testing with ongoing quality control of assessments by video review**
  - All training was performed prior to patient screening activity
- **The ATOM group certified all Clinical Evaluators after protocol-specific live training. As part of their initial training, Clinical Evaluators assessed a patient with DMD in order to have a quality review by the training expert**
  - Performed once, with repeat if not accurate
  - Graded according to standard criteria
  - Conducted in standard order
  - Videotaped for central review
- **Analysis was conducted for enrolled patients in the study with two valid functional measures**
  - After evaluator training, boys were screened, including completing the NSAA. Baseline NSAA was repeated 1 to 4 weeks later
  - Average duration between screening and baseline was 18.6 ± 8.2 days
  - If the Screening Visit was repeated, the assessments nearest to Baseline Visit (Day 1) was used

Results

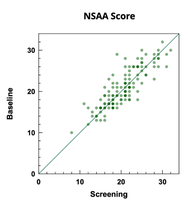
Baseline Characteristics in Phase 3 PolarisDMD Similar to Those Seen in the Phase 2 MoveDMD Trial

- **Phase 3 trial enrolled the expected patient population**
  - Comparison of baseline age and function (NSAA, time to stand, 4-stair climb, and 10-meter walk/run) were similar in both trials; there were no significant differences in baseline characteristics between the two trials*
- **Findings support the assumptions on which the Phase 3 trial was powered**

	PolarisDMD (n=131)	MoveDMD (n=23)
Age (years)	5.7 ± 1.0	6.0 ± 1.1
Percent enrolled patients that had not taken steroids	98%	100%
North Star Ambulatory Assessment (NSAA) score	20.8 ± 4.7	20.1 ± 5.5
10-Meter Walk/Run speed (1/s)	0.181 ± 0.037	0.168 ± 0.045
4-Stair Climb speed (1/s)	0.265 ± 0.097	0.254 ± 0.110
Time to Stand speed (1/s)	0.212 ± 0.070	0.193 ± 0.080

Means ± standard deviation shown
*Kolmogorov-Smirnov test used to assess for population distribution differences

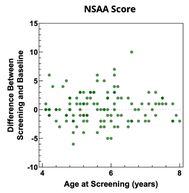
NSAA Reproducible Between Screening and Baseline Visits in Young Boys in PolarisDMD



- In 124 boys with valid paired assessments, screening and baseline generally show consistency
- Lines of identity shown with intraclass correlation coefficient = 0.84
- Between screening and baseline, there was a mean increase of 0.3 points, or 1.7%, which supports that there was no meaningful learning effect from performing the test after the first time in the clinical trial setting

Darker shade on graph shows overlap of patients.

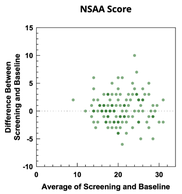
Intra-patient Variability of NSAA Between Screening and Baseline Did Not Depend on Age



- Change in NSAA between screening and baseline was not correlated with age

Darker shade on graph shows overlap of patients.

Intra-patient Variability of NSAA Did Not Depend on Baseline Functional Status

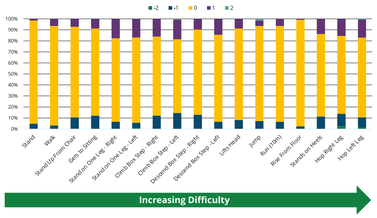


- Change in NSAA between screening and baseline was not correlated with baseline function as measured by the average of screening and baseline
- There did not appear to be a difference in variability that depended on baseline function

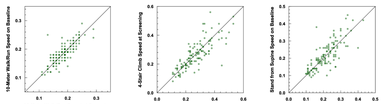
Darker shade on graph shows overlap of patients.

Variability of Individual NSAA Measures

- **Greater than 80% of individual measures were unchanged between screening and baseline**



Individual Timed Function Tests Are Generally Reproducible



- Change in Timed Function Tests between screening and baseline was not correlated with age
- Change in Timed Function Tests between screening and baseline was not correlated with baseline function as measured by the average of screening and baseline
- Mean differences between screening and baseline were small: 0.6, 1.0 and 2% for 10MWR, 4-SC and TTS, respectively, consistent with a lack of learning effect

Results

Reproducibility of Additional Functional Measures Between Screening and Baseline

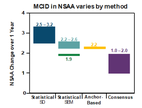
- The NSAA and Timed Function Tests were reproducible in the Phase 3 PolarisDMD study population
- NSAA was more reproducible than the Timed Function Tests in this population
- The Intraclass Correlation (ICC) allows determination of the Standard Error of the Measurement, considered to be a measure of the Minimum Clinically Important Difference

	Intraclass Correlation	Standard Error of the Measurement (% of mean)
North Star Ambulatory Assessment (NSAA) score	0.84	1.86 (9%)
10-Meter Walk/Run speed (1/s)	0.82	0.015 (9%)
4-Stair Climb speed (1/s)	0.81	0.037 (16%)
Time to Stand speed (1/s)	0.79	0.042 (17%)

Conclusions

Literature Estimates of Minimum Clinically Important Difference (MCID) in NSAA Over 1 Year

Method	Basis for Method	Sources	Results	
			Age	NSAA Change
Statistical: SD	Variability in population at Baseline: MCID = ½ standard deviation	Muntoni 2019	6 - 7	3.2
		Weng 2019		2.8
Statistical: SEM*	Reproducibility of measure: Based on modeling 1 year change in a progression model	Muntoni 2019	All ages	2.6
		Weng 2019		2.2
Statistical: SEM*	Reproducibility based on Standard Error of the Mean in Phase 3 PolarisDMD baseline dataset	Current Study	4 - 7	1.9
Anchor-Based	NSAA change for a defined change in a functional outcome measure	Weng 2019	N/A	2.2
Consensus	Parent/caregiver questionnaire on meaningful change	Pitchforth 2018	N/A	1 - 2



For parents, a meaningful change in NSAA was 1 – 2 points depending on the impact to function.

A meaningful change was 1, if that reflected loss of ability to perform a function, or 2, if that reflected worsening of ability to perform 2 of the NSAA functional measures

*The statistical SEM methods differ in the patient population measured. The SEM for PolarisDMD was measured in boys with DMD not on steroids, while the other SEM methods measured boys with DMD who were on steroids.

Muntoni WMS2018, Weng WMS2019, Pitchforth WMS2019

Conclusions

- Both the North Star Ambulatory Assessment and Timed Function Tests demonstrated reproducibility in 4 to 7 year olds (up to 8th birthday) after standardized training
- There were no significant learning effects for any of these functional measures, even at the youngest ages
- When functional measures were repeated, variability did not depend upon baseline functional level
- Based on the intraclass correlation of repeated measures, NSAA and the Timed Function Tests were reproducible, which supports use of their use as primary and secondary efficacy endpoints in the Phase 3 PolarisDMD trial

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- Maria Mancini, James MacDougall, and Joanne Donovan are employees or consultants of Catabasis and may hold stock in Catabasis
- Edasalonexent is an investigational agent that is not approved in any territory

Questions? MedInfo@catabasis.com

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