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LYNX Phase 2 Trial Results in DMD: Positive Effects of Sevasemten, an Investigational Agent, on Physical Function Defines Dose and Informs Design for Phase 3

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Background

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease caused by mutations in the *DMD* gene.[1,2] While there are currently approved therapies on the market for DMD, there remains high unmet need for additional therapies.

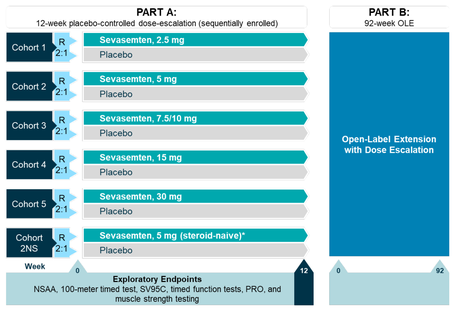
Sevasemten is an investigational, novel, oral, fast skeletal myosin inhibitor designed to protect muscle against contraction-induced damage while preserving function. [3]

Methods

Study Design & Objective:

- LYNX (NCT05540860) is an ongoing, multi-center, placebo-controlled, dose-finding Phase 2 trial to evaluate the effect of sevasemten on safety, biomarkers of muscle damage, and function.
- After safety and biomarker review in the 3 month double blind period, study participants were transitioned to the highest tolerated dose in an open-label period.
- Study goal: to explore a range of doses to assess safety and identify a potentially beneficial dose for Phase 3

LYNX Study Design



*Age 4-7
Doses listed were the starting doses for each cohort; changes were made to dosing as the trial continued. Additionally, a cohort of participants ages 4-7 who were not on corticosteroids were included as Cohort 2NS.
Abbreviations: NSAA, North Star Ambulatory Assessment; SV95C, strive velocity 95th centile; R, randomization; PRO, patient-reported outcomes

Endpoints:

- The primary endpoint is safety.
- Secondary endpoints: biomarkers of muscle damage (creatine kinase (CK), fast skeletal muscle troponin I (TNNI2)), stride velocity 95th centile (SV95C), North Star Ambulatory Assessment (NSAA), timed function tests, pharmacokinetics (PK)

Key Inclusion Criteria:

- Ambulatory participants ages 4-9 years old inclusive with a *DMD* gene mutation and DMD phenotype on stable corticosteroids for >6 months
- An additional cohort of participants ages 4-7 years old, who were not on corticosteroids, was included (cohort 2NS)

Cohorts 2 and 3:

Following dose modifications, participants in cohorts 2 and 3 were on the identified target dose of 10 mg the longest, with a total duration >18 months.

Baseline Characteristics*	Cohorts 2 and 3	All Cohorts**
Safety Population, N	23	66
Age, years:	7.7 (1.6)	7.5 (1.7)
Total NSAA Score:	27.0 (4.8)	24.8 (5.6)
4SC, seconds:	2.9 (1.0)	3.6 (1.6)
RFF seconds:	3.7 (1.4)	4.2 (1.8)
10MWR, seconds:	4.6 (0.8)	4.9 (1.1)
SV95C, meters/seconds:	1.8 (0.4)	1.8 (0.4)

*60/66 participants were on stable steroid background; 9/66 participants were on an approved exon skipper
Mean (SD)
**Includes Cohort 2NS
Abbreviations: NSAA, North Star Ambulatory Assessment; 4SC, 4-stair climb; RFF, rise from floor; 10MWR, 10-meter walk/run; SV95C, strive velocity 95th centile; SD, standard deviation

Results (3 months)

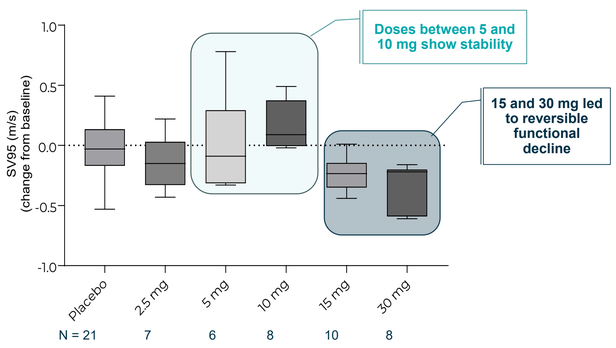
Biomarkers of muscle damage:

- Dose selection initially focused on safety and changes in biomarkers of muscle damage based on previous observations in Becker muscular dystrophy clinical trials.
- Biomarker changes were not observed below the 30 mg Cohort in those on a stable steroids.

Functional Measures:

- Over 3 months of sevasemten dosing, doses between 5 and 10 mg showed stability in SV95C.
- LYNX participants were continued on either 5 or 10 mg to explore long-term functional changes.
- Therefore, the focus of dose selection turned to functional changes at 5 and 10 mg of sevasemten.

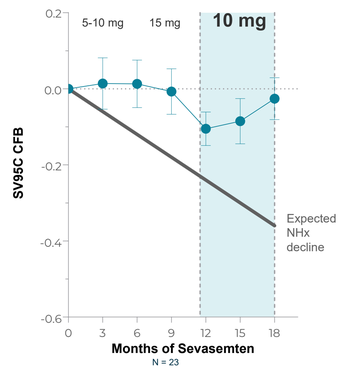
SV95C After 3 months of Sevasemten Dosing



Abbreviations: SV95C, stride velocity 95th centile

Results (18 months)

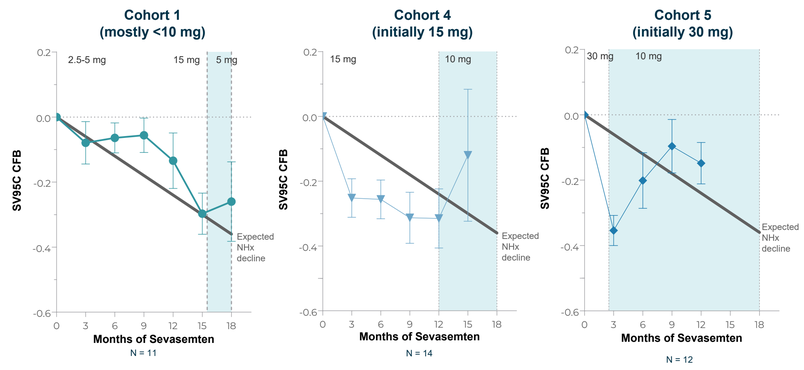
SV95C Changes During 18 Months For Cohorts Predominantly on 10 mg Sevasemten Dose



Target dosing period — Expected decline from natural history
Mean (95% CI); Day 0 is first dose of sevasemten for all graphs above
Abbreviations: CFB, change from baseline; SV95C, Stride Velocity 95th Centile; NHx, natural history

For those predominantly on sevasemten 10 mg (Cohorts 2 and 3), SV95C was stable at 18 months, which differed from expected natural history.

SV95C Changes Following 18 Months Sevasemten At Other Doses



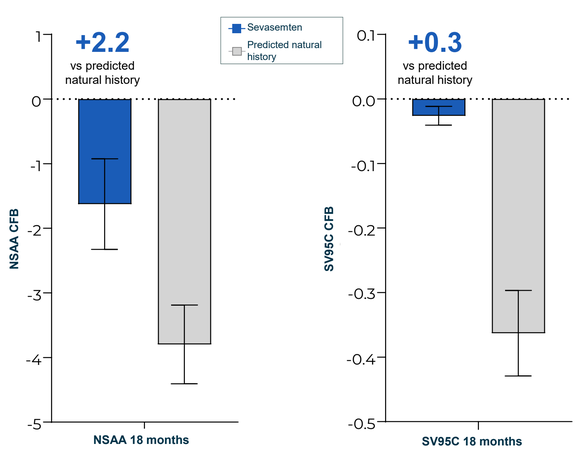
Target dosing period — Expected decline from natural history
Mean (95% CI); Day 0 is first dose of sevasemten for all graphs shown above
Abbreviations: CFB, change from baseline; SV95C, Stride Velocity 95th Centile; NHx, natural history

Reversible declines in SV95C were seen with the 15 and 30 mg doses of sevasemten.

Based on safety and SV95C, the 10 mg dose of sevasemten was identified as the target dose for further study.

- Participants on sevasemten in Cohorts 2 and 3, who started sevasemten at an average age of 7.7, predominantly on 10 mg, had improvements in NSAA and SV95C compared with expected natural history after 18 months (below, left).
- Sensitivity analyses showed that NSAA improved compared to predicted decline[4], independent of baseline NSAA or age (below, right).
- 4SC mean change from baseline was +0.5 seconds over 18 months in cohorts 2 and 3.

NSAA



SV95C

Mean predicted change from individual baseline values derived via DMD Prediction Model[4]
Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies (EMADOC-1700519818-1127132)
Mean ± SEM. LYNX cohorts included in analysis were cohorts 2 and 3.
Abbreviations: CFB, change from baseline, DMD, Duchenne muscular dystrophy; NSAA, NorthStar ambulatory assessment; SV95C, stride velocity 95th centile

Subgroup Sensitivity Analysis of NSAA Compared to Predicted Natural History Decline

Cohort	Observed	Predicted	Difference (Obs. – Pred.)	
	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Cohorts 2 & 3	-1.6 (2.8)	-3.8 (2.4)	+2.2 (2.5)	0.0036
Baseline NSAA < 25	-1.2 (1.6)	-3.6 (3.4)	+2.4 (2.9)	0.1370
Baseline NSAA ≥ 25	-1.8 (3.3)	-3.9 (2.1)	+2.0 (2.5)	0.0200
Age at Screening < 7	-0.7 (2.2)	-3.3 (2.6)	+2.6 (3.4)	0.0915
Age at Screening ≥ 7	-2.3 (3.1)	-4.2 (2.4)	+1.8 (1.7)	0.0110

Mean predicted change from individual baseline values derived via DMD Prediction Model[4]
P-values based on t-test. Results for Observed Case (vs LOCF) analyses are similar
Abbreviations: DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; LOCF, last observation carried forward; SD, standard deviation; Obs, observed; Pred, predicted

Safety

- With a dose of 10 mg, sevasemten was found to be well-tolerated.
- Most common adverse events were vomiting and dizziness.
- At doses of 15-30 mg, adverse events associated with excess pharmacology were observed, which resolved with dose reduction.
- Safety profile was similar for the 10 mg dose in the open-label period.

TEAEs Occurring in ≥5% of Total Active	Placebo (N=23)	Cohort 1 2.5 mg (N=7)	Cohort 2 5.0 mg (N=6)	Cohort 3 7.5/10.0 mg (N=8)	Cohort 4 15.0 mg (N=10)	Cohort 5 30.0 mg (N=8)	Cohort 2NS 5.0 mg (N=4)	Pooled Active (N=43)
Any TEAE	16 (70%)	5 (71%)	4 (67%)	7 (88%)	10 (100%)	8 (100%)	4 (100%)	38 (88%)
Gastrointestinal disorders								
Vomiting	3 (13%)	0	2 (33%)	3 (38%)	2 (20%)	2 (25%)	1 (25%)	10 (23%)
General disorders and administration site conditions								
Fatigue	1 (4%)	1 (14%)	0	0	2 (20%)	1 (13%)	0	4 (9%)
Infections and infestations								
Nasopharyngitis	0	2 (29%)	0	0	2 (20%)	0	2 (50%)	6 (14%)
Viral upper respiratory tract infection	0	0	0	0	3 (30.0%)	0	0	3 (7%)
Injury, poisoning and procedural complications								
Fall	2 (9%)	2 (29%)	0	0	1 (10%)	1 (13%)	1 (25%)	5 (12%)
Musculoskeletal and connective tissue disorders								
Muscle spasms	0	1 (14%)	0	0	2 (20%)	0	0	3 (7%)
Nervous system disorders								
Dizziness	3 (13%)	0	0	1 (13%)	3 (30%)	4 (50.%)	0	8 (19%)
Headache	6 (26%)	1 (14%)	0	0	2 (20%)	0	0	3 (7%)
Somnolence	0	1 (14%)	0	0	1 (10%)	3 (38%)	0	5 (12%)
Respiratory, thoracic and mediastinal disorders								
Cough	6 (26%)	0	0	0	1 (10%)	2 (25%)	0	3 (7%)

Abbreviation: TEAE, treatment emergent adverse event

Conclusions

- **SV95C appears to be a sensitive and responsive measure** of function for dose selection in this study.
- **Safety and functional observations support the 10 mg dose** of sevasemten as the dose to move forward with to a pivotal-stage program.
- Sevasemten will continue to be investigated in DMD with the LYNX trial, continuing with an **open-label extension to collect longer-term data**.

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