



Positive Topline Results from Pivotal Phase 3 SAPPHIRE Trial of Apitegromab in Spinal Muscular Atrophy (SMA)

October 7, 2024

Agenda

Introduction	Jay Backstrom, M.D., MPH, President & Chief Executive Officer
SAPPHIRE Results	Jing Marantz, M.D. Ph.D., Chief Medical Officer
Concluding Remarks	Jay Backstrom, M.D., MPH, President & Chief Executive Officer
Q&A Session	

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Apitegromab is an investigational drug candidate under evaluation. Apitegromab has not been approved for any use by the FDA or any other regulatory agency and the safety and efficacy of apitegromab has not been established.



Introduction

Jay Backstrom, M.D., MPH
President & Chief Executive Officer

Our Purpose: Create Possibilities for Those Living with Spinal Muscular Atrophy (SMA)

“ Muscle is everything. I want to live knowing that I have the strength **to take care of myself** if left alone.

- Lyza

”



Positive Phase 3 SAPPHIRE Trial: Transformative Benefit in SMA

MET PRIMARY ENDPOINT:

1.8
POINT
IMPROVEMENT
in HFMSE* vs. placebo
(p=0.0192)

CONSISTENT
clinically meaningful
benefit across
all age groups
(2-21)

30%
of apitegromab patients
ACHIEVED ≥3
POINT IMPROVEMENT IN
HFMSE†

FAVORABLE
SAFETY profile
consistent with >48
months experience in
Phase 2 TOPAZ trial

Apitegromab has the potential to alter the course of SMA

* Based on apitegromab combined dose (10 mg/kg and 20 mg/kg) + SOC versus placebo + SOC
† 12.5% of patients on placebo + SOC achieved a ≥3-point improvement in HFMSE
SOC=Standard of care (i.e., nusinersen or risdiplam)

A woman with blonde hair in a ponytail, wearing a black tank top and dark leggings, is sitting on a white folding chair. Her feet are resting on a red mat on the floor. The background is a plain wall. The image is partially obscured by a large white circular graphic on the right side of the slide.

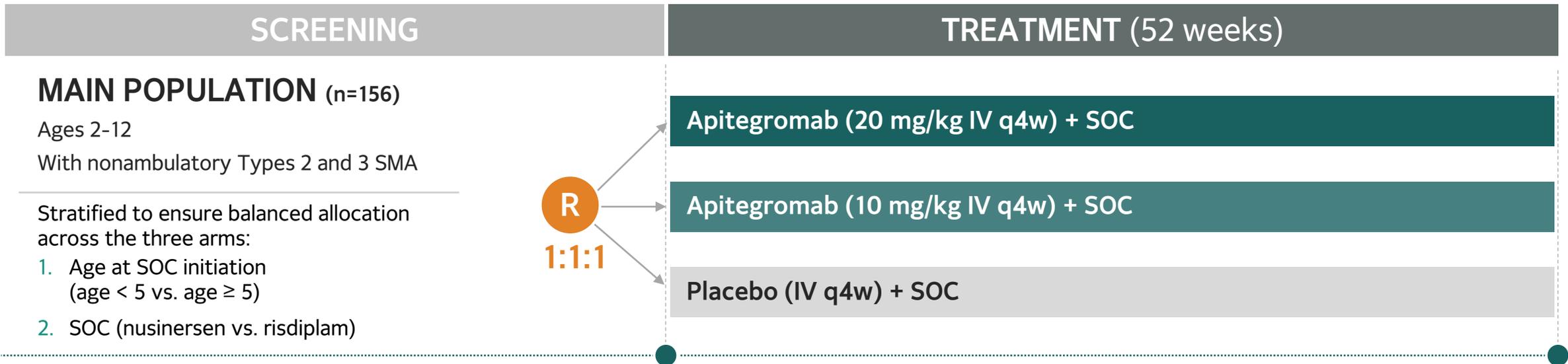
Phase 3 SAPPHIRE Topline Results

Jing Marantz, M.D., Ph.D.
Chief Medical Officer

Study Design



Randomized, double-blind, placebo-controlled, parallel arm design (n=188)
 Patients on standard of care (nusinersen or risdiplam)



ENDPOINTS

Primary Efficacy:

Mean HFMSE change from baseline at 12 months

Additional Efficacy Measures:

RULM, WHO, other outcome measures

Safety, PK/PD, ADA

Additional Study Objectives

Exploratory Population (n = 32, age 13-21)

Stratified by SOC, randomized 2:1 between apitegromab 20 mg/kg vs placebo

Endpoints: Safety & exploratory efficacy

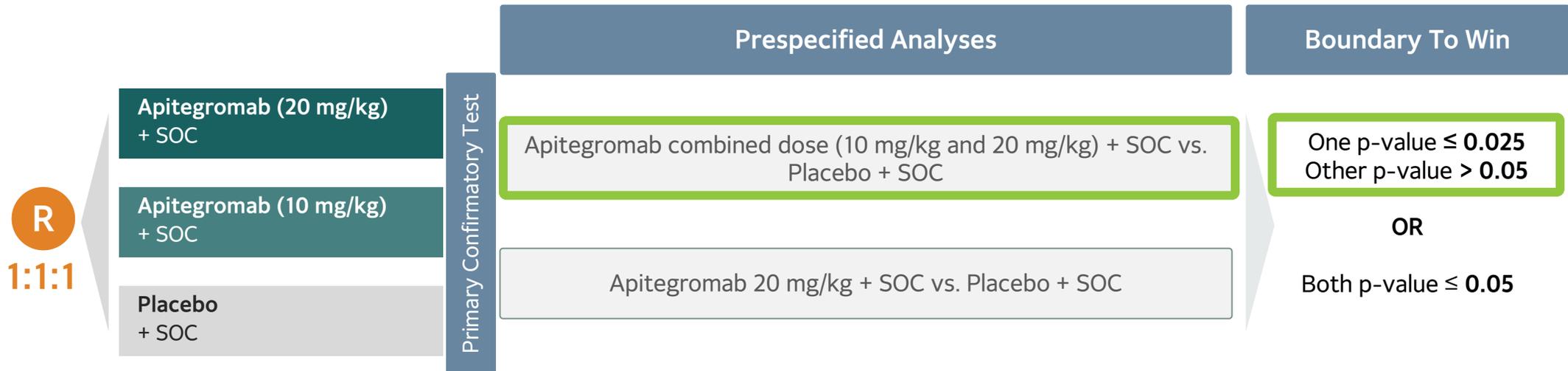
Separate open-label extension study (after patients complete 12-month treatment period)

Safety & exploratory long-term efficacy

Prespecified Statistical Analysis Plan

Primary Objective

To assess the efficacy of apitegromab compared with placebo using HFMSE in patients 2 through 12 years old

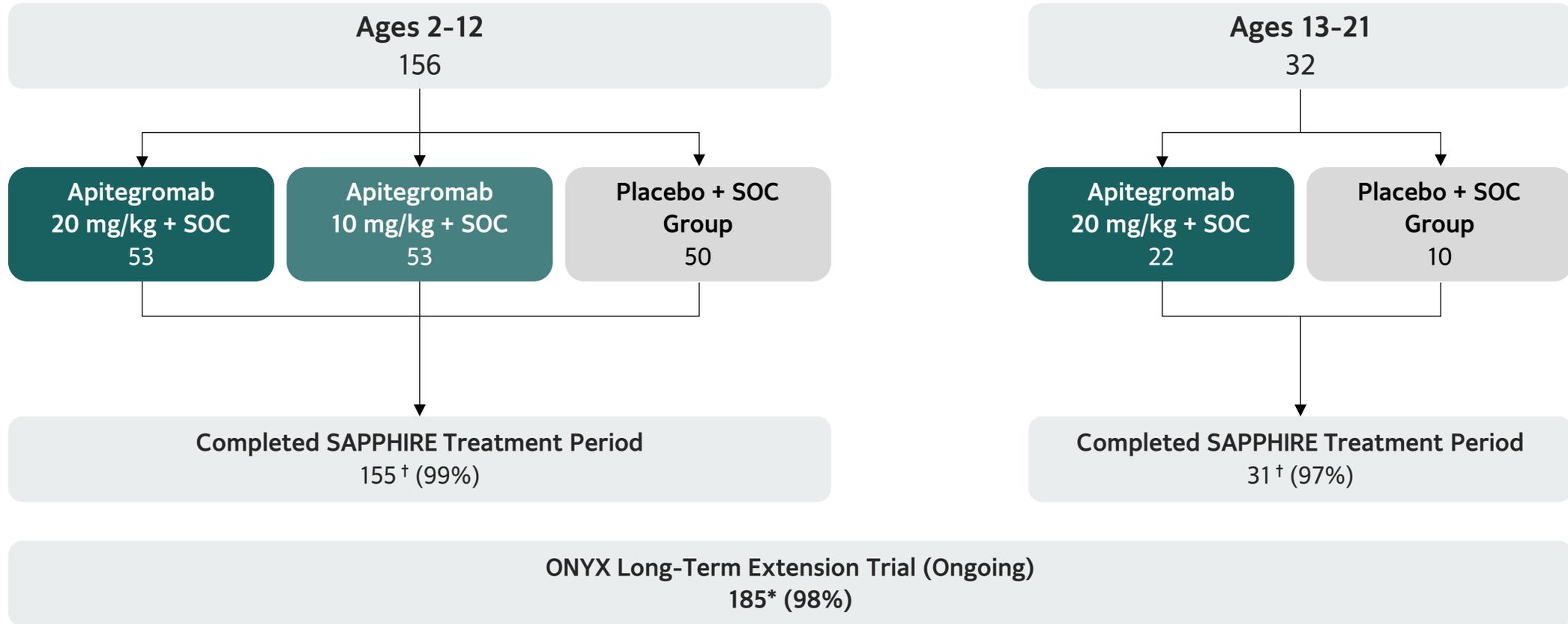


- Prespecified analyses to assess dose: combined apitegromab doses (10 mg/kg + 20 mg/kg), 20 mg/kg, and 10 mg/kg; 10 mg/kg and 20 mg/kg expected to be similar based on insights from TOPAZ
- Primary confirmatory test evaluates HFMSE for combined dose and 20 mg/kg concurrently by Hochberg, followed by RULM, HFMSE ≥ 3 proportion, WHO for 20 mg/kg, then HFMSE, RULM, HFMSE ≥ 3 , WHO for 10 mg/kg dose in a hierarchical order

The Hochberg procedure (Hochberg 1988) was used to test: 1) apitegromab combined dose (10 mg/kg and 20 mg/kg) vs placebo and 2) apitegromab 20 mg/kg dose vs placebo concurrently for the primary endpoint as the primary confirmatory test. The hierarchical testing procedure was applied to account for multiple confirmatory tests for the primary endpoint and key secondary endpoints. The testing procedure first evaluated the primary confirmatory test, followed by analyses of key secondary endpoints for apitegromab 20 mg/kg, and then the analyses of primary endpoint and key secondary endpoints for apitegromab 10 mg/kg.
SOC=standard of care

98% of Patients Continue on Long-Term Extension

188 Patients Underwent Randomization



*1 patient from 2-12 age group opted not to enroll in the ONYS study.

† 1 subject (1%) in the 20 mg/kg apitegromab arm in the 2-12 age group withdrew consent. 1 subject (3%) in the 20 mg/kg apitegromab arm in the 13-21 age group withdrew consent. Neither withdrew consent due to an adverse event.

SOC=standard of care.

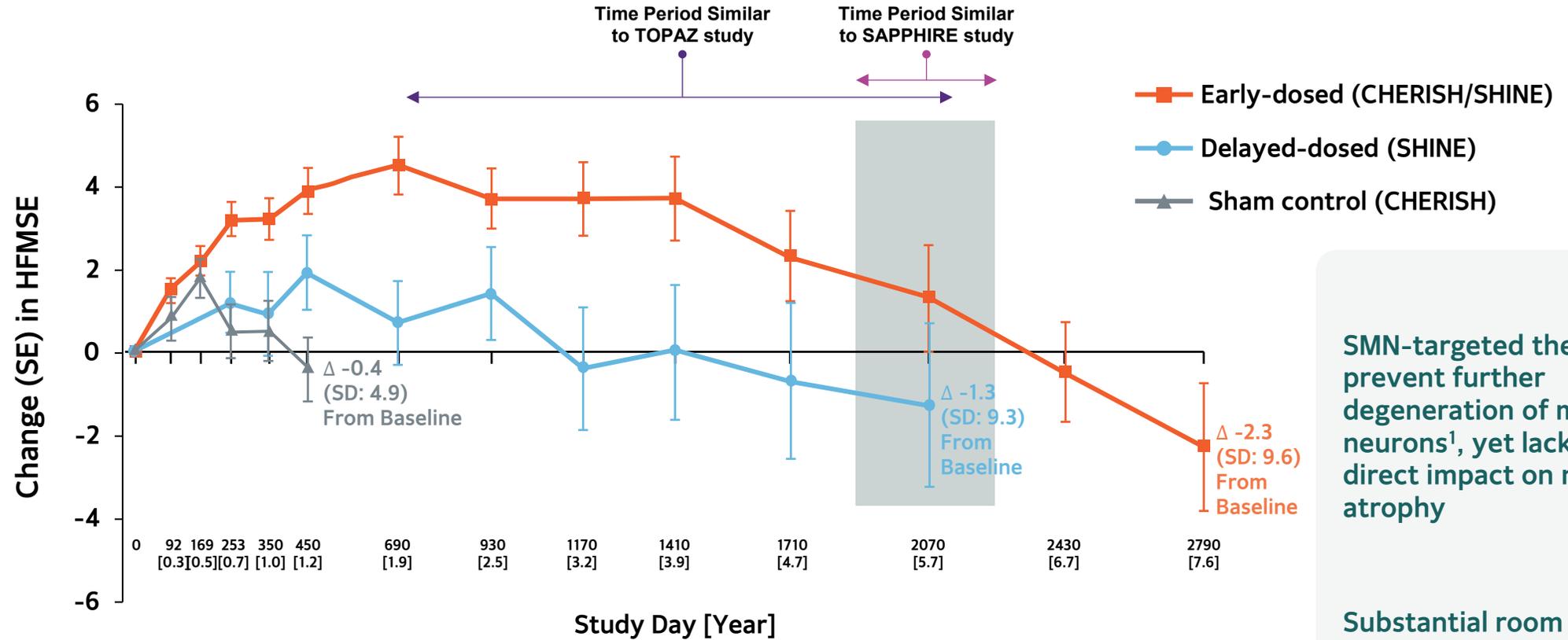
Baseline Demographics and Disease Characteristics Well Balanced

	Ages 2-12				Ages 13-21	
	Placebo + SOC (N = 50)	Apitegromab 10 mg/kg + SOC (N = 53)	Apitegromab 20 mg/kg + SOC (N = 53)	Apitegromab + SOC (N = 106)	Placebo + SOC (N = 10)	Apitegromab 20 mg/kg + SOC (N = 22)
Female Sex, n (%)	25 (50.0)	23 (43.4)	26 (49.1)	49 (46.2)	5 (50.0)	15 (68.2)
Age at Screening - years, mean (range)	8.1 (3, 12)	7.4 (2, 12)	7.9 (2, 12)	7.6 (2, 12)	15.2 (13, 18)	16.1 (13, 21)
SMN Therapy at Randomization						
Nusinersen / Risdiplam (%)	80 / 20	75.5 / 24.5	77.4 / 22.6	76.4 / 23.6	60 / 40	54.5 / 45.5
Duration of Nusinersen / Risdiplam - years, mean	5.5 / 2.7	4.4 / 3.0	5.3 / 3.5	4.8 / 3.2	6.7 / 3.3	5.9 / 3.8
SMN Therapy Initiation Age, <5 / ≥5 years (%)	88 / 12	86.8 / 13.2	84.9 / 15.1	85.8 / 14.2	N/A	N/A
Number of SMN Therapies, 1 / 2 (%)	86 / 14	86.8 / 13.2	84.9 / 15.1	85.8 / 14.2	80 / 20	90.9 / 9.1
SMA Type, Type 2 / 3 (%)	94 / 6	83 / 17	90.6 / 9.4	86.8 / 13.2	60 / 40	40.9 / 59.1
SMN2 Copy Number, 2 / 3 / 4 (%)	4 / 90 / 2	11.3 / 77.4 / 7.5	7.5 / 86.8 / 5.7	9.4 / 82.1 / 6.6	0 / 80 / 10	4.5 / 59.1 / 13.6
Baseline HFMSE Score, mean (range)	27.8 (9, 46)	25.5 (9, 48)	25.5 (10, 43)	25.5 (9, 48)	22.8 (10, 45)	20.6 (8, 43)
History of Scoliosis (%)	70	71.7	71.7	71.7	90	86.4

KEY • Study population was broadly representative of SMA population

TAKEAWAYS • Patients on the advanced phase of their SMN therapy journey

Despite Chronic SMN Therapy, SMA Patients Continue To Lose Function Over Time



Early-dosed (CHERISH/SHINE)	n=	84	84	84	84	83	76	83	83	79	74	75	54	61	39
Delayed-dose (SHINE)	n=	42		40	18	24	37	37	35	29	30	22		61	39
Sham control (CHERISH)	n=	42	41	41	41	42	39								

SMN-targeted therapies prevent further degeneration of motor neurons¹, yet lack any direct impact on muscle atrophy

Substantial room for improvement in the current approved treatment landscape exists

Finkel RS et al. "Final Safety and Efficacy Data From the SHINE Study in Participants With Infantile-Onset and Later-Onset SMA." Presented at Cure SMA Annual Conference, July 2024

*Patient age based on those received active treatment (mean or median)

1. This information from third-party studies is provided for background purposes only and is not intended to convey or imply a comparison to the SAPHIRE clinical trial results

SMN=survival motor neuron

Primary Endpoint Met

Clinically Meaningful and Statistically Significant Improvement in HFMSE

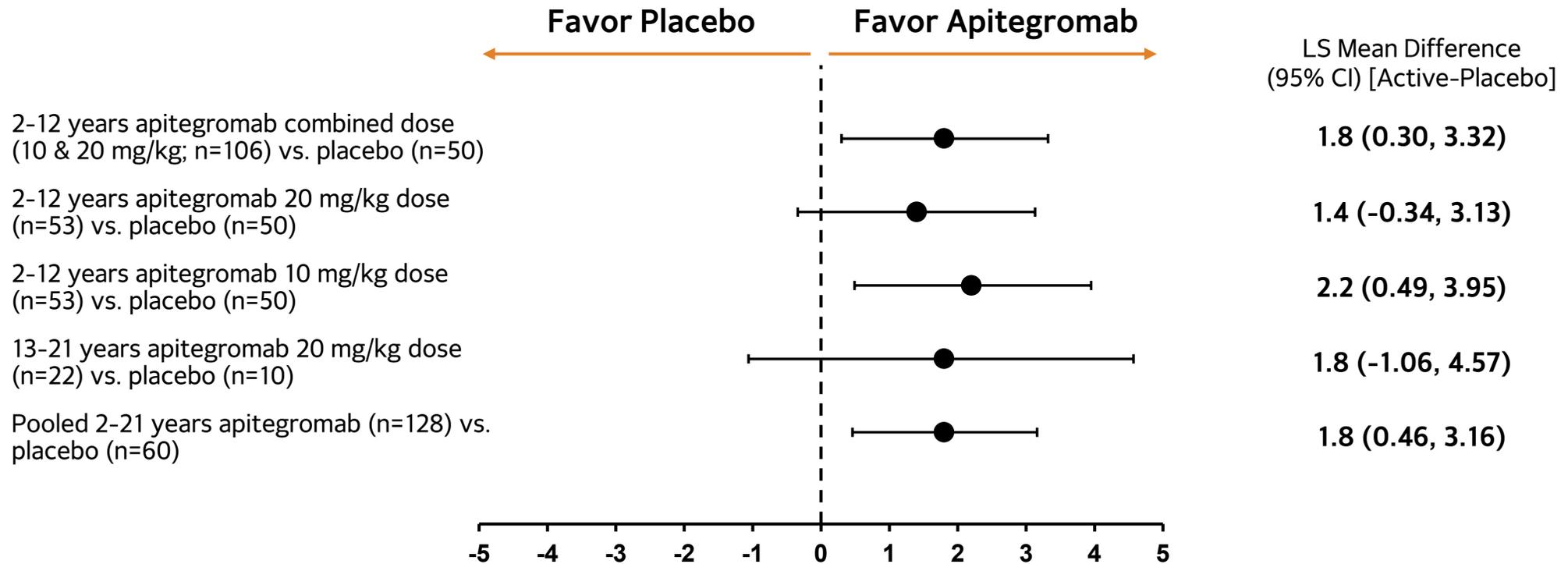
Change from Baseline in HFMSE Total Score

Analysis	n	Results (vs Placebo, n=50)	Unadjusted <i>P</i> -value		
Primary Analysis	Apitegromab 10+20 mg/kg combined	106	1.8	0.0192* 	Achieved Statistical Significance
	Apitegromab 20 mg/kg	53	1.4	0.1149*	
	Apitegromab 10 mg/kg	53	2.2	0.0121**	

*Hochberg method prespecified for multiplicity adjustment; **nominal p value
HFMSE=Hammersmith Functional Motor Scale Expanded.

Improvement in HFMSE Consistent Across Doses and Age Groups

Change from Baseline in HFMSE Total Score at 12 Months*

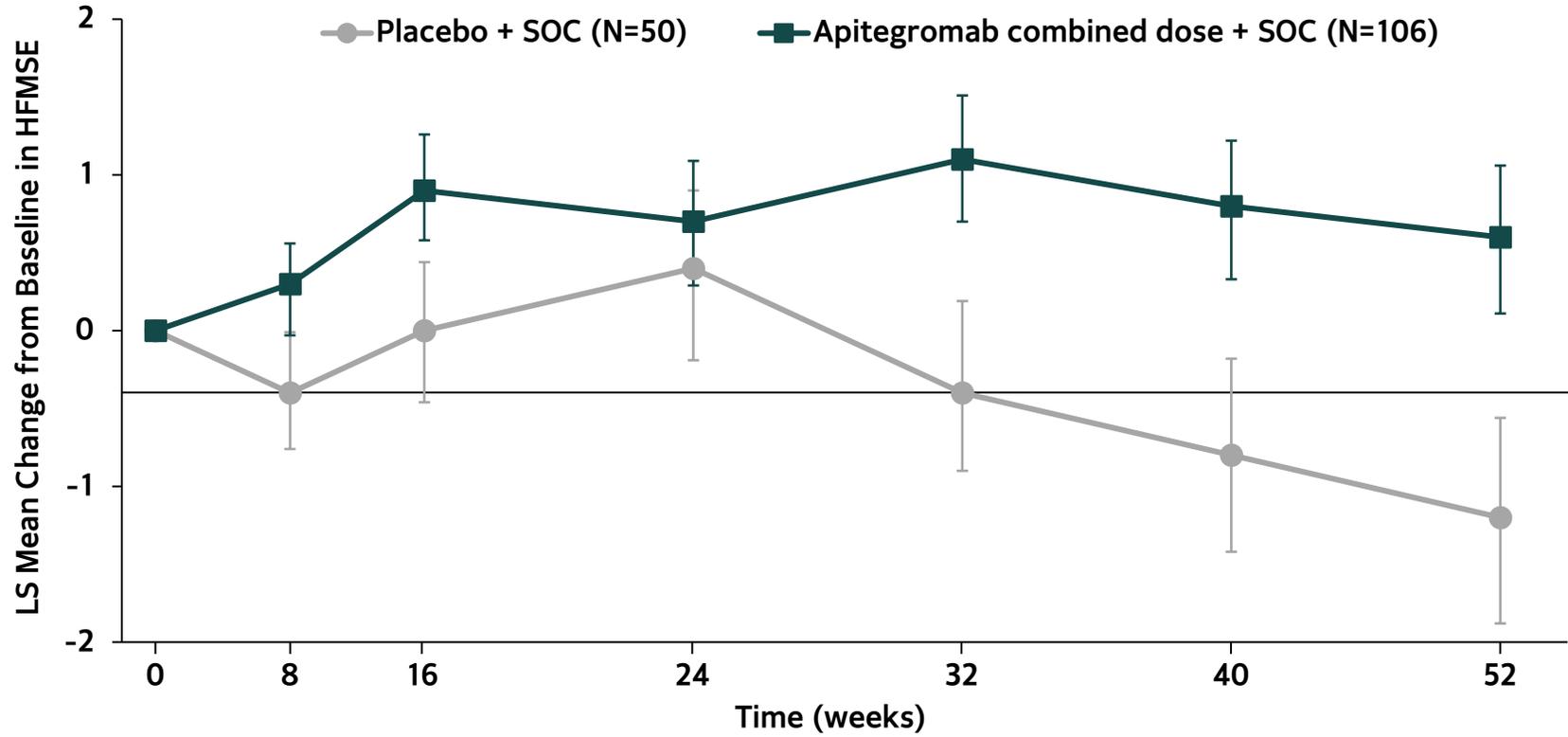


CI=Confidence Interval; EXP=Exploration Subpopulation; HFMSE=Hammersmith Functional Motor Scale Expanded; SOC=standard of care.

*n values at 12-month endpoint

Early and Increasing HFMSE Improvement vs. Placebo

Least Squares Mean (+/- SE) Change from Baseline in HFMSE Total Score by Visit (MITT Set)

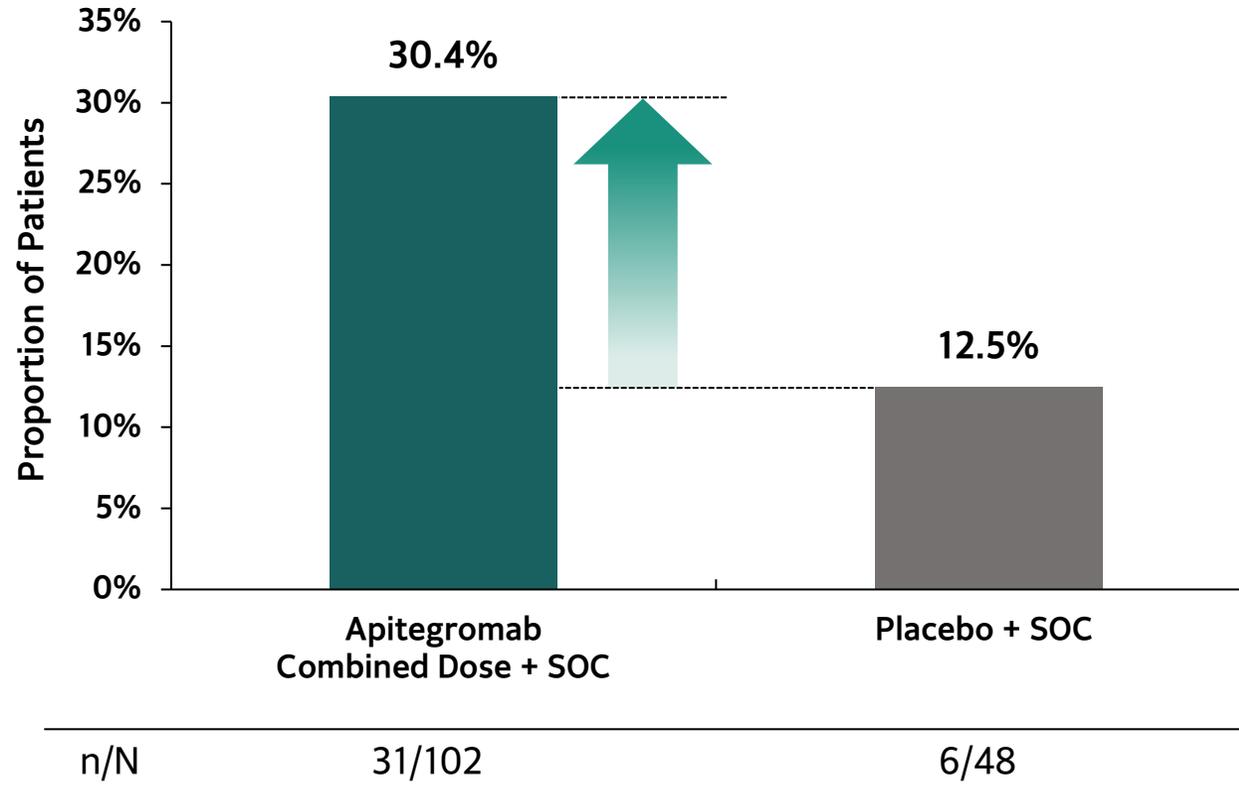


Apitegromab-treated patients improved on HFMSE, while placebo patients declined on HFMSE over 12 months

Placebo + SOC	50	50	50	48	50	49	48
Apitegromab + SOC	106	105	105	101	102	102	102

30% of Apitegromab Patients Achieved ≥ 3 Points on HFMSE

≥ 3 Point Improvement in HFMSE



Proportion of patients achieving ≥ 3 Point Improvement in HFMSE was higher for apitegromab vs. placebo in combined dose (odds ratio 3.0, $p=0.0256$)

Well-Tolerated Safety Consistent With Established Profile Observed in Phase 2 TOPAZ Trial

Summary of Adverse Events (AE)	Ages 2-12				Ages 13-21	
	Placebo + SOC (N = 50) n (%)	Apitegromab 10 mg/kg + SOC (N = 53) n (%)	Apitegromab 20 mg/kg + SOC (N = 53) n (%)	Apitegromab + SOC (N = 106) n (%)	Placebo + SOC (N = 10) n (%)	Apitegromab 20 mg/kg + SOC (N = 22) n (%)
AE	43 (86.0)	51 (96.2)	46 (86.8)	97 (91.5)	9 (90.0)	19 (86.4)
SAE	5 (10.0)	9 (17.0)	12 (22.6)	21 (19.8)	1 (10.0)	0
AE Grade \geq 3	5 (10.0)	9 (17.0)	11 (20.8)	20 (18.9)	1 (10.0)	1 (4.5)
AE Leading to treatment discontinuation	0	0	0	0	0	0
AE Leading to study withdrawal	0	0	0	0	0	0

- AE \geq 20% incidence in apitegromab-treated patients were pyrexia, nasopharyngitis, cough, vomiting, upper respiratory track infection, and headache
- SAEs pneumonia and dehydration were infrequent (<8%) and deemed unrelated to apitegromab

KEY TAKEAWAYS

- There were no clinically relevant differences in the adverse event profile by dose, 10 mg/kg vs 20 mg/kg
- SAEs were consistent with underlying disease and standard of care, and none were assessed as related to apitegromab
- There were no study drug discontinuations due to adverse events

Potential to Transform Standard of Care in SMA

Clear and Meaningful Improvement

1.8-point improvement in HFMSE (p=0.0192) compared to placebo

Patients improving on apitegromab vs. declining on placebo



Potential to be Suitable for Broad SMA Population*

Broadly representative study population

Improvement across all age groups (2-21)



Well-tolerated Safety Profile

Favorable safety profile supports durability of treatment

>48 months treatment experience in SMA¹



¹ Based on TOPAZ patients receiving combination therapy after 4 years of treatment. Data cutoff date: April 2024

* If approved by regulatory authorities



Conclusion

Jay Backstrom, M.D., MPH
President & Chief Executive Officer



We are a global leader in harnessing the life-changing potential of the TGFβ superfamily

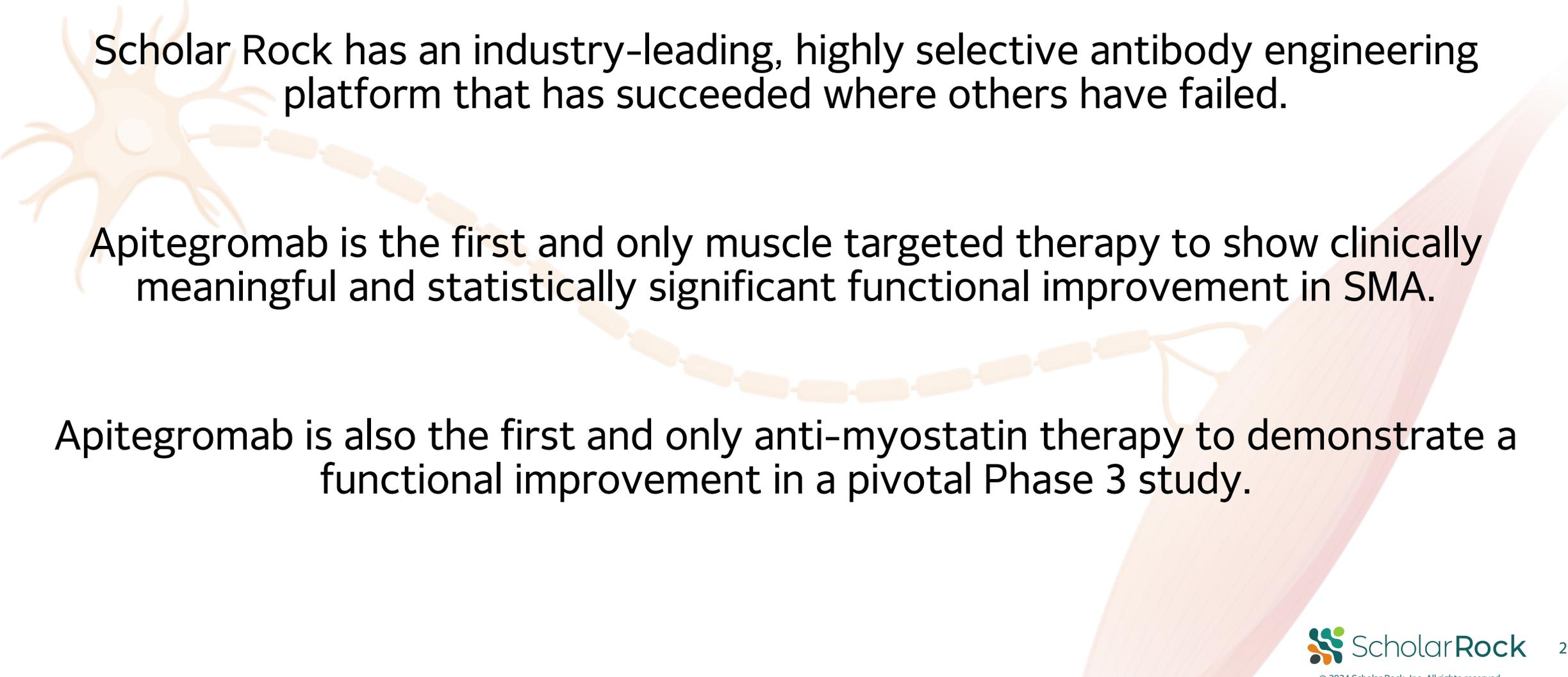


OUR MISSION

To discover, develop, and deliver life-changing therapies by harnessing cutting-edge science to create new possibilities for people living with serious diseases



Innovating a New Era in the Treatment of Spinal Muscular Atrophy

A stylized illustration of a neuron on the left, with its cell body and branching processes. A long, thin axon extends from the neuron, passing through a series of rectangular segments that represent the spinal cord. The axon ends on the right, where it connects to a large, pinkish-red muscle fiber. The background is white with a subtle gradient and a faint, larger-scale version of the neuron and muscle fiber illustration.

Scholar Rock has an industry-leading, highly selective antibody engineering platform that has succeeded where others have failed.

Apitegromab is the first and only muscle targeted therapy to show clinically meaningful and statistically significant functional improvement in SMA.

Apitegromab is also the first and only anti-myostatin therapy to demonstrate a functional improvement in a pivotal Phase 3 study.

Apitegromab Has the Potential to Transform Standard of Care in SMA

MET PRIMARY ENDPOINT:

1.8
POINT
IMPROVEMENT
in HFMSE* vs. placebo
(p=0.0192)

CONSISTENT
clinically meaningful
benefit across
all age groups
(2-21)

30%
of apitegromab patients
ACHIEVED ≥ 3
POINT IMPROVEMENT IN
HFMSE†

FAVORABLE
SAFETY profile
consistent with >48
months experience in
Phase 2 TOPAZ trial

Scholar Rock is working with a sense of urgency to bring
apitegromab to SMA patients

* Based on apitegromab combined dose (10 mg/kg and 20 mg/kg) + SOC versus placebo + SOC
† 12.5% of patients on placebo + SOC achieved a ≥ 3 -point improvement in HFMSE
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Upcoming Planned Key Milestones



Apitegromab Regulatory Submissions

- Submit FDA and EMA applications in Q1 2025
- Request priority review (FDA) and accelerated assessment (EMA)



Myostatin Clinical Momentum

- Obesity: EMBRAZE readout expected in Q2 2025
- SMA: Under 2 study initiation planned for mid-2025



Apitegromab Commercial Launch in SMA*

- US launch in Q4 2025 and EU launch to follow

* If approved by relevant health authorities



Q&A Session

Thank you!