Deep Insights Advancing Impactful Medicines

Company Overview | October 2024

ScholarRock™

Forward-Looking Statements

Various statements in this presentation concerning the future expectations, plans and prospects of Scholar Rock Holding Corporation and Scholar Rock, Inc. (collectively, "Scholar Rock"), including without limitation, Scholar Rock's expectations regarding its strategy, its product candidate selection and development timing, including timing for the initiation of and reporting results from its preclinical studies and clinical trials for SRK-439, apitegromab, SRK-181 and other product candidates and indication selection and development timing, its cash runway, the ability of any product candidate to perform in humans in a manner consistent with earlier nonclinical, preclinical or clinical trial data, and the potential of its product candidates and proprietary platform. The use of words such as "may," "could," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "project," "intend," "future," "potential," or "continue," and other similar expressions are intended to identify such forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. All such forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, without limitation, that preclinical and clinical data, including the results from the Phase 2 trial of apitegromab or Part A or Part B of the Phase 1 trial of SRK-181, are not predictive of, may be inconsistent with, or more favorable than, data generated from future or ongoing clinical trials of the same product candidate, including the Phase 3 clinical trial of apitegromab in SMA and Part B of the Phase 1 clinical trial of SRK-181, respectively, Scholar Rock's ability to provide the financial support, resources and expertise necessary to identify and develop product candidates on the expected timeline, the data generated from Scholar Rock's nonclinical and preclinical studies and clinical trials, information provided or decisions made by regulatory authorities, competition from third parties that are developing products for similar uses, Scholar Rock's ability to obtain, maintain and protect its intellectual property, the success of Scholar Rock's current and potential future collaborations, Scholar Rock's dependence on third parties for development and manufacture of product candidates including, without limitation, to supply any clinical trials, Scholar Rock's ability to manage expenses and to obtain additional funding when needed to support its business activities and establish, and maintain strategic business alliances and new business initiatives, and our ability to continue as a going concern as well as those risks more fully discussed in the section entitled "Risk Factors" in Scholar Rock's Form 10-K for the year ended December 31, 2023, and Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, as well as discussions of potential risks, uncertainties, and other important factors in Scholar Rock's subsequent filings with the Securities and Exchange Commission. Any forward-looking statements represent Scholar Rock's views only as of today and should not be relied upon as representing its views as of any subsequent date. All information in this press release is as of the date of the release, and Scholar Rock undertakes no duty to update this information unless required by law.

This presentation may also contain estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we compete are necessarily subject to a high degree of uncertainty and risk.

Apitegromab and SRK-181 are investigational drug candidates under evaluation. Apitegromab, SRK-181, SRK-373, SRK-256, and SRK-439 have not been approved for any use by the FDA or any other regulatory agency and the safety and efficacy of apitegromab, SRK-181, SRK-373, SRK-256, and SRK-439 have not been established.

ScholarRock

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

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

TGFβ=Transforming growth factor-beta.

Building a Fully Integrated Therapeutics Company

Revolutionary Scientific Platform

- **Pioneers in unparalleled selective** targeting of the **latent forms** of **growth factors**
- Robust pipeline of **novel** assets including **two clinical programs** and a **growing portfolio of preclinical programs**

Transformative Therapeutics in Development

Apitegromab in SMA

Potential therapy designed to **improve motor function to help address remaining unmet need** after receipt of existing SMA therapies

SRK- 439 in Obesity

Novel antimyostatin antibody with the potential to support **healthier weight management by preserving lean muscle**

SRK-181 in Immuno-Oncology

In Ph 1 development to **overcome resistance to checkpoint inhibitors** in multiple tumor types

Experienced and Focused

- Seasoned team with **track record** of **clinical** and **commercial success**
- **Deep** rare disease, R&D, FDA/EMA approval & launch **experience**
- **Focused, efficient approach** to scaling the organization

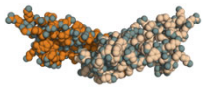
SMA=Spinal muscular atrophy; EMA=European Medicines Agency; FDA=United States Food and Drug Administration; R&D=research and development.

Our Approach

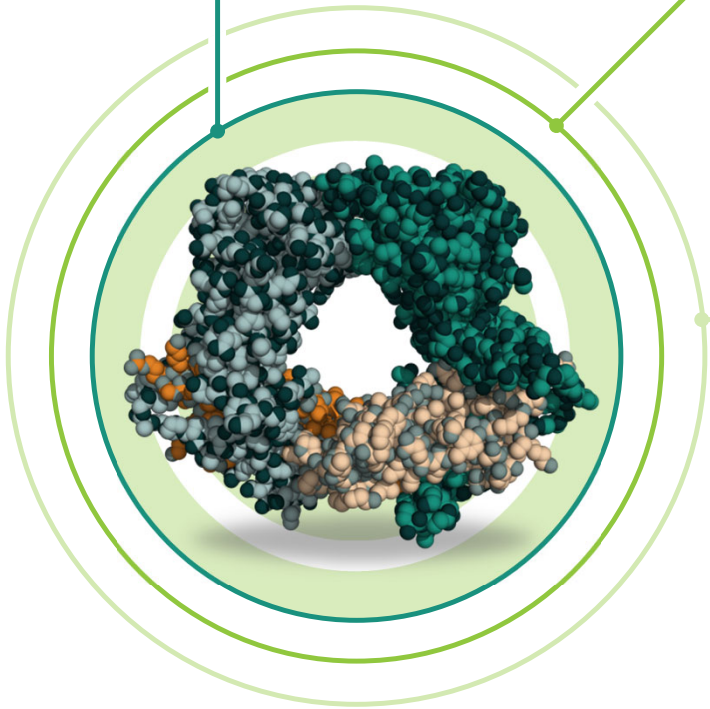
Selectivity Drives Success

RIGHT TARGET → **Validated Biology**

RIGHT TIME → **Latent Form**



Traditional Target
"mature" active growth factor



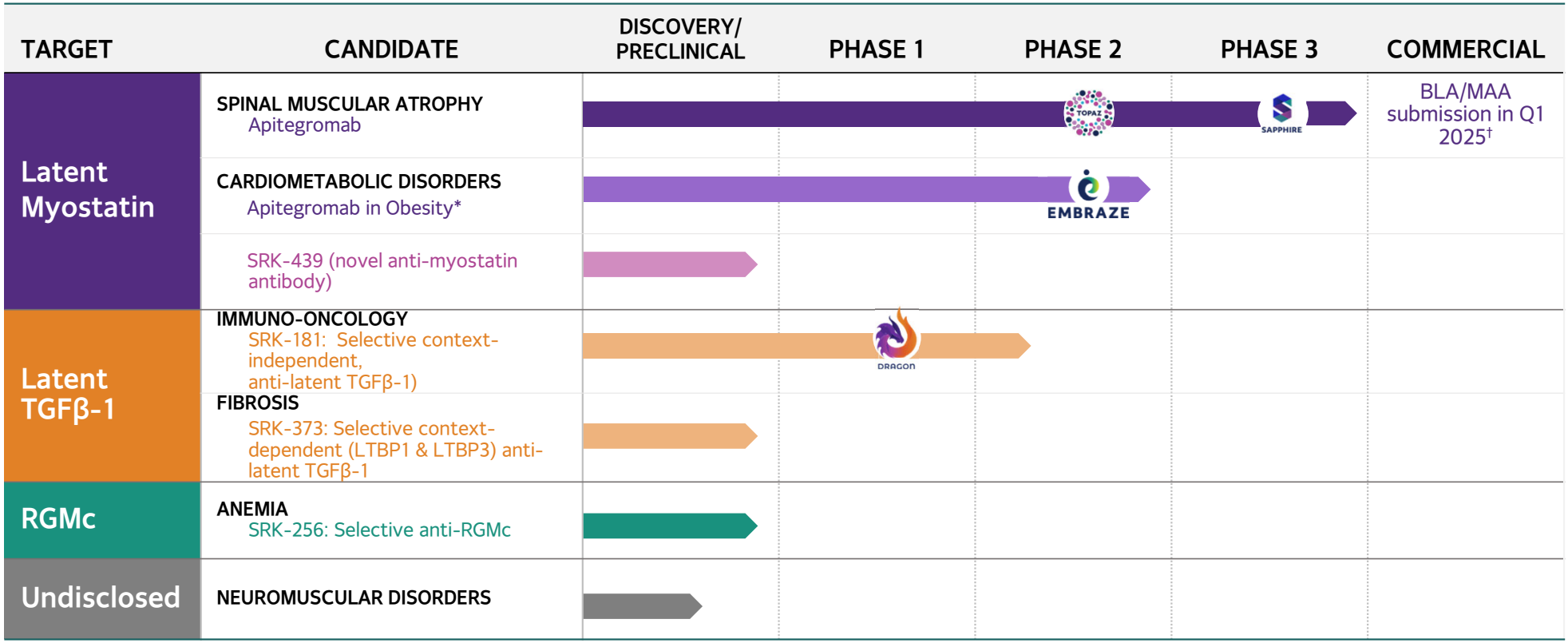
Scholar Rock's Target
Latent Growth Factor Complex

Deep structural insights to validated targets

Industry-leading antibody design and protein engineering to selectively target latent growth factors

Optimized for efficacy and mitigates off-target effects

Scientific Platform Yielding Growing Pipeline Across High Value Therapeutic Areas



*Utilized data from previously completed Ph 1 study in healthy volunteers and initiate a Ph 2 POC trial in 2024. † Anticipated milestones.
LTBP1=Latent transforming growth factor beta binding protein 1; LTBP3=Latent transforming growth factor beta binding protein 3; POC=Proof of concept; RGMc=Repulsive guidance molecule C; TGFβ-1=Transforming growth factor beta-1.

ScholarRock

Leveraging Our Building Blocks, Transformative 18 Months Ahead

Value Drivers

Significant Inflection Points in Next Year

Apitegromab BLA/MAA Submission

Proof of Concept in Obesity

Preparing to Launch SMA in US and EU*

Phased approach to building key capabilities

Well established presence within SMA Community

Powerful Building Blocks

Novel Scientific Platform

Robust Pipeline across 5 therapeutic areas

3 clinical programs

Multiple preclinical programs

Experienced Team

Deep rare disease, R&D, FDA/EMA approval experience

~150+ Employees

~74% R&D

Established Markets with High Unmet Need

Apitegromab in SMA

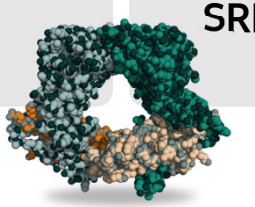
SRK-439 in Obesity

SRK-181 in Immuno-oncology

Global Rights Across the Portfolio

29 patent families pending

Exclusivity through 2036 to 2043 for key assets



* Subject to regulatory approval

ScholarRock

Strategic Roadmap: Our Vision for 2030

Scholar Rock Today

- Building Commercial Preparedness in US & EU
- 3 Clinical Programs
- Multiple Research Programs

Scholar Rock 2030

- **Multi-Billion Dollar Global Neuromuscular Franchise**
  Established in key major markets
- **5 Clinical Programs**
  Including additional neuromuscular assets
- **Multiple Research Programs**
  Across TGFβ superfamily of growth factors
- **New Targets**
  Leveraging our world-leading antibody engineering capabilities to pursue targets beyond TGFβ superfamily

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

EMBRAZE

OPAL

Apitegromab Commercial Launch in SMA*

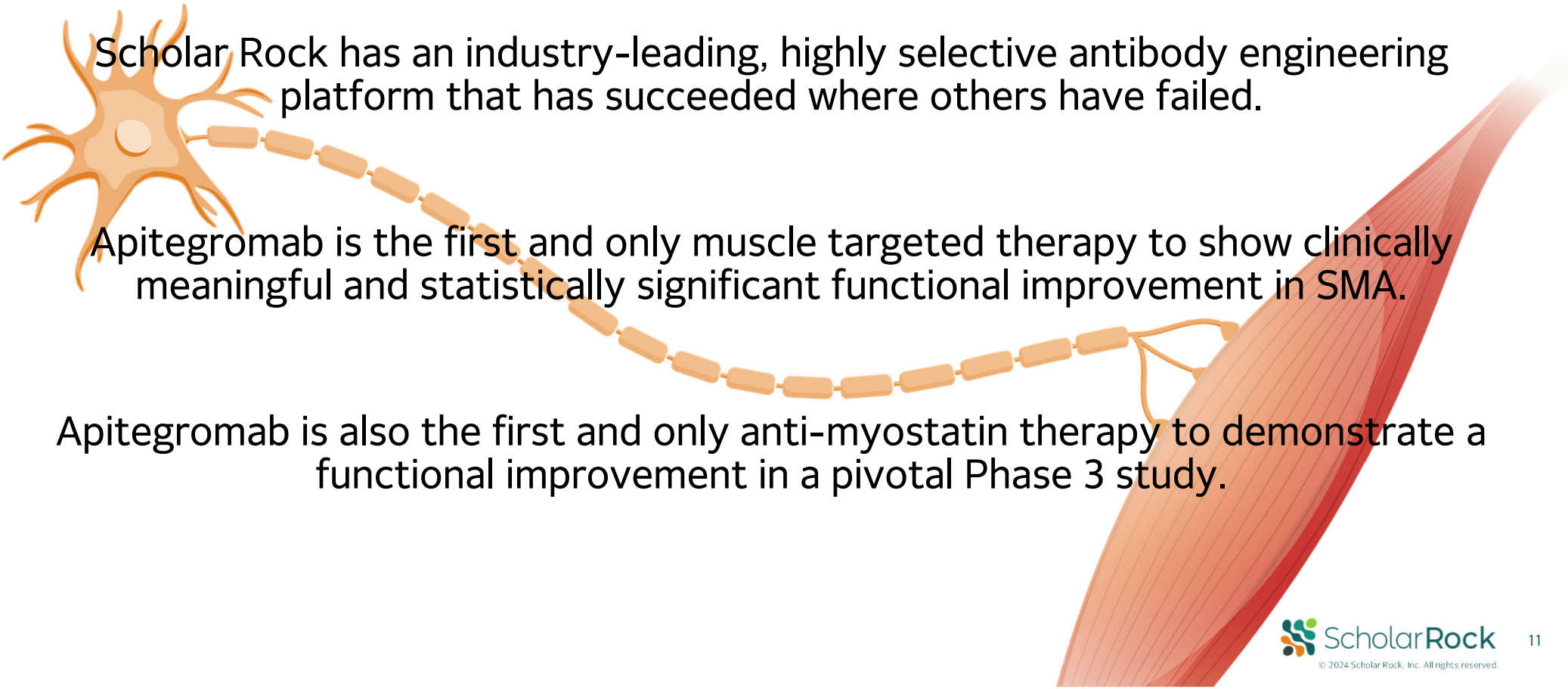
- US launch in Q4 2025 and EU launch to follow

* If approved by relevant health authorities

Antimyostatin Program: Apitegromab in Spinal Muscular Atrophy

ScholarRock™

Innovating a New Era in the Treatment of Spinal Muscular Atrophy



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.

Hallmarks of SMA

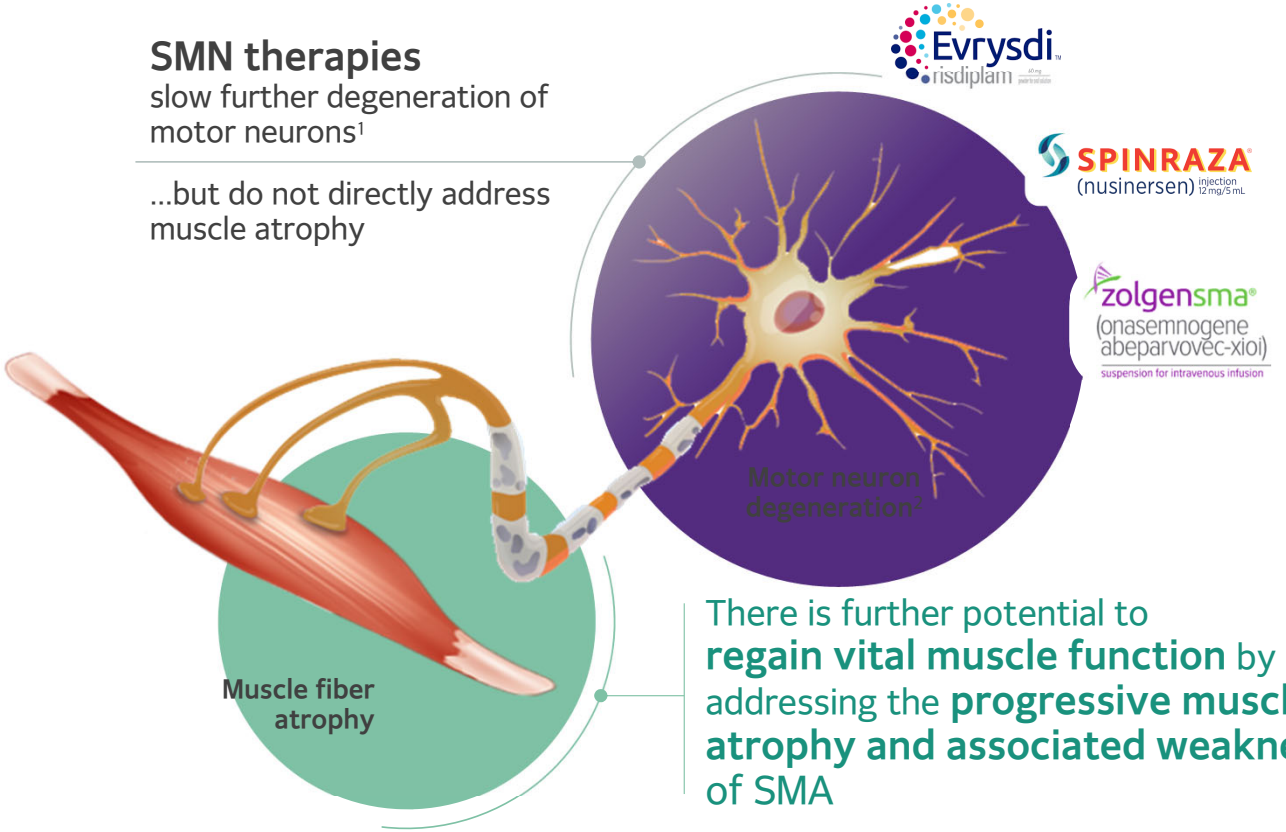
Motor Neuron Loss and Muscle Atrophy Leads to Progressive Muscle Weakness

Spinal Muscular Atrophy

Motor neuron impairment and loss due to SMN genetic deficiency leads to muscle atrophy and weakness

SMN therapies
slow further degeneration of motor neurons[1]

...but do not directly address muscle atrophy



There is further potential to **regain vital muscle function** by also addressing the **progressive muscle atrophy and associated weakness** of SMA

SMA=Spinal muscular atrophy; SMN=Survival motor neuron.
1. Hua Y, et al. Nature. 2011;478(7367):123-6.
2. Figure adapted from: SMA Foundation Overview. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf.; Accessed April 18, 2021.

SMA Leads to Deterioration in Essential Muscle Function

"What may seem like minimal gains in strength actually translate to **exponential gains in functional abilities.**

I often have to choose between taking a shower and doing homework because **I don't have the energy to do both.**

Small tasks are huge success in my life. If I could lift that 1L bottle of water at work instead of having to find a graduate student to move it for me…**things don't take a ton more muscle, but they are all muscle I still don't have**."

Despite significant advancements, **progressive muscle weakness** remains an unmet need in SMA

Muscle weakness can lead to deterioration in **mobility, swallowing, breathing** and cause **debilitating fatigue**

Quotes are from patient advocates who participated in 2022 Cure SMA FDA Patient-Led Listening Session and not from the pictured individuals. Summary of the listening session can be found on the FDA website at https://www.curesma.org/cure-sma-holds-patient-led-listening-session-with-fda/

SMA Today: More Patients Screened and Treated

GLOBAL DISEASE:

>20,000 affected

in US and Europe[1, 2]

Three treatments to address SMN loss

SPINRAZA® (nusinersen) injection 12 mg/5 mL

>13,000 patients
treated WW

$1.8 billion
annual revenue (LTM)[3]

Evrysdi® risdiplam

> 11,000 patients
treated WW

~CHF1.4 billion
annual revenue (LTM)[4]

zolgensma® (onasemnogene abeparvovec-xioi) suspension for intravenous infusion

> 3,500 patients
treated WW

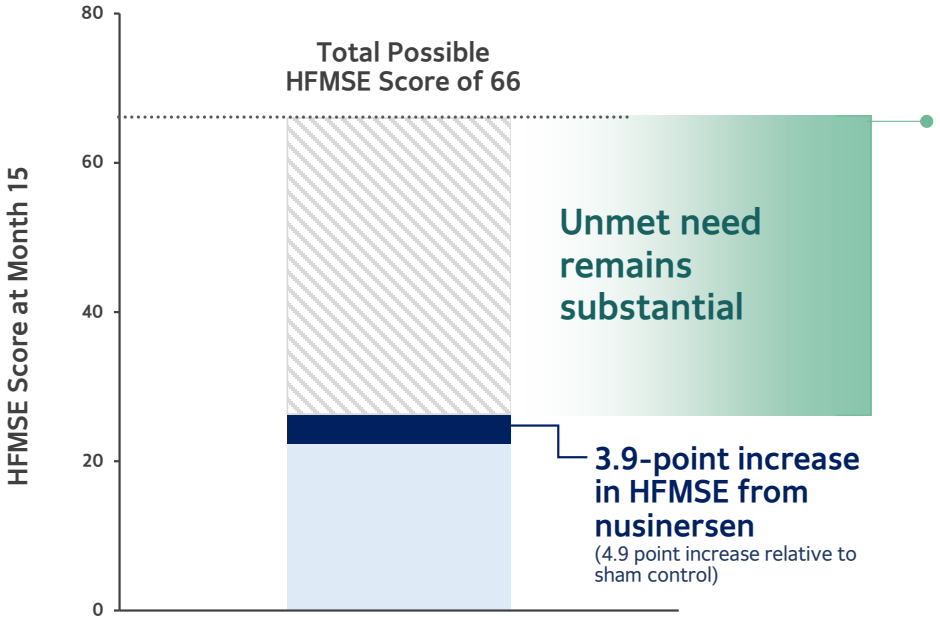
~$1.2 billion
in revenues (LTM)[5]

Established market dynamics support Scholar Rock's first potential commercial launch

CHF=Swiss franc; LTM=last twelve months; SMA=Spinal muscular atrophy; SMN=Survival motor neuron; WW=worldwide.

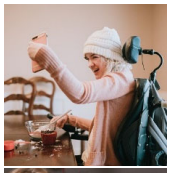
1. Cure SMA 2022 Report: 9042022_State-of-SMA_vweb.pdf (curesma.org)
2. Lally et al. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet J Rare Dis. 2017 Nov 28;12(1):175. doi: 10.1186/s13023-017-0724-z.
3. Revenue as of Biogen 3Q23 financial update; includes patients treated worldwide in post-marketing setting, expanded access program, and clinical trials as of May 2022.
4. Revenue as of Roche 3Q23 financial update; includes patients treated worldwide as of July 2023.
5. Revenue as of Novartis 3Q23 financial update; includes patients treated worldwide including clinical trials, commercially, and managed access programs as of August 2023.

Muscle-Targeted Therapy: A New Treatment Frontier



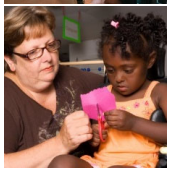
Mean improvement in HFMSE experienced by patients in nusinersen Phase 3 CHERISH trial[1]

Patients and caregivers want new therapies to address the following unmet needs[2]:



INCREASE muscle strength

IMPROVE daily activities



STABILIZE or GAIN new motor function

REDUCE fatigue

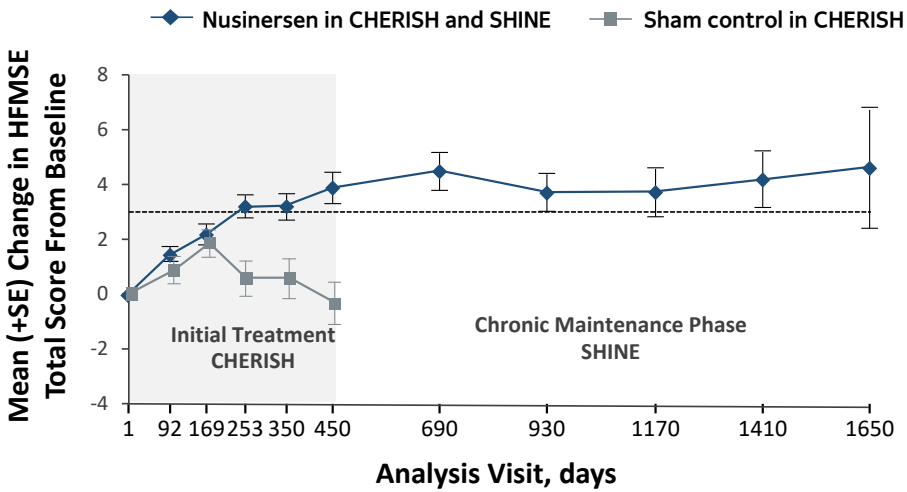
*Percentages represent percent of patients who named these unmet needs when asked, "What are your most significant current unmet needs that you hope new therapies would address?"
HFMSE=Hammersmith Functional Motor Scale-Expanded.
1. Mercuri E et al.; N Engl J Med 2018; 378:625-635; DOI: 10.1056/NEJMoa1710504; cherish trial results; 2. 2023 Community Update Survey, Cure SMA.
This third-party information is provided for background only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results.

Motor Function With SMN Therapies as Assessed by HFMSE

HFMSE appears to Plateau After Initial Gains

Change in HFMSE Over Four Years with Nusinersen[1]

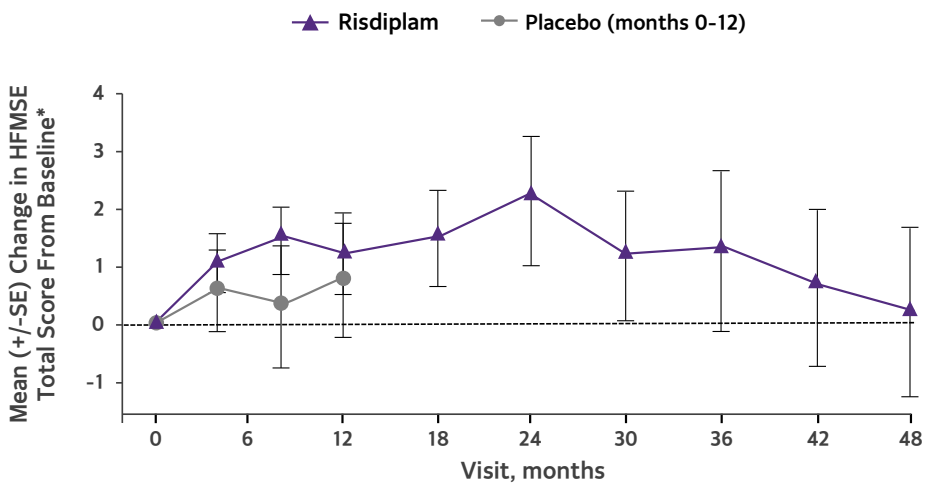
Overall population age 2-12



Nusinersen	n=	84	82	84	84	83	76	83	83	79	61	20
Placebo	n=	42	41	41	42	42	39					

Change in HFMSE* Over Four Years with Risdiplam[2]

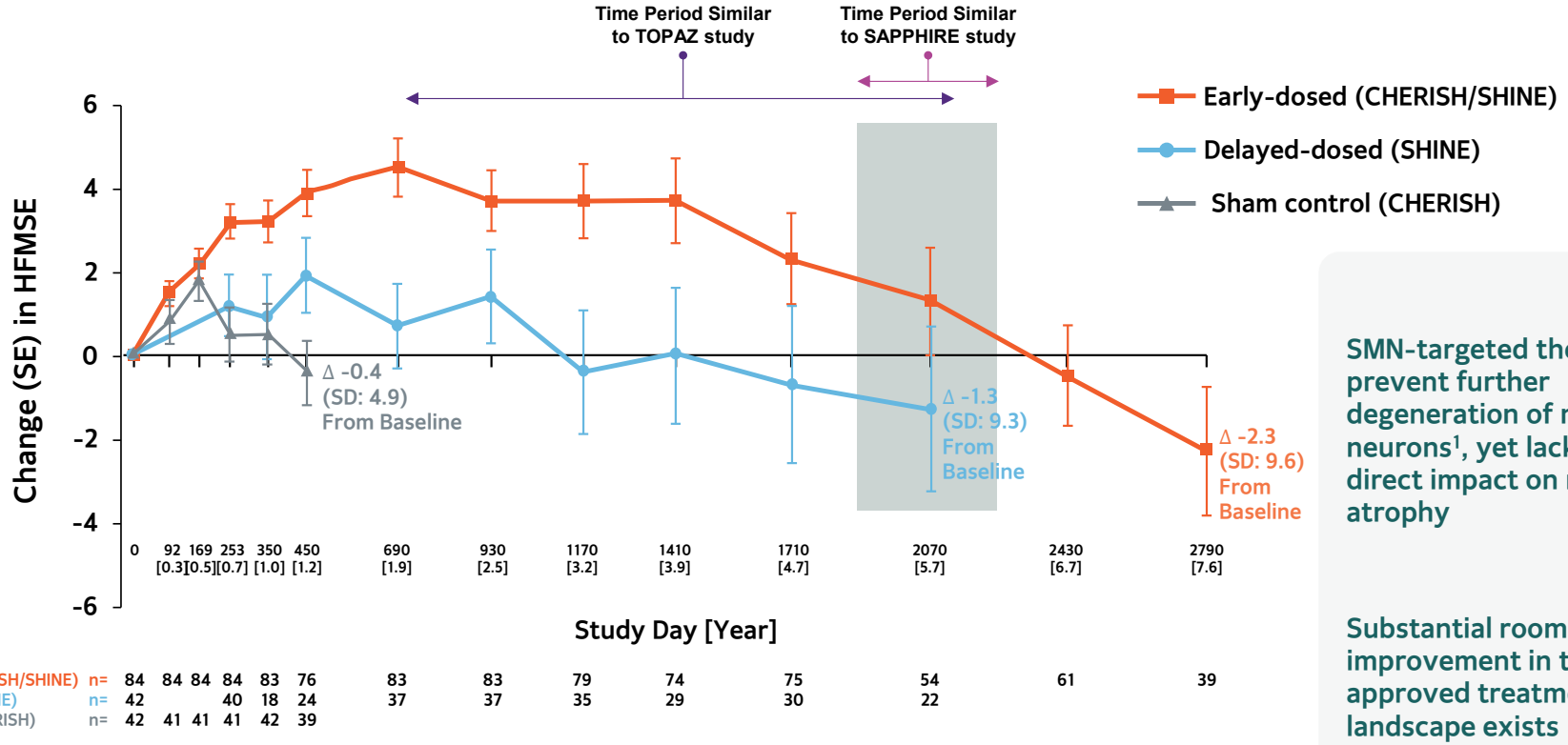
Overall population age 2-25



Risdiplam	n=	120	120	119	117	109	106	89	99	101	97	
Placebo	n=	60	60	58	58							

1. Mercuri E, et al. Presented at: World Muscle Society Congress 2020, P. 257
2. Oskoui M, et al. Presented at: 2021 Muscular Dystrophy Association Clinical & Scientific Conference; March 15-18, 2021. Poster 80.
HFMSE, Hammersmith Functional Motor Scale–Expanded; SE, standard error.
*MFM was primary efficacy endpoint of SUNFISH. HFMSE was a secondary endpoint. This third-party information is provided for background only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results.

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		
Sham control (CHERISH)	n=	42	41	41	41	42	39								

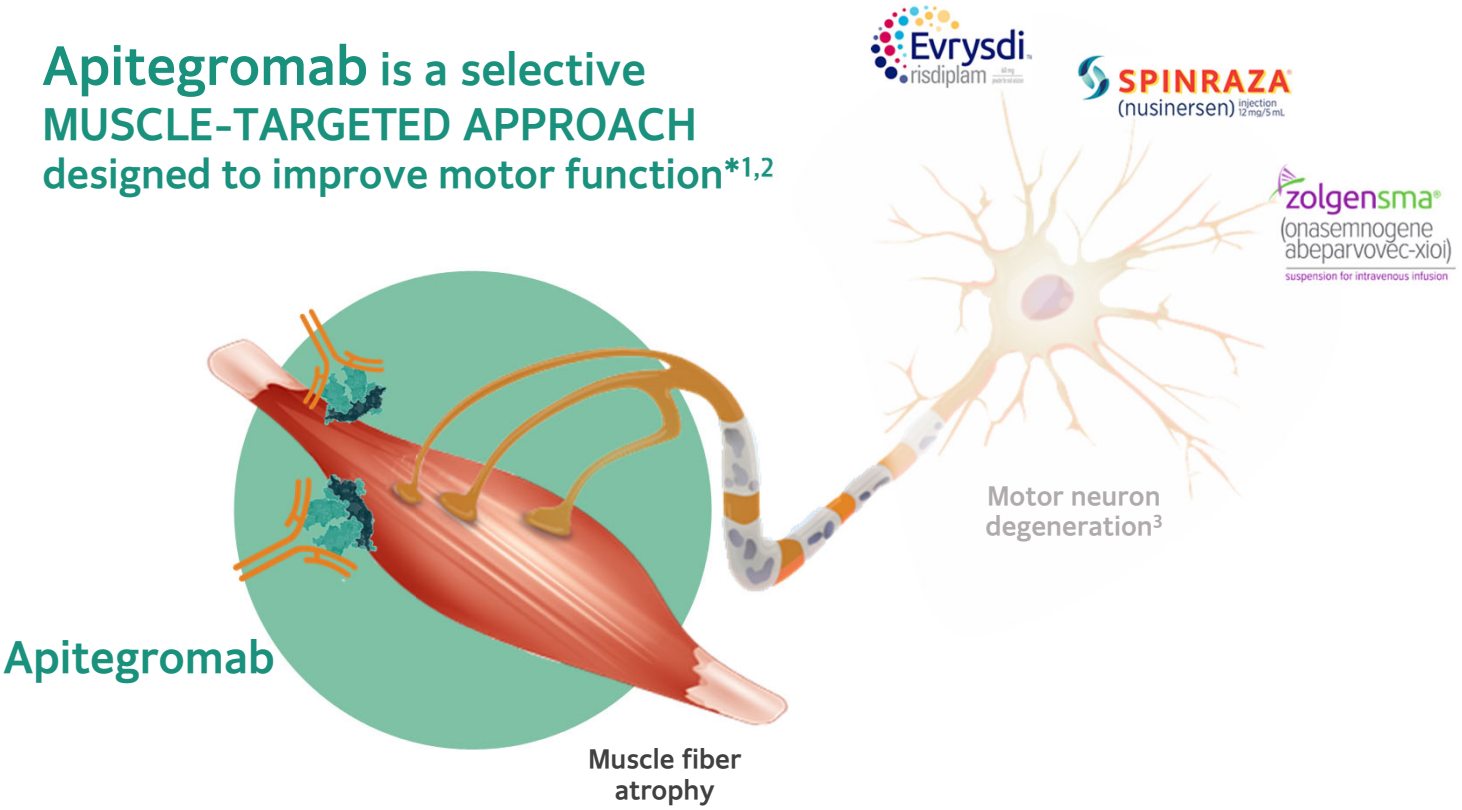
SMN-targeted therapies prevent further degeneration of motor neurons[1], yet lack any direct impact on muscle atrophy

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 SAPPHIRE clinical trial results
SMN=survival motor neuron

Apitegromab Offers Significant Potential to Address Unmet Needs

Apitegromab is a selective
MUSCLE-TARGETED APPROACH
designed to improve motor function*[1,2]



Myostatin is a negative modulator of muscle growth

Strong clinical and preclinical evidence indicates upstream targeting of structurally differentiated pro- and latent myostatin avoids undesirable off-target effects

Apitegromab specifically and only inhibits myostatin and has the potential to build muscle and strength to improve patient outcomes

* Based on Animal Model Data; 1. Long KK, et al. Hum Mol Genet. 2019;28(7):1077-1088; 2. Pirruccello-Straub M, et al. Sci Reports. 2018;8(1):2292. doi:10.1038/s41598-018-20524-9 3. Figure adapted from: SMA Foundation Overview. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf.; Accessed April 18, 2021. For illustrative purposes only.

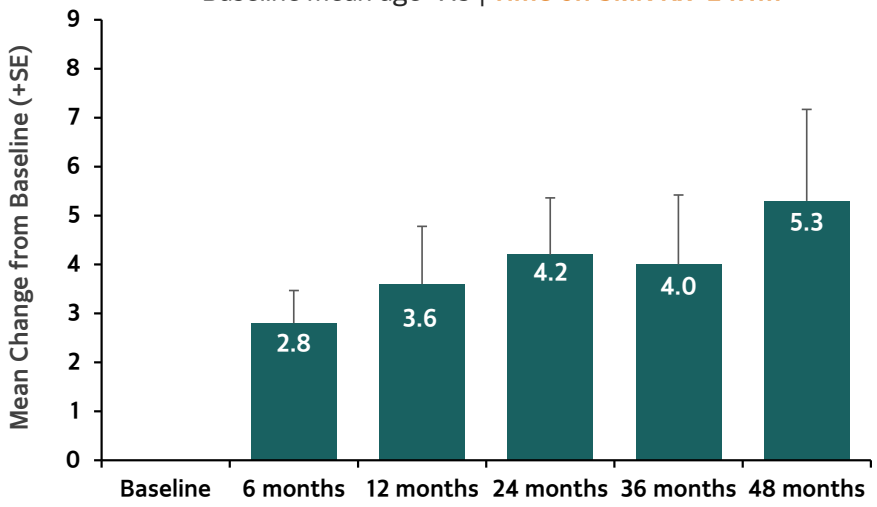
Apitegromab TOPAZ Clinical Trial: Motor Function Outcomes by HFMSE Over 48 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients[1]

Age 2-21 Years
All Doses (N=35)

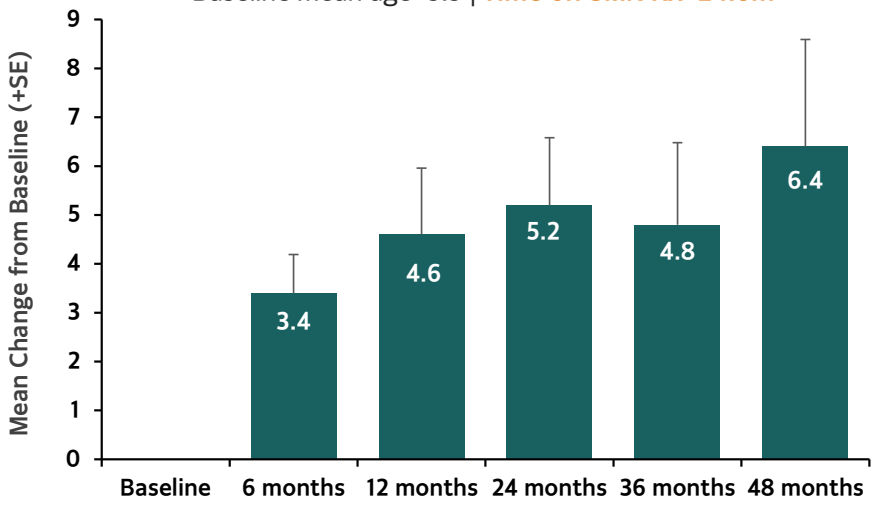
Baseline mean age=7.3 | **Time on SMN Rx=24.1m**



n=	35	29	32	29	28	23
95% CI=		(1.4, 4.1)	(1.2, 6.0)	(1.9, 6.6)	(1.0, 6.9)	(1.5, 9.2)

Age 2-12 Years
All Doses (N=29)

Baseline mean age=5.5 | **Time on SMN Rx=24.6m**



n=	29	23	26	23	23	19
95% CI=		(1.8, 5.0)	(1.8, 7.4)	(2.3, 8.0)	(1.3, 8.3)	(1.8, 11.0)

1. For the 48-month evaluation, an observed case analysis was conducted using available data by analysis timepoint, censoring any HFMSE assessments after the patient received scoliosis surgery. The analysis population pooled the nonambulatory patients (Cohorts 2 and 3) and included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who switched from 2 mg/kg to 20 mg/kg in Year 2). A total of 11 patients in the population had scoliosis surgery during the study and their data was excluded from any HFMSE assessments at 48 months. Visit windows were applied to utilize data from unscheduled or early termination visits if the patient was missing the HFMSE total score at the scheduled visit. Error bars represent standard error (SE) and CI represents confidence interval. SMN Rx=SMN therapy. Apitegromab is an investigational drug candidate being evaluated for the treatment of spinal muscular atrophy. Apitegromab has not been approved for any use by the US FDA or any other health authority, and its safety and efficacy have not been established.

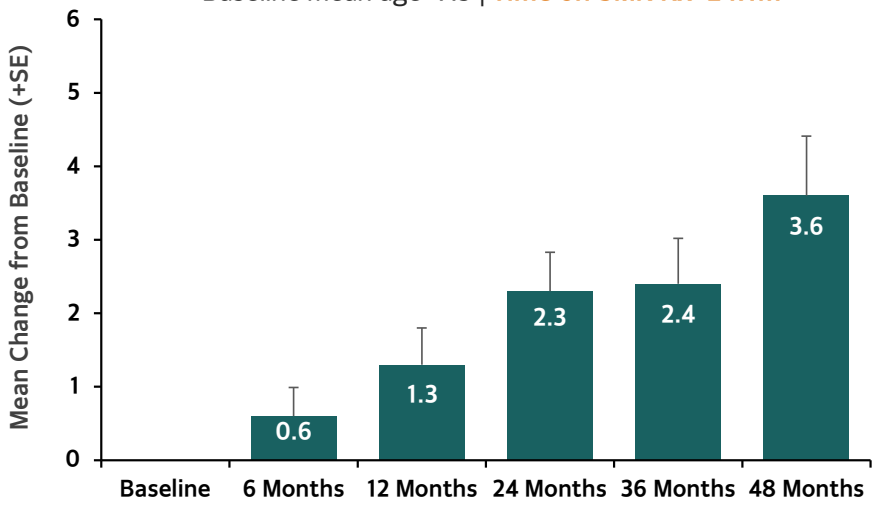
Apitegromab TOPAZ Clinical Trial: Motor Function Outcomes by RULM Over 48 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients[1]

Age 2-21 Years
All Doses (N=35)

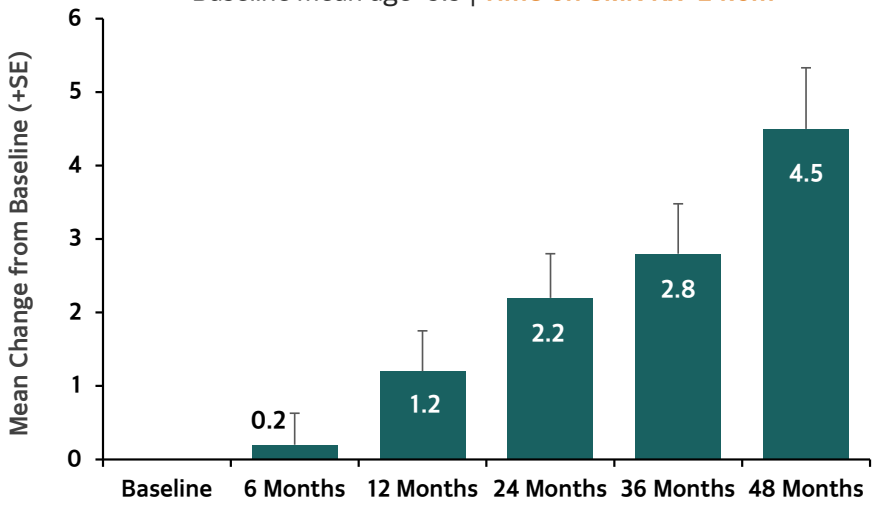
Baseline mean age=7.3 | Time on SMN Rx=24.1m



n=	34	28	31	31	27	22
95% CI=		(-0.2, 1.4)	(0.2, 2.3)	(1.2, 3.3)	(1.1, 3.7)	(2.0, 5.3)

Age 2-12 Years
All Doses (N=29)

Baseline mean age=5.5 | Time on SMN Rx=24.6m



n=	28	22	25	25	22	18
95% CI=		(-0.7, 1.1)	(0.1, 2.4)	(1.0, 3.5)	(1.4, 4.2)	(2.7, 6.3)

1. For the 48-month evaluation, an observed case analysis was conducted using available data by analysis timepoint, censoring any RULM assessments after the patient received scoliosis surgery. The analysis population pooled the nonambulatory patients (Cohorts 2 and 3) and included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who switched from 2 mg/kg to 20 mg/kg in Year 2). A total of 11 patients in the population had scoliosis surgery during the study and their data was excluded from any RULM assessments at 48 months. Visit windows were applied to utilize data from unscheduled or early termination visits if the patient was missing the RULM total score at the scheduled visit. One patient did not have baseline RULM due to young age. Error bars represent standard error (SE) and CI represents confidence interval. SMN Rx=SMN therapy. Apitegromab is an investigational drug candidate being evaluated for the treatment of spinal muscular atrophy. Apitegromab has not been approved for any use by the US FDA or any other health authority, and its safety and efficacy have not been established.

SAPPHIRE Phase 3 Design is Optimized by Insights from TOPAZ

TOPAZ Learnings

STUDY POPULATION

Substantial HFMSE gains observed in the nonambulatory Type 2/3 SMA cohorts

AGE

Exploratory age 2-12 analysis in nonambulatory Type 2/3 showed transformative potential

DURATION

HFMSE gains substantial by 12 months of treatment

DOSE

Dose response seen (greater effect observed with 20 mg/kg over 2 mg/kg)

Phase 3 SAPPHIRE Trial

Registrational trial with topline 12-month data readout expected in Q4 2024

SAPPHIRE Design Elements

STUDY POPULATION

- Nonambulatory Type 2/3 SMA
- Primary efficacy endpoint: HFMSE

AGE

Age 2-12 main efficacy population
Age 13-21 exploratory population

DURATION

12-month treatment duration

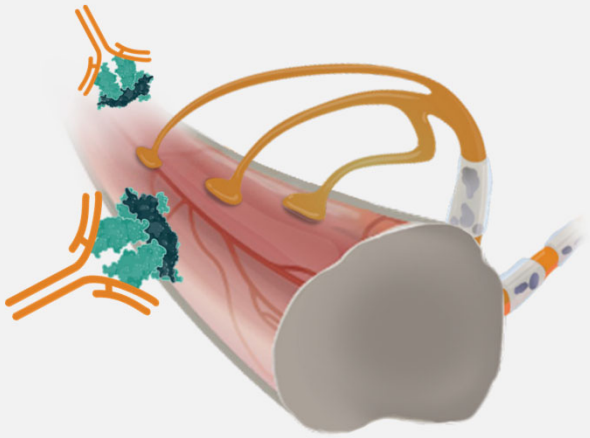
DOSE

- 20 mg/kg apitegromab dose
- 10 mg/kg apitegromab dose

HFMSE=Hammersmith Functional Motor Scale Expanded.

Summary of TOPAZ Data

Substantial and Sustained Improvement over 48 MONTHS[1]



TOPAZ

Data to date has shown substantial clinical benefit that is dose-dependent

Clinical benefit continued to improve or was sustained over 48 months

Consistency across functional scales and patient-reported outcomes

Well tolerated profile and low discontinuation rate supports durability of treatment

>90% of patients remained on therapy*

TOPAZ data suggest that apitegromab has the potential to transform care in SMA by directly addressing progressive muscle weakness

1- A total of 11 patients in the population had scoliosis surgery during the study and their data was excluded from any HFMSE and RULM assessments at 48 months.
PRO=Patient Reported Outcome
*Pooled non-ambulatory cohorts

ScholarRock

SAPPHIRE

Positive Topline Results from Pivotal Phase 3 SAPPHIRE Trial of Apitegromab SMA

ScholarRock™

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

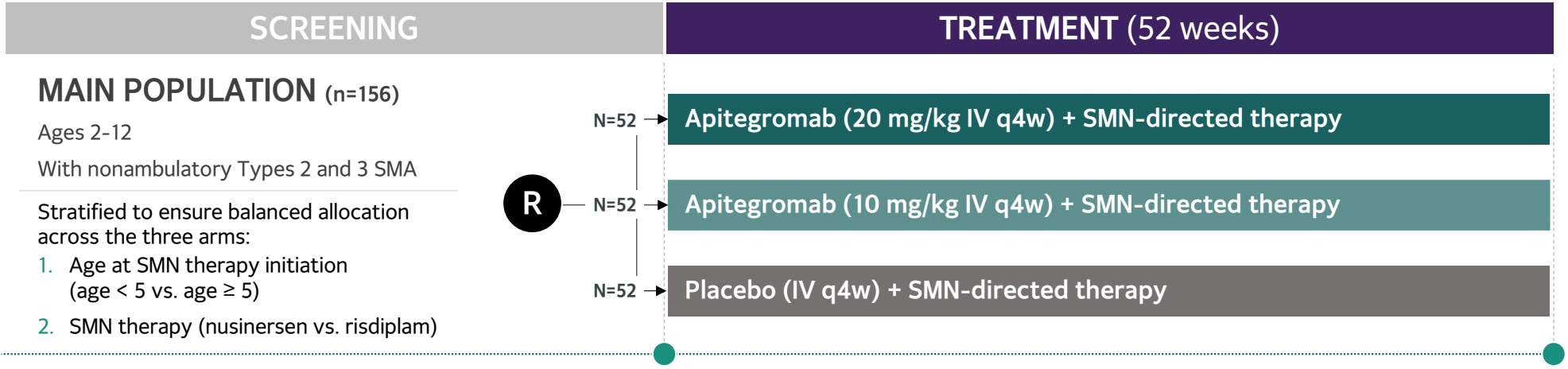
Scholar Rock is working with a sense of urgency to bring apitegromab to SMA patients

* 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
SOC=Standard of care (i.e., nusinersen or risdiplam)

SAPPHIRE Trial Designed for Clinical Success

SAPPHIRE

Randomized, double-blind, placebo-controlled, parallel arm design (n=204)
Enrolling patients who are on SMN-directed therapy (nusinersen or risdiplam)
Completed enrollment in Q3 2023



ENDPOINTS

Primary Efficacy:
Mean HFMSE change from baseline at 12 months

Additional Efficacy Measures:
RULM, WHO, other outcome measures

Safety, PK/PD, ADA

Additional Data Opportunities

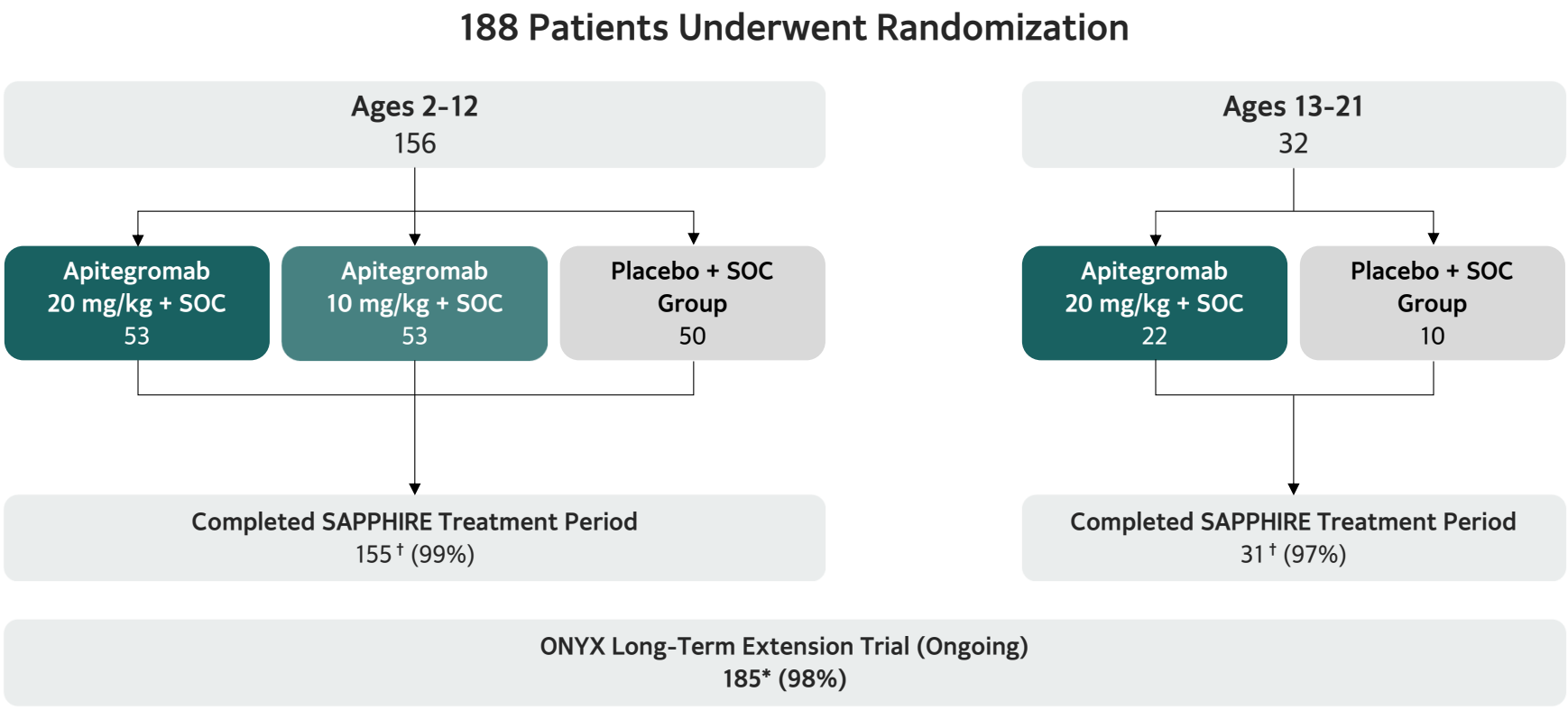
Exploratory population (age 13-21), in patients using SMN therapy
Focused upon safety & exploratory efficacy (n=48; 2:1 randomization between apitegromab 20 mg/kg vs placebo)

Separate open-label extension study (after patients complete 12-month treatment period)
Focused upon safety & exploratory long-term efficacy

ClinicalTrials.gov Identifier: NCT05156320
HFMSE=Hammersmith Functional Motor Scale Expanded; RULM=Revised Upper Limb Module; R=randomization; SMA=spinal muscular atrophy; SMN=survival motor neuron.

SAPPHIRE – APITEGROMAB IN SMA

98% of Patients Continue on Long-Term Extension



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

SAPPHIRE – APITEGROMAB IN SMA

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 TAKEAWAYS

- Study population was broadly representative of SMA population
- Patients on the advanced phase of their SMN therapy journey

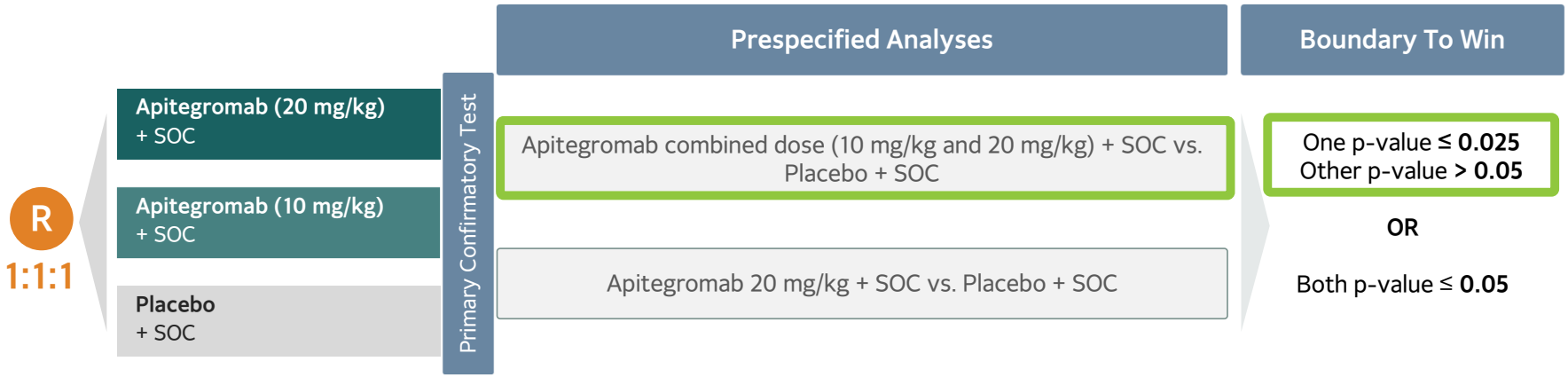
Max=Maximum; Min=Minimum; SD=standard deviation; SMN=Survival Motor Neuron; SMA=Spinal Muscular Atrophy, SOC=standard of care.

SAPPHIRE – APITEGROMAB IN SMA

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

SAPPHIRE – APITEGROMAB IN SMA

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 *P*-value
Apitegromab 10+20 mg/kg combined	106	1.8	0.0192* ✓
Apitegromab 20 mg/kg	53	1.4	0.1149*
Apitegromab 10 mg/kg	53	2.2	0.0121**

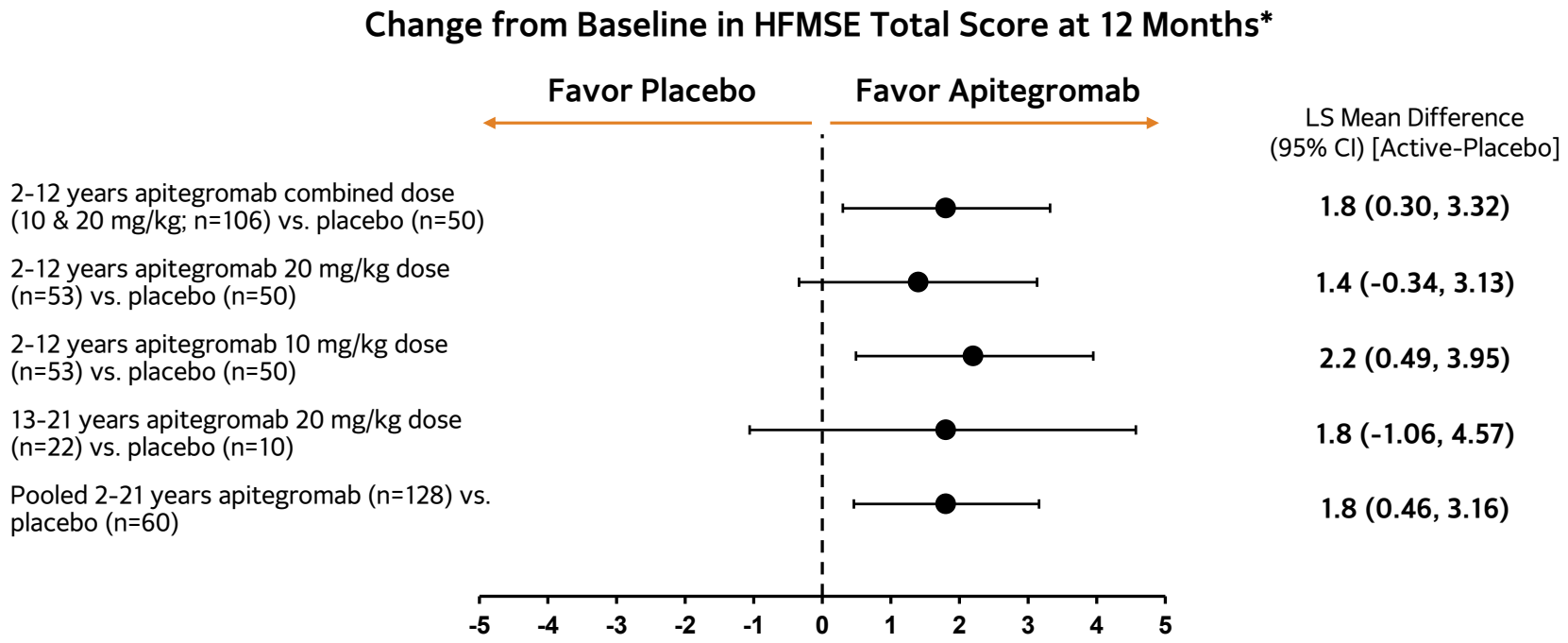
Primary Analysis

Achieved Statistical Significance

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

SAPPHIRE – APITEGROMAB IN SMA

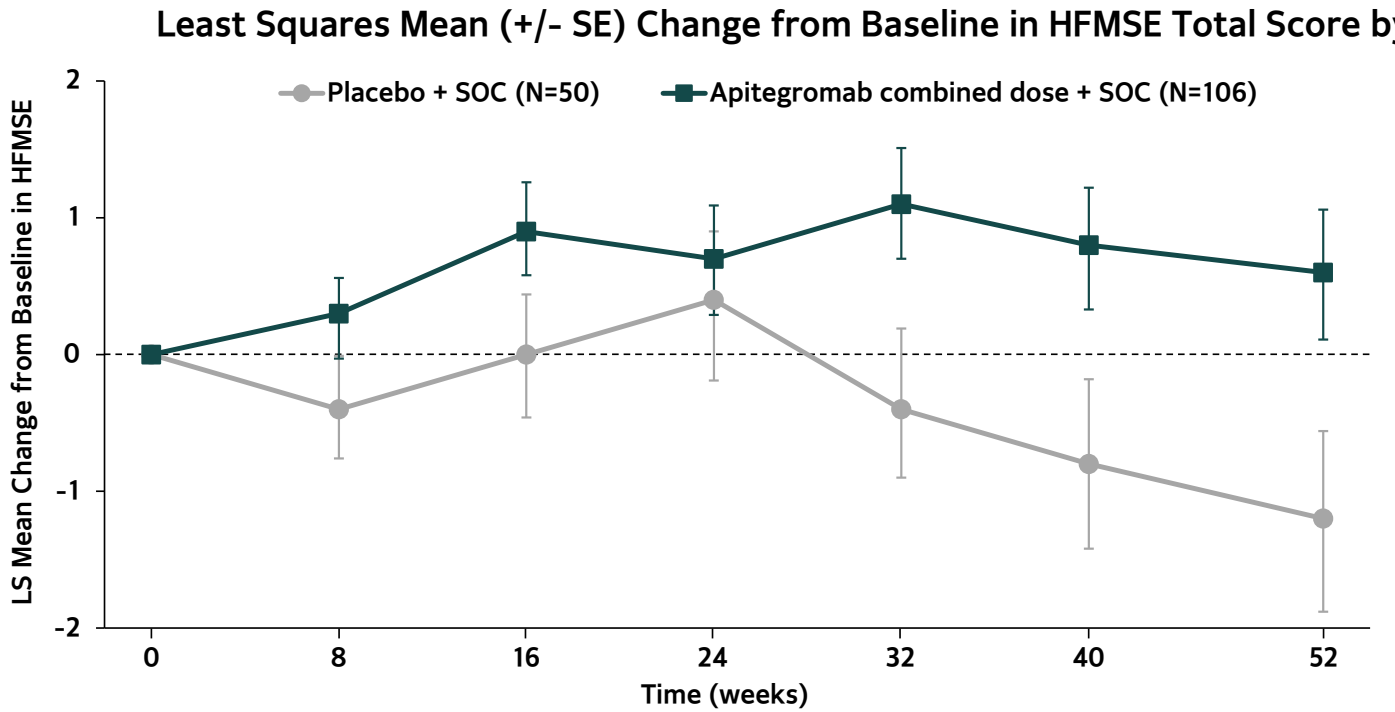
Improvement in HFMSE Consistent Across Doses and Age Groups



CI=Confidence Interval; EXP=Exploration Subpopulation; HFMSE=Hammersmith Functional Motor Scale Expanded; SOC=standard of care.
*n values at 12-month endpoint

SAPPHIRE – APITEGROMAB IN SMA

Early and Increasing HFMSE Improvement vs. Placebo



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

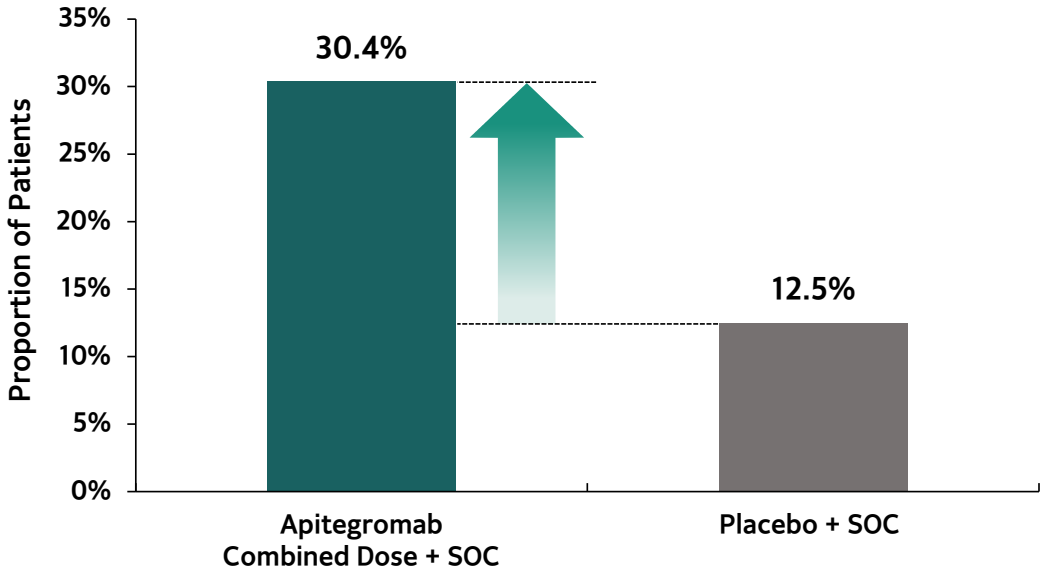
Apitegromab-treated patients improved on HFMSE, while placebo patients declined on HFMSE over 12 months

CI=Confidence Interval; EXP=Exploration Subpopulation; HFMSE=Hammersmith Functional Motor Scale Expanded; LS=Least Squares; MEP=Main Efficacy Population; SOC=standard of care.

SAPPHIRE – APITEGROMAB IN SMA

30% of Apitegromab Patients Achieved ≥3 Points on HFMSE

≥3 Point Improvement in HFMSE



n/N	31/102	6/48

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)

HFMSE=Hammersmith Functional Motor Scale Expanded; SOC=standard of care.

SAPPHIRE – APITEGROMAB IN SMA

Well-Tolerated Safety Consistent With Established Profile

Summary of Adverse Events	Main Efficacy Population (ages 2-12)				Exploratory Subpopulation (ages 13-21)	
	Placebo + SOC (N = 50) n (%)	10 mg/kg + SOC (N = 53) n (%)	20 mg/kg + SOC (N = 53) n (%)	SRK-015 + SOC (N = 106) n (%)	Placebo + SOC (N = 10) n (%)	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 ≥ 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 with highest incidence						
Pyrexia	16 (32.0)	18 (34.0)	13 (24.5)	31 (29.2)	1 (10.0)	2 (9.1)
Nasopharyngitis	10 (20.0)	15 (28.3)	11 (20.8)	26 (24.5)	4 (40.0)	6 (27.3)
Cough	11 (22.0)	15 (28.3)	11 (20.8)	26 (24.5)	1 (10.0)	4 (18.2)
SAE with highest incidence						
Pneumonia	0	3 (5.7)	4 (7.5)	7 (6.6)	0	0
Dehydration	0	2 (3.8)	1 (1.9)	3 (2.8)	0	0

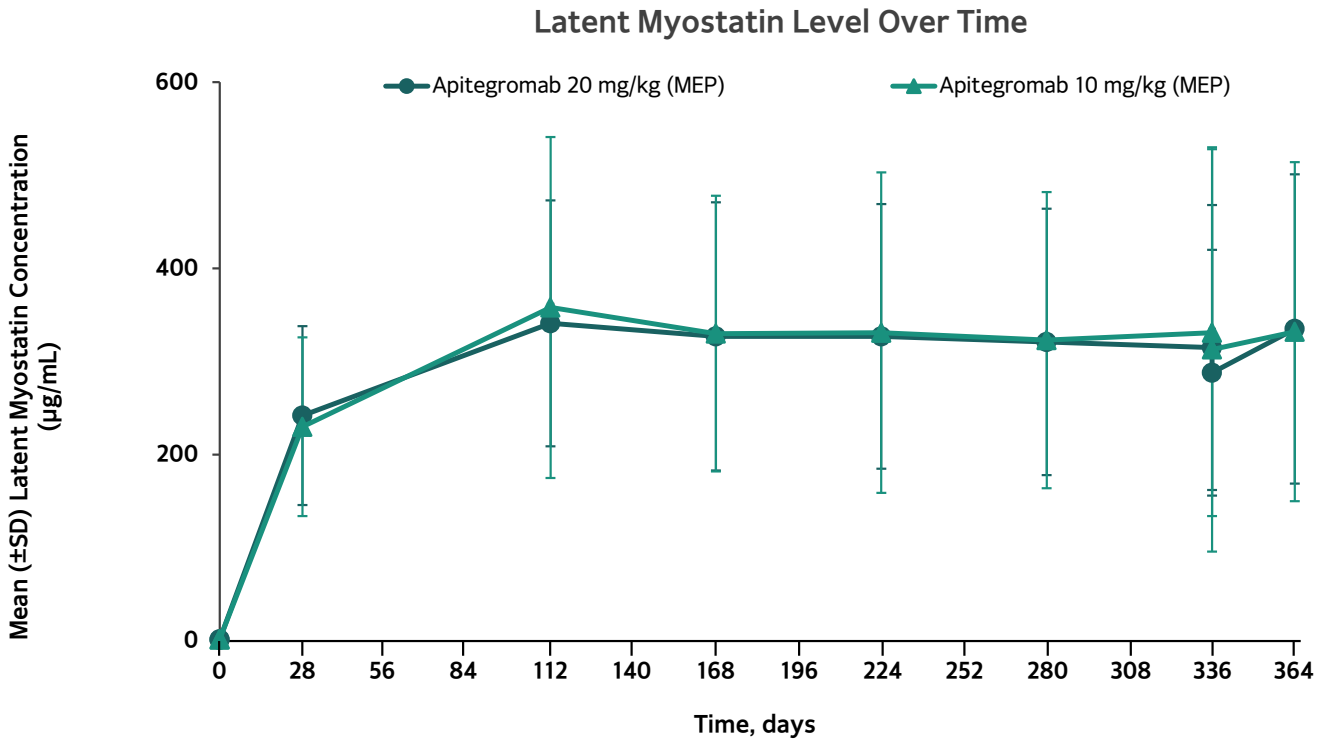
KEY TAKEAWAYS

- Treatment with apitegromab was well-tolerated across all age groups, with a safety profile consistent with established safety profile
- There were no clinically relevant differences in the adverse event profile by dose, 10 mg/kg vs 20 mg/kg
- Serious adverse events (SAEs) were consistent with underlying disease and SMN treatment; no SAEs were assessed as related to apitegromab
- There were no deaths or study drug discontinuations due to adverse events
- 1 patient tested positive for ADA; the samples were further assessed and determined to be below the sensitivity cutoff point

AE=Adverse Event; SAE= serious adverse event; SOC=standard of care; SMN=survival motor neuron; ADA=anti-drug antibodies; all AEs are coded using the MedDRA version 26.1.

SAPPHIRE – APITEGROMAB IN SMA

Total Latent Myostatin Levels Over Time



KEY TAKEAWAYS

- Robust and sustained target engagement were observed following apitegromab dosing
- Similar levels of target engagement were observed for 10 mg/kg and 20 mg/kg

MEP=main efficacy population; SD=standard deviation.

SAPPHIRE – APITEGROMAB IN SMA

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

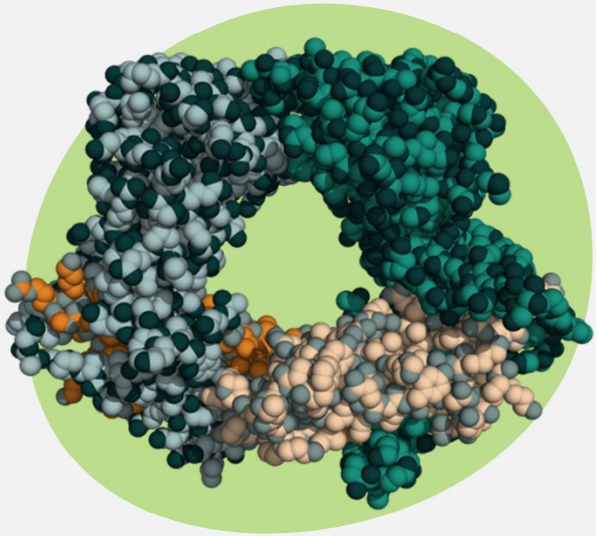
>48 months treatment experience in SMA[1]

[1] Based on TOPAZ patients receiving combination therapy after 4 years of treatment. Data cutoff date: April 2024
* If approved by regulatory authorities

Next Horizon in Antimyostatin Therapies: Cardiometabolic Disorders

ScholarRock™

Differentiated Expertise Developing Muscle-Targeted Therapies



Myostatin is a member of the TGFβ superfamily known to be a negative regulator of muscle mass and promotes muscle catabolism

Next Frontier in Antimyostatin

Leveraging Our R&D Platform to Expand into Cardiometabolic Disorders

Pioneered unique approach to develop antibodies that bind to pro- and latent forms of myostatin with exquisite selectivity and inhibit its activation

Apitegromab is being developed as a highly selective inhibitor of latent myostatin activation, to enhance muscle growth and function in neuromuscular disorders

- To date apitegromab has been evaluated in approximately 250 patients ages 2 to 21 living with spinal muscular atrophy (SMA), showing sustained benefit over 36 months, a well tolerated profile and low discontinuation rate

Discovered multiple additional anti-pro/latent myostatin inhibitory antibodies including:

- SRK-439: Being developed as a novel, highly potent and selective antibody tailored for cardiometabolic disorders

Obesity is Recognized as a Top Global Public Health Issue

Obesity is a common, serious, and costly chronic disease affecting adults and children worldwide

BY 2030, OBESITY WILL AFFECT:

>1 BILLION adults

>250 MILLION children and adolescents[1]

Adult obesity associated with more than **$170 billion in excess costs** annually in the U.S.[2]

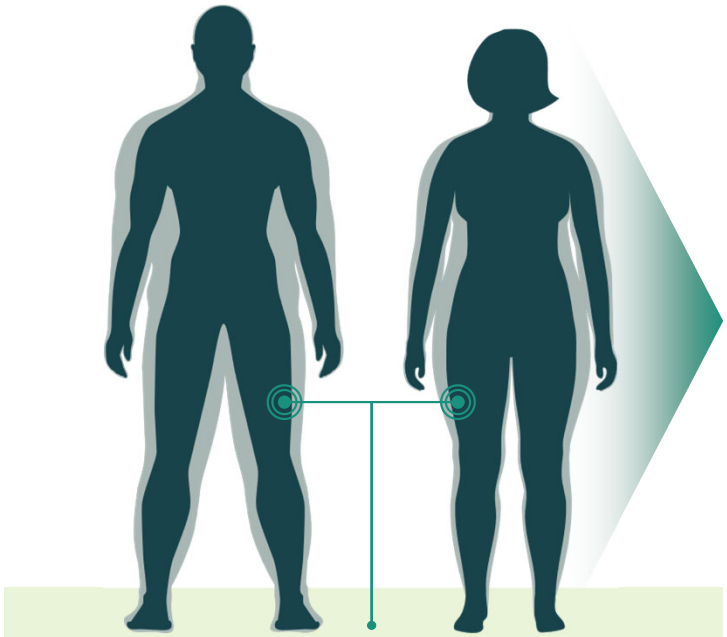
In the US, **1 in 5** children and more than **1 in 3** adults are obese

Obesity can increase the risk of comorbidities, such as some cancers, heart disease, and type 2 diabetes

1. The World Obesity Foundation, World Obesity Atlas 2022; 2. Ward ZJ, Bleich SN, Long MW, Gortmaker SL (2021) Association of body mass index with health care expenditures in the United States by age and sex. PLoS ONE 16(3): e0247307.

Loss of Lean Muscle Significant with GLP-1 RA Therapy

Lean muscle is essential to healthy metabolic function



Significant proportion of weight loss due to loss of lean muscle mass

Current Weight Loss Strategies *Challenged by:*

- Tolerability
- Lack of durability
- **Significant muscle loss**[1-3]

Recently approved **GLP-1 RAs are highly effective** in weight loss & experiencing rapid uptake

But 25%-40% of total body weight loss mediated by GLP-1 RA therapy may be attributed to **loss of lean muscle mass**[2,3]

Preserving lean muscle mass is important to promote long-term metabolic benefits, sustainable weight management and health outcomes[4-7]

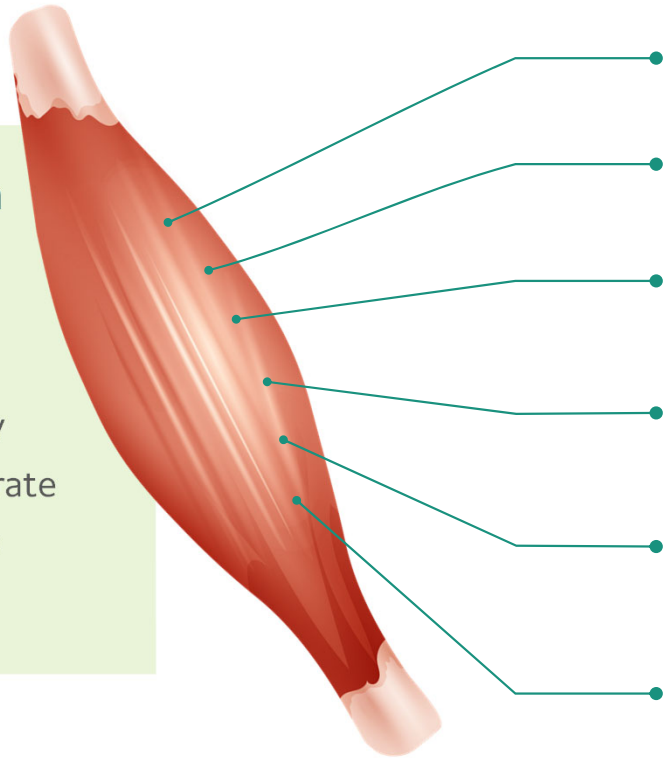
GLP-1 RA=Glucagon-like peptide-1 receptor agonists.

1. Muller TD, et al Anti-obesity drug discovery: advances and challenges. Nature Reviews Drug Discovery 2022; 21, 201–223; 2. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384(11):989-1002; 3. Jastreboff AM, et al Tirzepatide Once Weekly for the Treatment of Obesity. NEJM 2022; 387 (3): 205-216; 4. Cava et al. Preserving healthy muscle during weight loss. Adv Nutr 2017;8:511-19; 5. Lundgren JR et al. Healthy Weight Loss Maintenance with Exercise, Liraglutide or Both Combined. NEJM 2021;384:1719-30; 6. Beal JW et al. Dietary weight loss-induced improvements in metabolic function are enhanced by exercise in people with obesity and prediabetes. Nat Metab. 2022;5(7):1221-1235; 7. Dulloo AG, et al How dieting makes some fatter: from a perspective of human body composition autoregulation. Proc Nutr Soc. 2012 Aug;71(3):379-89.

Maintaining Muscle is Important for Healthy Weight Loss

The preservation of lean mass has many benefits for overall health:

- Improved strength
- Improved insulin sensitivity
- Increased basal metabolic rate
- Improved metabolic profile
- Reduced total body fat



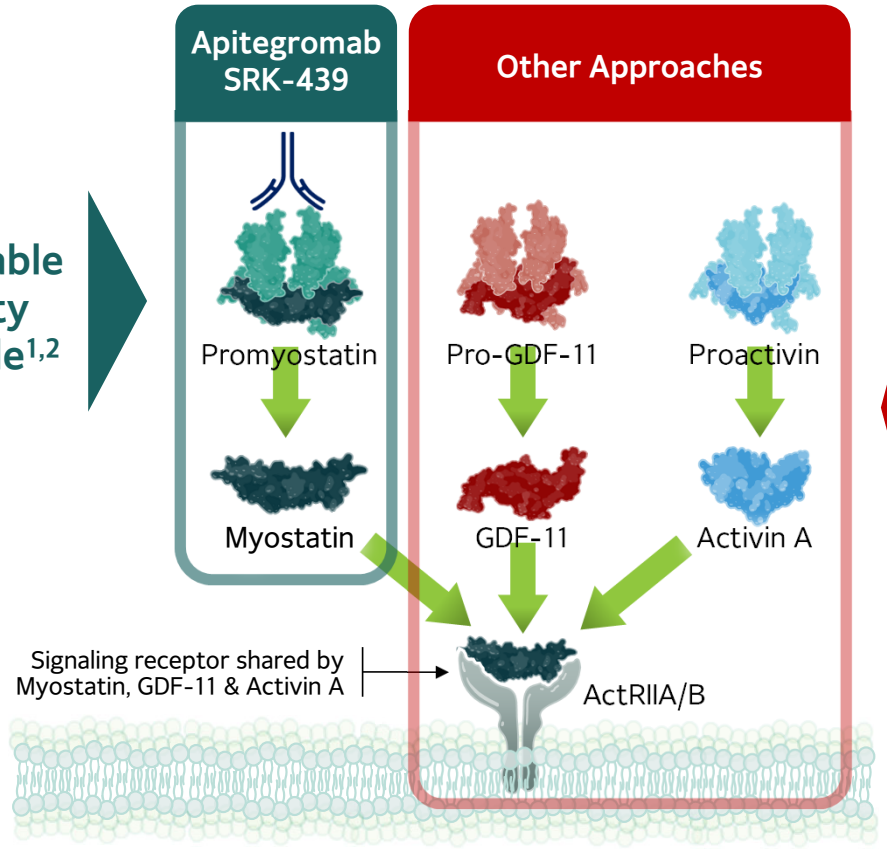
- Increased basal metabolic rate (BMR)[1]
- Enhanced glucose homeostasis[2]
- Better insulin sensitivity and lower risk of prediabetes[3]
- Reduced visceral fat[4]
- Increased caloric expenditure post-exercise[5]
- Increased bone density, strength, function, and longevity and decreased risk of injury, and disability[6-8]

GLP-1 RA=Glucagon-like peptide-1 receptor agonist.

1. Aristizabal JC, Freidenreich DJ, Volk BM, et al. Effect of resistance training on resting metabolic rate and its estimation by a dual-energy X-ray absorptiometry metabolic map. Eur J Clin Nutr.2015; 69, 831–836. https://doi.org/10.1038/ejcn.2014.216; 2. Lindegaard B, Hansen T, Hvid T, et al. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-infected patients with lipodystrophy. J Clin Endocrinol Metab. 2008; 93:3860–9; 3. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. J Clin Endocrinol Metab. 2011; 96:2898–903. doi: 10.1210/jc.2011-0435; 4. Wewege MA, Desai I, Honey C, et al. The effect of resistance training in healthy adults on Body fat percentage, fat mass and visceral fat: A systematic review and meta-analysis. Sports Med. 2022(Feb);52(2):287-300. doi: 10.1007/s40279-021-01562-2; 5. Zurlo, F., Larson, K., Bogardus, C., et al. Skeletal muscle metabolism is a major determinant of resting energy expenditure. J Clin Invest. 1990;86(5), 1423-1427; 6. Fukushima Y, Kurose S, Shinno H, et al. Importance of lean muscle maintenance to improve insulin resistance by body weight reduction in female patients with obesity. Diabetes Metab J. 2016;40: 147-153; 7. Roh E, Choi KM. Health consequences of sarcopenic obesity: a narrative review. Front. Endocrinol. 2020;11: 332; 8. Volpi E, Nazemi R, Fujita S. Muscle tissue changes with aging. Curr Opin Clin Nutr Metab Care. 2004;7(4): 405-410.

SELECTIVITY TO MYOSTATIN IS CRITICAL

Multiple Risks Associated with Non-Selective Targeting



Health Risks Observed with Non-Selective Inhibition of ActRII Pathway:

- GI problems, e.g., diarrhea, pancreatitis [3-6]
- Nose bleeds (epistaxis), low platelet count, telangiectasias[7-10]
- Reduction in reproductive hormones in males and females[3, 7, 11, 12]
- Acne, rash, skin abscesses[5, 13, 14]
- Madarosis (loss of eyebrows or eyelashes)[14]

1. Barrett et al., Adv Therapy 2021; 2. Crawford et al., Neurology 2024; 3. Garito T et al Clin Endocrinol 2018; 4. Amato AA et al Neurology 2021; 5. Heymsfield SB et al. JAMA 2021; 6. Vanhoutte F et al. J Clin Pharmacol 2020; 7. Attie KM et al Muscle Nerve 2013; 8. Attie KM et al Am J Hematol 2014; 9. Campbell C et al. Muscle Nerve 2017; 10. Hoeper MM et al NEJM 2023; 11. Ruckle J et al, JBMR 2009; 12. Sherman ML et al J Clin Pharm 2013; 13. Muntoni F et al. Neurol Ther. 2024. 14. Rocco MD et al Nat Med 2023;

Why We Are Confident in SRK-439

Scholar Rock's Unique Approach

- A new anti-myostatin specifically suited for obesity

Exquisite Selectivity

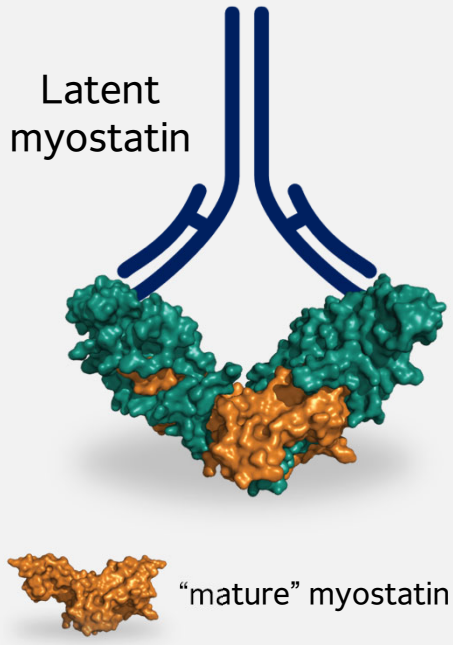
- Targets pro and latent forms of myostatin designed to minimize undesirable off-target effects

Strong Scientific Validation

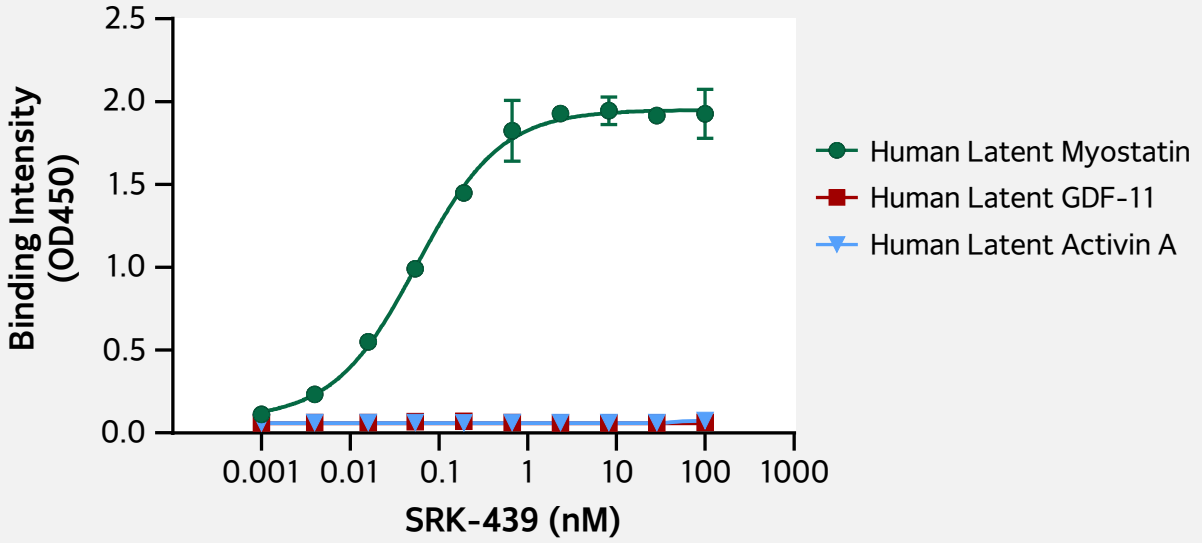
- Preclinical data demonstrated favorable muscle mass preservation and metabolic effects

SRK-439: Exquisite Selectivity for Myostatin

Scholar Rock's Target: Latent Myostatin



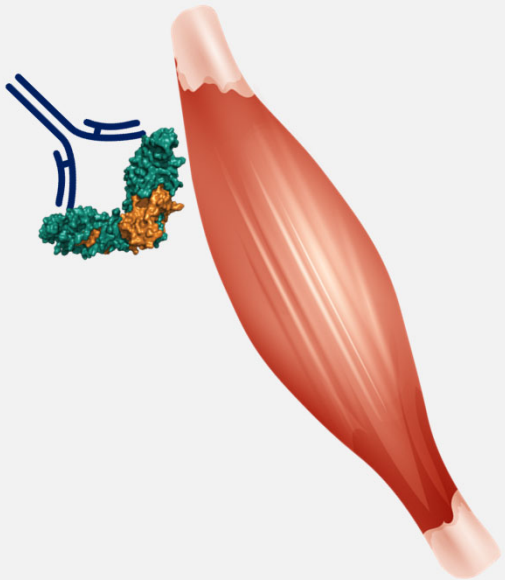
SRK-439 Selectively Binds Latent Myostatin



- Increasing SRK-439 concentrations lead to increased signal of binding to myostatin with no signal observed for GDF-11 or Activin A

Strong Scientific Validation and Promising Preclinical Evidence

Give Us Confidence in SRK-439

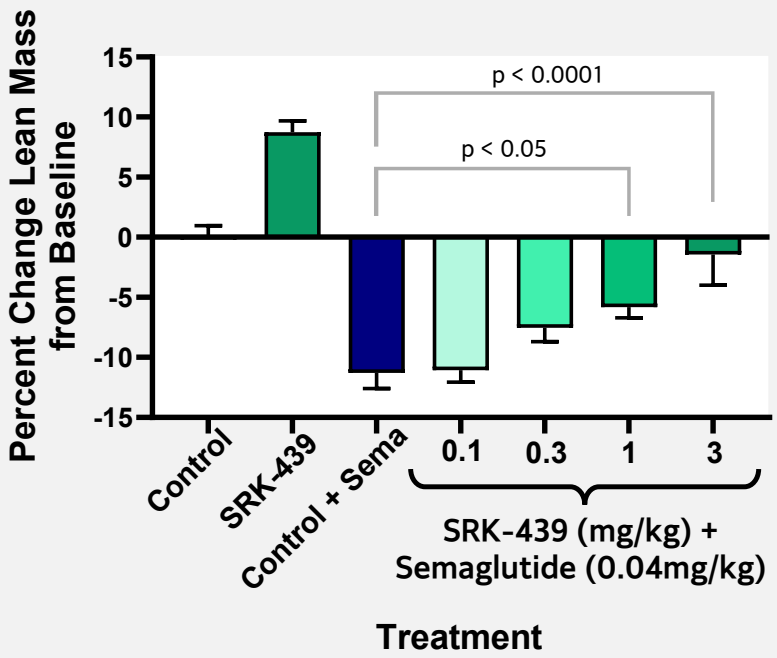


Preclinical data to date show strong potential to support healthier weight loss in combination with GLP-1 RA:

- **Preservation of lean mass** during GLP-1 RA-induced weight loss and **improvement in metabolic parameters**
- **Increase in lean mass** and attenuation of fat mass regain following GLP-1 RA withdrawal
- **Greater potency** compared to an anti-ACTRII antibody

SRK-439: Potential for Healthier Weight Loss Management in Combination with GLP-1 RA

SRK-439 Maintained Lean Mass in Semaglutide Treated Animals



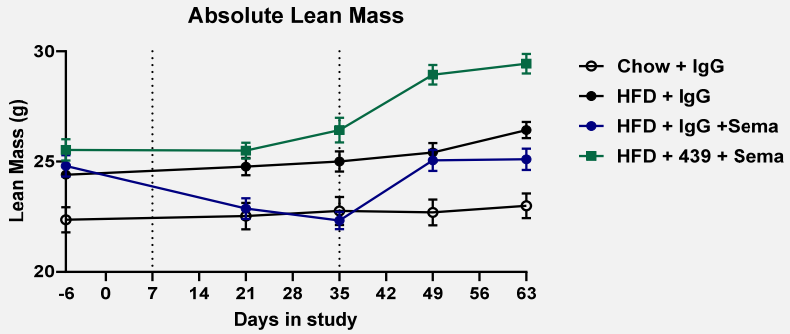
Key Observations

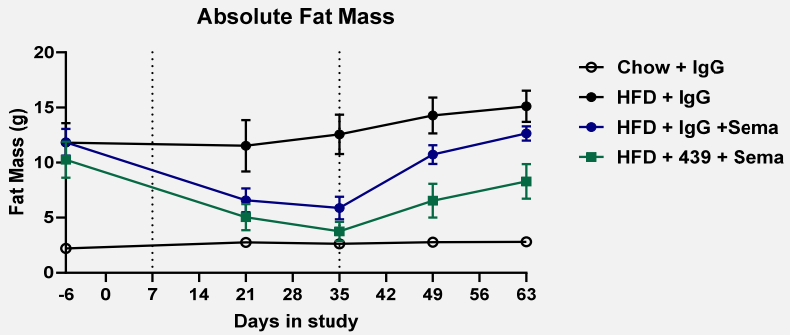
- Considerable lean mass loss with semaglutide treatment
- Combination with SRK-439 led to dose-dependent lean mass preservation
  - Effects seen with doses as low as 0.3 mg/kg
- Dose dependent enhancement of fat mass loss also observed, improving overall body composition

Study conducted in Diet Induced Obesity (DIO) mouse model utilizing a murine chimera of SRK-439
GLP-1 RA: GLP1 receptor agonist

SRK-439 Increased Lean Mass and Attenuated Regain of Fat Mass After GLP-1 RA Withdrawal in Obesity Mouse Model

SRK-439 Increased Absolute Lean Mass and Attenuated Regain of Absolute Fat Mass





Key Observations

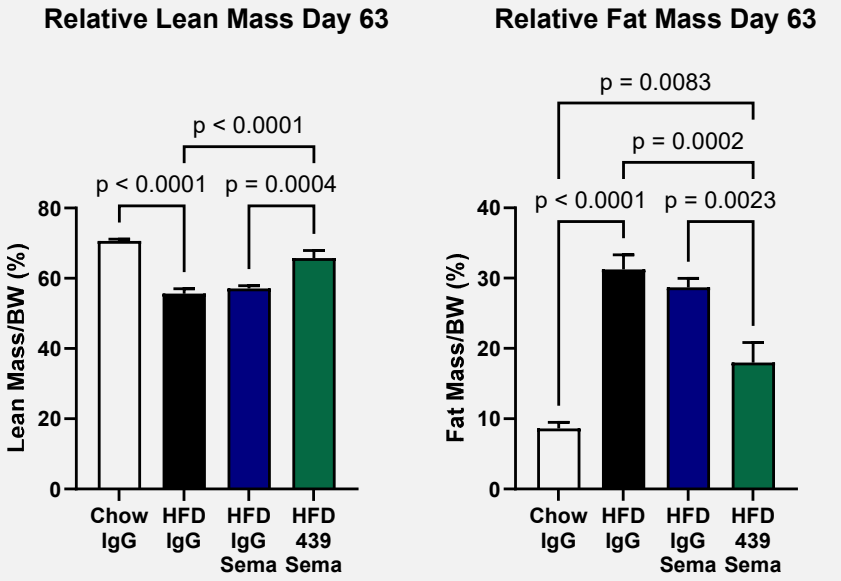
- Considerable lean mass loss seen with semaglutide treatment as expected
- Treatment with SRK-439 led to:
  - Preservation of lean mass during semaglutide treatment
  - Significant increase in lean mass upon semaglutide discontinuation
  - Attenuation of fat mass regain upon semaglutide discontinuation

American Diabetes Association®

Study conducted in Diet Induced Obesity (DIO) mouse model utilizing a murine chimera of SRK-439
GLP-1 RA: GLP1 receptor agonist. Day 7 is start of semaglutide and SRK-439 treatment. Day 35 is discontinuation of semaglutide treatment.

SRK-439 Improved Body Composition After GLP 1-RA Withdrawal

SRK-439 Improved Proportion of Lean and Fat Mass to Total Body Weight



Key Observations

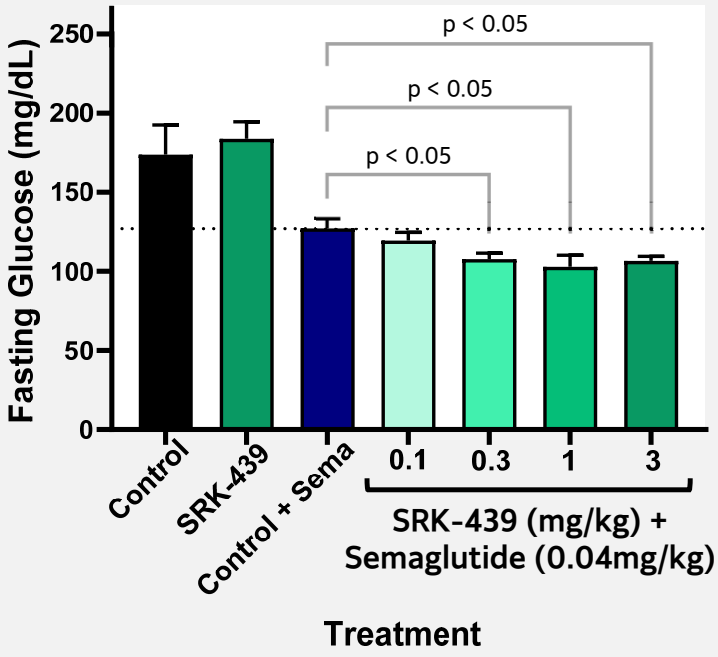
- SRK-439 attenuates regain of fat mass after withdrawal of semaglutide compared to IgG control
- SRK-439 leads to higher lean mass proportion after withdrawal of semaglutide compared to IgG control

American Diabetes Association®

Study conducted in Diet Induced Obesity (DIO) mouse model utilizing a murine chimera of SRK-439
GLP-1 RA: GLP1 receptor agonist. HFD: High Fat Diet

SRK-439: Further Improvement of Metabolic Health

SRK-439 Further Improved Fasting Glucose in Semaglutide Treated Animals



Key Observations

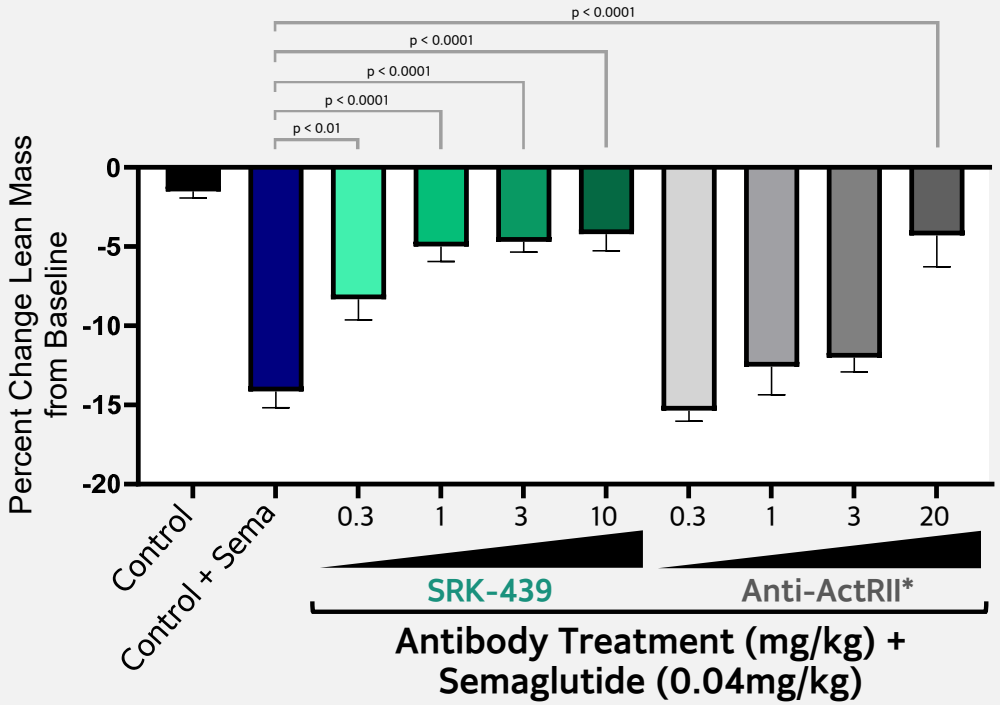
- Semaglutide reduced fasting glucose levels as expected
- Combination with SRK-439 led to further improvement in fasting glucose levels by ~20% in a dose-dependent manner
- Highlights the role of muscle preservation in improving long term metabolic profile

Study conducted in Diet Induced Obesity (DIO) mouse model utilizing a murine chimera of SRK-439

LOW EFFICACIOUS DOSE AND COMPETITIVE PROFILE

SRK-439 Is More Potent than Anti-ActRII Antibody at Maintaining Lean Mass During GLP-1 RA-Induced Weight Loss

Head-to-Head Comparison to Non-Selective Myostatin Inhibitor in DIO Mouse Model



Key Observations

- SRK-439 preserved semaglutide-driven lean mass loss dose-dependently and at lower doses than anti-ActRII
- Highlights efficacy of SRK-439 and avoids potential liabilities of non-selective approach of anti-ActRII antibodies
- Low target dose of SRK-439 supports subcutaneous and potentially best-in-class profile

*Murine chimera of Bimagrumab
Study conducted in Diet Induced Obesity (DIO) mouse model utilizing a murine chimera of SRK-439

SRK-439: Best in Class Potential

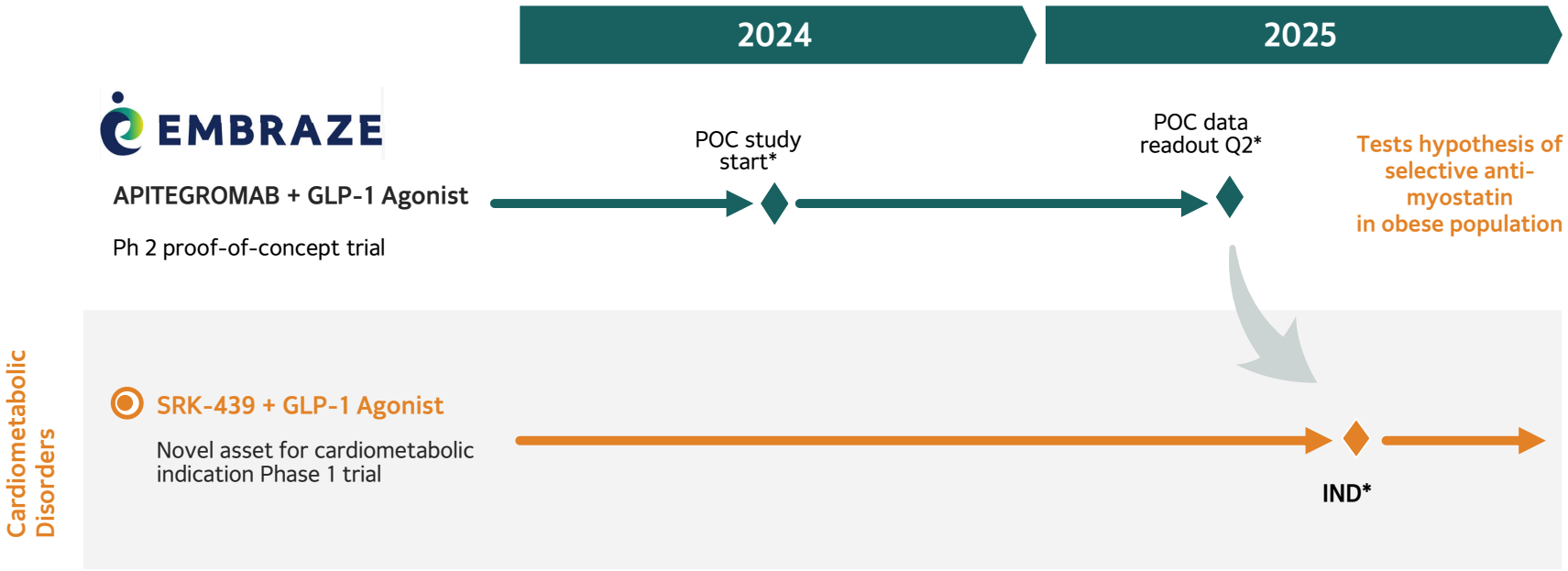
	SRK-439	ActRII Ab	Ligand Trap	Adnectin
Selectivity for myostatin	✓	✗	✗	✗
Action limited to muscle	✓	✗	✗	✗
Combination GLP-1 RA data in obesity preclinical models[1-3]	✓	✓	✓	✓
Low efficacious dose in preclinical obesity models[1-3]	✓	✗	✗	✗
Lower risk of potential undesirable effects in clinic[4]	✓	✗	✗	✗

GLP-1 RA: GLP1 receptor agonist
1. Nunn E, et al., Mol Metab 2024; 2. Schang G., et al, J. Endoc Soc 2023; 3. Ackerman, P, et al. Obesity Week 2023 Poster 211;
4. See also references on slide titled, "Multiple Risks Associated with Non-Selective Targeting" in this presentation.

PIPELINE OVERVIEW

OBESITY

Leveraging Apitegromab to Inform Obesity Program



*Expected timelines
POC = Proof of Concept

OBESITY

CARDIOMETABOLIC DEVELOPMENT PROGRAM

Goals of the EMBRAZE Proof-of-Concept Study

EMBRAZE Study Aims to Demonstrate

- Effect of apitegromab to preserve lean mass in obese or overweight patients receiving a GLP-1 agonist
- Safety and tolerability data to provide initial support for long-term chronic use
- Explore the potential effect of apitegromab to improve metabolic profile and physical function

INSIGHTS GAINED FROM EMBRAZE STUDY

to inform SRK-439 development

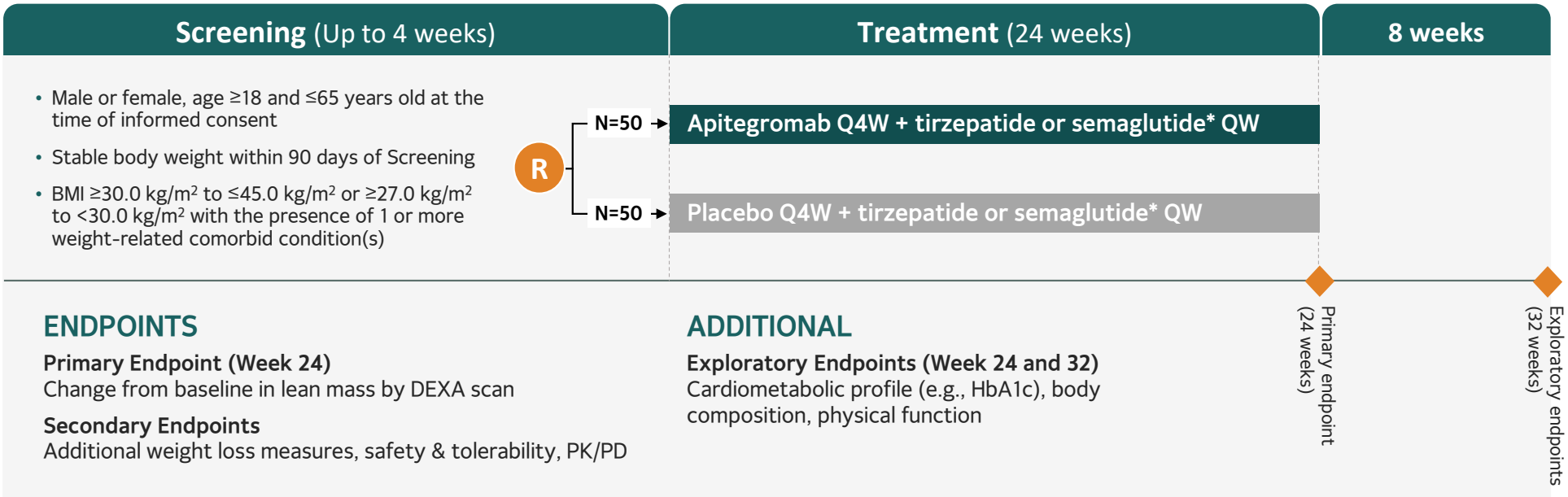
Initiated trial in May 2024, ahead of target timeline	**Strong enrollment momentum**	**Updating guidance for topline data to Q2 2025**

EMBRAZE TRIAL DESIGN

Enrolling Phase 2 Proof-of-Concept Study of Apitegromab in Obesity

EMBRAZE

Randomized, double-blind, placebo-controlled (n=100)
Enrolling patients who are overweight or obese
Enrollment ahead of schedule; topline data expected in Q2 2025



ENDPOINTS

Primary Endpoint (Week 24)
Change from baseline in lean mass by DEXA scan

Secondary Endpoints
Additional weight loss measures, safety & tolerability, PK/PD

ADDITIONAL

Exploratory Endpoints (Week 24 and 32)
Cardiometabolic profile (e.g., HbA1c), body composition, physical function

*Participating patient will be assigned to either tirzepatide or semaglutide depending on availability.
Apitegromab dose regimen will be 10 mg/kg Q4W, based on projected exposure in the obese population comparable to that of 20 mg/kg Q4W in SMA
Tirzepatide and semaglutide dose regimen will follow the United States Prescribing Information.

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Regulatory Pathway

FDA Guidelines

A clinical outcome assessment is a measure that describes or reflects how a patient feels, functions, or survives.*

- FDA guidance supports combination strategy
- Need to demonstrate the added clinical benefit of the combination

Added Clinical Benefit

Incremental Weight Loss

- Current weight management drugs approved based on total body weight loss
- Incremental weight loss as primary endpoint – preservation of lean mass may lead to additional weight loss incremental to that mediated by GLP-1 agonist

Incremental Clinical Benefit

- Increased muscle mass has the potential to improve metabolic profile (e.g., HbA1c)
- Preserving lean body mass is expected to improve physical function

*Clinical Outcome Assessment: Frequently Asked Questions: https://www.fda.gov/about-fda/clinical-outcome-assessment-coa-frequently-asked-questions#Consideration1

IN SUMMARY

SRK-439: The Right Molecule for Healthy Weight Loss

The right target

→ Highly selective approach

The right tissue

→ Targets muscle

The right safety profile

→ Efficacy without potential liabilities of non-selective approaches

The right product profile

→ Designed for subcutaneous low frequency dosing with robust subcutaneous exposure and long half life

Fibrosis

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TGFβ is Established as Key Driver of Fibrosis Across Multiple Diseases

Nature Reviews , April 25, 2016 NATURE REVIEWS | NEPHROLOGY

TGF-β: the master regulator of fibrosis

Xiao-ming Meng[1], David J. Nikolic-Paterson[2] and Hui Yao Lan[3]

Int. J. Mol. Sci. August 27, 2018

Targeting TGF-β Signaling in Kidney Fibrosis

Yoshitaka Isaka

Nature Reviews. August 19, 2014 NATURE REVIEWS | RHEUMATOLOGY

Transforming growth factor β—at the centre of systemic sclerosis

Robert Lafyatis

J. Am. Soc. Nephrol. December 3, 2017

Targeting Anti-TGF-β Therapy to Fibrotic Kidneys with a Dual Specificity Antibody Approach

Steve McGaraughty,* Rachel A. Davis-Taber,† Chang Z. Zhu,* Todd B. Cole,* Arthur L. Nikkel,* Meha Chhaya,† Kelly J. Doyle,* Lauren M. Olson,* Gregory M. Preston,† Chrisine M. Grinnell,† Katherine M. Salte,* Anthony M. Giamis,* Yanping Luo,* Victor Sun,† Andrew D. Goodearl,† Murali Gopalakrishnan,* and Susan E. Lacy†

J Pathol, July 25, 2021

TGF-β as a driver of fibrosis: physiological roles and therapeutic opportunities

Erine H Budi[1], Johanna R Schaub[1], Martin Decaris[1], Scott Turner[1], Rik Derynck[2]

J Receptors Sign Trans, Feb 13, 2020

Inevitable role of TGF-β in progression of nonalcoholic fatty liver disease

Bhagyalakshmi Nair and Lekshmi R. Nath

Proc Am Thorac Soc, July 3, 2006

Transforming Growth Factor β
A Central Modulator of Pulmonary and Airway Inflammation and Fibrosis

Dean Sheppard

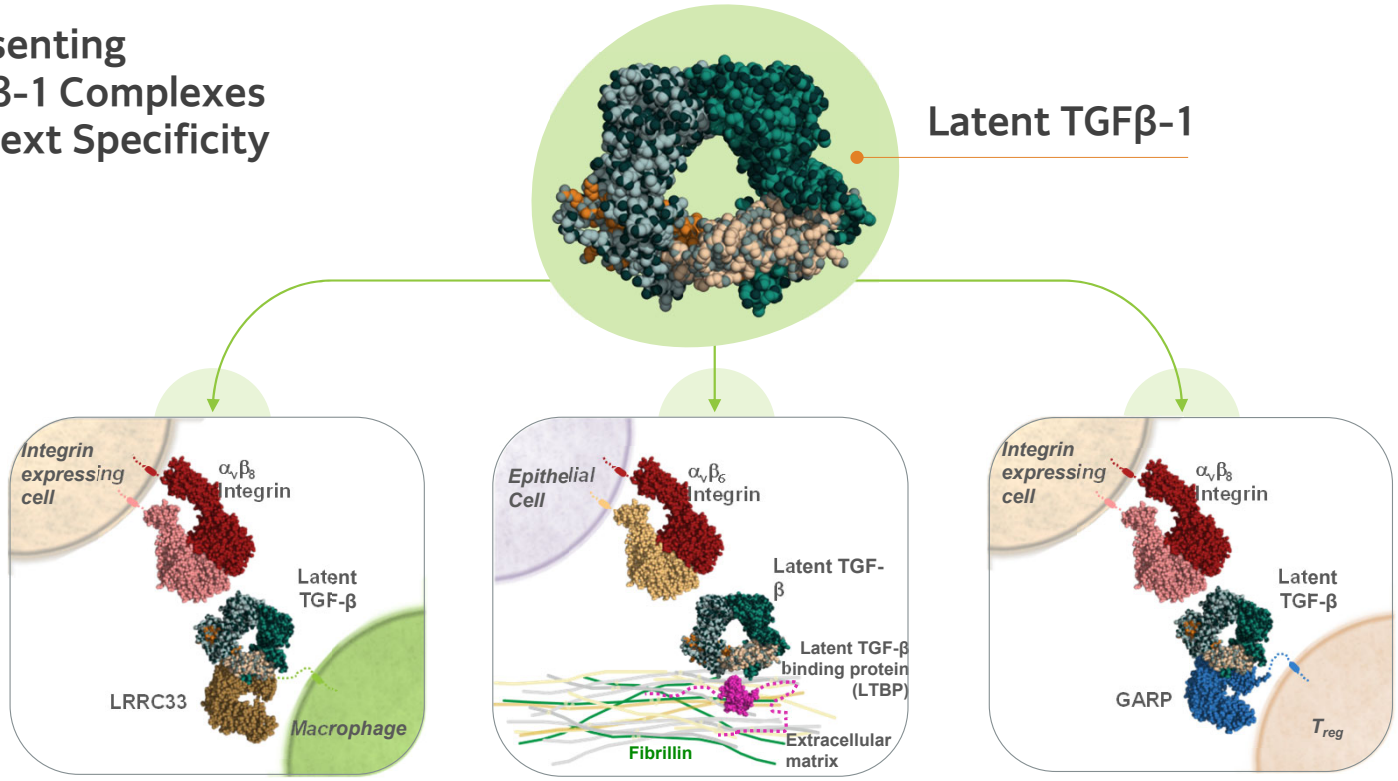
PNAS, February 24, 1986 PNAS

Transforming growth factor type β: Rapid induction of fibrosis and angiogenesis in vivo and stimulation of collagen formation in vitro

ANITA B. ROBERTS* MICHAEL B. SPORN*, RICHARD K. ASSOIAN*, JOSEPH M. SMITH*, NANETTE S. ROCHE*, LALAGE M. WAKEFIELD*, URSULA I. HEINE*, LANCE A. LIOTTA*, VINCENT FALANGA†, JOHN H. KEHRL‡, AND ANTHONY S. FAUCI‡

Targeting Latent TGFβ-1 Complexes Creates Multiple "Handles" For Selectivity

Targeting Presenting Molecule/TGFβ-1 Complexes Provides Context Specificity



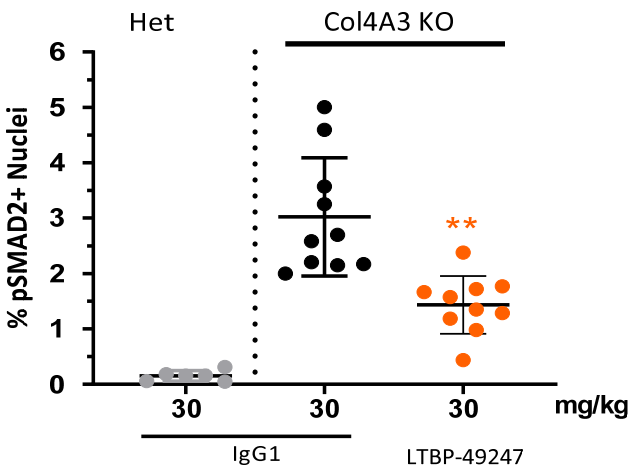
LRRC33 Presents TGFβ on Macrophages

LTBP1 & 3 Present TGFβ in Connective Tissue

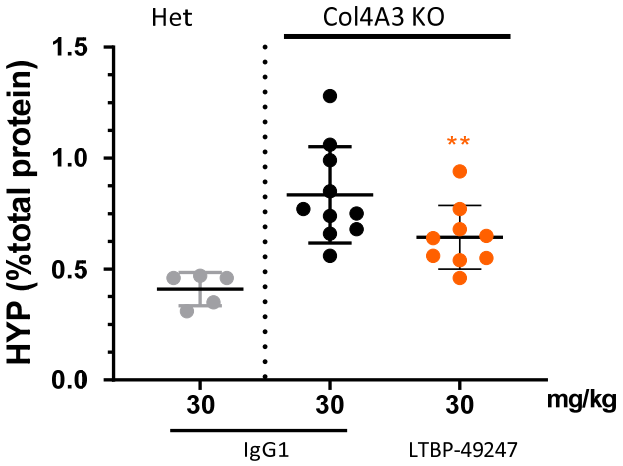
GARP Presents TGFβ on Tregs

LTBP-49247 Reduced TGFβ Signaling and Fibrosis in Preclinical Models of Kidney Fibrosis

LTBP-49247 reduced a TGFβ PD biomarker in kidneys of *Col4a3* KO mice (Alport Syndrome model)



LTBP-49247 reduced fibrosis in kidneys of Alport model

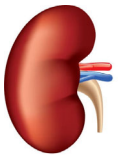


** p < 0.01
One way ANOVA vs. IgG
HYP=hydroxyproline

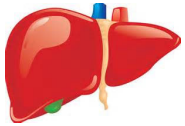
- Efficacy also seen in rat model of kidney fibrosis
- No observed toxicity in mouse 13-week non-GLP repeat dose study
- Favorable PK in cynomolgus monkeys (t1/2 ~28 days) suggests LTBP-49247 is amenable to clinical subcutaneous dosing with promising developability profile

FIBROSIS

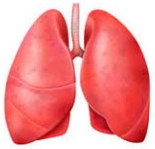
Significant Opportunities to Address High Unmet Need Across Multiple Fibrotic Indications



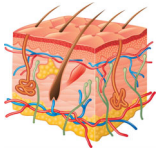
Alport Syndrome (AS)
Focal Segmental Glomerulosclerosis (FSGS)
IgA Nephropathy (IgAN)



Primary Sclerosing Cholangitis (PSC)



Idiopathic Pulmonary Fibrosis (IPF)



Diffuse Cutaneous Systemic Sclerosis (dcSSc)

Collectively, significant commercial potential given large patient population with clear high unmet need given poor outcomes and lack of effective therapeutics

- Significant impact to delay or stop progression to end-stage disease and organ transplant
- Expansion opportunities via other indications given shared etiologies

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

EMBRAZE

OPAL

Apitegromab Commercial Launch in SMA*

- US launch in Q4 2025 and EU launch to follow

* If approved by relevant health authorities

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