



Deep Insights Advancing Impactful Medicines

Company Overview | August 2024

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, 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.



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



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 in Ph 3 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

Our Approach

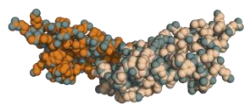
Selectivity Drives Success

**RIGHT
TARGET** →

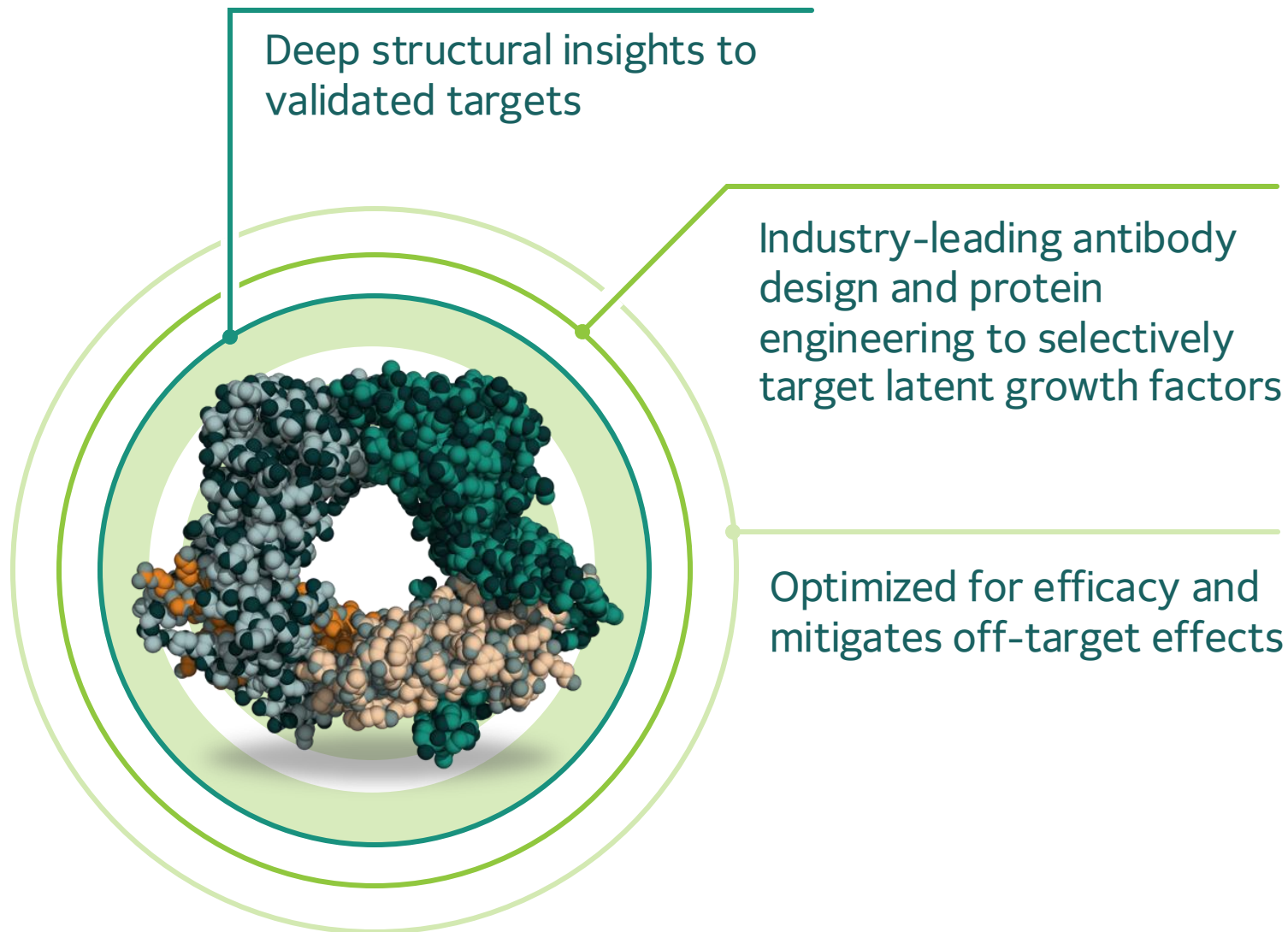
**Validated
Biology**

**RIGHT
TIME** →

**Latent
Form**



Traditional Target
“mature” active growth factor



Scholar Rock's Target
Latent Growth Factor
Complex

Scientific Platform Yielding Growing Pipeline Across High Value Therapeutic Areas

TARGET	CANDIDATE	DISCOVERY/ PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
Latent Myostatin	SPINAL MUSCULAR ATROPHY Apitegromab				
	CARDIOMETABOLIC DISORDERS Apitegromab in Obesity*				
	SRK-439 (novel anti-myostatin antibody)				
Latent TGFβ-1	IMMUNO-ONCOLOGY SRK-181: Selective context-independent, anti-latent TGFβ-1)				
	FIBROSIS SRK-373: Selective context-dependent (LTBP1 & LTBP3) anti-latent TGFβ-1				
RGMc	ANEMIA SRK-256: Selective anti-RGMc				
Undisclosed	NEUROMUSCULAR DISORDERS				

*Utilized data from previously completed Ph 1 study in healthy volunteers and initiate a Ph 2 POC trial in 2024.
 LTBP1=Latent transforming growth factor beta binding protein 1; LTBP3=Latent transforming growth factor beta binding protein3; POC=Proof of concept; RGMc=Repulsive guidance molecule C;
 TGFβ-1=Transforming growth factor beta-1.

Leveraging Our Building Blocks, Transformative 18 Months Ahead

Value Drivers



Significant Inflection Points in Next Year

Phase 3 SAPPHIRE Trial
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

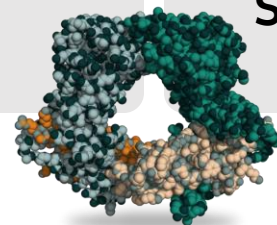
Established Markets with High Unmet Need

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

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

2024 & 2025 Anticipated Milestones

Milestones	2024	2025
SRK-181 data at ASCO - Oral presentation June 3 - Developmental Therapeutics-Immunotherapy	 	
SRK-439 data at American Diabetes Association - Oral presentation June 23 - New Insights into Therapeutic Strategies for Obesity and Diabetes	 	
SRK-439 IND submission		
EMBRAZE Ph 2 Trial (apitegromab in obesity) - Trial open for enrollment - Topline data expected in Q2 2025	 	
SAPPHIRE Ph 3 Trial (apitegromab in SMA) Topline readout expected in Q4 2024		
Potential SMA launch in Q4 2025, if successful & approved		
Study in SMA Patients < 2 Years of Age - Study design endorsed by EMA's paediatric committee - Study initiation planned for 2025		



Antimyostatin Program: Apitegromab in Spinal Muscular Atrophy

Why We Are Confident

1. Muscle Targeting

Selective muscle-targeting designed to improve motor function while minimizing off-target effects



2. Clinical Proof-Of-Concept

TOPAZ clinical proof-of-concept with substantial and durable effect across broad SMA patients ages 2-21



3. SAPPHIRE Optimized for Success

Trial design informed by insights from TOPAZ



4. TOPAZ Safety Profile

>90% patient retention,¹ well tolerated profile supports durability of treatment



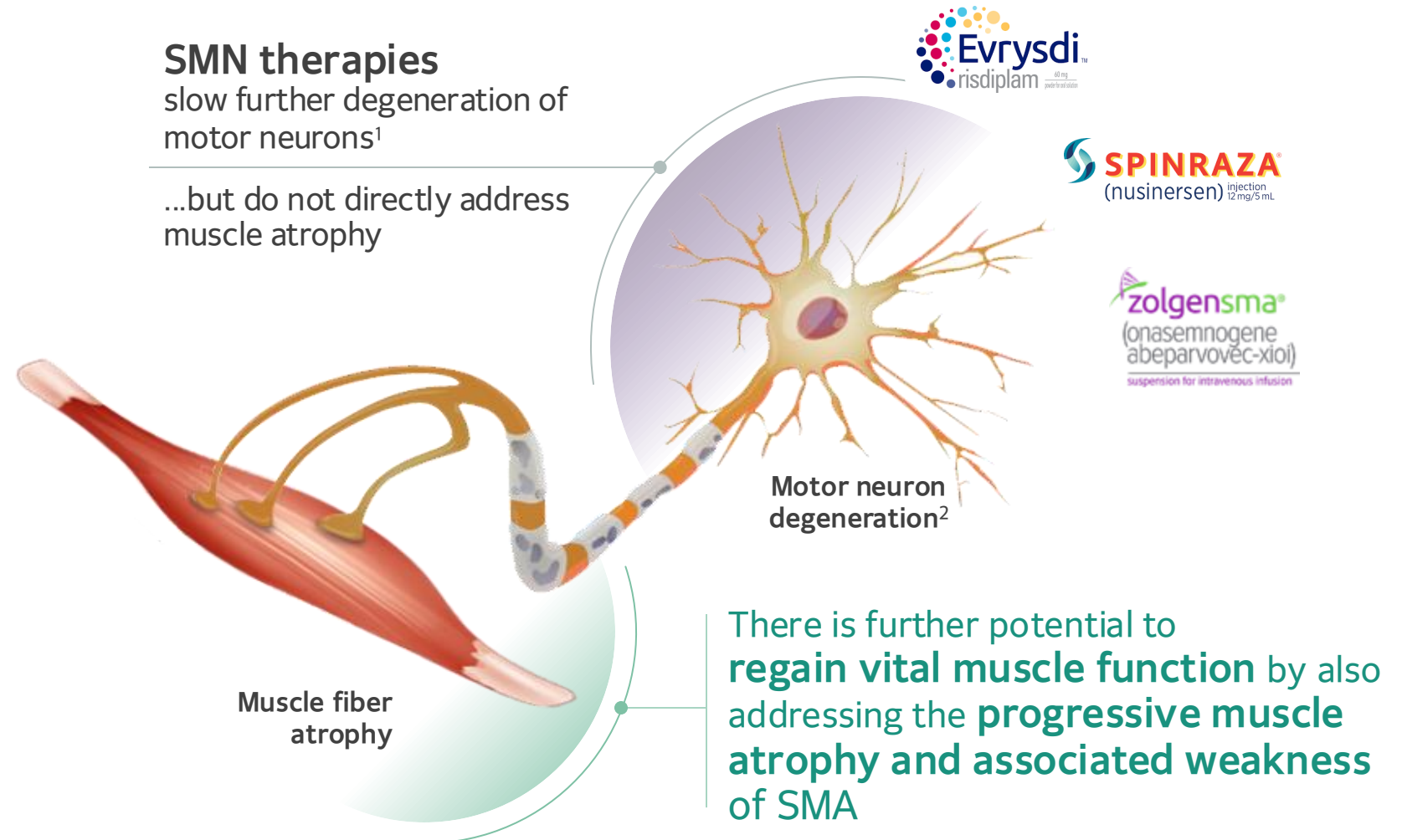
¹ Pooled nonambulatory patients

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



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**

SMA Today: More Patients Screened and Treated

GLOBAL DISEASE:
>20,000 affected
 in US and Europe^{1, 2}

Three treatments to address SMN loss



>13,000 patients
treated WW

\$1.8 billion
annual revenue (LTM)³



> 11,000 patients
treated WW

~CHF1.4 billion
annual revenue (LTM)⁴



> 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 \(curesma.org\)](https://www.curesma.org/9042022-State-of-SMA-vweb.pdf)

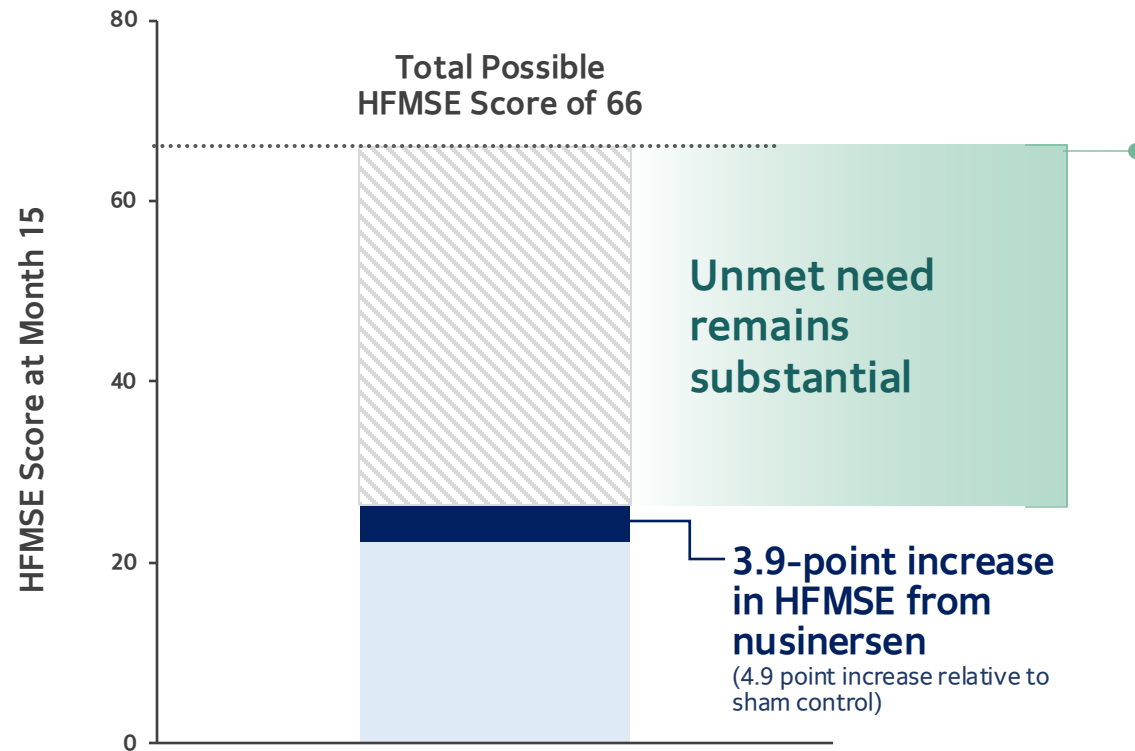
2. Lally et al. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet J Rare Dis. 2017 Nov 28;12(1):175. doi: 10.1186/s13023-017-0724-z.

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 trial¹

Patients and caregivers want new therapies to address the following unmet needs²:



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?"

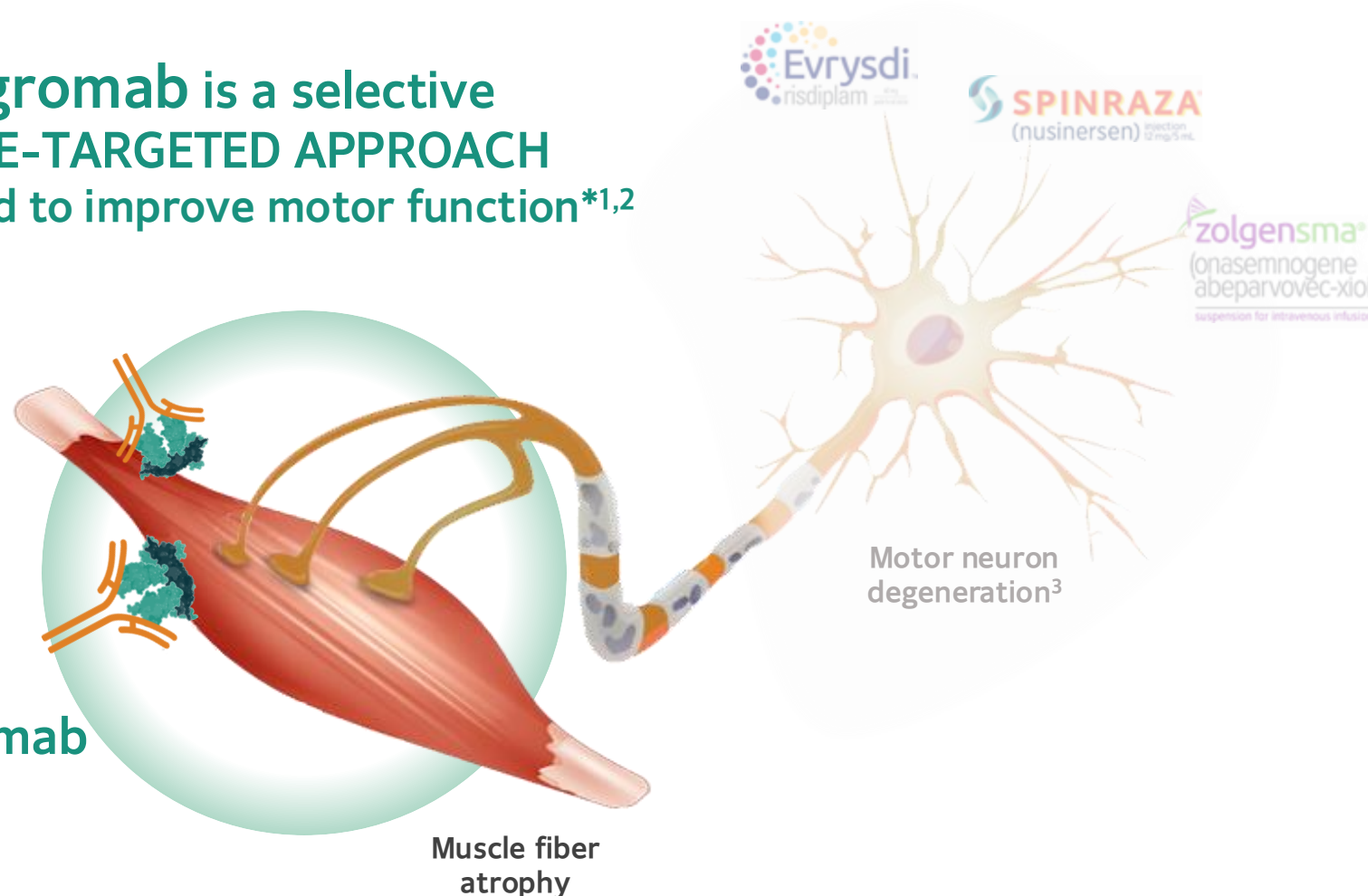
HFMSSE=Hammersmith Functional Motor Scale-Expanded.

1. Mercuri E et al.; N Engl J Med 2018; 378:625-635; DOI: 10.1056/NEJMoa1710504; cherish trial results; 2. 2022 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.

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



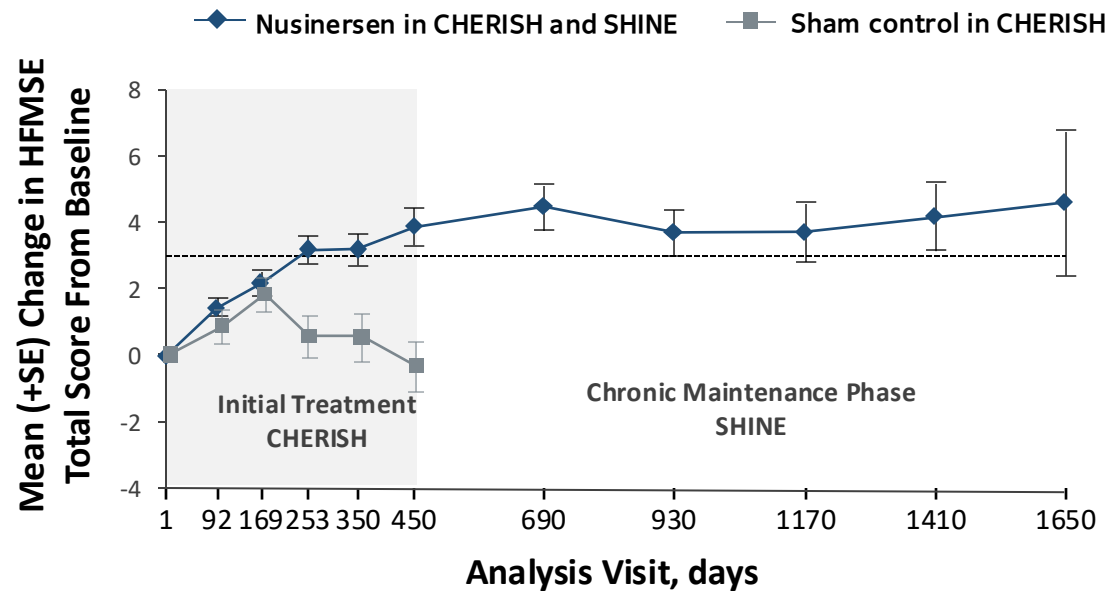
Apitegromab specifically and only inhibits myostatin and has the potential to build muscle and strength to improve patient outcomes

* 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.

Motor Function With SMN Therapies as Assessed by HFMSE

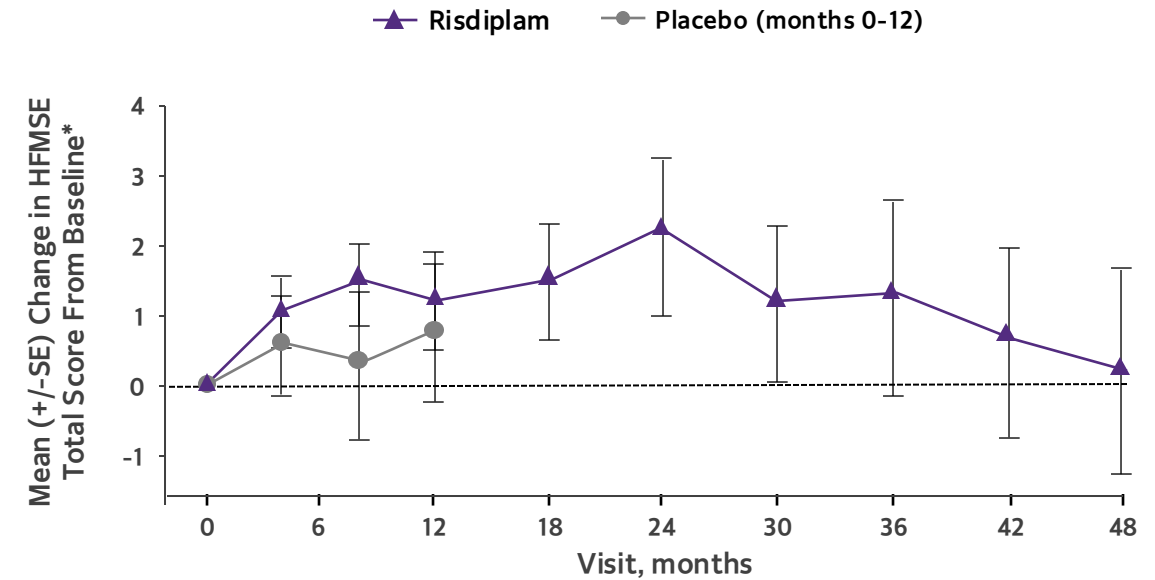
HFMSE appears to Plateau After Initial Gains

Change in HFMSE Over Four Years with Nusinersen¹
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 Risdiplam²
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

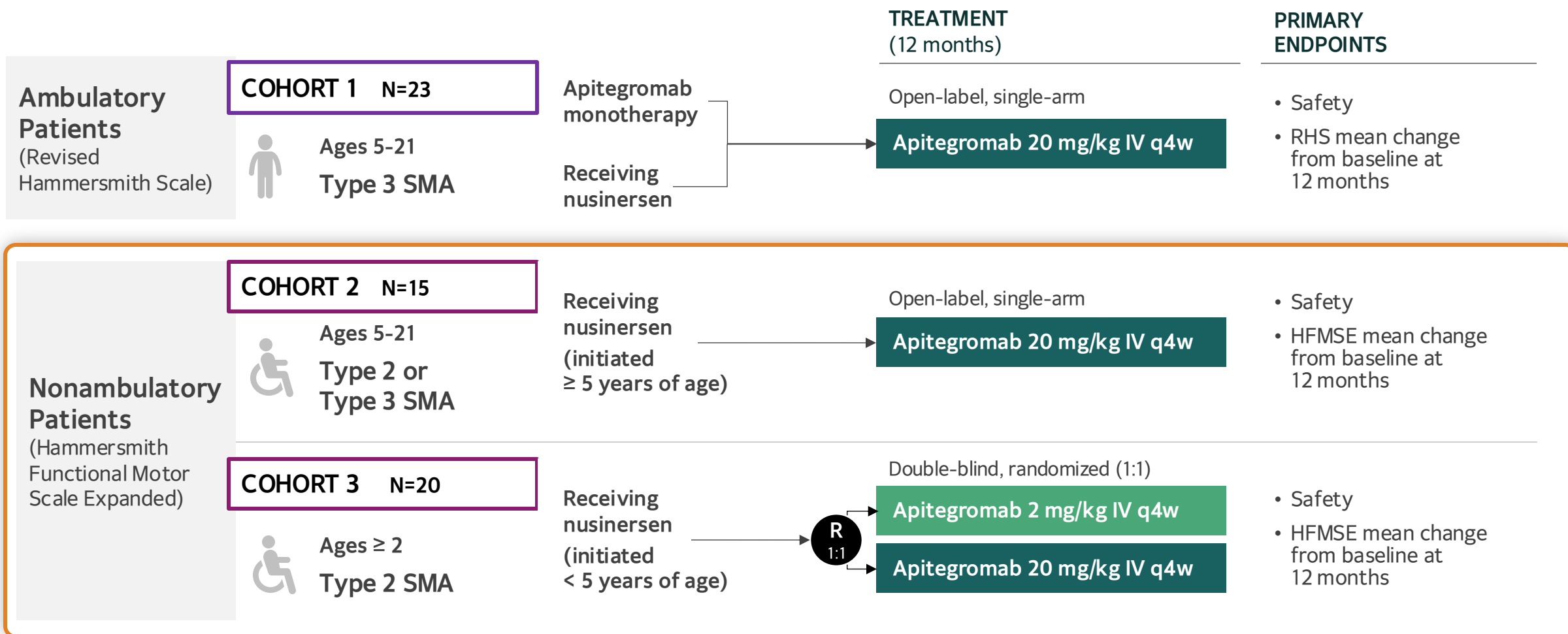
2. Oskoui M, et al. Presented at: 2021 Muscular Dystrophy Association Clinical & Scientific Conference; March 15-18, 2021. Poster 80.

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.



Phase 2 TOPAZ Trial: Safety and Efficacy Data from Muscle-Targeted Treatment Candidate in SMA



All SMA Types 2/3, cohorts defined by age and present ambulatory status at time of enrollment. HFMSE, Hammersmith Functional Motor Scale Expanded; IV, intravenous; q4w, every 4 weeks; SMA, spinal muscular atrophy; SMN, survival motor neuron.

1. Place A, et al. Eu J Neurol. 2021;28(Suppl1):207-334 (EPR-184). 2. Crawford T, et al. TOPAZ Extension: 24-month Efficacy and Safety of Apitegromab in Patients With Later-onset SMA (Type 2 and Type 3 SMA). Presented at CureSMA Annual Conference; June 16-19, 2022.

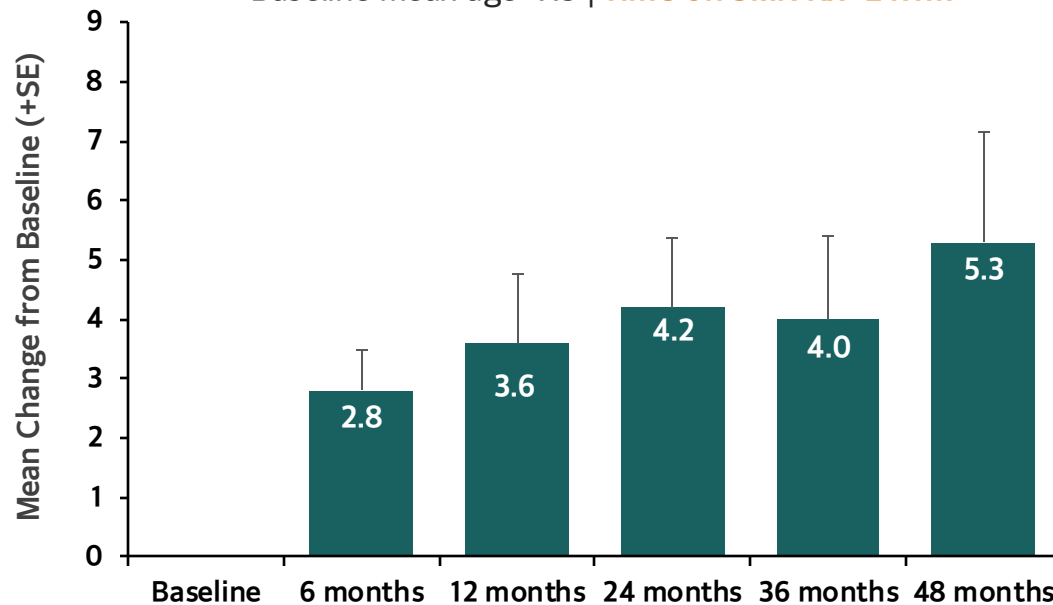
Apitegromab TOPAZ Clinical Trial: Motor Function Outcomes by HFMSE Over 48 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients¹

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

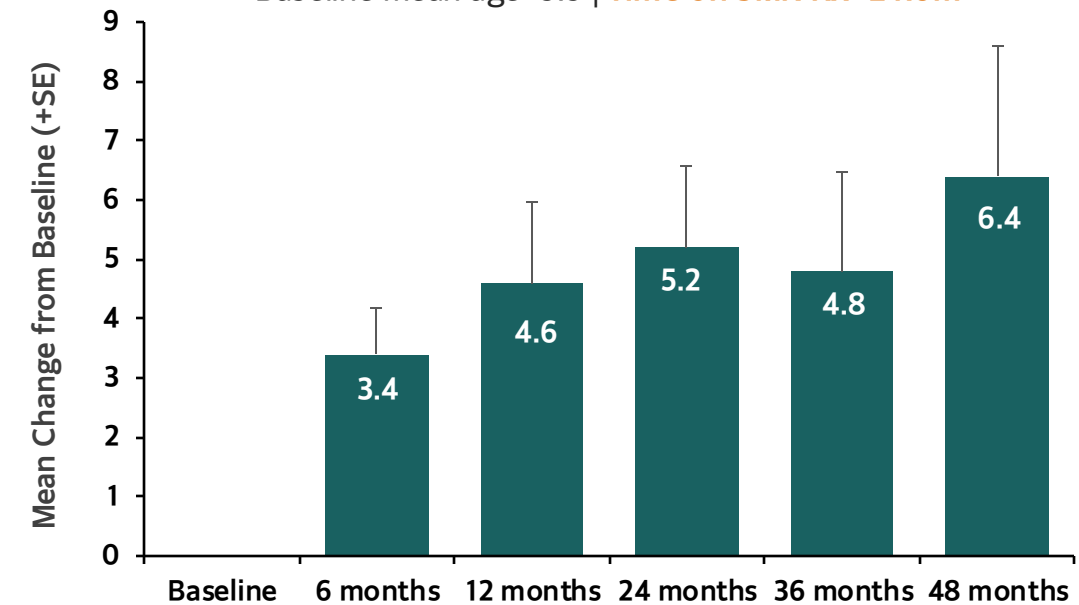
Baseline mean age=7.3 | Time on SMN Rx=24.1m



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.

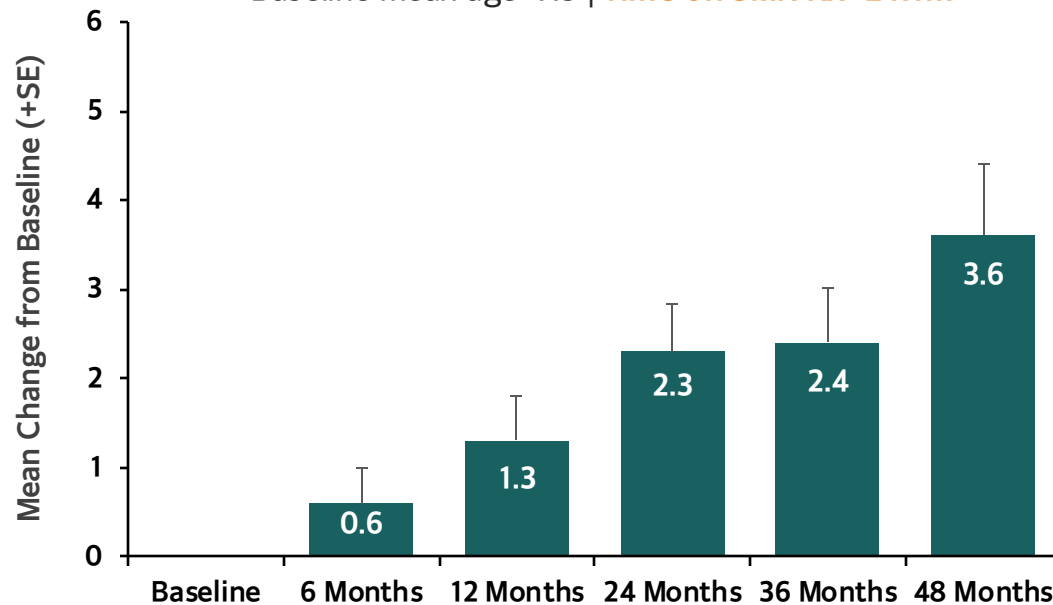
Apitegromab TOPAZ Clinical Trial: Motor Function Outcomes by RULM Over 48 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients¹

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

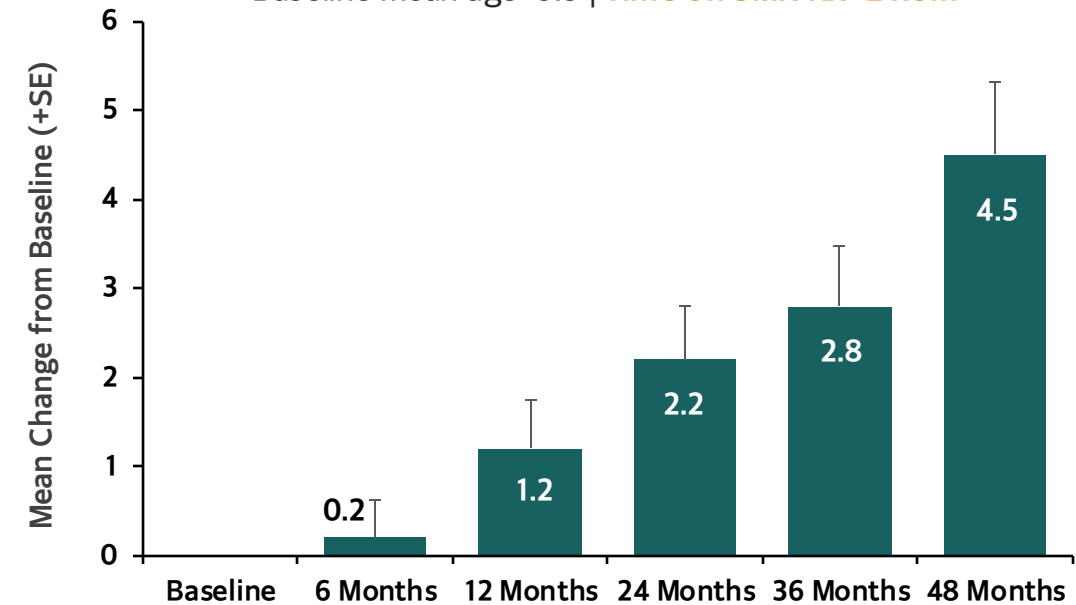
Baseline mean age=7.3 | Time on SMN Rx=24.1m



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.

TOPAZ Over 48 Months

Well Tolerated Safety Profile & Low Discontinuation Rate

**RIGHT
TARGET** →

Myostatin

**RIGHT
TIME** →

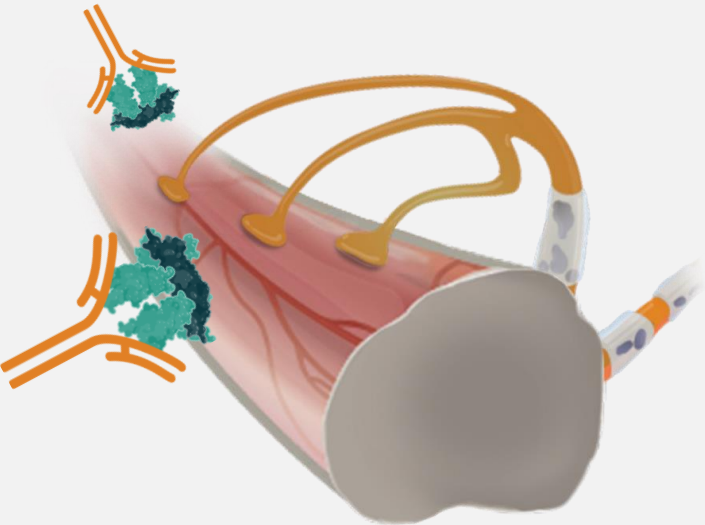
Latent Form

- >90% of patients remain on extension study¹
- Treatment-emergent adverse events (TEAEs) were consistent with previous reports with no new findings after over 200 patient-years of exposure
 - Most frequently reported TEAEs included COVID-19, pyrexia, upper respiratory tract infection, headache, cough, and nasopharyngitis
 - TEAEs were generally consistent with the underlying patient population and nusinersen therapy
- No treatment-related serious AEs or hypersensitivity reactions
- No report of positive apitegromab antibodies (ADA)²

1. Pooled nonambulatory patients. 2. No ADAs reported as above detection on titer assessment.

Summary of TOPAZ Data

Substantial and
Sustained
Improvement over
48 MONTHS¹



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 remain 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



SAPPHIRE

Sapphire Phase 3 Pivotal Trial



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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)



SAPPHIRE

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

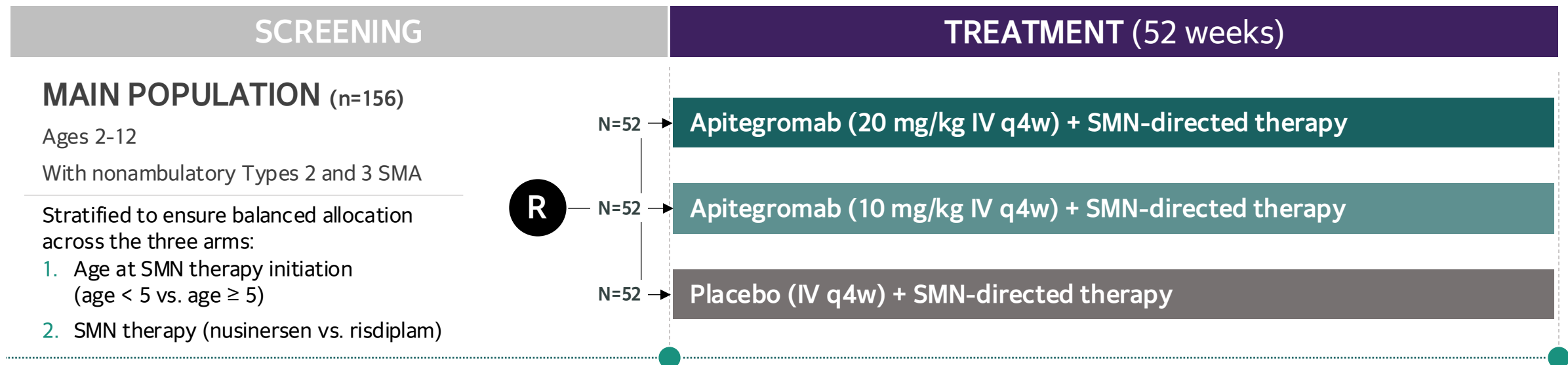
DOSE

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

SAPPHIRE Trial Designed for Clinical Success



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

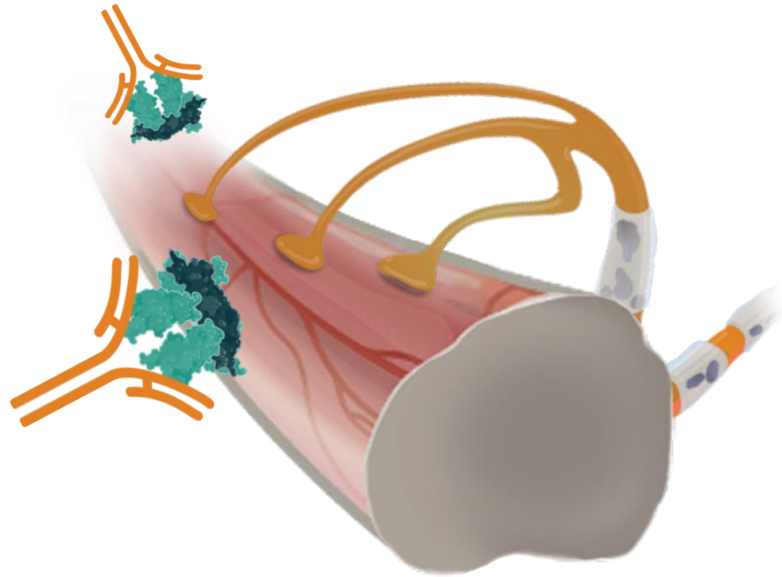
Focused upon safety & exploratory efficacy (n=48; 2:1 randomization between apitegromab 20 mg/kg vs placebo)

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

Focused upon safety & exploratory long-term efficacy

Apitegromab: Potential to Maximize Outcomes for People Living with Spinal Muscular Atrophy (SMA)

Transformative
Potential to Change
the Standard of Care



First and only muscle-targeted investigational treatment to demonstrate clinical proof-of-concept in SMA



Phase 3 SAPPHIRE Trial

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



Phase 2 TOPAZ Trial

Demonstrated **substantial and sustained functional improvements** in Type 2 and nonambulatory Type 3 SMA patients



ONYX Open-Label Extension Study

Evaluating the **long-term safety and efficacy** of apitegromab in patients who have completed TOPAZ or SAPPHIRE

Where We Plan to Go: Expanding to Benefit More People Living with SMA

2024



SAPPHIRE

Q4 Data
Readout

2025

- BLA /MAA Filing
- Regulatory Approval*
- Study in SMA Patients < 2 Years of Age
 - Study design endorsed by EMA's paediatric committee
 - Study initiation planned for 2025

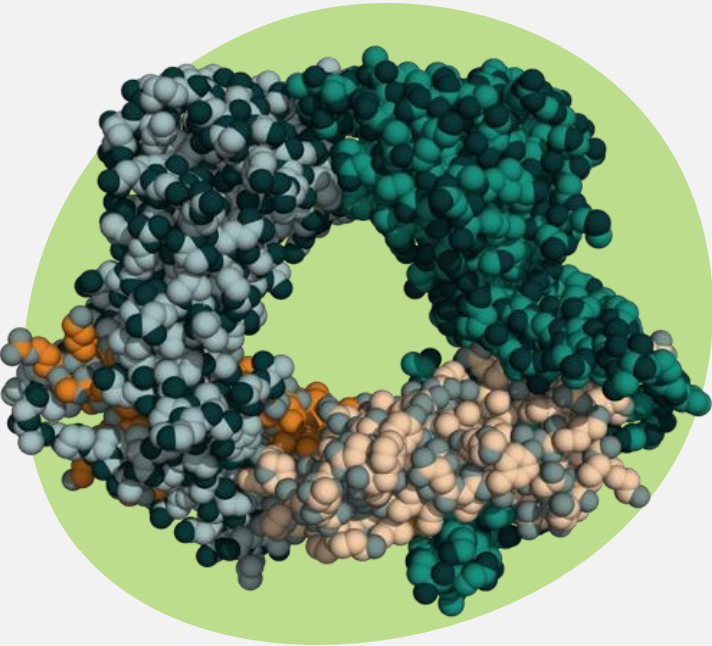


*Pending approval



Next Horizon: Cardiometabolic Disorders

Differentiated Expertise Developing Muscle-Targeted Therapies



Myostatin is a member of the TGF β 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

BY 2030, OBESITY WILL AFFECT:

>1 BILLION
adults

>250 MILLION
children and
adolescents¹



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

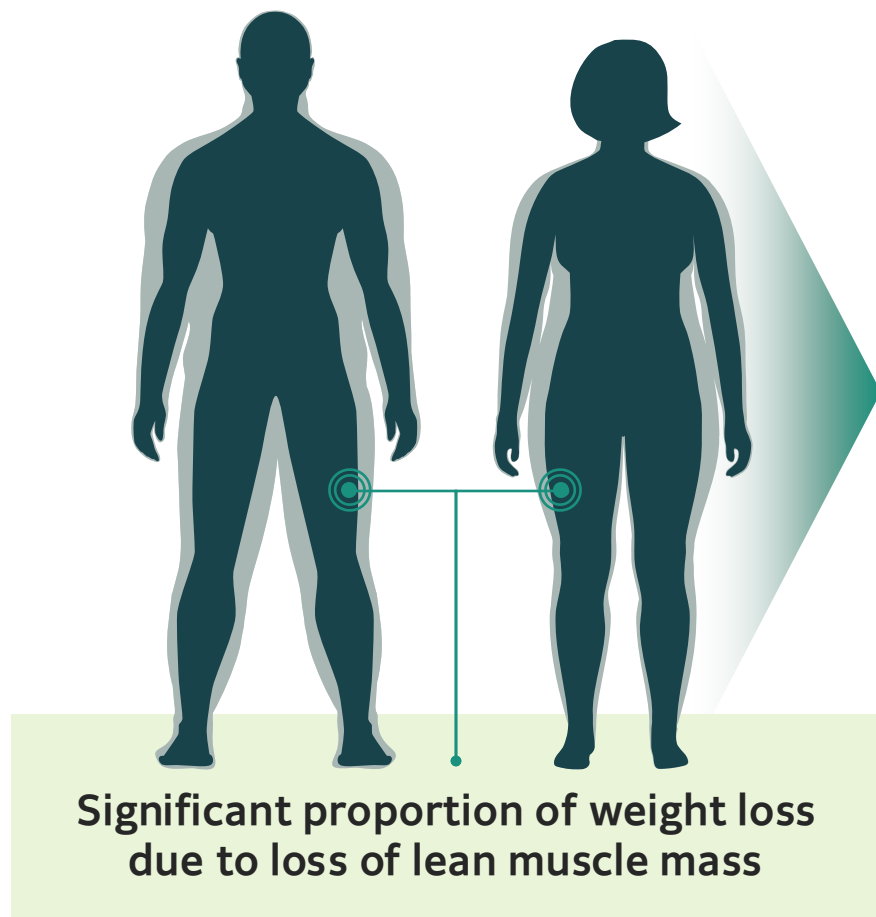
Adult obesity
associated with more
than **\$170 billion**
in excess costs
annually in the U.S.²

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

Loss of Lean Muscle Significant with GLP-1 RA Therapy

Lean muscle is essential to healthy metabolic function



Current Weight Loss Strategies *Challenged by:*

- ⚠ Tolerability
- ⚠ Lack of durability
- ⚠ Significant muscle loss¹⁻³

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 outcomes⁴⁻⁷

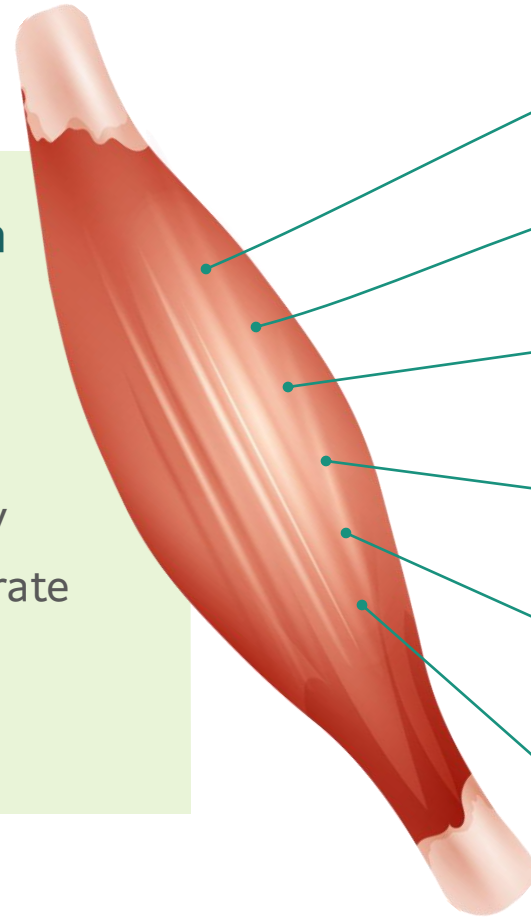
GLP-1 RA=Glucagon-like peptide-1 receptor agonists.

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



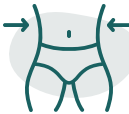
Increased basal metabolic rate (BMR)¹



Enhanced glucose homeostasis²



Better insulin sensitivity and lower risk of prediabetes³



Reduced visceral fat⁴



Increased caloric expenditure post-exercise⁵

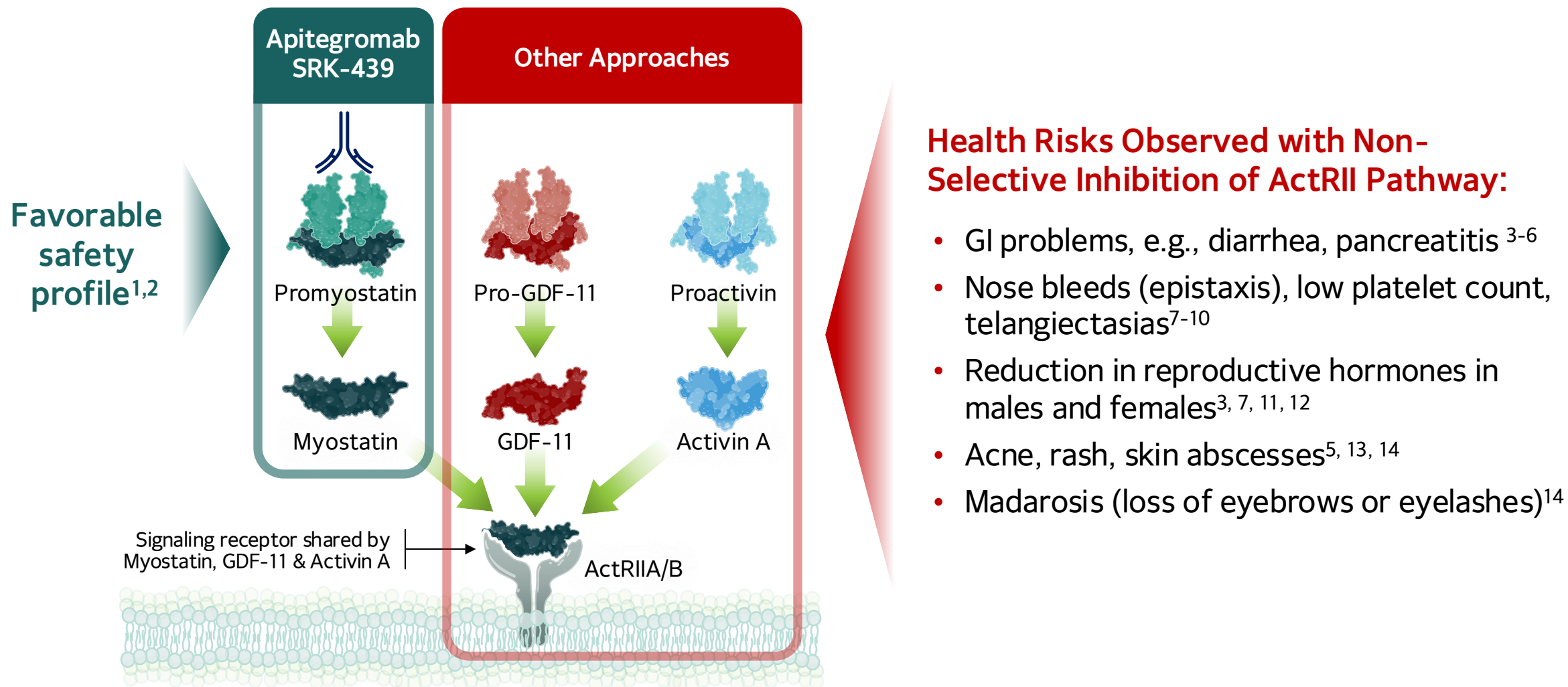


Increased bone density, strength, function, and longevity and decreased risk of injury, and disability⁶⁻⁸

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.

Multiple Risks Associated with Non-Selective Targeting



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



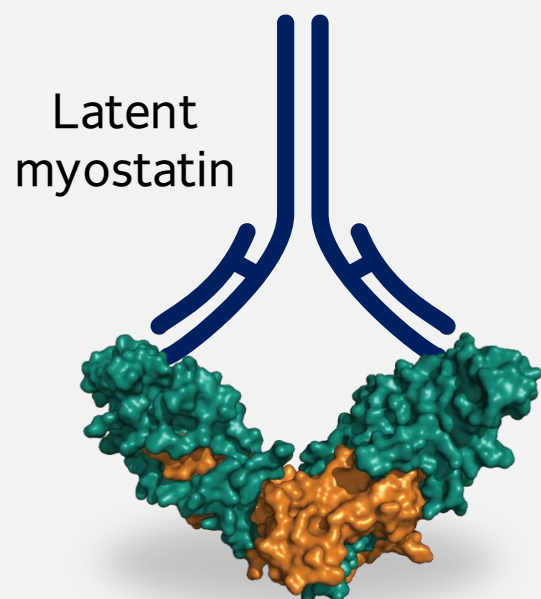
Strong Scientific Validation

- Preclinical data demonstrated favorable muscle mass preservation and metabolic effects

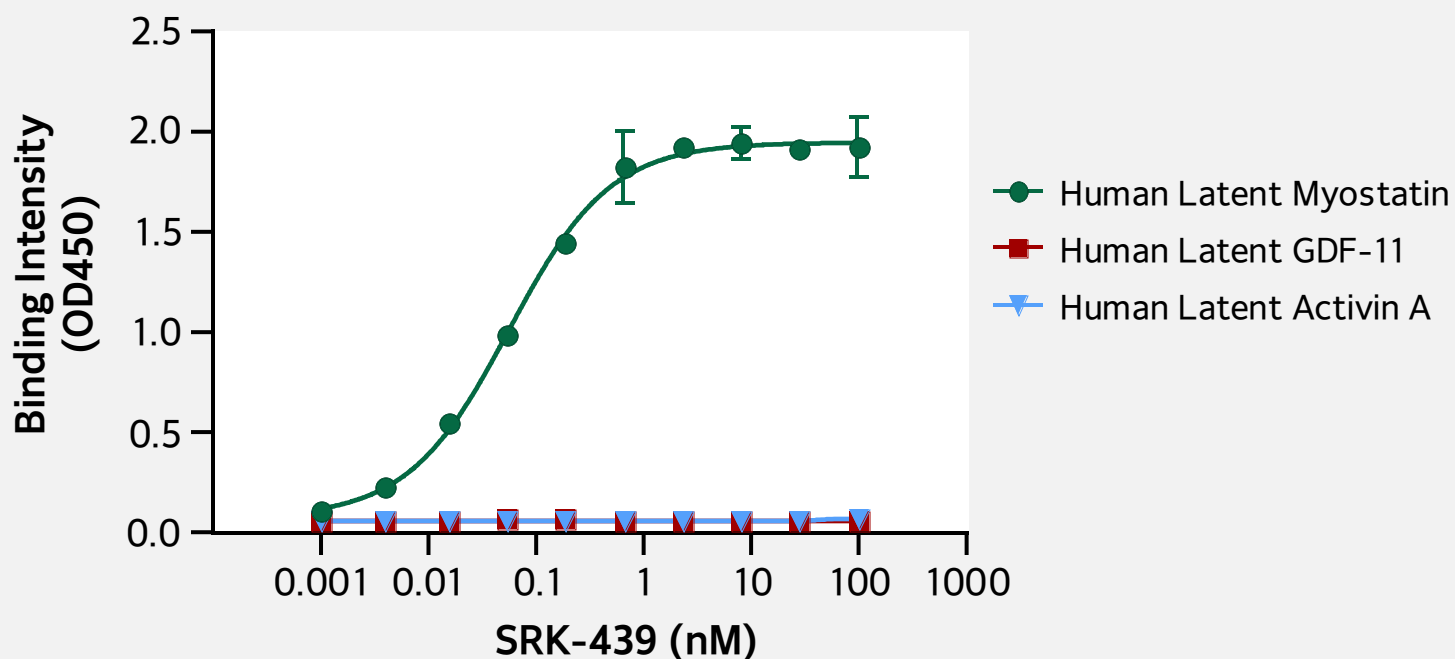


SRK-439: Exquisite Selectivity for Myostatin

Scholar Rock's Target: Latent Myostatin



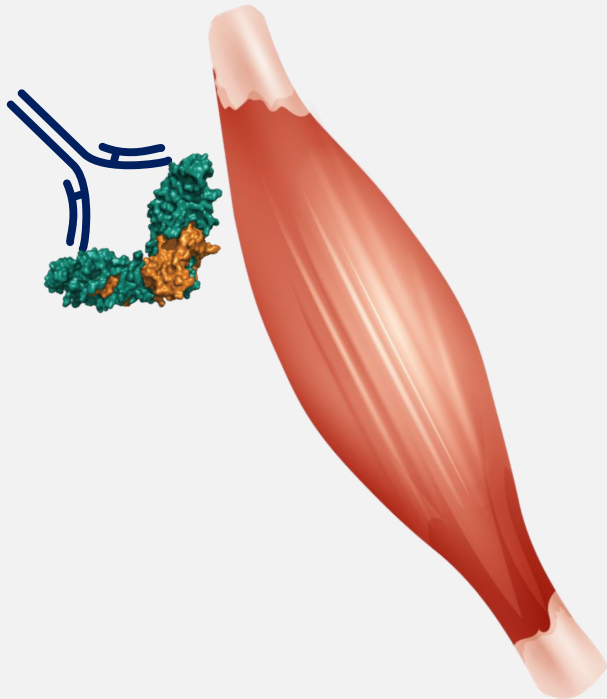
SRK-439 Selectively Binds Latent Myostatin



- 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

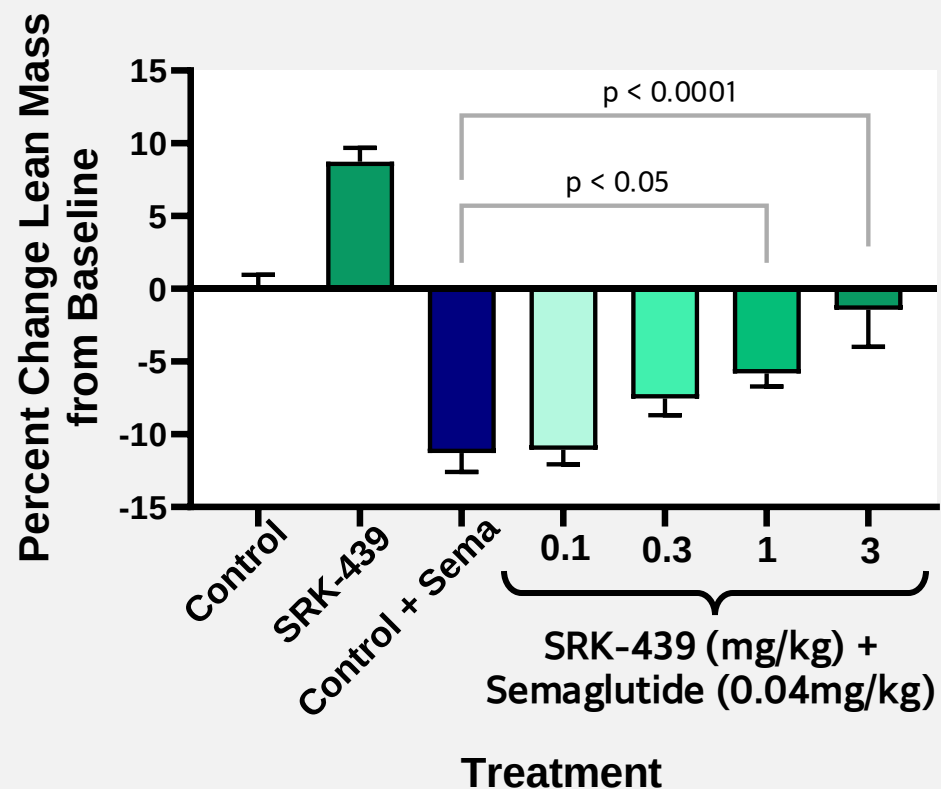


Preclinical data to date show strong potential to support healthier weight loss in combination with GLP-1 RA:

- ✓ **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-ACTR11 antibody

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

SRK-439 Maintained Lean Mass in Semaglutide Treated Animals

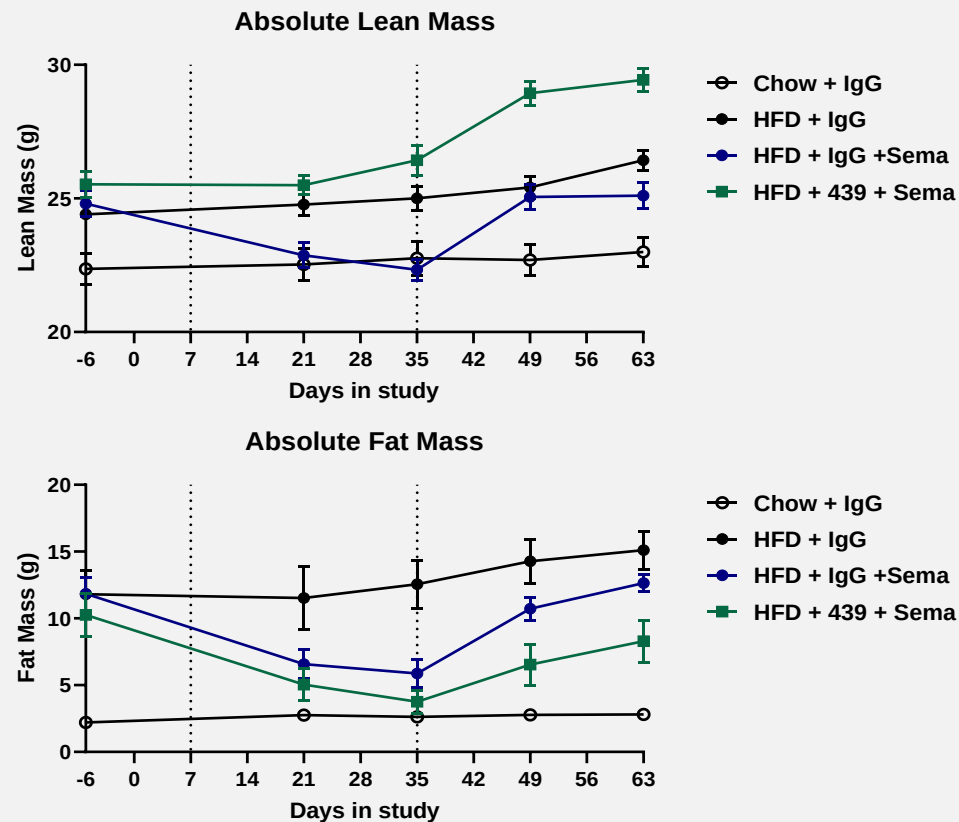


Key Observations

- 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

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



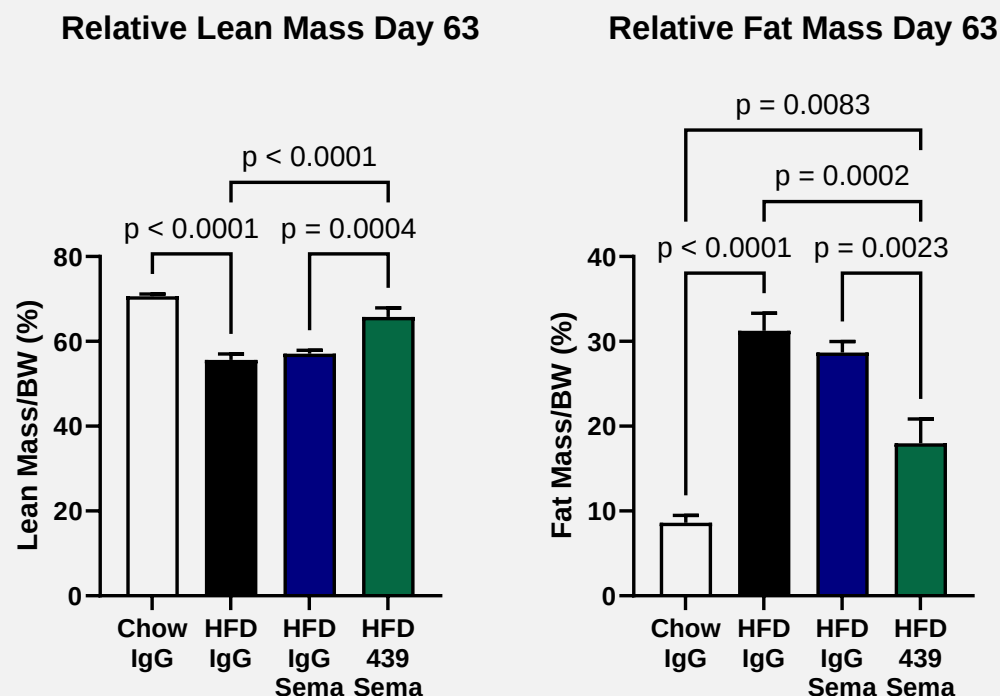
Key Observations

- 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



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

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



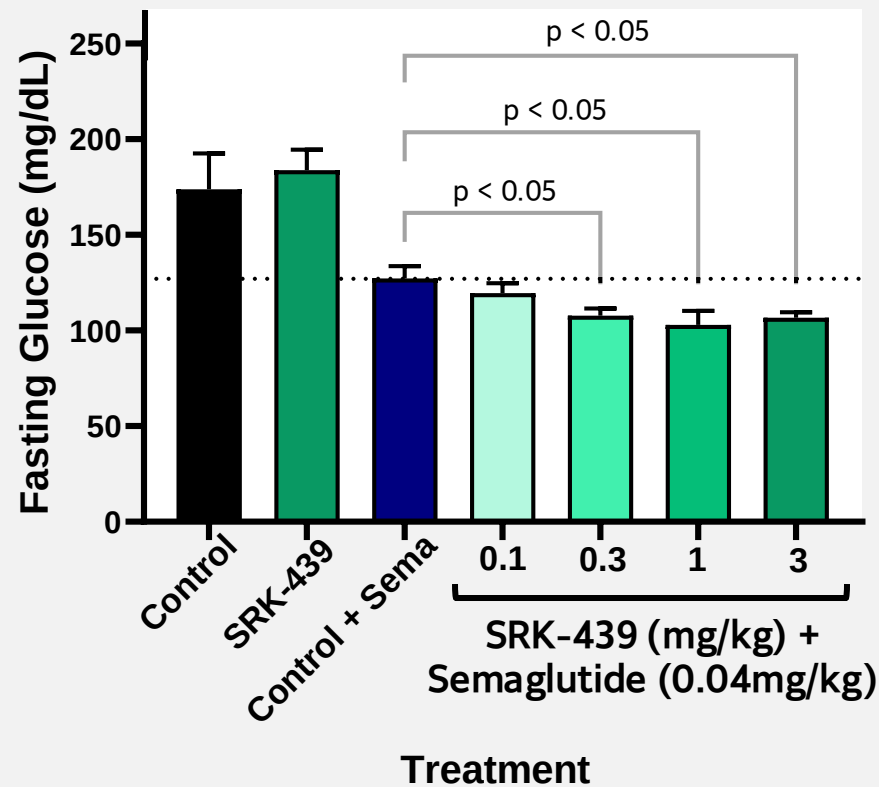
Key Observations

- 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



SRK-439: Further Improvement of Metabolic Health

SRK-439 Further Improved Fasting Glucose in Semaglutide Treated Animals



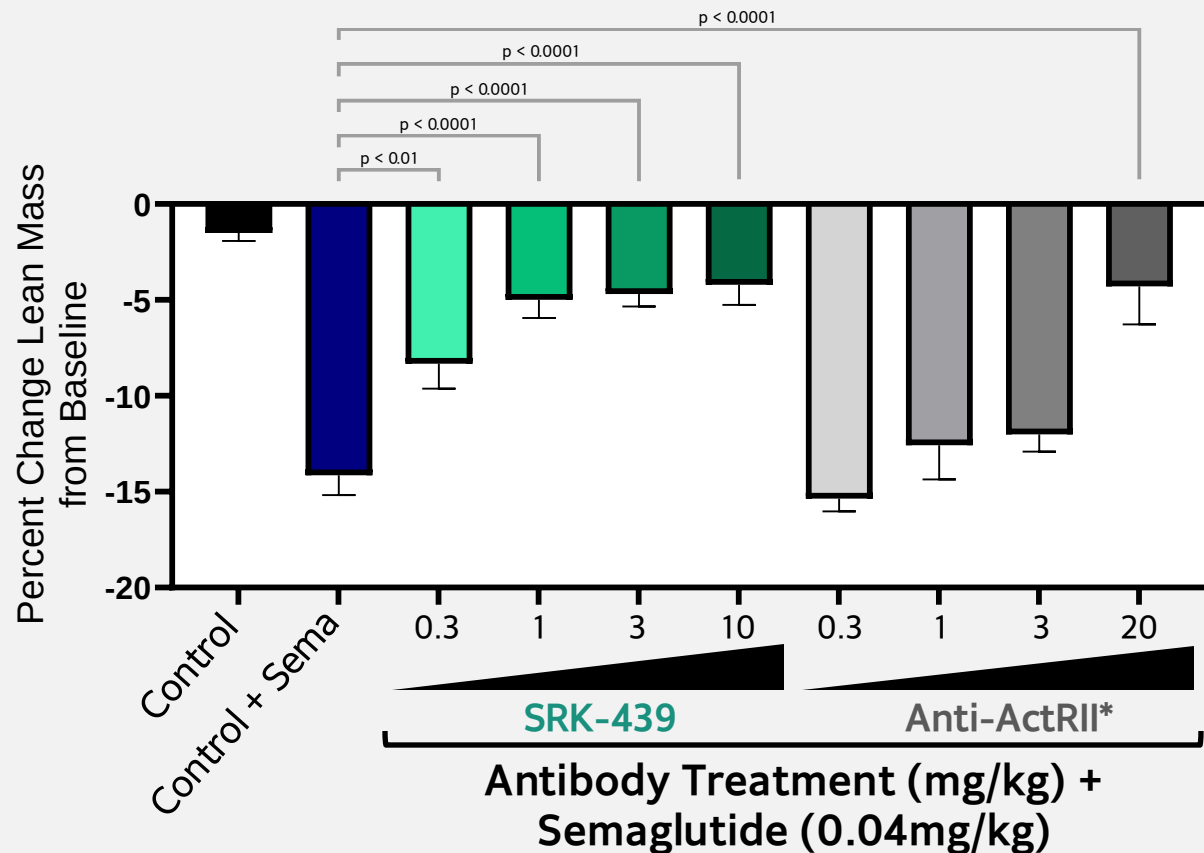
Key Observations

- 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

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

SRK-439: Best in Class Potential

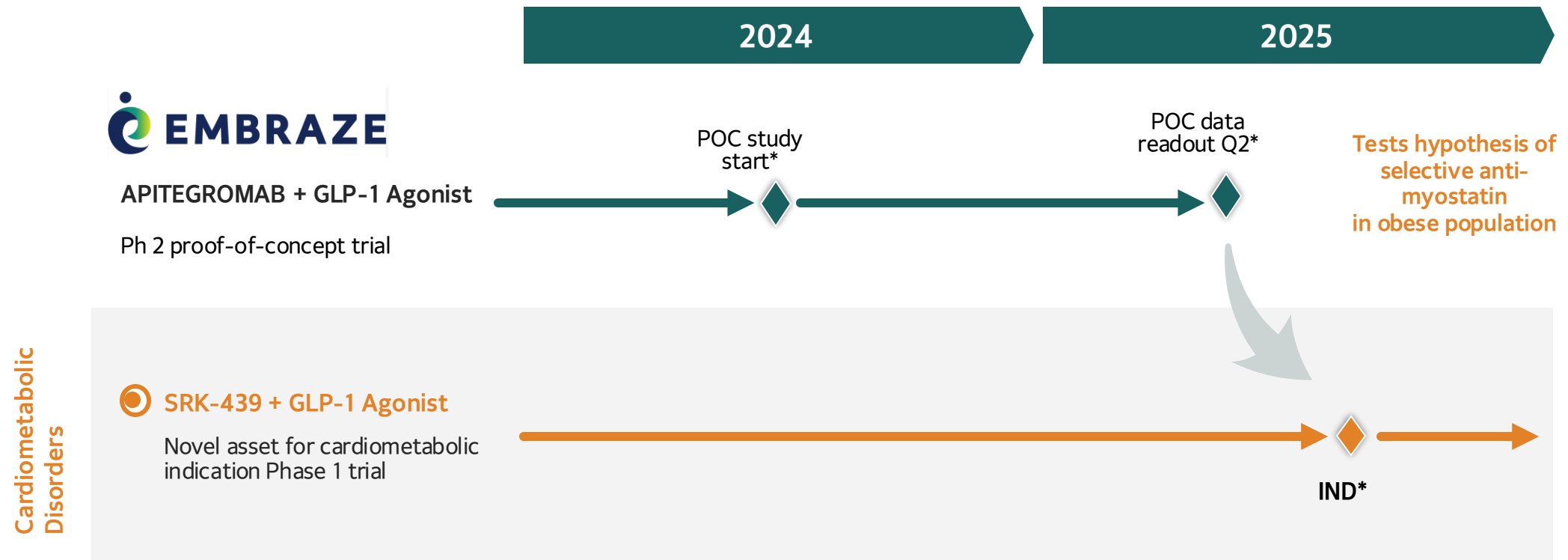
	SRK-439	ActRII Ab	Ligand Trap	Adnectin
Selectivity for myostatin	✓	✗	✗	✗
Action limited to muscle	✓	✗	✗	✗
Combination GLP-1 RA data in obesity preclinical models ¹⁻³	✓	✓	✓	✓
Low efficacious dose in preclinical obesity models ¹⁻³	✓	✗	✗	✗
Lower risk of potential undesirable effects in clinic ⁴	✓	✗	✗	✗

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.

Leveraging Apitegromab to Inform Obesity Program



*Expected timelines
POC = Proof of Concept

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

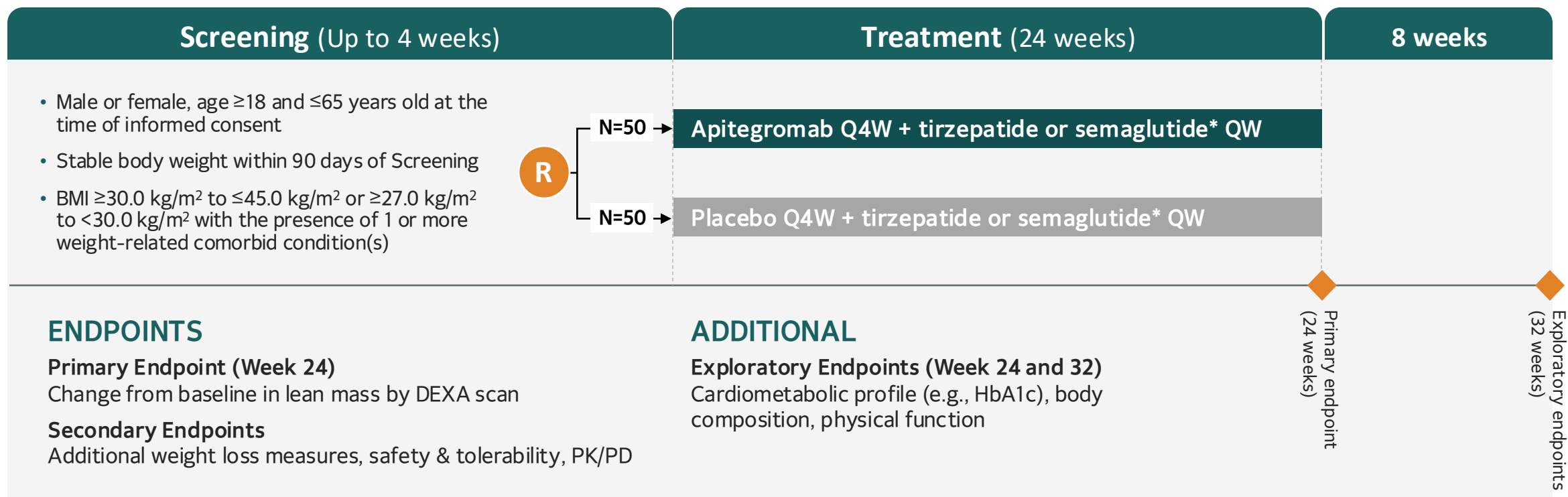
Strong enrollment
momentum

Updating guidance for
topline data to Q2 2025

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



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



*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.

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>

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

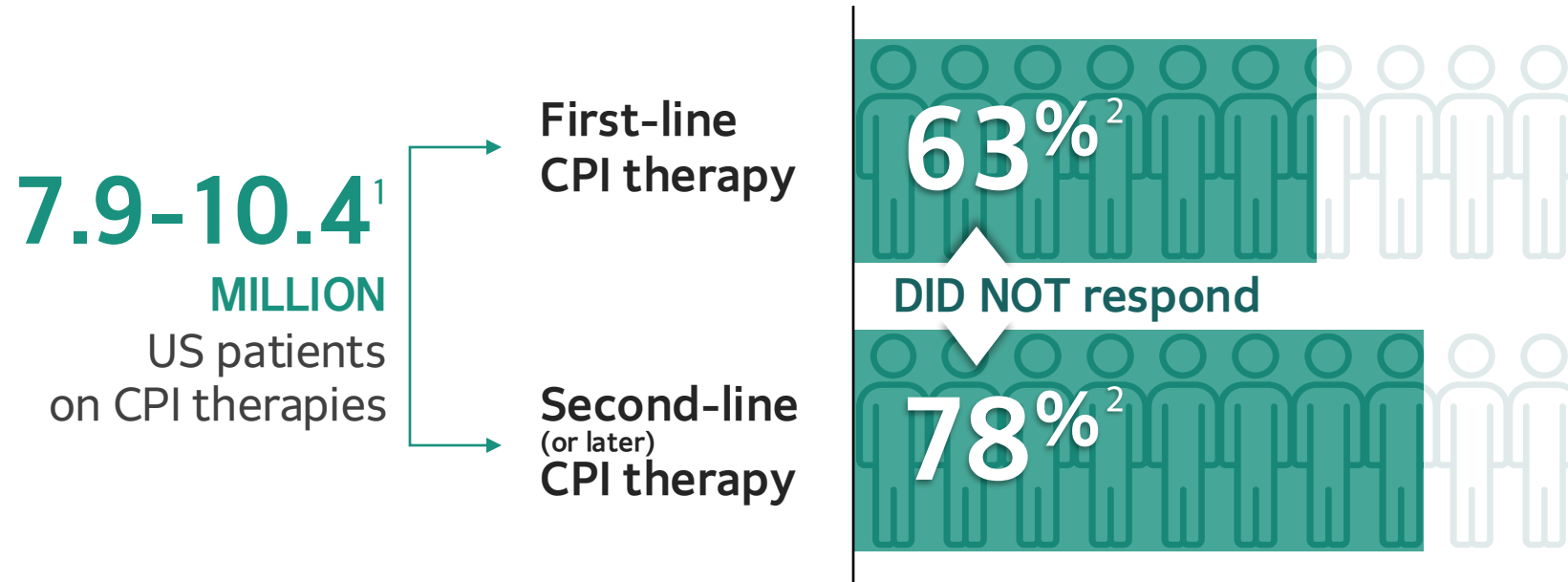




DRAGON

SRK-181: Potential Transformative Backbone for a New Era of Cancer Immunotherapy

Resistance to Checkpoint Inhibitor (CPI) Therapies Remains a Significant Clinical Challenge



Clinically derived rationale points to significant opportunity to
increase checkpoint therapy responses by targeting TGFβ-1

1. Source: Gores, M. (2022). *In the eye of the storm: PD-(L)1 inhibitors weathering turbulence* [White paper]. IQVIA. <https://www.iqvia.com/library/white-papers/in-the-eye-of-the-storm-pd-l-1-inhibitors-weathering-turbulence>

2. Source: Carretero-Gonzalez et al. (2018) *Oncotarget* 9:8706-8715

Meta-analysis of twelve randomized trials with control arm or adequate safety profile (includes nivolumab, pembrolizumab, and atezolizumab)

Strong Scientific Rationale for the Role of TGFβ Inhibition in Immuno-Oncology

Nature (online), February 14, 2018.

TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells

Sanjeev Mariathasan^{1*}, Shannon J. Turley^{1*}, Dorothee Nickles^{1*}, Alessandra Castiglioni¹, Kobe Yuen¹, Yulei Wang¹, Edward E. Kadel III¹, Hartmut Koeppen¹, Jillian L. Astarita¹, Rafael Cubas¹, Suchit Jhunjhunwala¹, Romain Banchereau¹, Yagai Yang¹, Yinghui Guan¹, Cecile Chalouni¹, James Ziai¹, Yasin Şenbabaoğlu¹, Stephen Santoro¹, Daniel Sheinson¹, Jeffrey Hung¹, Jennifer M. Giltman¹, Andrew A. Pierce¹, Kathryn Mesh¹, Steve Lianoglou¹, Johannes Riegler¹, Richard A. D. Carano¹, Pontus Eriksson², Mattias Höglund², Loan Somarriba³, Daniel L. Halligan³, Michiel S. van der Heijden⁴, Yohann Loriot⁵, Jonathan E. Rosenberg⁶, Lawrence Fong⁷, Ira Mellman¹, Daniel S. Chen¹, Marjorie Green¹, Christina Dedeth¹, Gregg D. Fine¹, Priti S. Hegde¹, Richard Bourgon¹ & Thomas Powles⁸

Science Translational Medicine, March 25, 2020.

Selective inhibition of TGFβ-1 activation overcomes primary resistance to checkpoint blockade therapy by altering tumor immune landscape

Constance J. Martin, et al.

Vol 12, Issue 536. DOI: [10.1126/scitranslmed.aay8456](https://doi.org/10.1126/scitranslmed.aay8456)

June 2019.

“Merck to Acquire Tilos Therapeutics: Merck Gains Portfolio of Investigational Antibodies Modulating TGFβ”

- \$773 million total potential deal value

Cell

Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma

Willy Hugo, Jesse M. Zaretsky, Lu Sun, Douglas B. Johnson, Antoni Ribas, Roger S. Lo

Volume 165, Issue 1, 24 March 2016, Pages 35-44

Nature Reviews, July 24, 2020 NATURE REVIEWS | CLINICAL ONCOLOGY

TGFβ: biology in cancer progression and immunotherapy

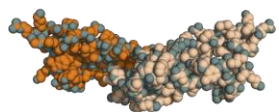
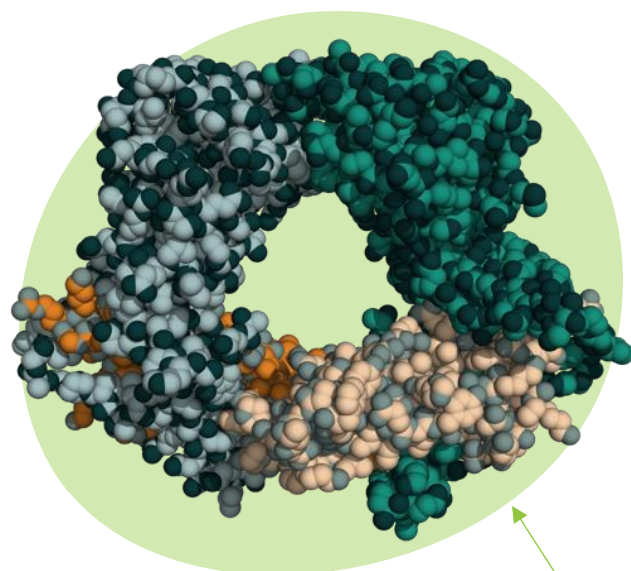
Rik Derynck^{1,2,3}, Shannon J. Turley⁴ and Rosemary J. Akhurst^{2,3}

July 24, 2020: <https://doi.org/10.1038/s41571-020-0403-1>

August 2022.

“Bristol Myers Squibb Enters Agreement to Acquire Forbuis TGF-beta Program”

SRK-181: Unique Latent TGF β -1 Selective Approach Designed to Overcome Checkpoint Inhibitor Resistance



Traditional Target
“Mature” growth factor

SRK-181: Latent TGF β -1 Inhibitor

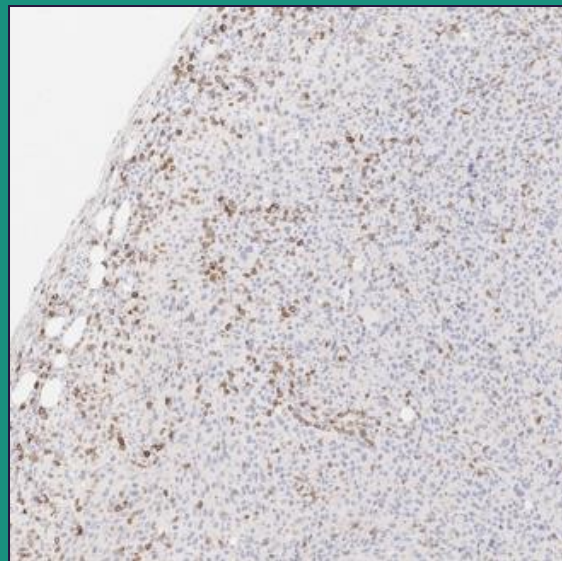
Targets TGFβ-1	Potential to overcome CPI resistance	SRK-181 inhibits the TGF β -1 implicated in check point inhibitor resistance	
Selective to β-1 isoform	Highly selective to β -1 isoform vs. 2 and 3	Increases therapeutic window and potentially avoids toxicities associated with non-selective TGF β inhibition	Other programs target multiple isoforms of TGF β
Targets the latent form of TGFβ-1	Increases opportunity to inhibit TGF β -1	Selectively targeting the latent form shuts off the growth factor before activation	Most other programs target the mature form of TGF β -1
Context-independent	Inhibits all sources of TGF β -1	SRK-181 targets all TGF β -1 sources (LRRC33, GARP and LTBP1 and 3)	Some programs only target one source

1. Wakefield LM, Winokur TS, Hollands RS, Christopherson K, Levinson AD, Sporn MB. Recombinant latent transforming growth factor beta 1 has a longer plasma half-life in rats than active transforming growth factor beta 1, and a different tissue distribution. *J Clin Invest*. 1990 Dec;86(6):1976-84. doi: 10.1172/JCI114932. PMID: 2254455; PMCID: PMC329834.

SRK-181-mIgG1 + Anti-PD1 Overcomes Immune Exclusion

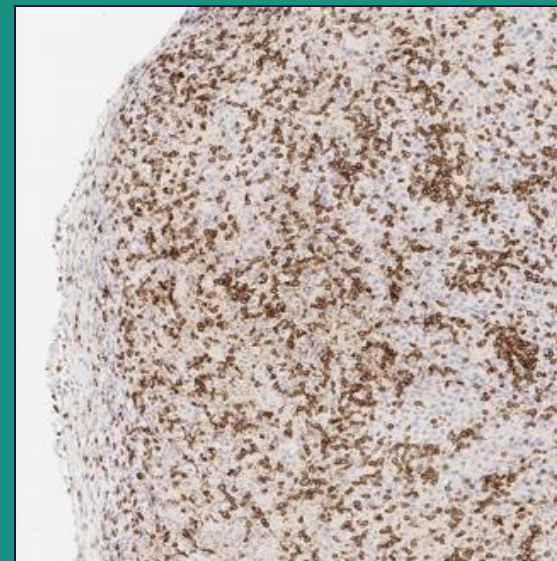
Overcoming immune exclusion Tumor micro-environment

Anti-PD1



Immune Exclusion

Anti-PD1/ SRK-181-mIgG1



Overcome Exclusion

SRK-181-mIgG1 combination therapy led to influx and amplification of cytotoxic CD8+ cells in preclinical bladder tumor model

Phase 1 Clinical Trial Overview

Dose Escalation (3+3)

Part A1: SRK-181 Single Agent
(80-3000 mg q3w/2000 mg q2w)

All advanced solid tumor
n=19



Part A2: SRK-181 + anti-PD-(L)1
(SRK-181: 240-2400mg q3w)

Advanced solid tumor non-responders to prior anti-PD-(L)1
n= 15



Dose Expansion

Part B: SRK-181 (1500mg q3w) + Pembrolizumab
n=up to 40/cohort

Key Eligibility Criteria

- ≥18-year-old and ECOG 0-1
- Measurable disease per RECIST v1.1
- At least 1 prior line of anti-PD-1 antibody
- Part B Cohort **ccRCC** and **HNSCC**:
 - Must have had PD on the most recent prior anti-PD-1
- Part B Cohorts **NSCLC**, **UC** and **MEL**:
 - Non-responders to all prior anti-PD-1

Cohort ccRCC

Cohort HNSCC

Cohort MEL

Cohort UC

Cohort NSCLC

Cohort Any Other*

Study Endpoints

Primary:

- Safety and tolerability

Secondary:

- Anti-tumor activity (BOR, ORR, DoR, and DCR)
- PK and ADA

Exploratory:

- Biomarker
- PFS, OS, etc.

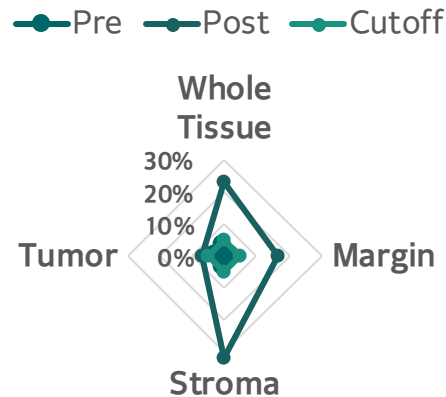
*Cohort Any Other was terminated early and HNSCC was added.

ADA, anti drug antibody; BOR, best overall response; ccRCC, clear cell renal cell carcinoma; DCR, disease control rate; DoR, duration of response; ECOG, eastern cooperative oncology group; HNSCC, head and neck squamous cell carcinoma; MEL, melanoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-(L)1, PD-1/PD-L1; PFS, progression-free survival; PK, Pharmacokinetic; q2w, every 2 weeks; q3w, every 3 weeks; RECIST, response evaluation criteria in solid tumors; UC, urothelial carcinoma.

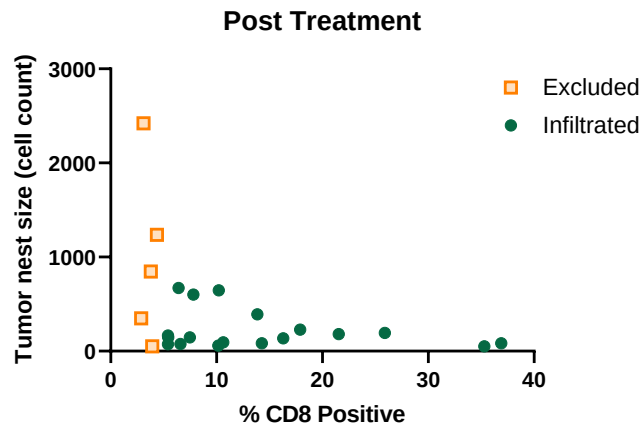
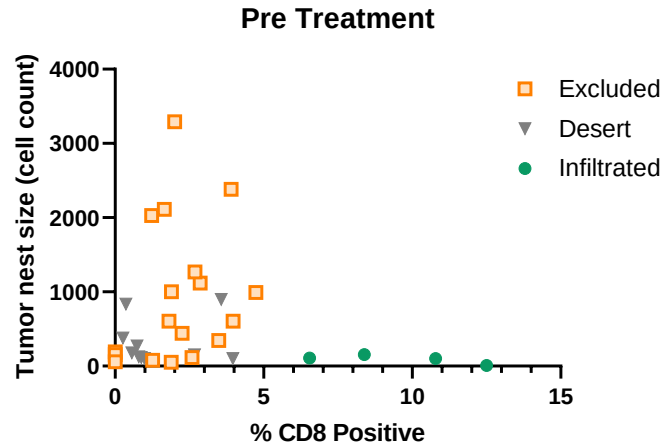
SRK-181 in Combination with Anti-PD1 Increases Infiltration of CD8+ T Cells in Melanoma

- Paired biopsies from 2 melanoma patients were analyzed for CD8 content.
- An increase in CD8+ T cell infiltration was observed in both biopsy pairs, overcoming an initially excluded or desert phenotype and resulting in more infiltrated tumor nests.
- Shown here is the representative quantification and images from one melanoma patient.

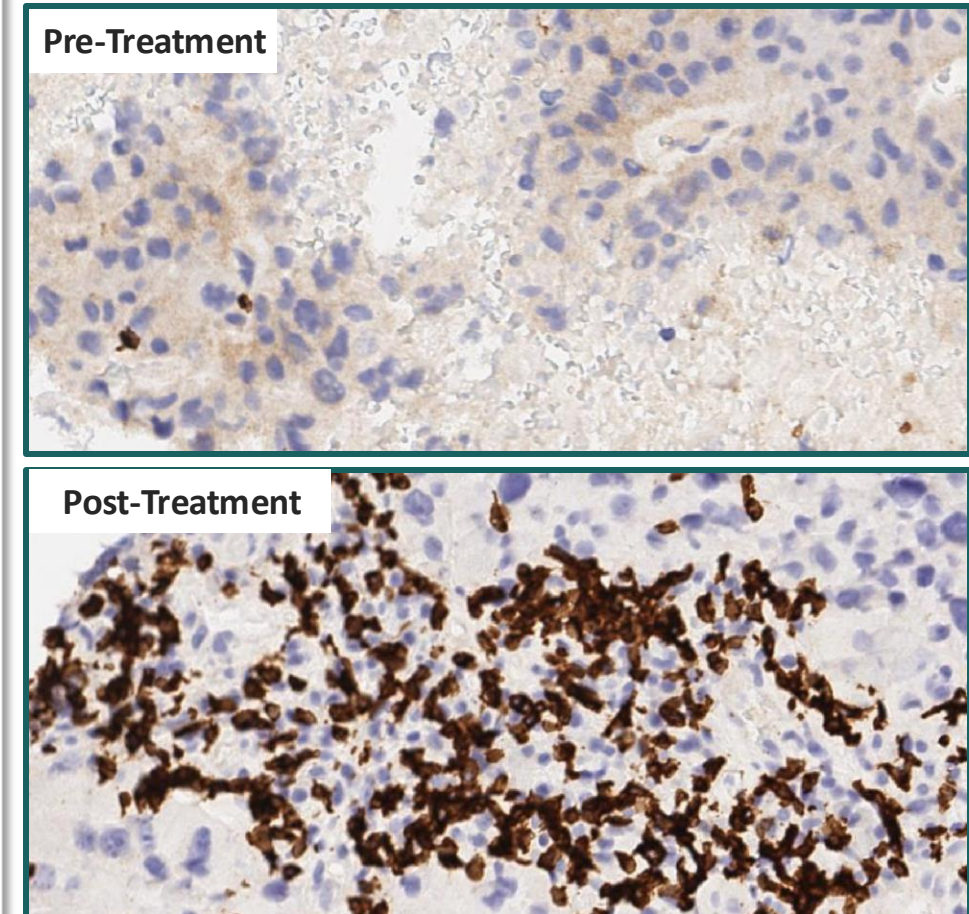
Primary Compartmental Analysis % CD8+ T cells per compartment



Tumor Nest Analysis



CD8 Stain – Melanoma, Pre and Post Treatment



Preliminary Safety and Efficacy

Phase 1 *Dose Escalation Phase*

Safety

- SRK-181 was well tolerated:** No DLTs observed; no Grade 4 or 5 treatment-related AEs

MAD/MTD

- MAD:** 3000mg q3w and 2000mg q2w for single SRK-181 and 2400mg q3w for SRK-181 in combination with anti-PD-1
- MTD not reached; recommended Part B dose** at 1500 mg q3w or 1000 mg q2w

PK

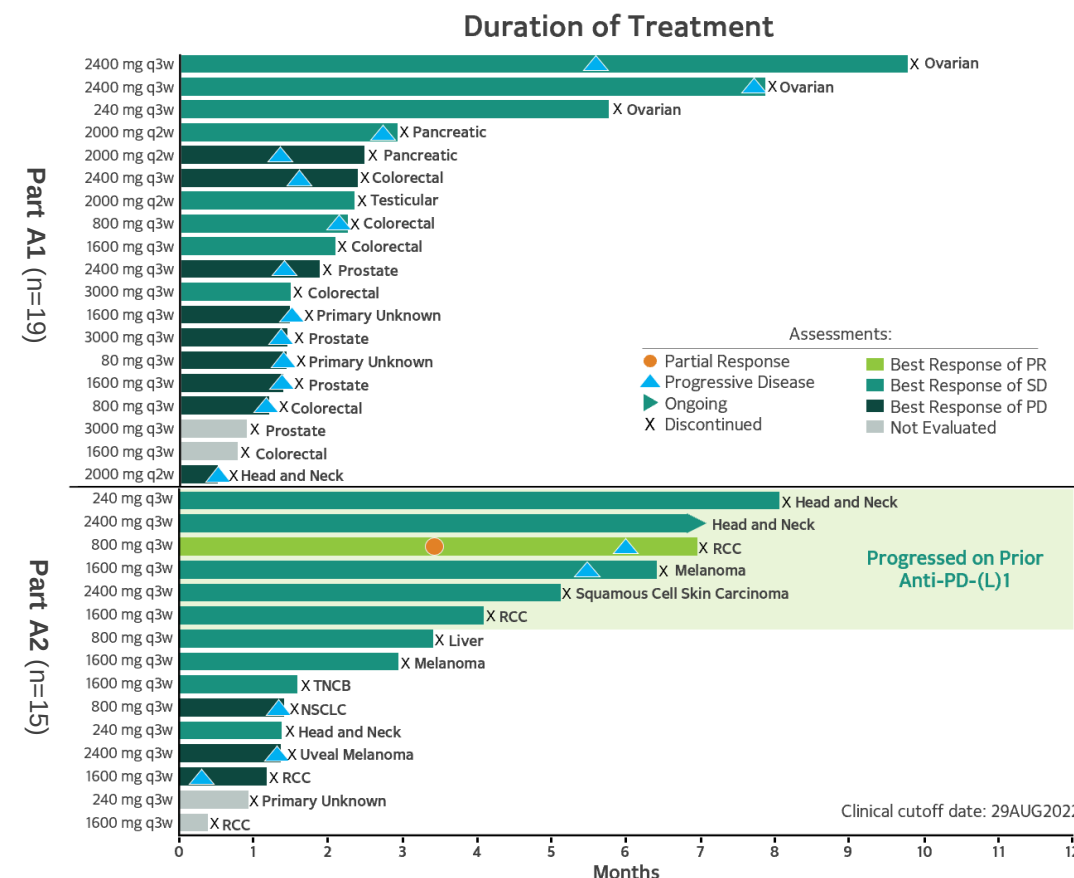
- Exposure was similar between monotherapy and combination
- Approximately dose proportional exposure over 240 mg q3w
- Minimal to no accumulation was observed after multiple doses

Efficacy

- Part A1, Single-Agent Dose Escalation**
 - All 3 ovarian cancer patients were stable beyond ~ 6-month cutoff
- Part A2, Combination Treatment Dose Escalation**
 - 1 PR in anti-PD-1 resistant ccRCC patient
 - 5 (33%) patients had SD for 4+ months
 - 1 HNSCC patient had a 29.4% tumor reduction

Martin CJ, et al. *Sci Transl Med*. 2020;12:eaay8456.
Yap T, et al. *J Immunotherapy of Cancer* 2022;10:doi: 10.1136/jitc-2022-SITC2022.0780.

AE, adverse event; ccRCC, clear cell renal cell carcinoma; DLT, dose-limiting toxicity; HNSCC, head and neck squamous cell carcinoma; MAD, maximum administered dose; MTD, maximum tolerated dose;
PK, Pharmacokinetic; PD, progressive disease; PR, partial response; q2w, every 2 weeks; q3w, every 3 weeks; SD, stable disease.
Data cut date: Apr 10, 2024



Patient Demographics and Disposition

Phase 1 Dose Expansion Phase

Category	All#
N	78
Age, median (range)	65y (32-81y)
Gender, M, n (%)	56 (71.8)
Prior Lines of Therapy, median (range)	3 (1-9)
Number of Lines of Prior Anti-PD-(L)1, n (%)	
1	48 (61.5)
2	23 (29.5)
3	6 (7.7)
4	1 (1.3)
Best Response to Prior Anti-PD-(L)1, n (%)	
Partial Response	1 (1.3)^
Stable Disease	40 (51.3)
Progressive Disease	37 (47.4)
Disease Progressed from the Last Prior Anti-PD-1, n (%)	76 (97.4)*

#Includes patients of 30 ccRCC, 11 HNSCC, 11 MEL, 11 UC, 11 NSCLC and 4 Any Other Cohorts.

^1 HNSCC patient had best response of PR to prior anti-PD-(L)1.

*2 MEL patients discontinued the last prior anti-PD-(L)1 due to other reason instead of disease progression.

AE, adverse event; ccRCC, clear cell renal cell carcinoma; HNSCC, head and neck squamous cell carcinoma; MEL, melanoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-(L)1, PD-1/PD-L1; RECIST, response evaluation criteria in solid tumors; UC, urothelial carcinoma.

Data cut date: Apr 10, 2024

Category	All
Enrolled	78
On Study, n (%)	10 (12.8)
Stopped Treatment, n (%)	68 (87.2)
Reason for Completion/Discontinuation, n (%)	
Disease Progression Based on RECIST 1.1	40 (51.3)
Clinical Progression	6 (7.7)
Adverse Event ^{&}	17 (21.8)
Investigator Decision	1 (1.3)
Withdrawal of Consent	4 (5.1)

[&]10 patients (12.8%) discontinued from the study due to treatment-related AEs: rash maculopopular and pneumonitis (2 patients), bullous pemphigoid, colitis, erythroderma, generalized erythematous rash, invasive squamous cell carcinoma, mucositis oral (1 patient each).

Manageable Safety Profile

Phase 1 Dose Expansion Phase

Treatment-Emergent AEs Related to SRK-181 or Anti-PD(L)1

Adverse Event	All Grades (>5%) N=78	≥Grade 3 N= 78
Rash [#]	25 (32.1%)*	10 (12.8%)*
Pruritus	20 (25.6%)*	1 (1.3%)*
Fatigue	16 (20.5%)	1 (1.3%)
Diarrhoea	11 (14.1%)	0 (0%)
Nausea	5 (6.4%)	1 (1.3%)
ALT increased	4 (5.1%)	2 (2.6%)
AST increased	4 (5.1%)	1 (1.3%)
Arthralgia	4 (5.1%)	0 (0%)
Vomiting	4 (5.1%)	0 (0%)

[#]Rash includes rash, rash macular, rash maculo-papular, rash erythematous, and rash pruritic.

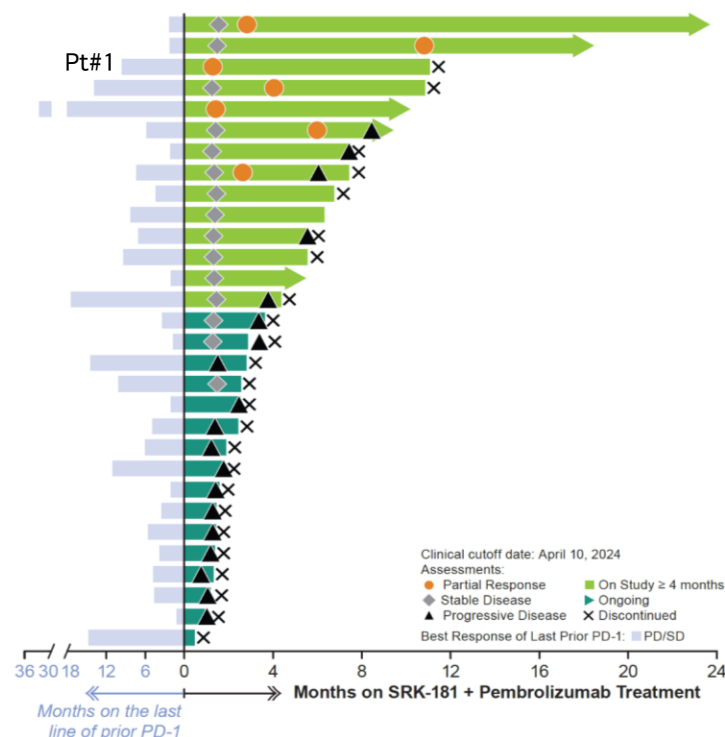
*Treatment-related irAE.

- There was 1 treatment-related Grade 4 AE (Dermatitis exfoliative generalised)
- There was no treatment-related Grade 5 AE
- Treatment-related SAE >2% (2 patients) were Pemphigoid (irAE)

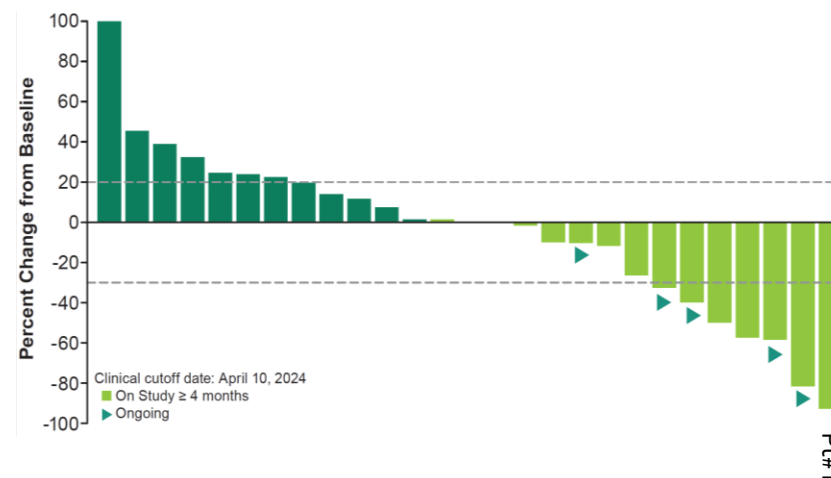
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-(L)1, PD-1/PD-L1; SAE, serious adverse event
Data cut date: Apr 10, 2024

Efficacy in Cohort ccRCC

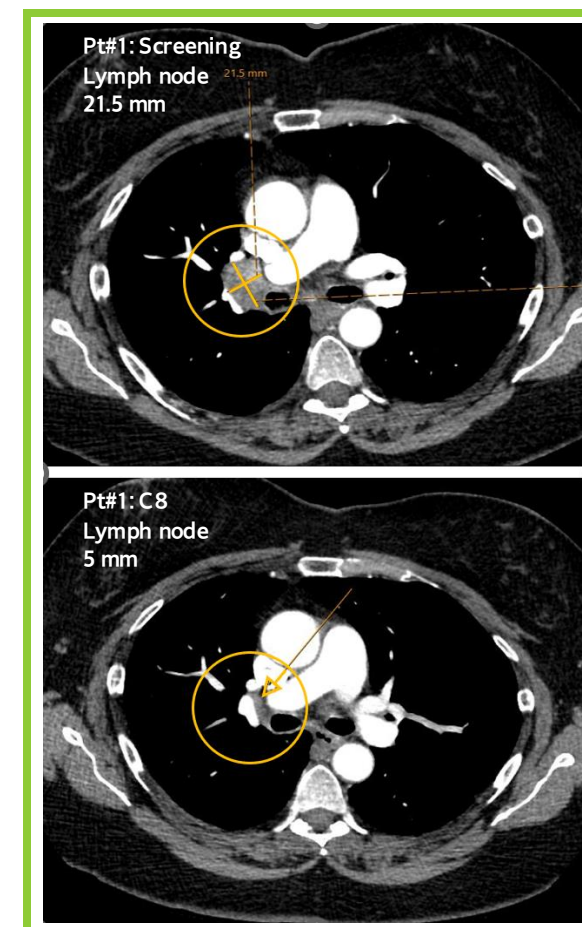
Clinical Responses in Heavily Pre-treated and Anti-PD-1 Resistant Patients



Efficacy	Intent To Treat N=30
ORR	7 (23.3%)
Confirmed PR	6 (20%)
mDoR (Months)	7.7+ (2.5+, 20.9+)
DCR	17 (56.7%)



- IMDC score: intermediate 67%; poor 30%
- Median lines of prior cancer therapy: 2 (range 1 – 9)
 - 29 (97%) received at least 1 prior anti-PD-1 and TKI
 - All had SD or PD as BOR to the last prior anti-PD-1
 - All had PD from the last prior anti-PD-1



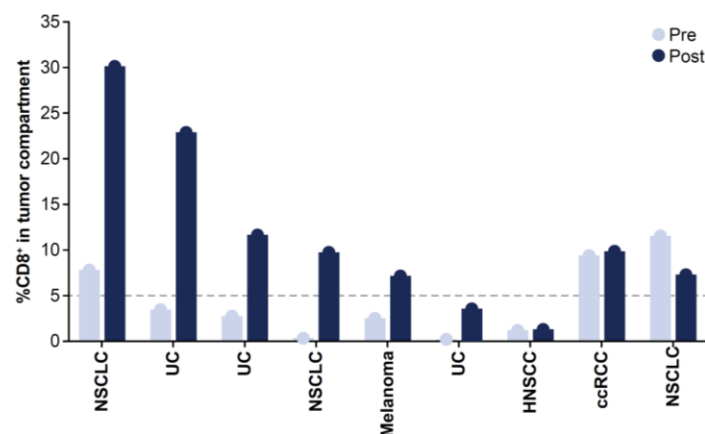
BOR, best overall response; DCR, disease control rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mDoR, median duration of response; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor. Data cut date: Apr 10, 2024

Proof of Mechanism

SRK-181 and Pembrolizumab Treatment Creates a Proinflammatory Microenvironment

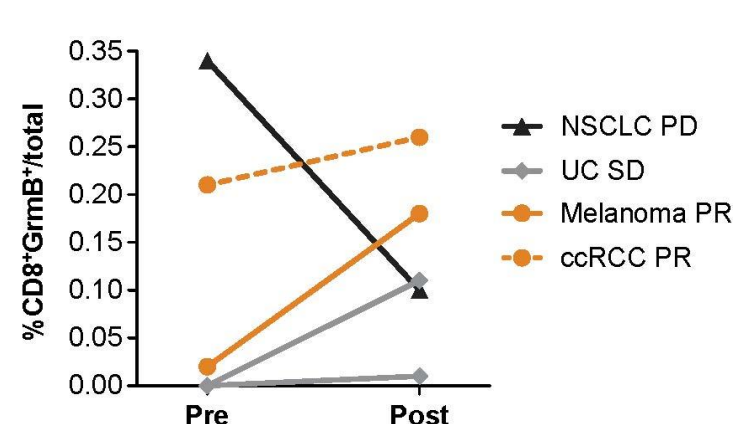
- SRK-181 and pembrolizumab increase CD8+ T-cells infiltration into tumors across multiple tumor types
- CD8+ T-cell were activated (CD8+GrmB+) in responding patients across multiple cohorts
- The number of CD8+GrmB+ cells correlates with tumor shrinkage

SRK-181 and Pembrolizumab Increased CD8+ Infiltration

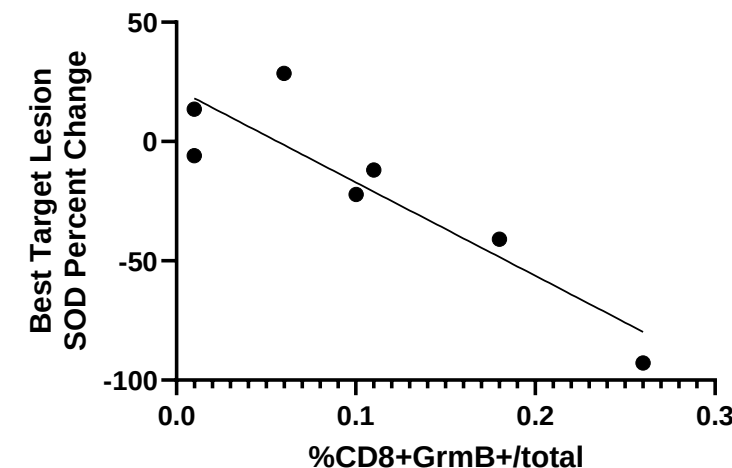


Line indicates cutoff that defines infiltrated status.
Data generated from available paired biopsies that were evaluated using a chromogenic assay.

CD8+ Cytotoxic T-cells were Activated in Responding Patients



Data generated from available paired biopsies that were evaluated using a multiplex fluorescent assay.



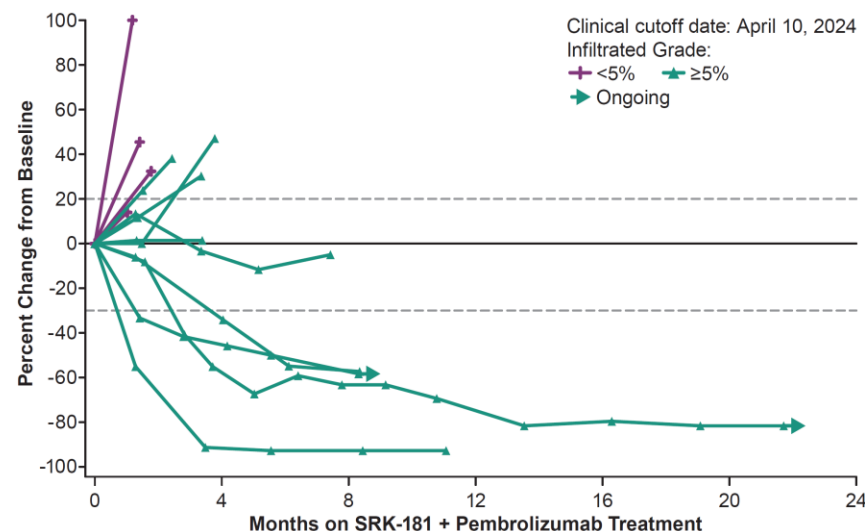
Data generated from available post treatment biopsies that were evaluated using a multiplex fluorescent assay.

ccRCC, clear cell renal cell carcinoma; CD, cluster of differentiation; GrmB, Granzyme B; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; UC, urothelial carcinoma.
Data cut date: Apr 10, 2024

Biomarker Data May Inform Patient Selection Strategy

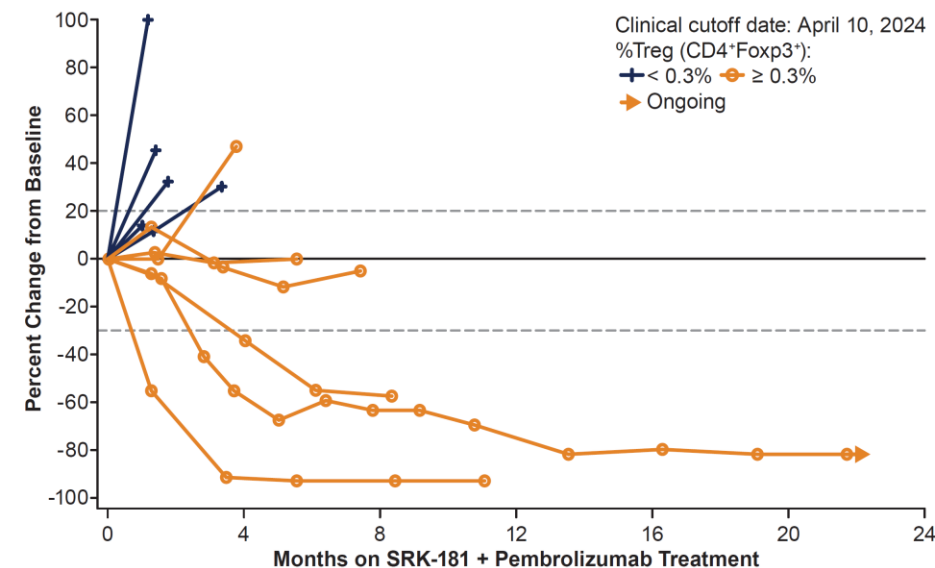
Baseline CD8+ T-cell Infiltration Status and Baseline Treg Levels Suggest a Higher Chance of Clinical Response

Baseline CD8+ Infiltration Status Suggest a Higher Chance of Response in ccRCC Patients



- Baseline data was available from 14 patients and 10 were infiltrated
- If enrollment had been limited to patients who were infiltrated at baseline:
 - ORR is increased from **23.3%** (7/30) to **40%** (4/10)
 - mDoR is improved from **7.7** months to **9.3** months

Elevated Baseline Treg (CD4+Foxp3+) Levels within Tumor Compartment Suggest a Higher Chance of Response in ccRCC Patients



- Baseline data was available from 11 patients and 6 had elevated Treg levels
- If enrollment had been limited to patients with elevated Treg at baseline:
 - ORR is increased from **23.3%** (7/30) to **50%** (3/6)
 - mDoR is improved from **7.7** months to **9.8** months

*1 patient progressed prior to 1st scan, so not represented on spider plot.

ccRCC, clear cell renal cell carcinoma; CD, cluster of differentiation; mDoR, median duration of response; Foxp3, forkhead box p3; ORR, objective response rate; TGFβ1, transforming growth factor beta-1; Treg, T regulatory cells
Data cut date: Apr 10, 2024

SRK-181 Summary

Differentiation

- Monoclonal antibody selectively targeting latent and context-independent binding to TGFβ1
- Novel and highly selective inhibition of TGFβ-1 targeting latent form
- Offers potential to avoid toxicity and dose-limiting challenges of non-selective TGFβ inhibition approaches



Ph1 DRAGON Demonstrated Proof-of-Concept in multiple tumor types

- **Showed objective, durable clinical responses above what is expected from continuing PD-1 alone¹**
- **Biomarker data supports proof-of-mechanism in multiple tumor types**

NEXT STEPS

**Enrollment
completed
December 2023**

**Present ongoing
emerging data at future
medical meetings**

**Conduct an end of Phase 1
meeting with regulatory
authorities to inform next steps**

PD-1=Programmed cell death ligand 1; TGFβ=Transforming growth factor-beta; ccRCC=Clear cell renal cell carcinoma.

1.Sumanta Kumar Pal et al. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. The Lancet, Volume 402, Issue 10397, 2023, Pages 185-195, [https://doi.org/10.1016/S0140-6736\(23\)00922-4](https://doi.org/10.1016/S0140-6736(23)00922-4)

PD-1/PD-L1)



Fibrosis

TGF β 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 Meng¹, David J. Nikolic-Paterson² and Hui Yao Lan³

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 McGaraghty,* Rachel A. Davis-Taber,[†] Chang Z. Zhu,* Todd B. Cole,* Arthur L. Nikkel,* Meha Chhaya,[†] Kelly J. Doyle,* Lauren M. Olson,* Gregory M. Preston,[†] Christine 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 Budi¹, Johanna R Schaub¹, Martin Decaris¹, Scott Turner¹, Rik Derynck²

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

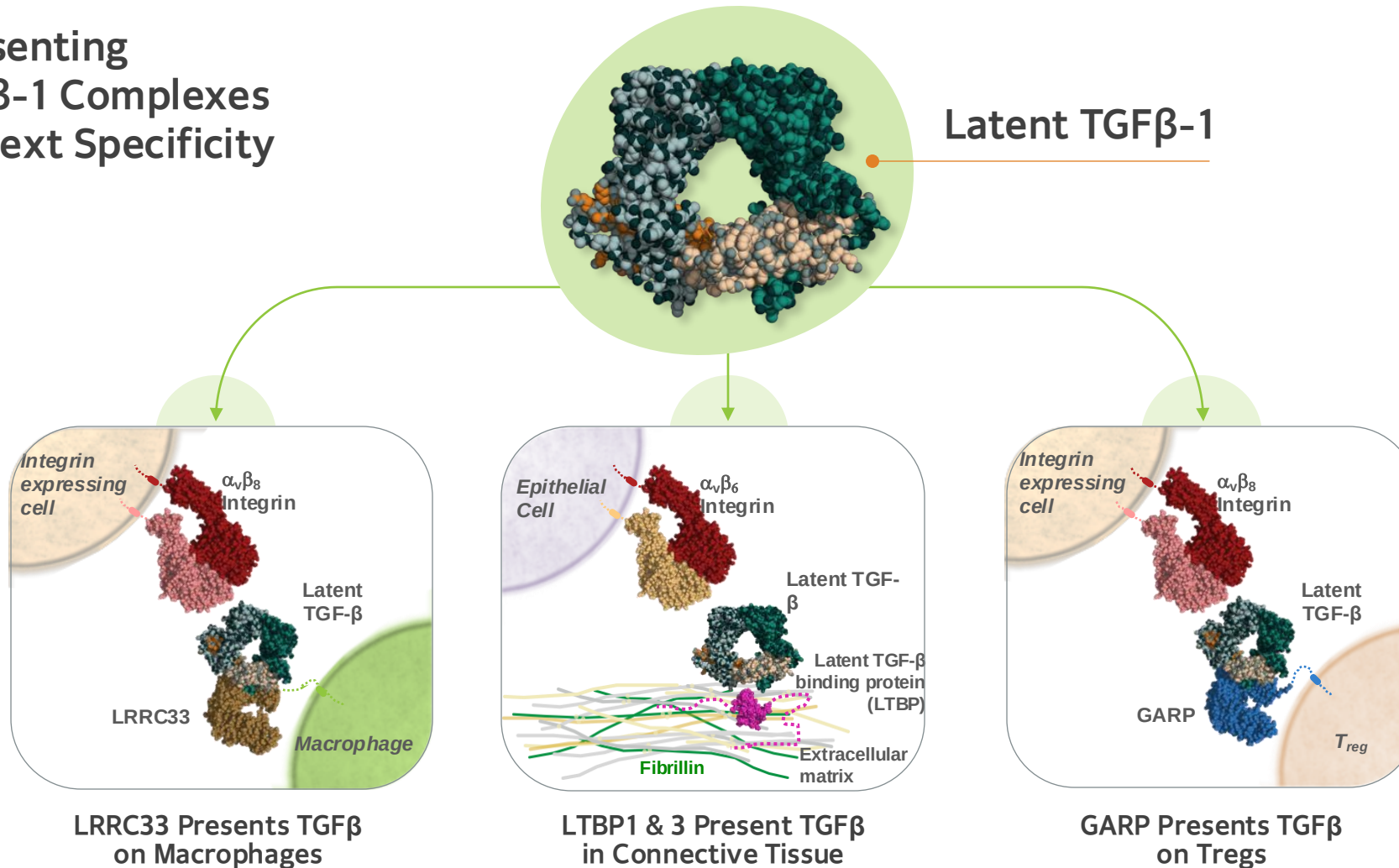
PNAS

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[‡]

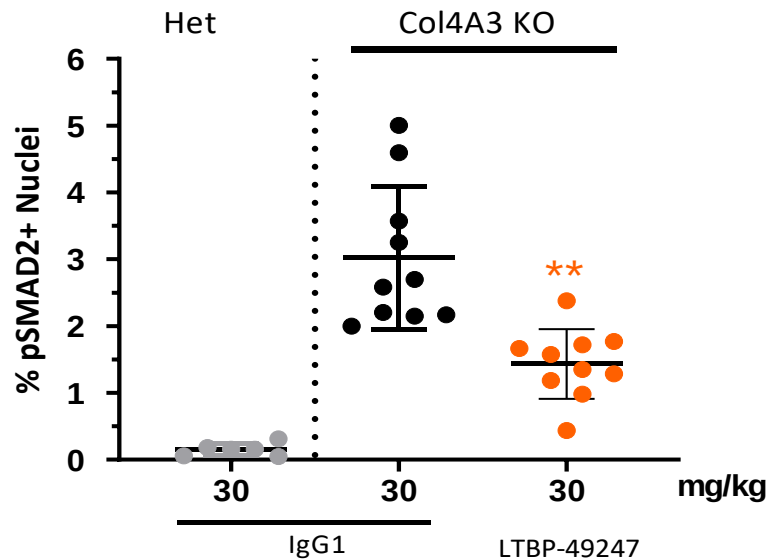
Targeting Latent TGF β -1 Complexes Creates Multiple “Handles” For Selectivity

Targeting Presenting Molecule/TGF β -1 Complexes Provides Context Specificity



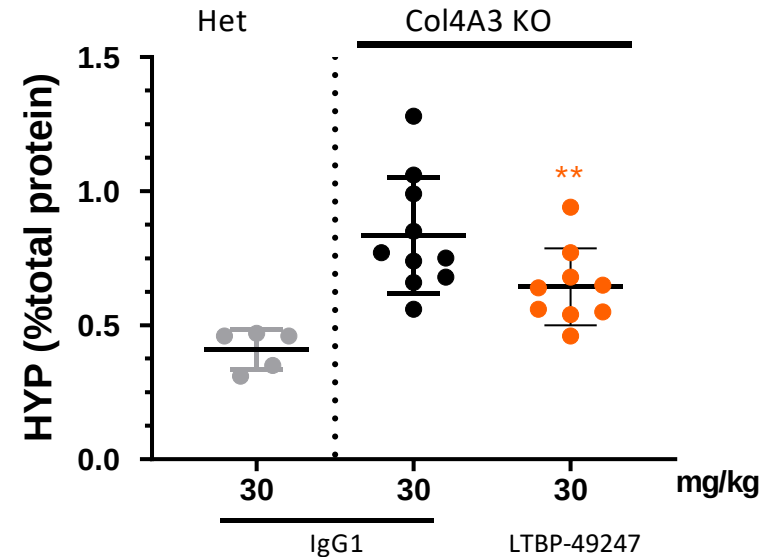
LTBP-49247 Reduced TGF β Signaling and Fibrosis in Preclinical Models of Kidney Fibrosis

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



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

LTBP-49247 reduced fibrosis in kidneys of Alport model

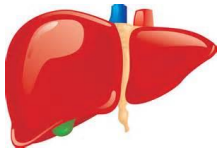


- Efficacy also seen in rat model of kidney fibrosis
- No observed toxicity in mouse 13-week non-GLP repeat dose study
- Favorable PK in cynomolgus monkeys ($t_{1/2}$ ~28 days) suggests LTBP-49247 is amenable to clinical subcutaneous dosing with promising developability profile

Significant Opportunities to Address High Unmet Need Across Multiple Fibrotic Indications



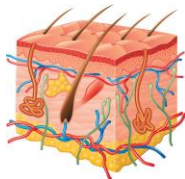
Alport Syndrome (AS)
Focal Segmental Glomerulosclerosis (FSGS)
IgA Nephropathy (IgAN)



Primary Sclerosing Cholangitis (PSC)



Idiopathic Pulmonary Fibrosis (IPF)



Diffuse Cutaneous Systemic Sclerosis (dcSSc)

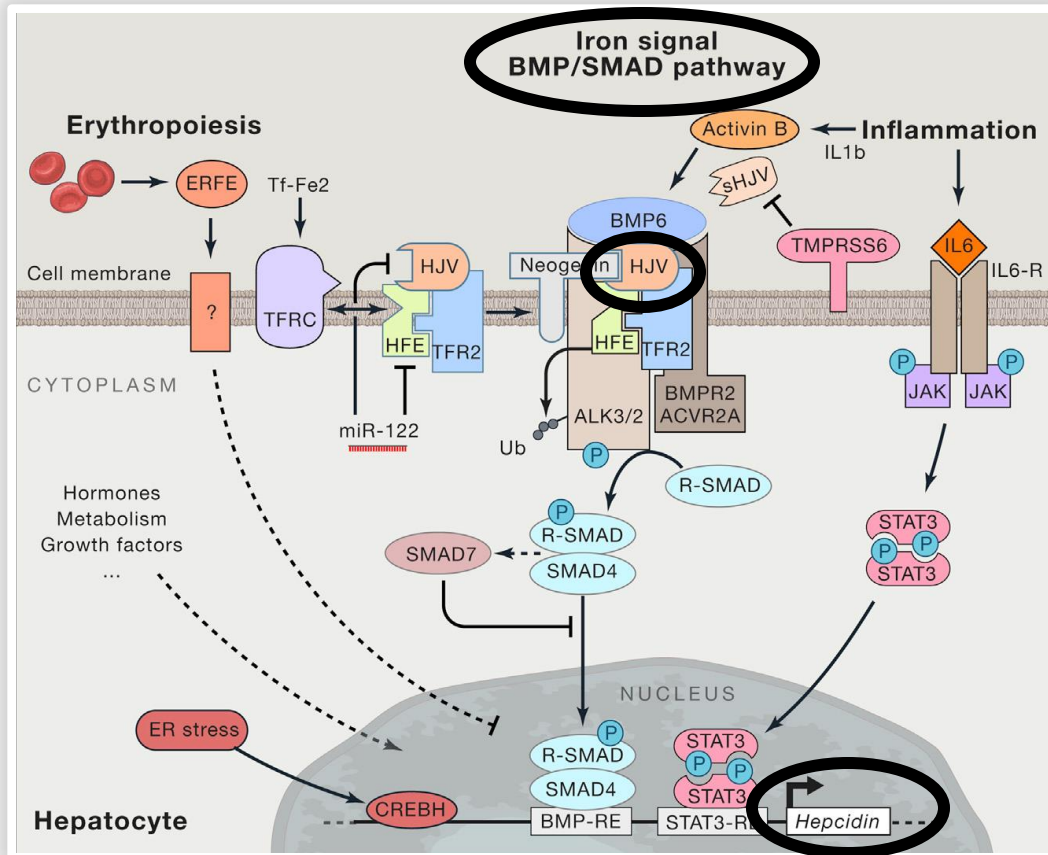
Collectively, significant commercial potential given large patient population with clear high unmet need given poor outcomes and lack of effective therapeutics

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



Iron-Restricted Anemia

BMP6/RGMc Pathway is a Well Validated Regulator of Systemic Iron Homeostasis



HJV/RGMc is a key player in the regulation of hepcidin expression

- Human mutations in HJV/RGMc establish it as a central player in hepcidin regulation¹
- Knockout phenotypes and tissue-specific expression pattern demonstrate that its predominant role is in iron homeostasis²
- Member of repulsive guidance molecule (RGM) family (RGMa, RGMb, RGMc/HJV) that act as BMP co-receptors to modulate BMP signaling³

Anemia of Inflammation/ Chronic Disease

- Elevation of proinflammatory cytokines drives increased hepcidin expression and results in anemia due to functional iron deficiency⁴

Untreated

↑ Hepcidin

↓ Serum iron

Ab treated

↓ Hepcidin

↑ Serum iron

Fig: Muckenthaler, M.U., Rivella, S., Hentze, M.W. and Galy, B. (2017) A Red Carpet for Iron Metabolism. *Cell*, 168(3): 344-361

1: Kuns-Hashimoto R, et al. (2008) Selective binding of RGMc/hemojuvelin, a key protein in systemic iron metabolism, to BMP-2 and neogenin. *Am J Physiol Cell Physiol* 294(4):C994-C1003

2: Constante M, et al. (2007) Repression of repulsive guidance molecule C during inflammation is independent of Hfe and involves tumor necrosis factor- α . *Am J Pathol* 170(2):497-504

3: Core A.B., et al. (2014) Hemojuvelin and bone morphogenetic protein (BMP) signaling in iron homeostasis. *Front Pharmacol*. 5:104.

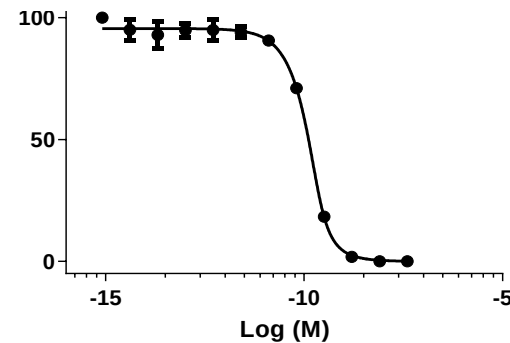
4. Wang CY and Babitt JL. (2016) Hepcidin Regulation in the Anemia of Inflammation. *Curr Opin Hematol* 23(3): 189-197.

HJV-35202: An Investigational High-Affinity Antibody Demonstrating Selective Inhibition of HJV/RGMC and Robust PK/PD in Cynos

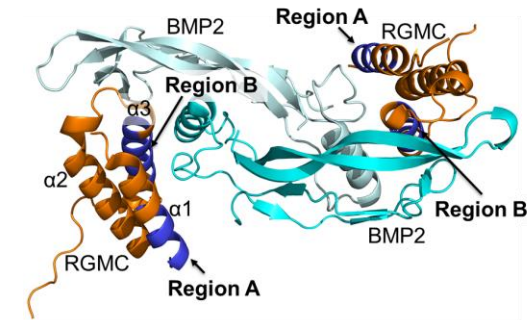
Key Attributes of HJV-35202:^{1,2}

- High-affinity antibody
- Specific to RGMC, with mechanism of specificity understood
- Cross-reactive to human, mouse, rat and cyno
- Sustained PD observed in healthy rats and cynos, with clear PK/PD relationship
- Highly manufacturable framework with no sequence liabilities
- Formulatable into a subcutaneous format (150 mg/mL)

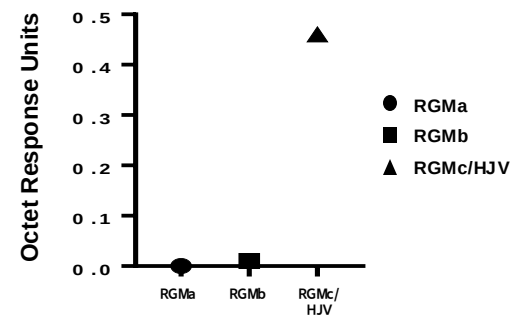
Potent in vitro binding affinity
($K_D=3.9E-11$)



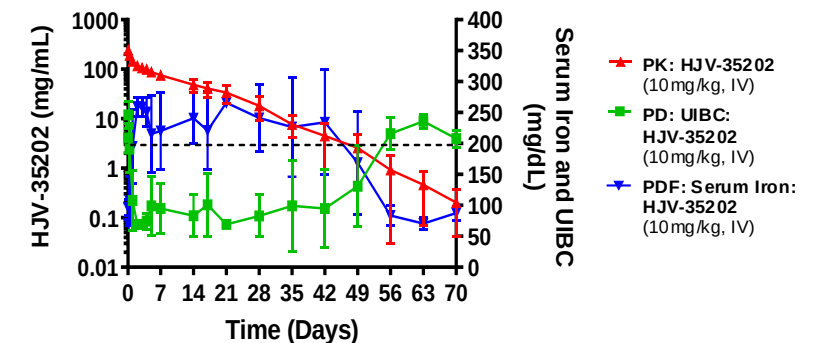
Highly specific to RGMC/HJV with well understood mechanism



Specific to RGMC over other RGM family members



Sustained PD effect in single dose Cyno study



1. Nicholls S.B., et al. Poster: RGMC-selective antibodies modulate iron homeostasis in vivo, *12th International BMP Conference, Tokyo, October 2018*
 2. Scholar Rock, Data on File

Significant Opportunities to Target Iron-Restricted Anemias Across Multiple Indications



Chronic Kidney Disease (CKD)



Anemia of Chronic Inflammation (AI)



Myelofibrosis (MF)

Targeting RGMc/HJV for anemia is well validated and relatively de-risked

- High levels of hepcidin, the main regulator of systemic iron metabolism, are associated with anemia across various diseases

Safe and convenient RGMc inhibitor has promise of improving patient outcomes across multiple indications as stand alone or in combination with SoC

- Significant and clear unmet need given lack of approved treatments or severe limitations of current treatments
- Well defined patient population

Collectively, sizeable commercial opportunity given relatively large population

- Potential for rapid POC with clear regulatory path
- Opportunity to build an anemia franchise with initial POC and indication expansion in the future

Key Accomplishments and 2024 Strategic Priorities

2023

ACCOMPLISHMENTS

- ✓ COMPLETED
SAPPHIRE enrollment
- ✓ EXPANDED
antimyostatin program
into cardiometabolic
disorders
- ✓ SUCCESSFUL
\$98M public offering,
extending projected
runway into second half
of 2025

Building on
this success,
in 2024 >>
we are
focused on



SAPPHIRE
Readout in Q4



Prepare for
commercialization



Initiate Ph 2 POC
trial with
apitegromab in
obesity



Advance
IND-enabling studies
for SRK-439