Deep Insights Advancing Impactful Medicines

Company Overview | January 2025

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 apitegromab, SRK-439, linavonkibart 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 3 trial of apitegromab or Part A or Part B of the Phase 1 trial of linavonkibart, 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; 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, including from the EMBRAZE clinical trial; 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; its ability to establish or maintain strategic business alliances; its ability to receive priority or expedited regulatory review or to obtain regulatory approval of apitegromab; its ability to expand globally and the anticipated commercial launch in the United States of apitegromab in the fourth quarter of 2025; 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 September 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, linavonkibart, SRK-256, SRK-373, 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, linavonkibart, SRK-256, SRK-373, and SRK-439 have not been established.

ScholarRock

ScholarRock™

Industry-leading technology, life-changing potential

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

TODAY'S FOCUS

Scholar Rock is Moving with a Sense of Urgency

To Bring Transformative Medicines to Patients

1 COMMERCIALIZE

Execute a Successful Commercial Launch*

Building off **successful Phase 3 SAPPHIRE results**

BLA and MAA 1Q 2025 submission on track

$2B+ Opportunity in **SMA**

2 EXPAND

Apitegromab Development Program: Building a Pipeline in a Product

Initiate earlier treatment with OPAL study for patients under 2 years of age with SMA

Pursuing opportunities for apitegromab in additional rare neuromuscular diseases

3 ADVANCE

Anti-myostatin Program into Cardiometabolic Indications

2Q 2025 EMBRAZE Phase 2 study results expected

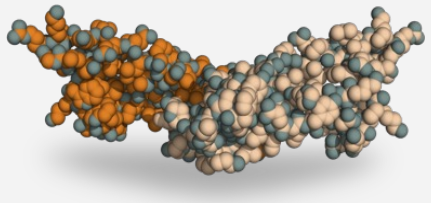
IND submission on track for 3Q 2025 for **SRK-439**, a highly innovative myostatin inhibitor

*Pending regulatory approval.

Scholar Rock Has Succeeded Where Others Have Failed

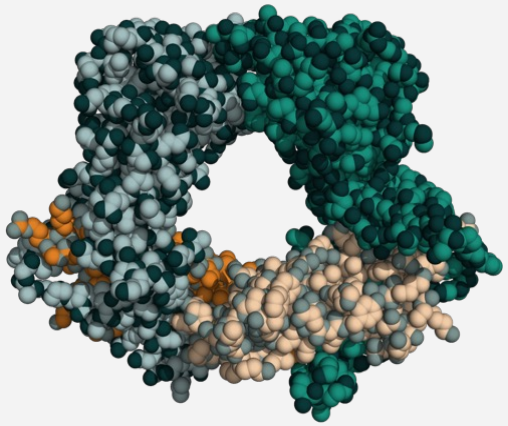
Selectivity Drives Success

Traditional Target
"Mature" Active Growth Factor



Challenging to target because of high homology across super-family

Scholar Rock's Target
Latent Growth Factor



Targeting the 'cage' before growth factor is released allows for exquisite selectivity

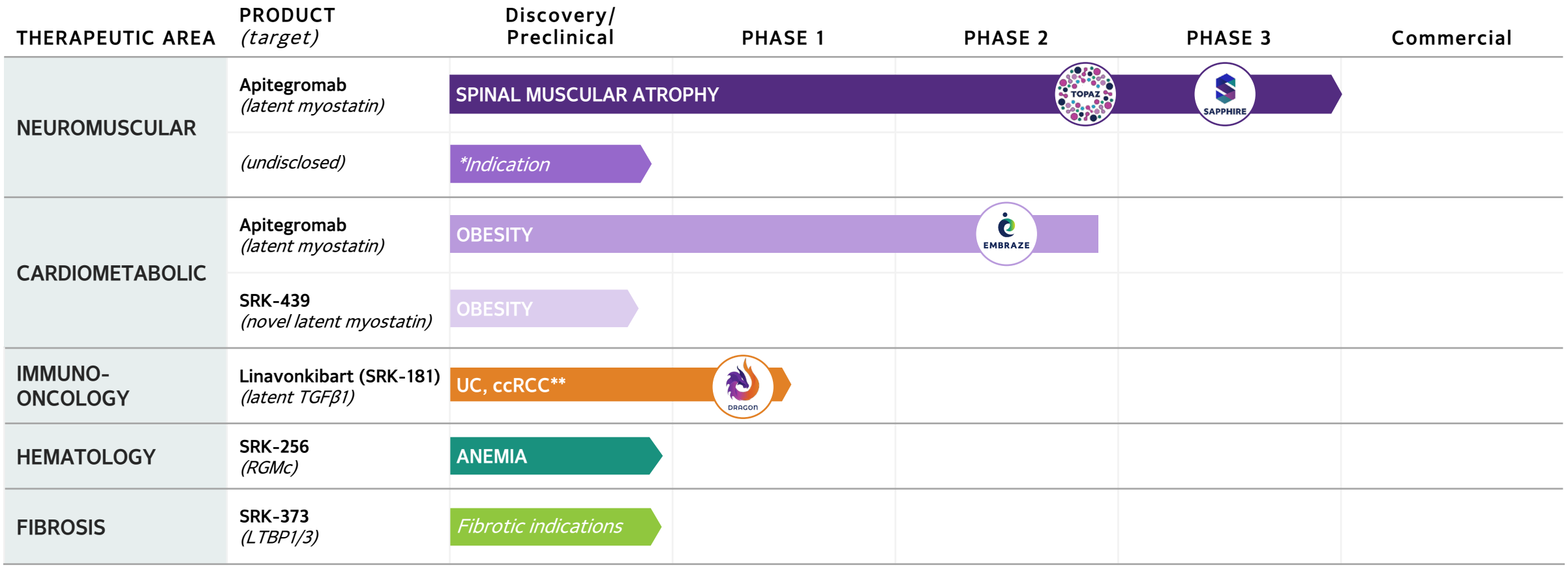
RIGHT TARGET → Validated Biology

RIGHT TIME → Latent Form

Growing Pipeline Across High Value Therapeutic Areas

Industry-leading Anti-myostatin Programs

Our Differentiated Approach: Target Latent Growth Factor



*undisclosed indication
**UC=urothelial cell carcinoma; RCC=renal cell carcinoma.

2025 Milestones: A Transformative Year for Scholar Rock

1 COMMERCIALIZE
Apitegromab in SMA

- Submit FDA and EMA applications in 1Q 2025
- US launch expected in 4Q 2025 and EU launch to follow*

2 EXPAND
Apitegromab Development Program: Building a Pipeline in a Product

- SMA: Under 2 study initiation planned for mid-2025
- Exploring additional neuromuscular indications

3 ADVANCE
Anti-myostatin Program into Cardiometabolic Indications

- Obesity: EMBRAZE readout expected in 2Q 2025
- SRK-439 IND filing planned for 3Q 2025

* Pending regulatory approval.
Apitegromab is an investigational drug candidate under evaluation and has not been approved by any regulatory agency.

Delivering on the Mission of Bringing Transformative Medicines to Patients

Leveraging R&D success to build a multi-billion dollar biopharmaceutical company

INNOVATE

- ✓ Developed platform based on selective targeting of latent growth factors
- ✓ Advanced industry-leading antibody design & protein engineering

DEVELOP

- ✓ Successfully executed positive Phase 3 trial in SMA

COMMERCIALIZE

- ☐ Successful commercial launch*
- ☐ Setting the stage for a multi-billion dollar opportunity

EXPAND

- ☐ Expanding neuromuscular franchise
- ☐ Advancing anti-myostatin program in obesity
- ☐ Advancing the pipeline

* Pending approval from regulatory agencies.
Apitegromab is an investigational drug candidate under evaluation and has not been approved by any regulatory agency.

Transforming the Treatment of Spinal Muscular Atrophy with Muscle-Targeted Therapy

Apitegromab

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

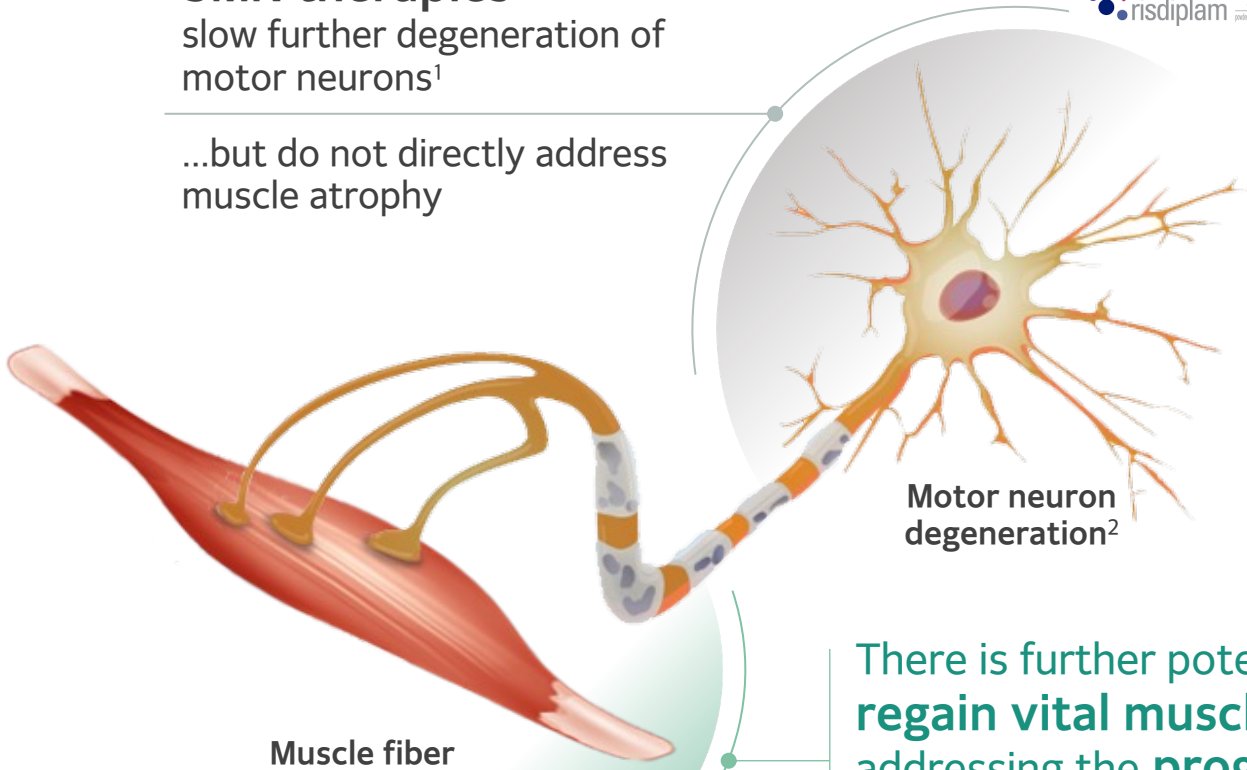
SMN therapies
slow further degeneration of motor neurons[1]

...but do not directly address muscle atrophy

Evrysdi risdiplam

SPINRAZA (nusinersen) injection 12 mg/5 mL

zolgensma (onasemnogene abeparvovec-xioi) suspension for intravenous infusion



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.

ScholarRock

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 60 mg powder for oral solution

> 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

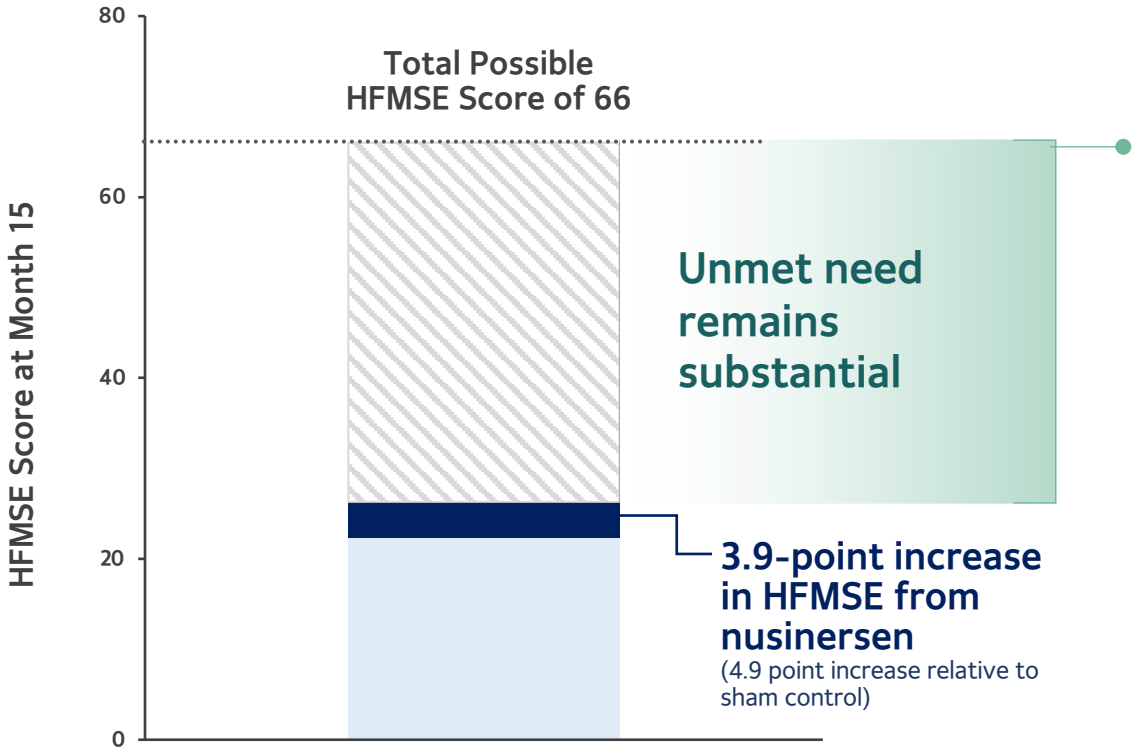
~$1.2 billion
in revenues (LTM)[5]

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.

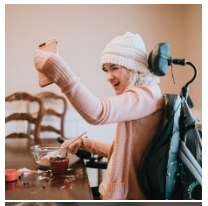
1. Cure SMA 2022 Report: 9042022_State-of-SMA_vweb.pdf (curesma.org)
2. Lally et al. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet J Rare Dis. 2017 Nov 28;12(1):175. doi: 10.1186/s13023-017-0724-z.
3. Revenue as of Biogen 3Q23 financial 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. 2022 Community Update Survey, Cure SMA.

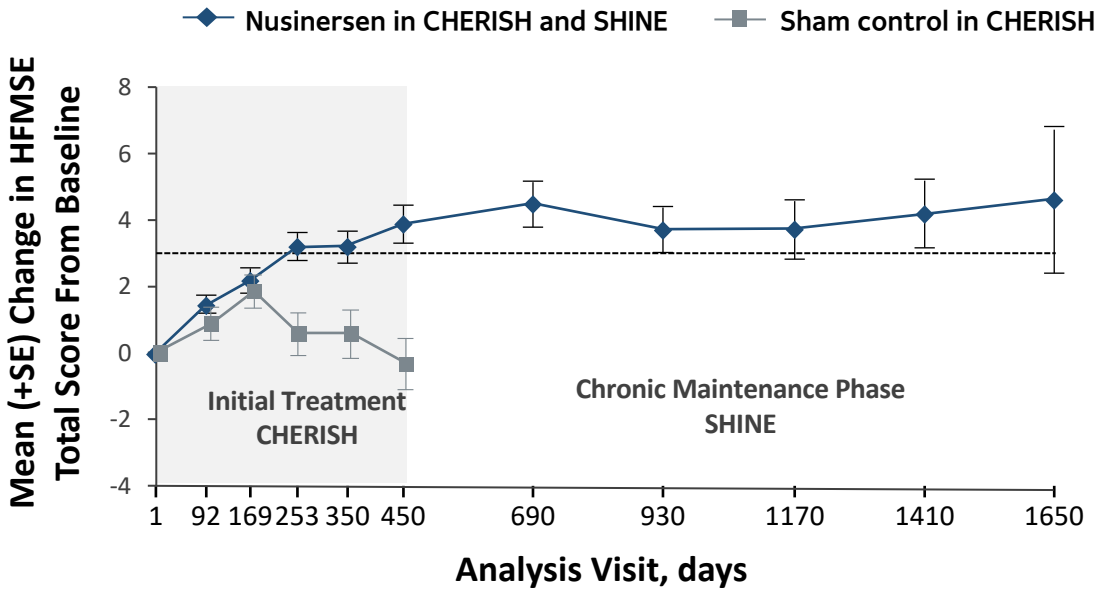
This third-party information is provided for background only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results.

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]

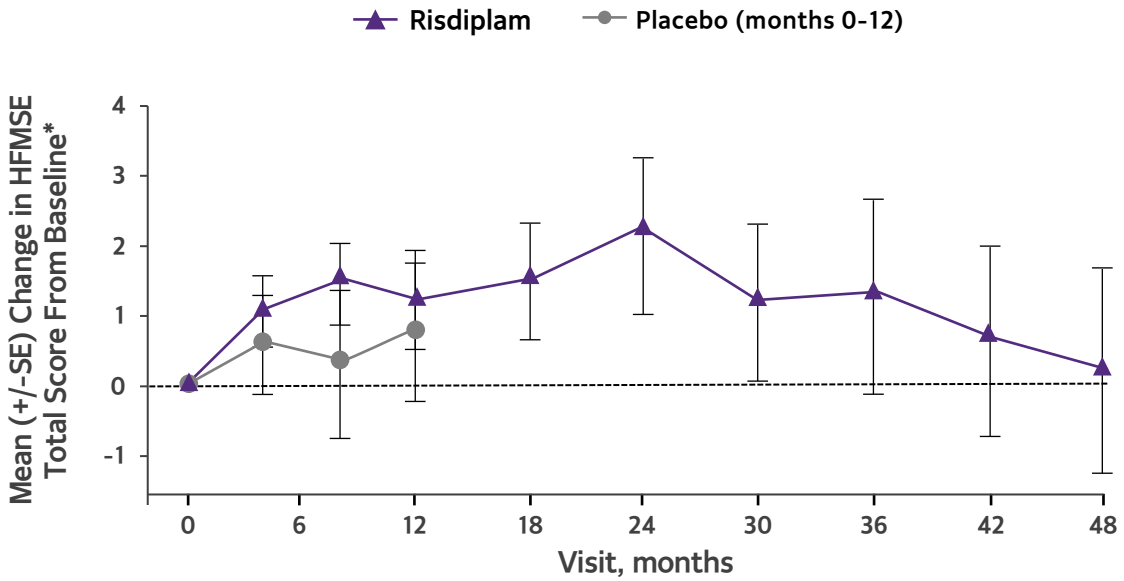
Overall population age 2-12



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						

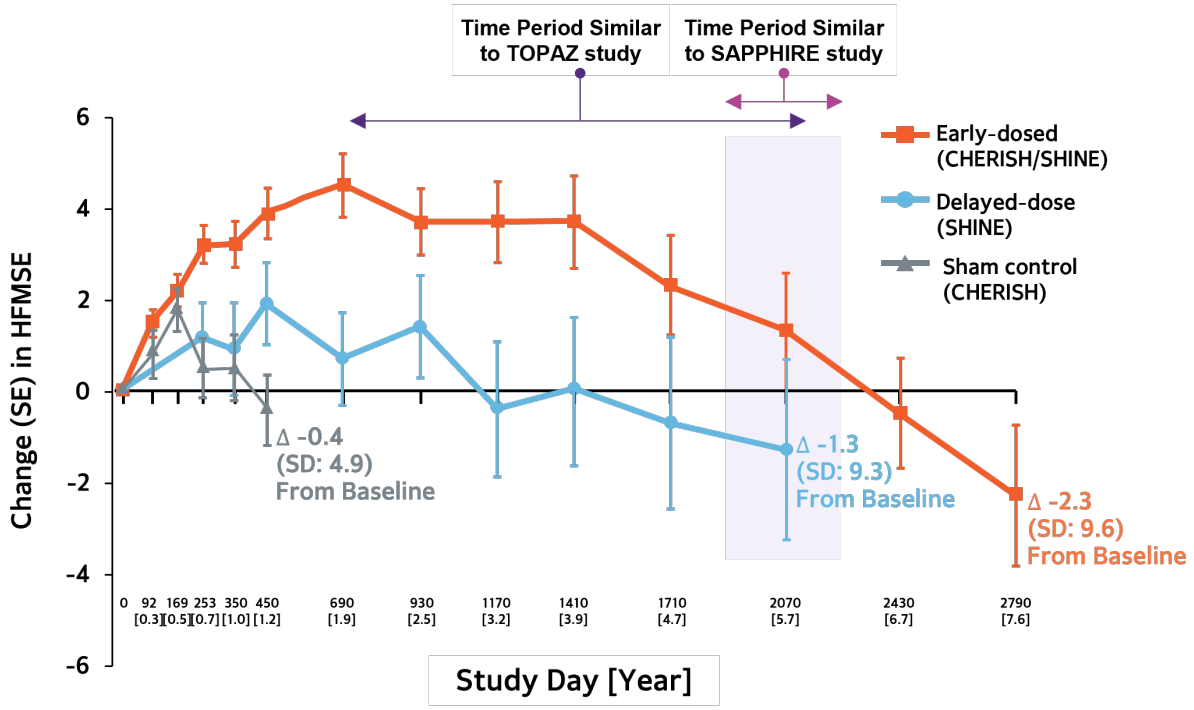
1. Mercuri E, et al. Presented at: World Muscle Society Congress 2020, P. 257
2. Oskoui M, et al. Presented at: 2021 Muscular Dystrophy Association Clinical & Scientific Conference; March 15-18, 2021. Poster 80.

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.

Apitegromab: Potential to Transform the Standard of Care in SMA

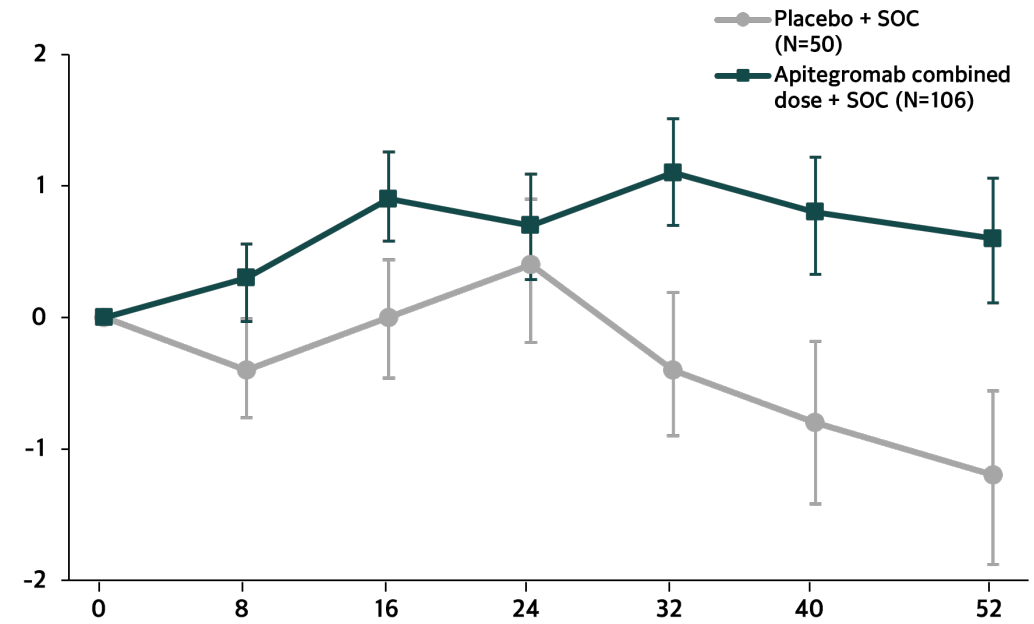
Motor Function Over Time of Patients Treated with Nusinersen



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

	0	92 [0.3]	169 [0.5]	253 [0.7]	350 [1.0]	450 [1.2]	690 [1.9]	930 [2.5]	1170 [3.2]	1410 [3.9]	1710 [4.7]	2070 [5.7]	2430 [6.7]	2790 [7.6]

Motor Function Over Time of Patients in SAPPHIRE



		0	8	16	24	32	40	52
Placebo + SOC	n=	50	50	50	48	50	49	48
Apitegromab + SOC	n=	106	105	105	101	102	102	102

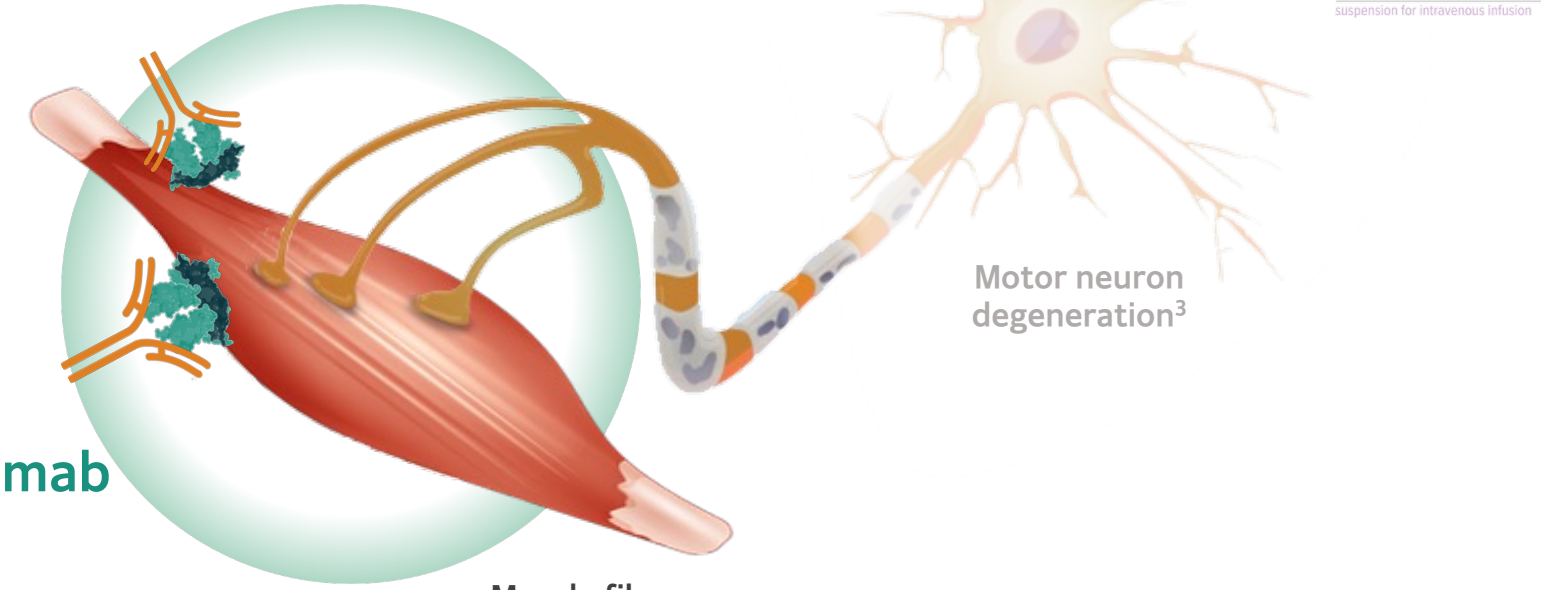
KEY TAKEAWAYS

- Despite effective SMN-targeted therapy, long-term trajectory of SMA patients remains that of progressive decline in motor function
- Treatment with apitegromab has improved motor function vs. placebo

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

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.

$2B+ Global Opportunity for Apitegromab in SMA

~$4.5B[1]

Global revenue for three SMN-targeted therapies

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Evrysdi® risdiplam 60 mg powder/solution

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

1st

And only muscle-targeted treatment to show clinical benefit in SMA

Apitegromab global revenue potential

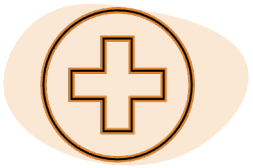
$2B+[2]

SMA patients are diagnosed, treated, and still need more to continue to improve their lives

[1] Revenue as of Biogen 4Q23 financial update, Roche 4Q23 financial update, and Novartis 4Q23 financial update.
[2] Scholar Rock internal estimates as of December 2024.
SMA=Spinal muscular atrophy; SMN=Survival motor neuron.

SMA is a Defined Market and Optimal For Apitegromab Launch

Patients are diagnosed and treated, but still need more



1. Patients Identified and Treated

~25K patients in US and EU

100% US newborn screening

2/3 of US patients on treatment

2. Clear Unmet Need

Patient, HCP, and payers recognize remaining need to improve function

3. Engaged Patient Community

Organized community aligned on need for muscle targeted therapy

4. Payer Receptivity

Established value for improving function

The SMA community is calling for new treatments to improve function

Preparing for a Successful Launch

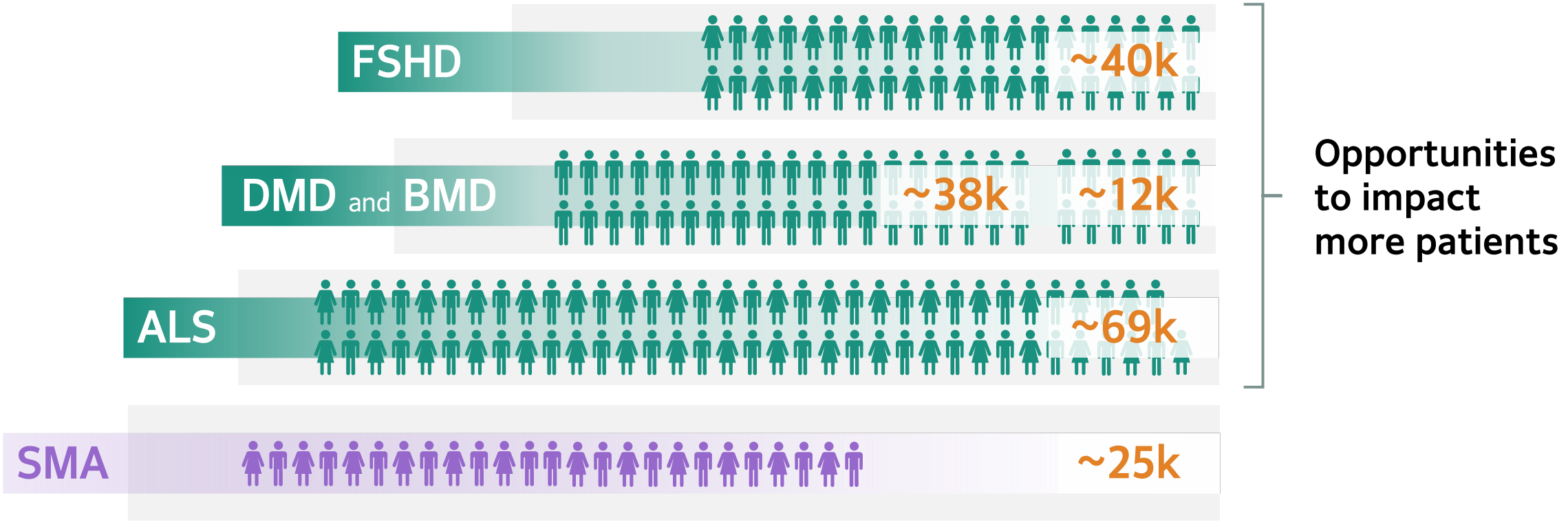
Delivering Apitegromab

- Commercial launch supply secured
- Rare disease distribution partners selected
- Home infusion at launch

Customer Engagement

- Account team with average 30 years experience engaging with US commercial and federal payers
- Efficient US customer-facing footprint of ~50 FTEs planned
- Establishing European presence

SMA is Only the Beginning: Creating Possibilities with Apitegromab in Additional Neuromuscular Diseases



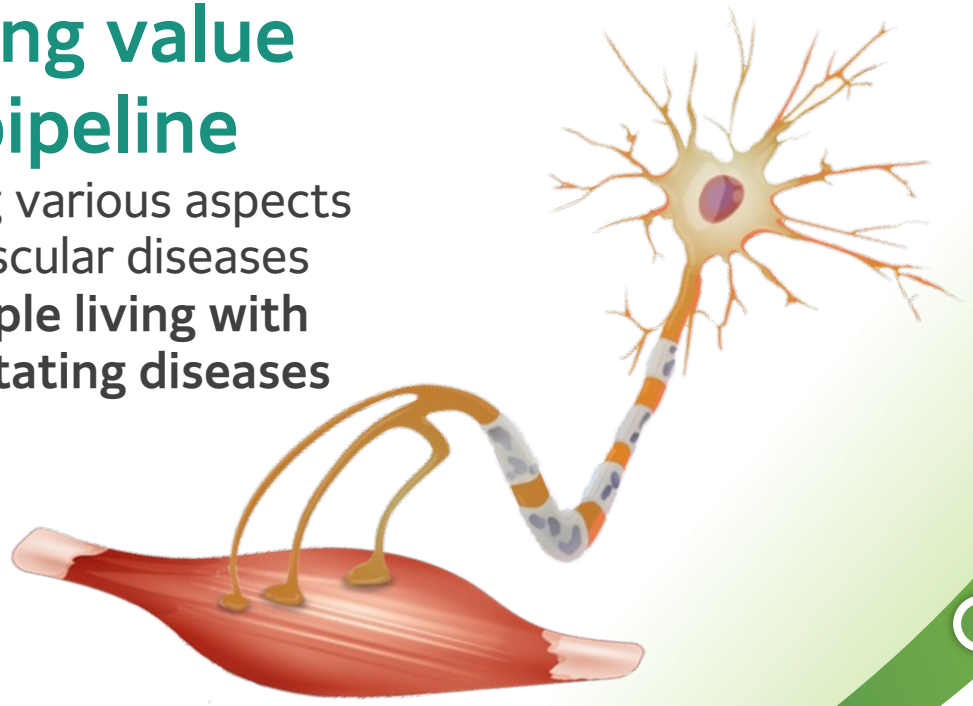
Building a neuromuscular franchise is a key driver towards future growth

*Numbers represent prevalence in the US and Europe based on internal market research.
SM=Spinal Muscular Atrophy; ALS=Amyotrophic Lateral Sclerosis; DMD=Duchenne Muscular Dystrophy; BMD=Becker's Muscular Dystrophy; FSHD=Facioscapulohumeral muscular dystrophy.

Apitegromab is the Foundation of a Future Multi-Billion Dollar Neuromuscular Franchise*

Unlocking value in our pipeline

by targeting various aspects of neuromuscular diseases **to help people living with rare, devastating diseases**



Neuromuscular expansion of apitegromab into additional indications

SMA expansion with Ph 2 OPAL trial for patients under 2 and subcutaneous formulation

Global expansion, starting with Europe

Commercial Launch*

*Subject to regulatory approval.

SAPPHIRE

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

ScholarRock™

The Only Muscle-Targeted Therapy with Clinical Success in SMA

Positive Phase 3 Trial Using Gold Standard SMA Scale

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

CONSISTENT
clinically meaningful benefit observed 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

SUCCESSFUL PIVOTAL TRIAL
On Track to Submit BLA and MAA in 1Q 2025

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

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

SCREENING

MAIN POPULATION (n=156)

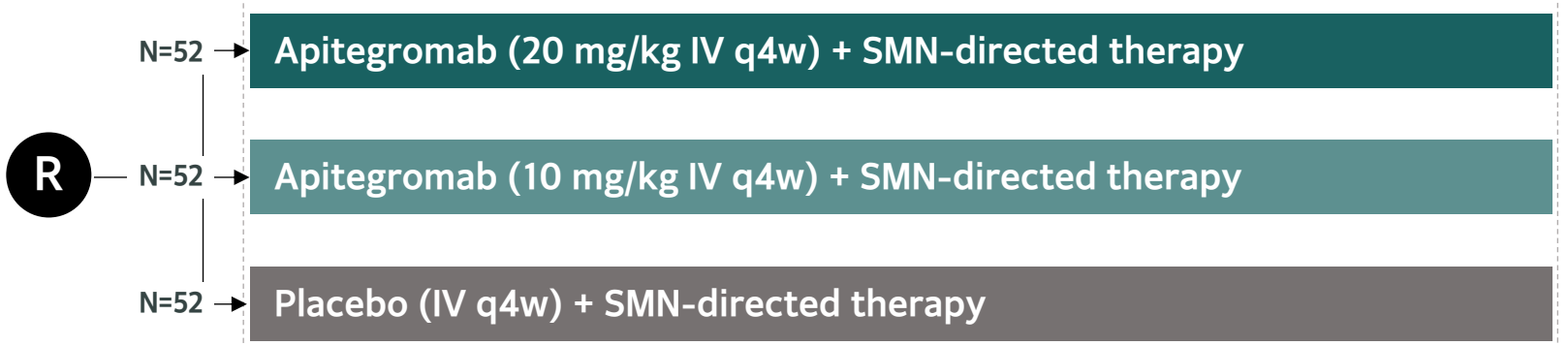
Ages 2-12

With nonambulatory Types 2 and 3 SMA

Stratified to ensure balanced allocation across the three arms:

1. Age at SMN therapy initiation (age < 5 vs. age ≥ 5)
2. SMN therapy (nusinersen vs. risdiplam)

TREATMENT (52 weeks)



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

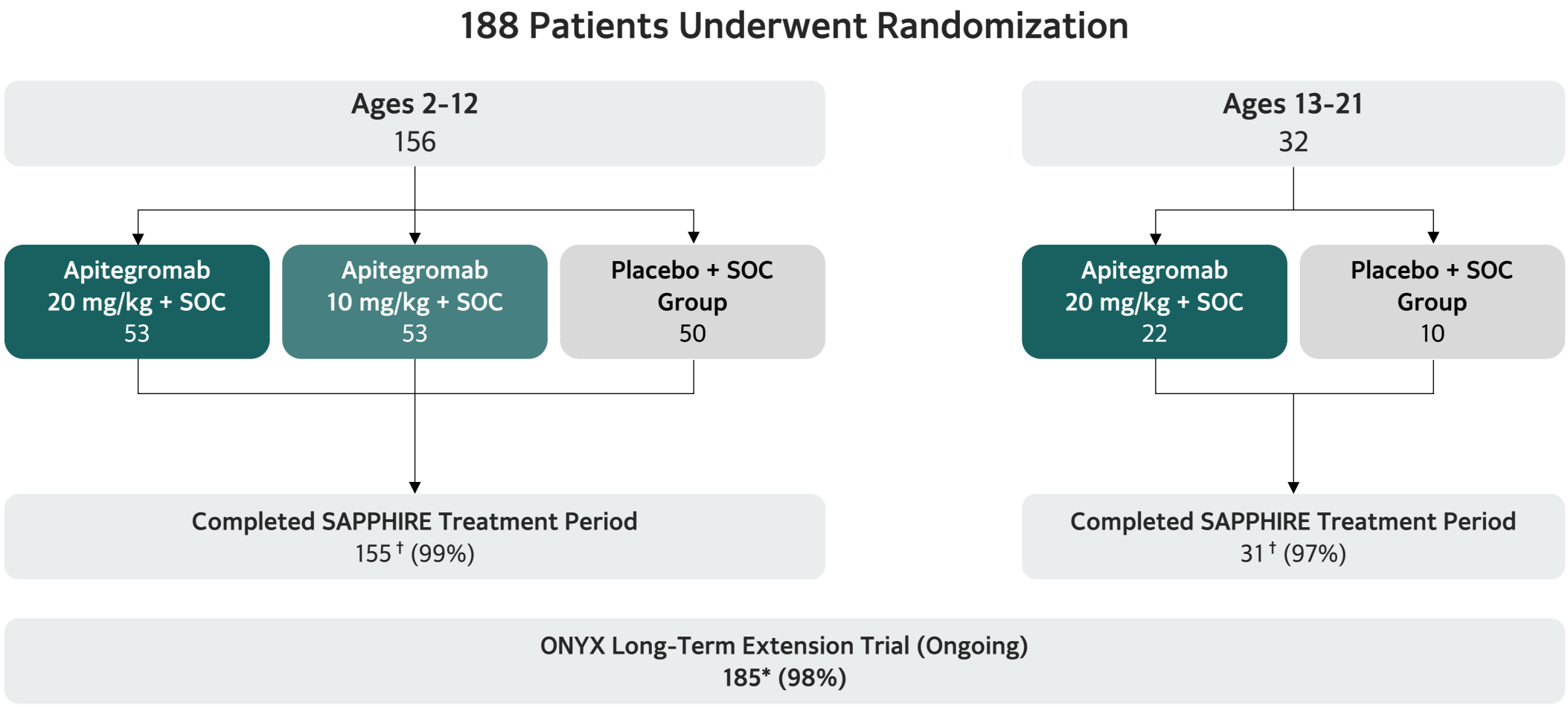
Exploratory population (age 13-21), in patients using SMN therapy
Focused upon safety & exploratory efficacy (n=48; 2:1 randomization between apitegromab 20 mg/kg vs placebo)

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.

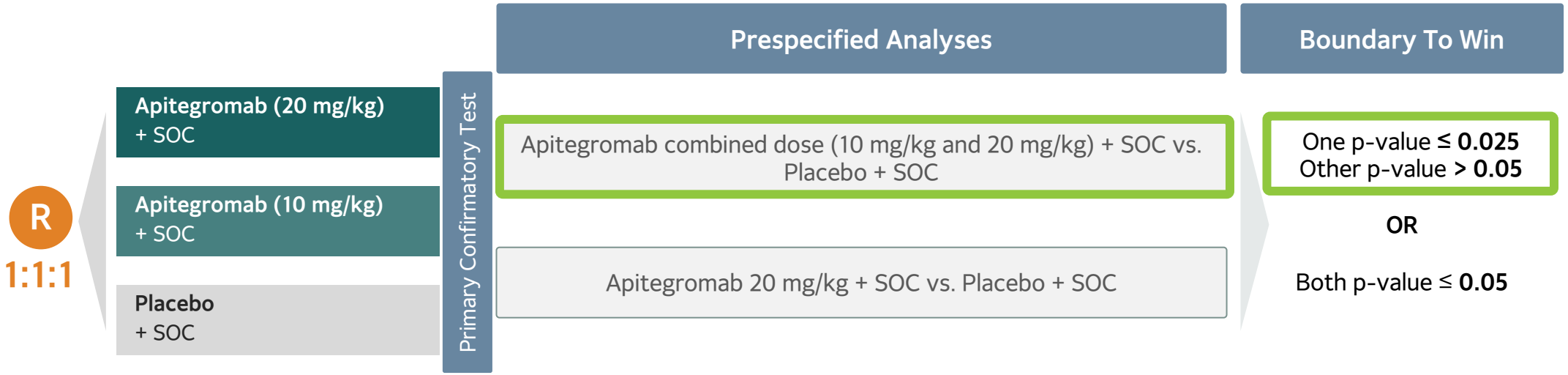
ScholarRock

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

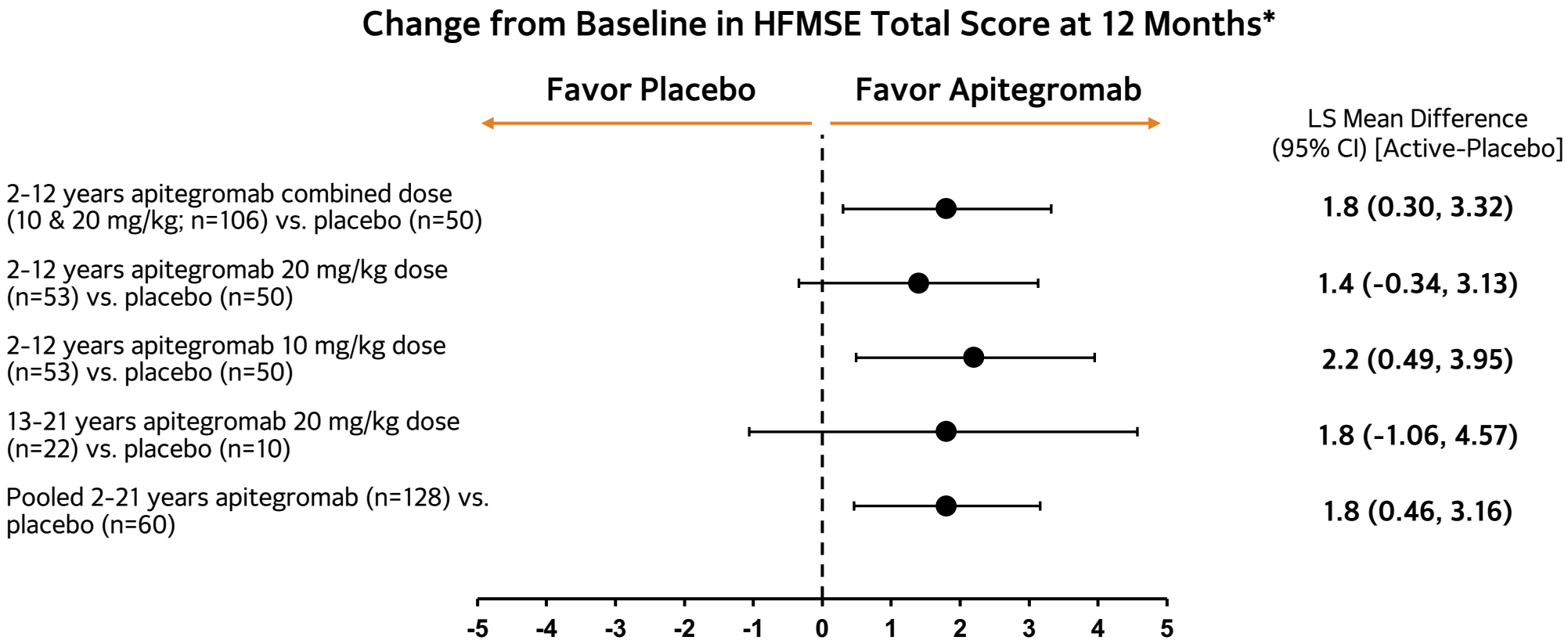
Analysis	n	Results (vs Placebo, n=50)	Unadjusted *P*-value	
Apitegromab 10+20 mg/kg combined	106	**1.8**	**0.0192***	✓
Apitegromab 20 mg/kg	53	1.4	0.1149*	
Apitegromab 10 mg/kg	53	2.2	0.0121**	

Primary Analysis

Achieved Statistical Significance

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

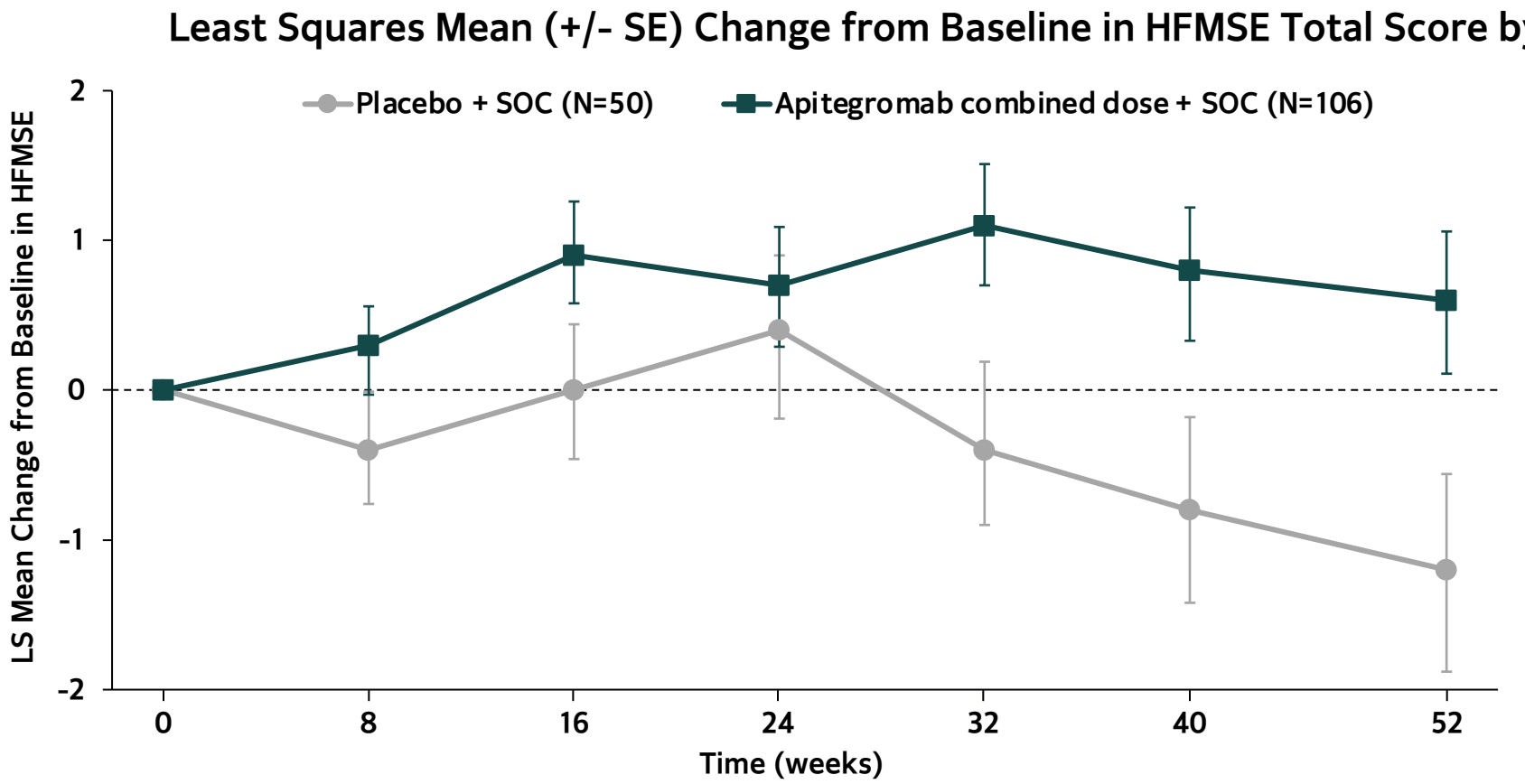
Improvement in HFMSE Consistent Across Doses and Age Groups



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

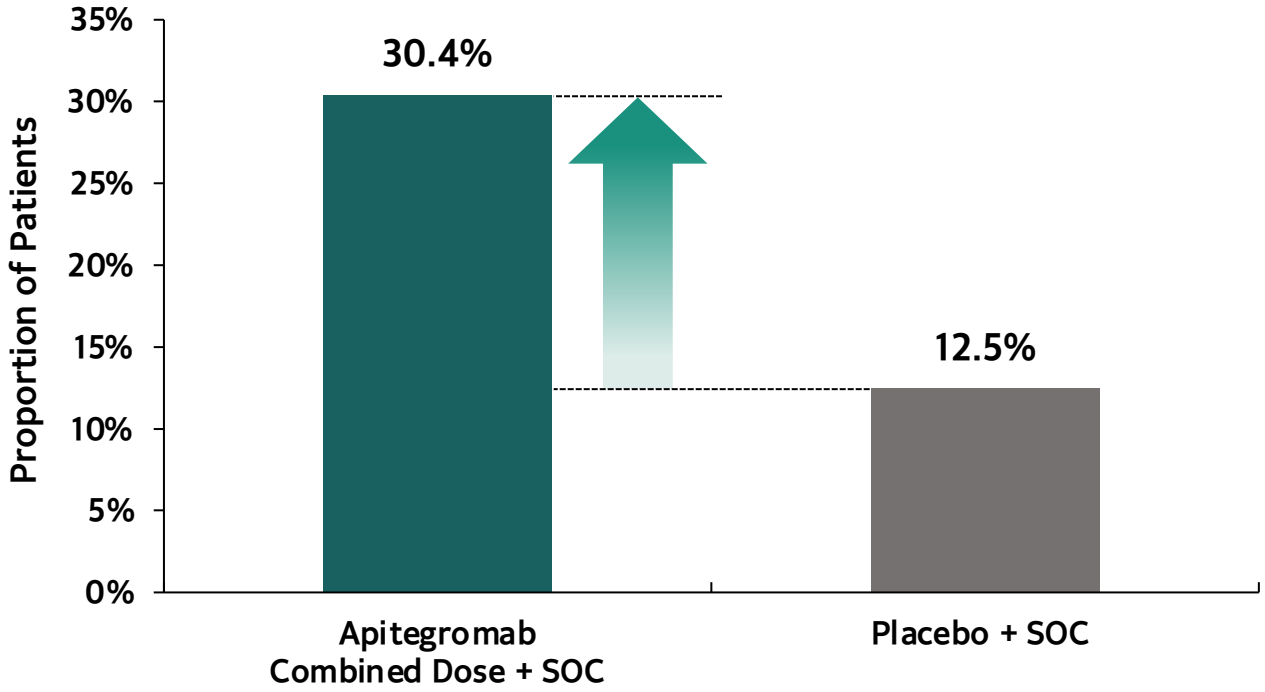
Apitegromab-treated patients improved on HFMSE, while placebo patients declined on HFMSE over 12 months

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

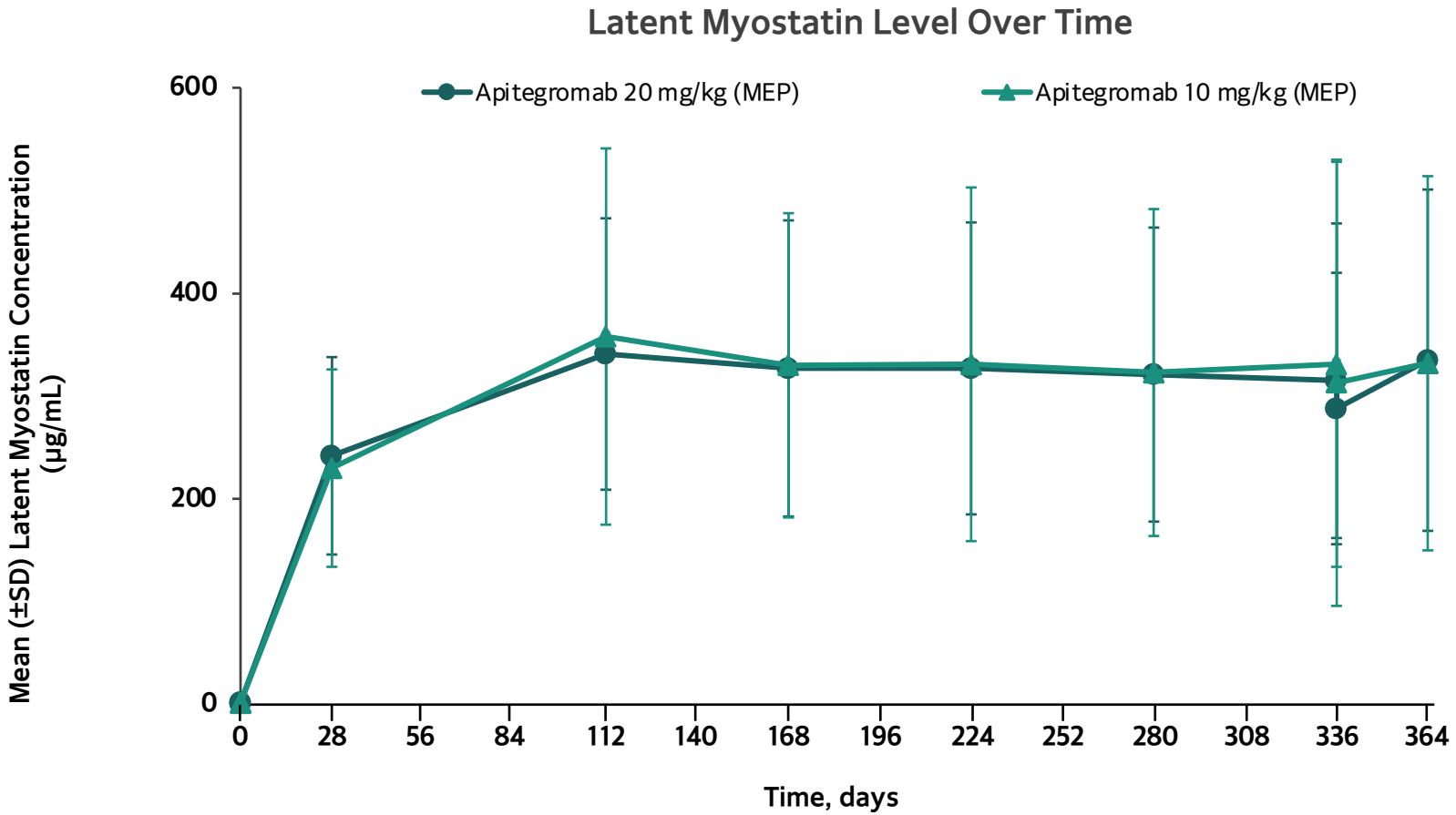
- Treatment with apitegromab was well-tolerated across all age groups, with a safety profile consistent with established safety profile
- There were no clinically relevant differences in the adverse event profile by dose, 10 mg/kg vs 20 mg/kg
- Serious adverse events (SAEs) were consistent with underlying 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.

ScholarRock

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

Expanding our Impact: Initiating Phase 2 OPAL Trial in mid-2025

Studying apitegromab in patients under 2 years old

TIME Is Muscle

Reaching patients earlier in their treatment journey

EXPANDING Our Impact

Including patients who received gene therapy

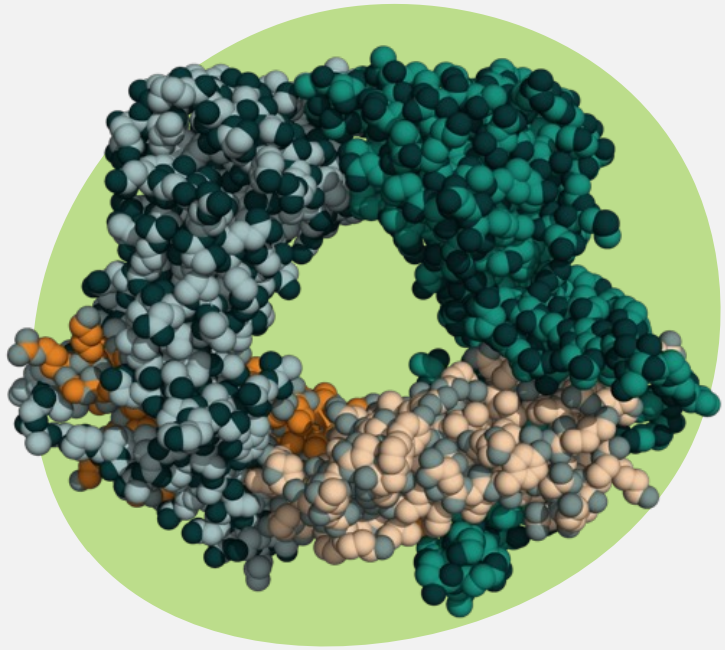
CHANGING More Lives

Potential to alter the course of SMA in a broad population

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

GLP-1 RAs are Transforming Weight Loss for Millions of People

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

ONCE-WEEKLY
wegovy®
semaglutide injection 2.4 mg

Lilly

once weekly
zepbound™
(tirzepatide) injection 0.5 mL
2.5 mg | 5 mg | 7.5 mg | 10 mg | 12.5 mg | 15 mg

novo nordisk®

BY 2029...

40 million people on GLP-1 RAs

$126 billion in Sales*

Source: UBS Bank, GLP-1: A medication worth $126 billion in sales by 2029? https://www.ubs.com/global/en/investment-bank/insights-and-data/2024/glp-1-a-medication.html.
GLP-1 RA=GLP-1 receptor agonist.

However, Patients Want Healthier Weight Loss*

WEAKNESS is a Concern

Patients complain of reduced strength after GLP-1 RA treatment

Improved LEAN MASS

Patients hope for a combination treatment approach to address this need

Significant Weight REGAIN

in 40-100% of patients after stopping GLP-1 RA treatment

> *Patients feel good about the number on the scale, but **there are issues with muscle loss** … they complain of **weakness** or **reduced strength**.*
>
> Obesity Clinician

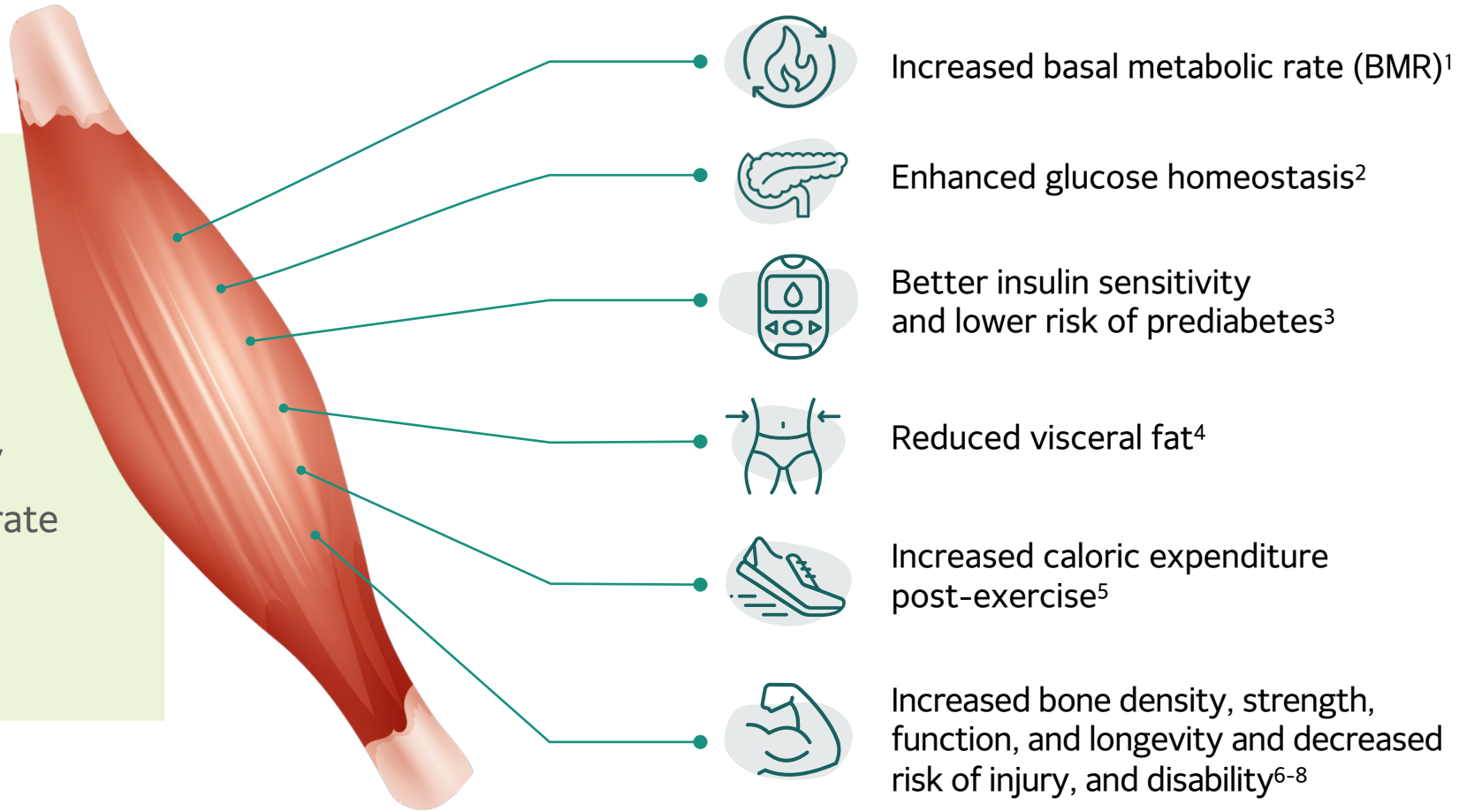
Scholar Rock's unique highly selective approach to targeting latent myostatin has the potential to address these patient needs

*Source: Scholar Rock market research, completed December 2024.
GLP-1 RA=GLP-1 receptor agonist.

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



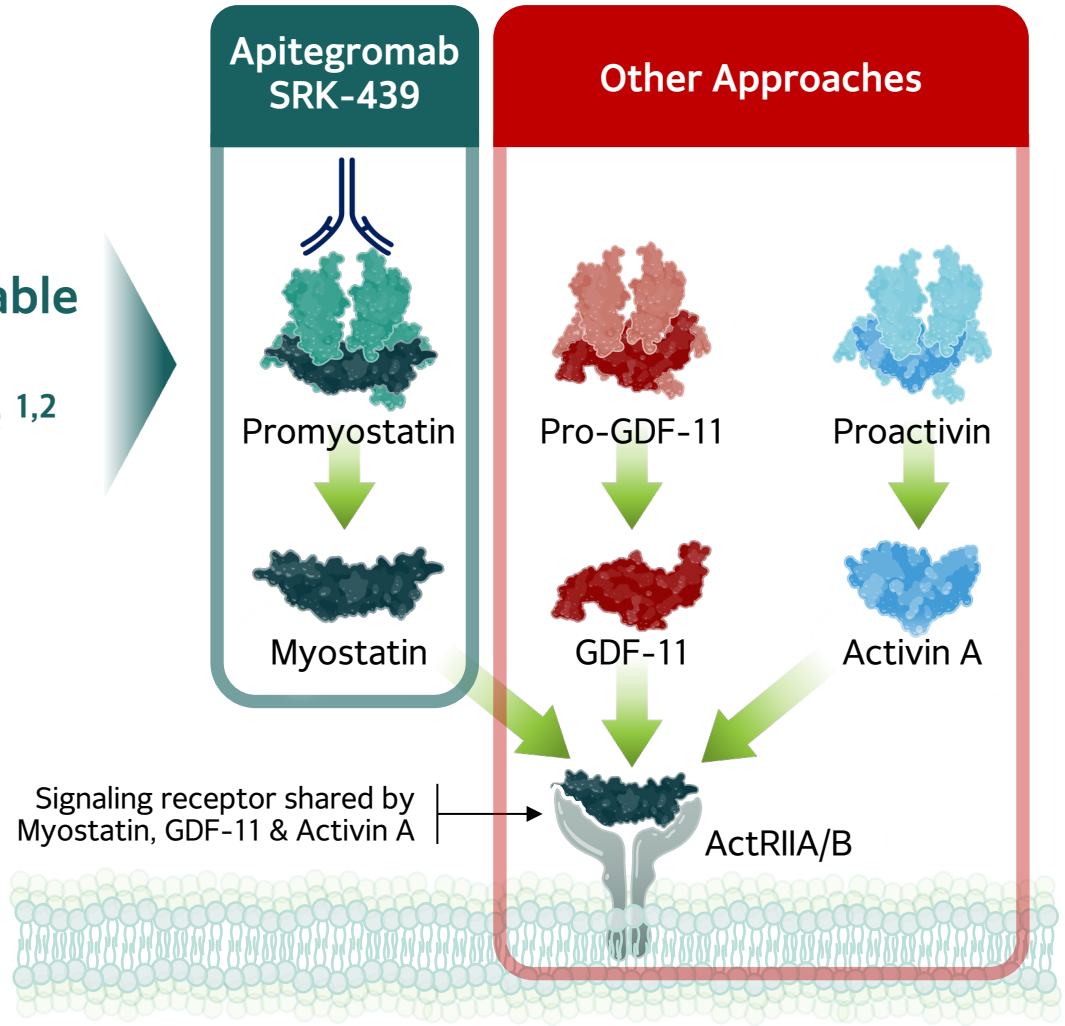
- Increased basal metabolic rate (BMR)[1]
- Enhanced glucose homeostasis[2]
- Better insulin sensitivity and lower risk of prediabetes[3]
- Reduced visceral fat[4]
- Increased caloric expenditure post-exercise[5]
- Increased bone density, strength, function, and longevity and decreased risk of injury,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

Potential to Optimize Benefit-Risk with Myostatin Selectivity

Favorable safety profile [1,2]



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 T et al. *Neurology.* 2024; 3. Garito T et al. *Clin Endocrinol (Oxf).* 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. *N Engl J Med.* 2023; 11. Ruckle J et al. *J Bone Miner Res.* 2009; 12. Sherman ML et al. *J Clin Pharmacol.* 2013; 13. Muntoni F et al. *Neurol Ther.* 2024. 14. Di Rocco M 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

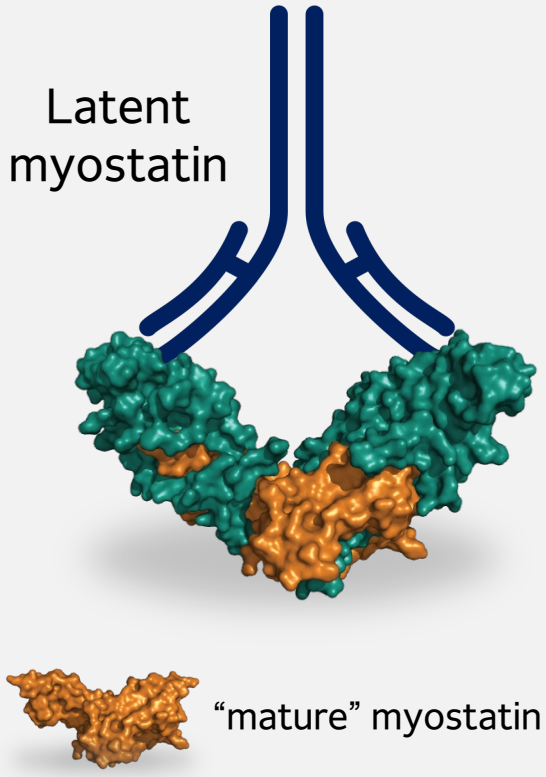
- Targets pro and latent forms of myostatin designed to minimize undesirable off-target effects

Strong Scientific Validation

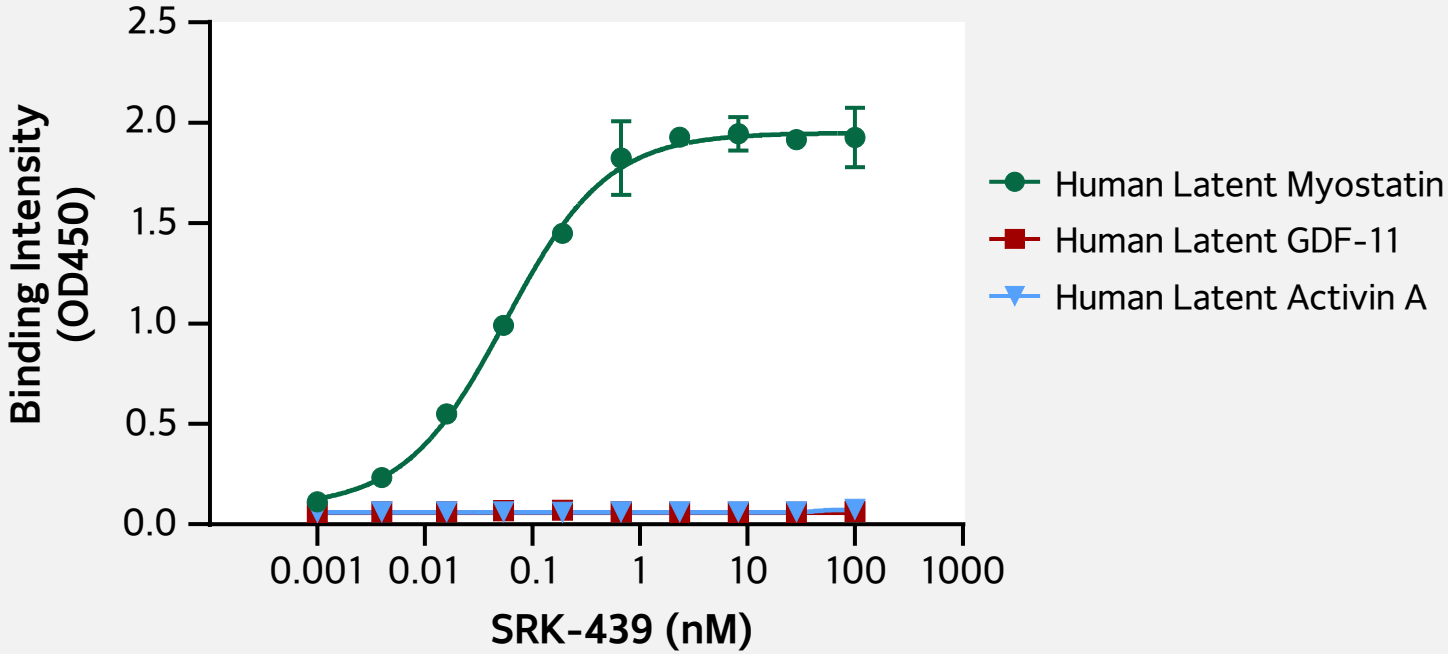
- Preclinical data demonstrated favorable muscle mass preservation and metabolic effects

SRK-439: Exquisite Selectivity for Myostatin

Scholar Rock's Target: Latent Myostatin



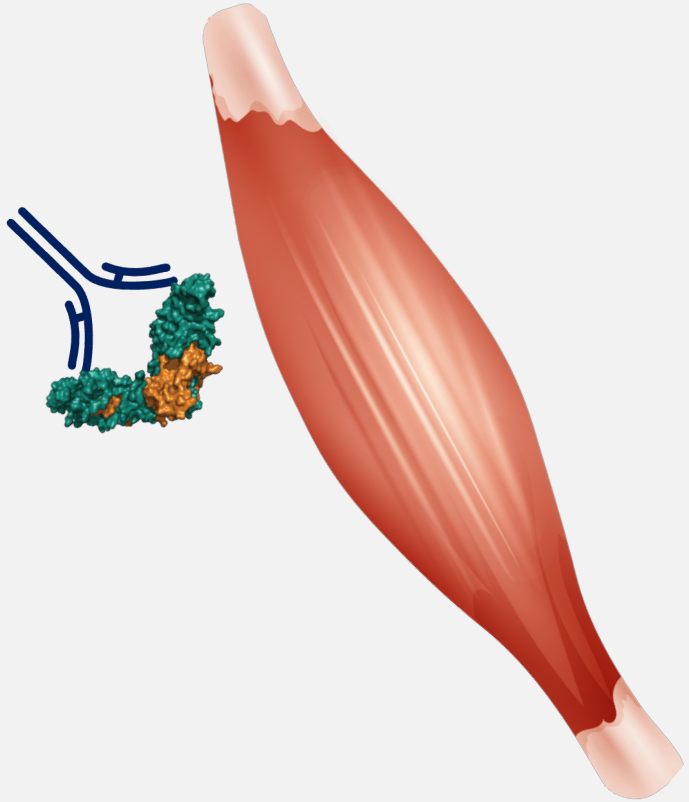
SRK-439 Selectively Binds Latent Myostatin



- 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

Potential Best in Class



KEYSTONE SYMPOSIA | American Diabetes Association® | obesityweek®

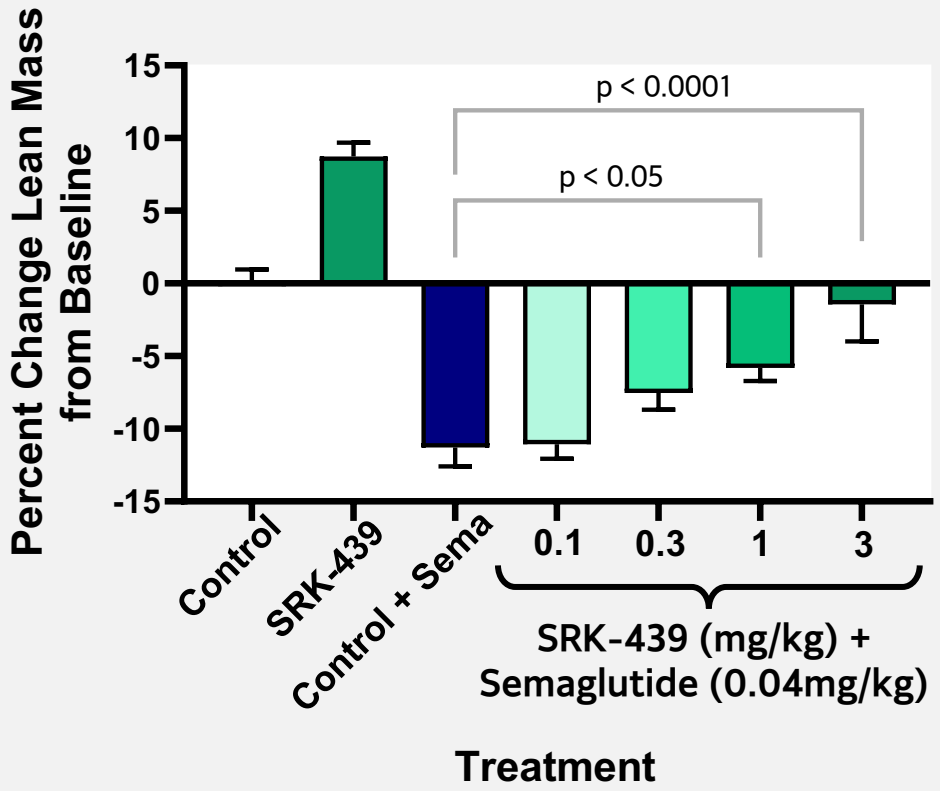
Preclinical data to date show strong potential to support healthier weight loss in combination with GLP-1 RAs:

- **Preservation of lean mass**
- **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
- **Works across the class** of GLP-1 RAs

GLP-1 RA: GLP-1 receptor agonist.

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

SRK-439 Maintained Lean Mass in Semaglutide Treated Animals



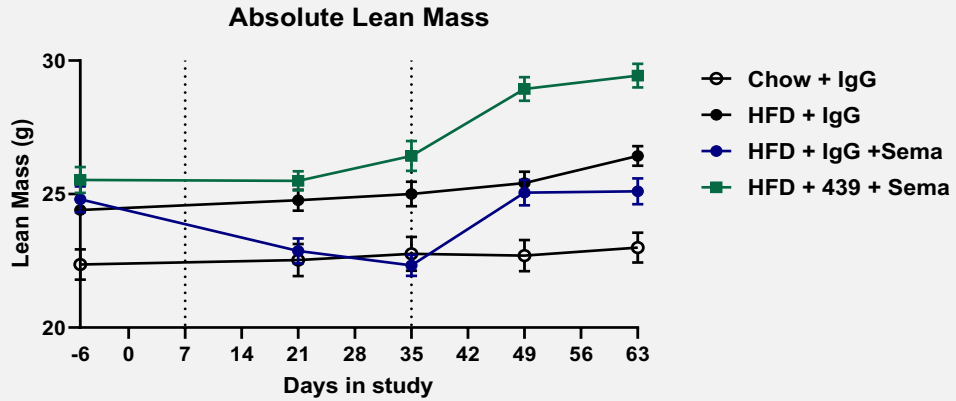
Key Observations

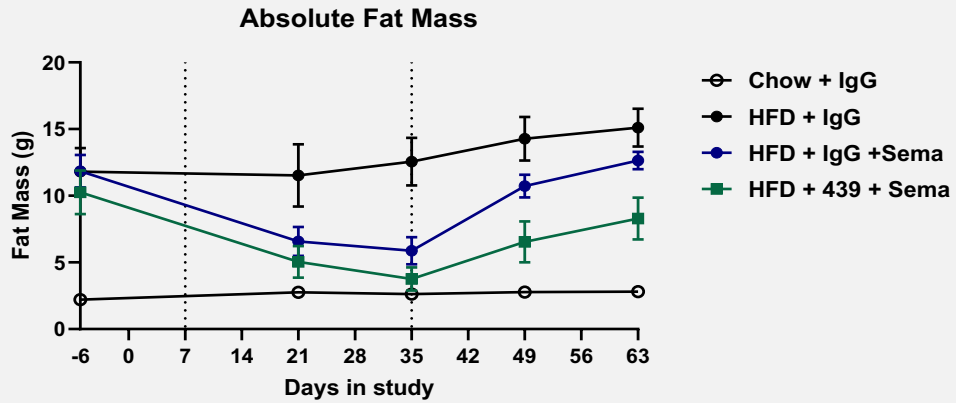
- Considerable lean mass loss with semaglutide treatment
- Combination with SRK-439 led to dose-dependent lean mass preservation
  - Effects seen with doses as low as 0.3 mg/kg
- Dose dependent enhancement of fat mass loss also observed, improving overall body composition

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

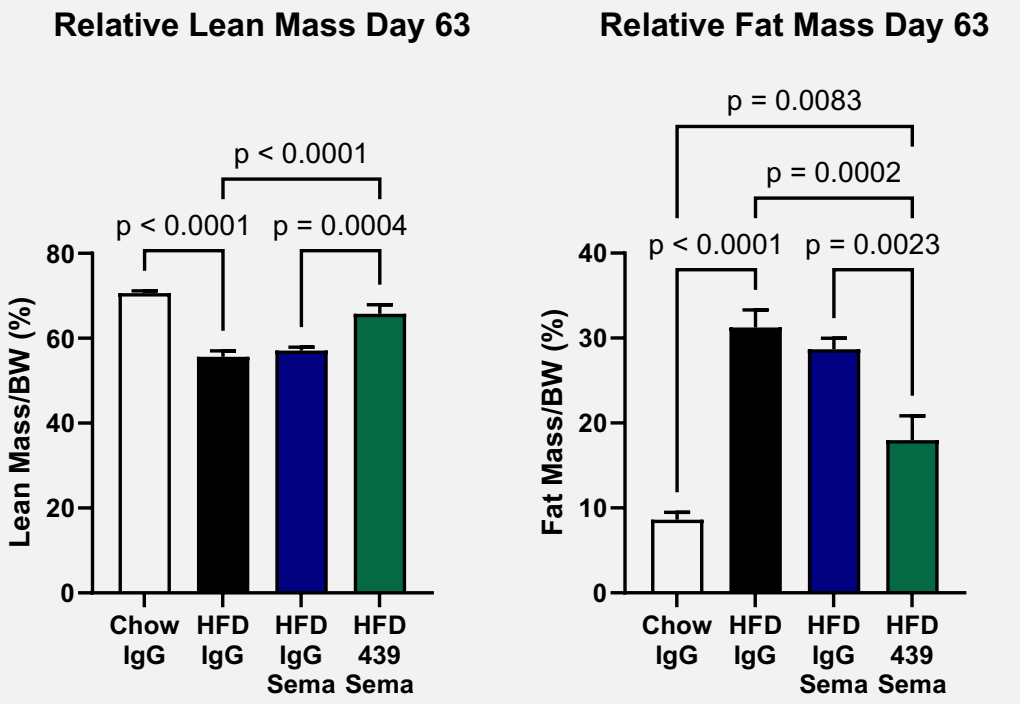
- Considerable lean mass loss seen with semaglutide treatment as expected
- Treatment with SRK-439 led to:
  - Preservation of lean mass during semaglutide treatment
  - Significant increase in lean mass upon semaglutide discontinuation
  - Attenuation of fat mass regain upon semaglutide discontinuation

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

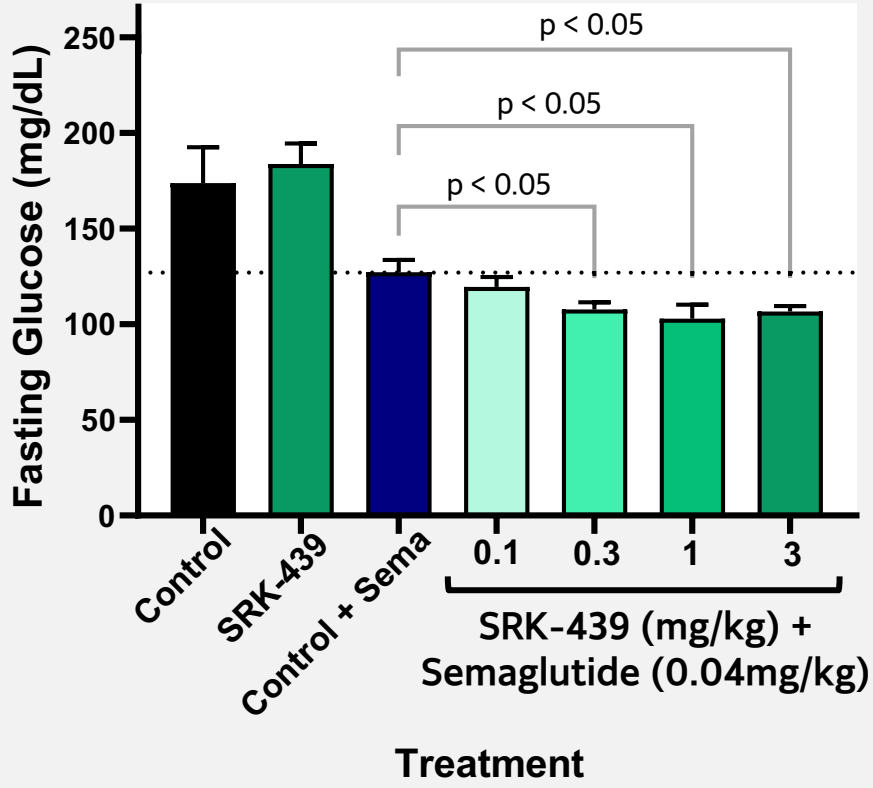
- SRK-439 attenuates regain of fat mass after withdrawal of semaglutide compared to IgG control
- SRK-439 leads to higher lean mass proportion after withdrawal of semaglutide compared to IgG control

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

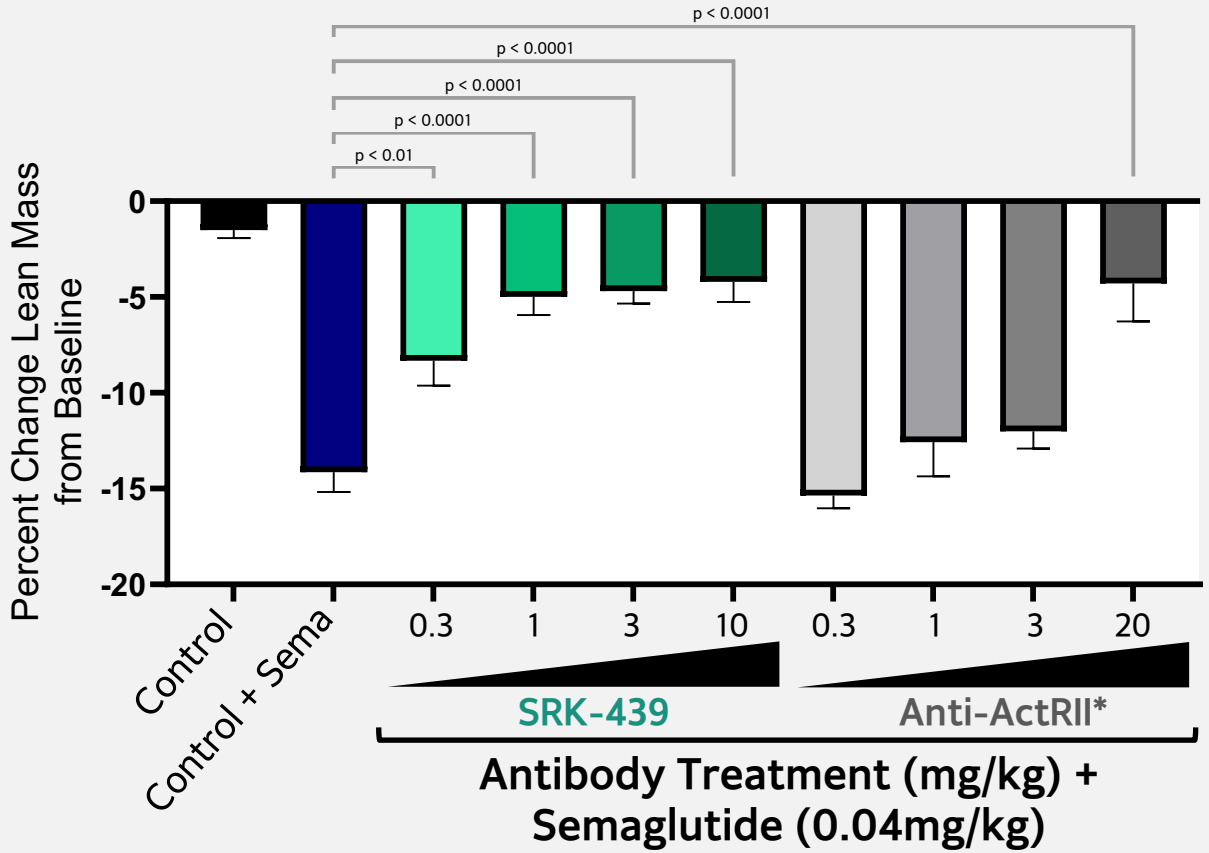
- Semaglutide reduced fasting glucose levels as expected
- Combination with SRK-439 led to further improvement in fasting glucose levels by ~20% in a dose-dependent manner
- Highlights the role of muscle preservation in improving long term metabolic profile

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

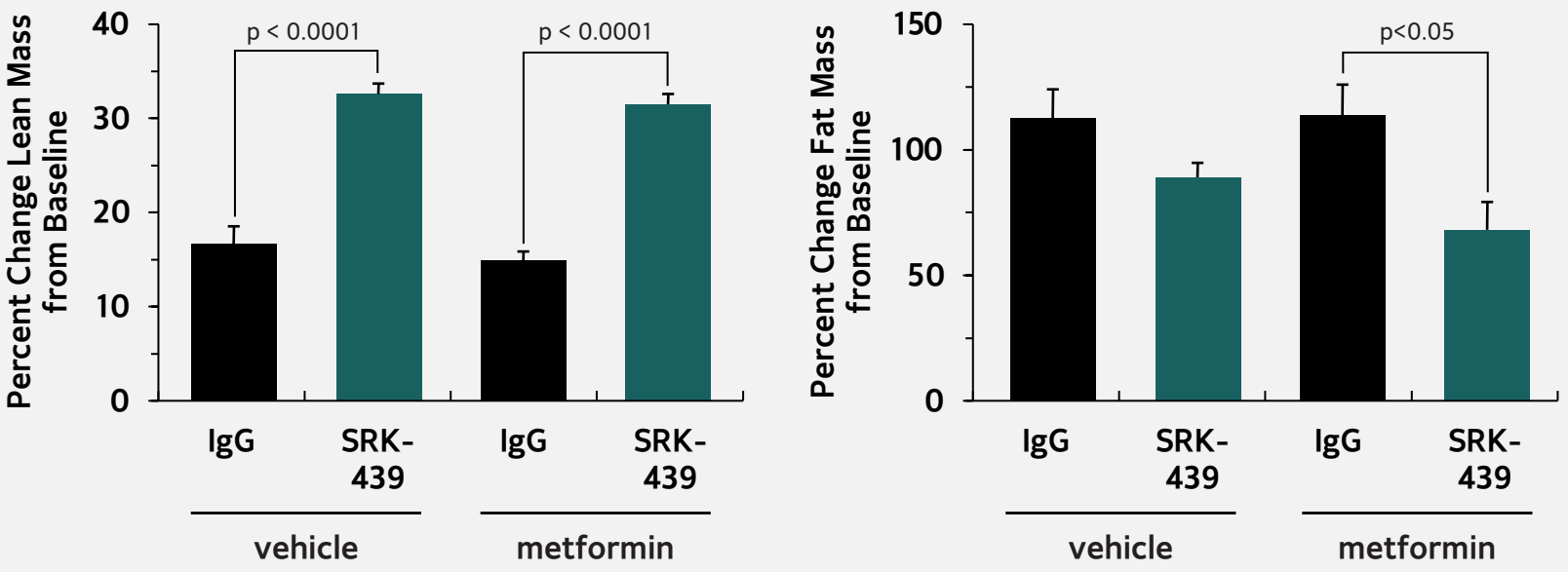
- SRK-439 preserved semaglutide-driven lean mass loss dose-dependently and at lower doses than anti-ActRII
- Highlights efficacy of SRK-439 and avoids potential liabilities of non-selective approach of anti-ActRII antibodies
- Low target dose of SRK-439 supports subcutaneous and potentially best-in-class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

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

LOW EFFICACIOUS DOSE AND COMPETITIVE PROFILE

SRK-439: Selective Inhibition of Myostatin in Combination with Metformin Increased Lean Mass

Lean and Fat Mass Change in Young DIO Mice Treated with SRK-439 and Metformin



Key Observations

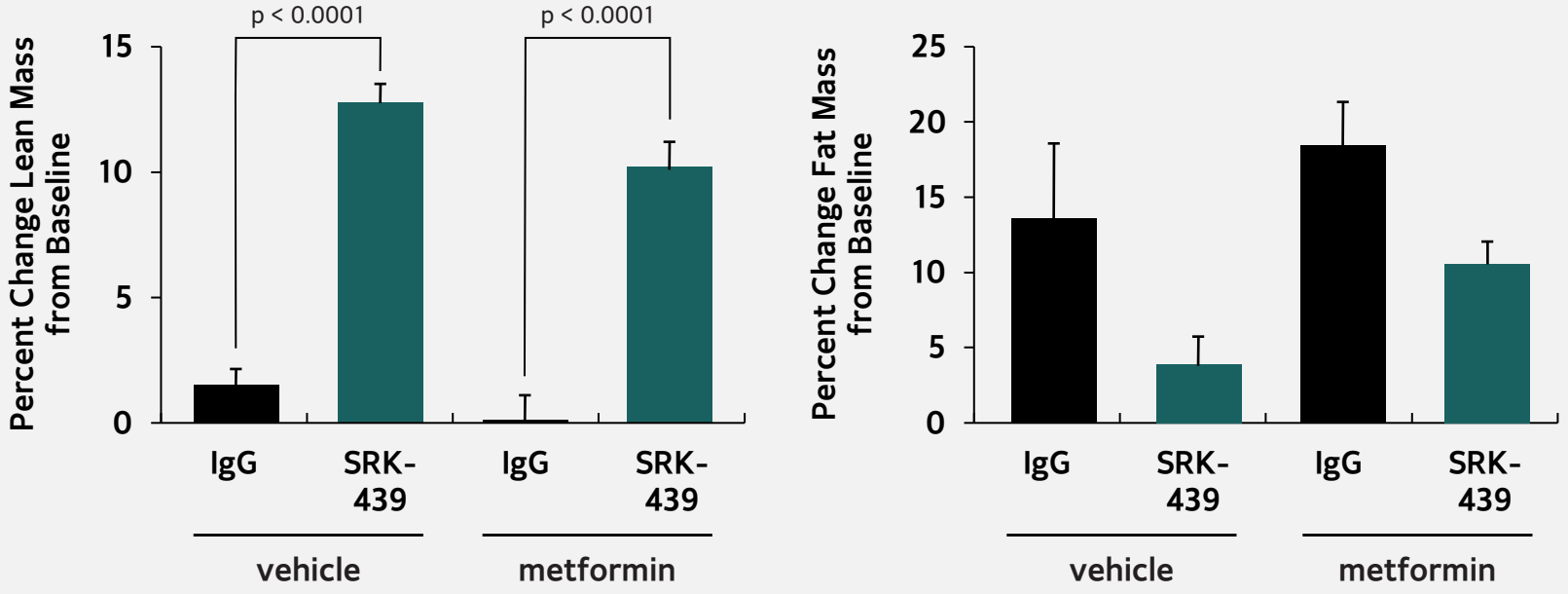
- Young animals treated with SRK-439 and metformin demonstrated a 2-fold increase in lean mass over the duration of the study
- The combination of SRK-439 and metformin also resulted in lower fat mass gain than was seen with metformin alone
- SRK-439 has the potential to improve body composition and contribute to healthier weight management in the context of both obesity and type 2 diabetes

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

LOW EFFICACIOUS DOSE AND COMPETITIVE PROFILE

SRK-439: Selective Inhibition of Myostatin in Combination with Metformin Increased Lean Mass

Lean and Fat Mass Change in Older DIO Mice Treated with SRK-439 and Metformin



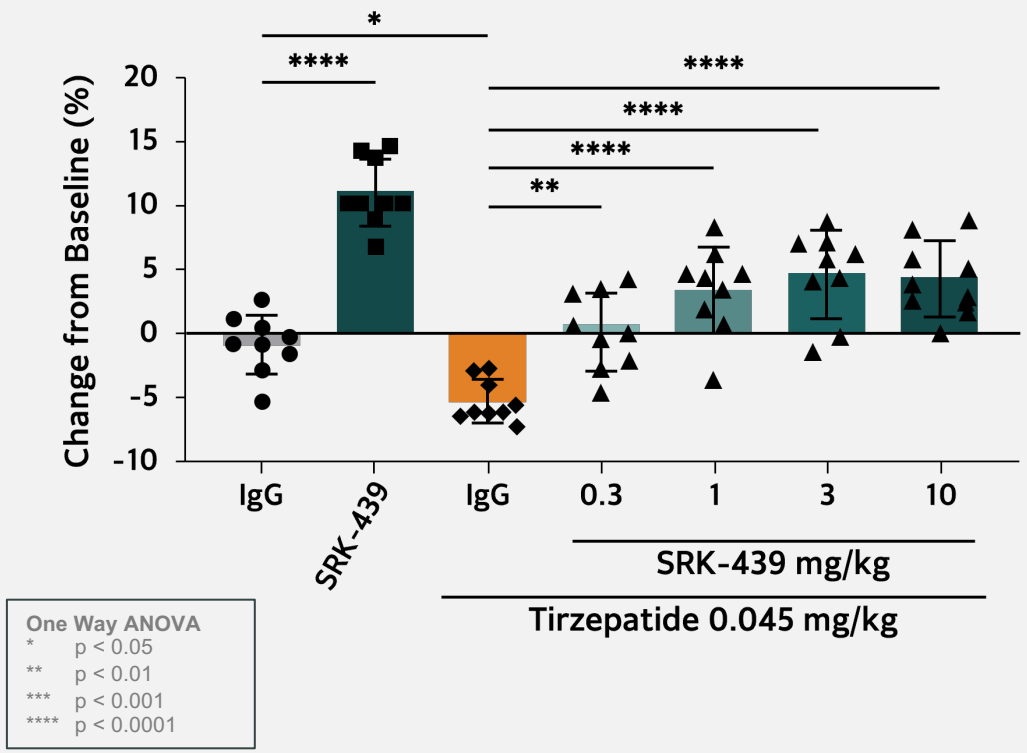
Key Observations

- Older animals treated with SRK-439 and metformin demonstrated a 50-fold increase in lean mass over the duration of the study
- The combination of SRK-439 and metformin also resulted in a trend toward lower fat mass gain than was seen with metformin alone

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

SRK-439 Protects from Tirzepatide-Induced Muscle Loss in DIO Mice

qNMR % Lean Mass Change from Baseline



Key Observations

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

DIO=Diet-induced obesity.

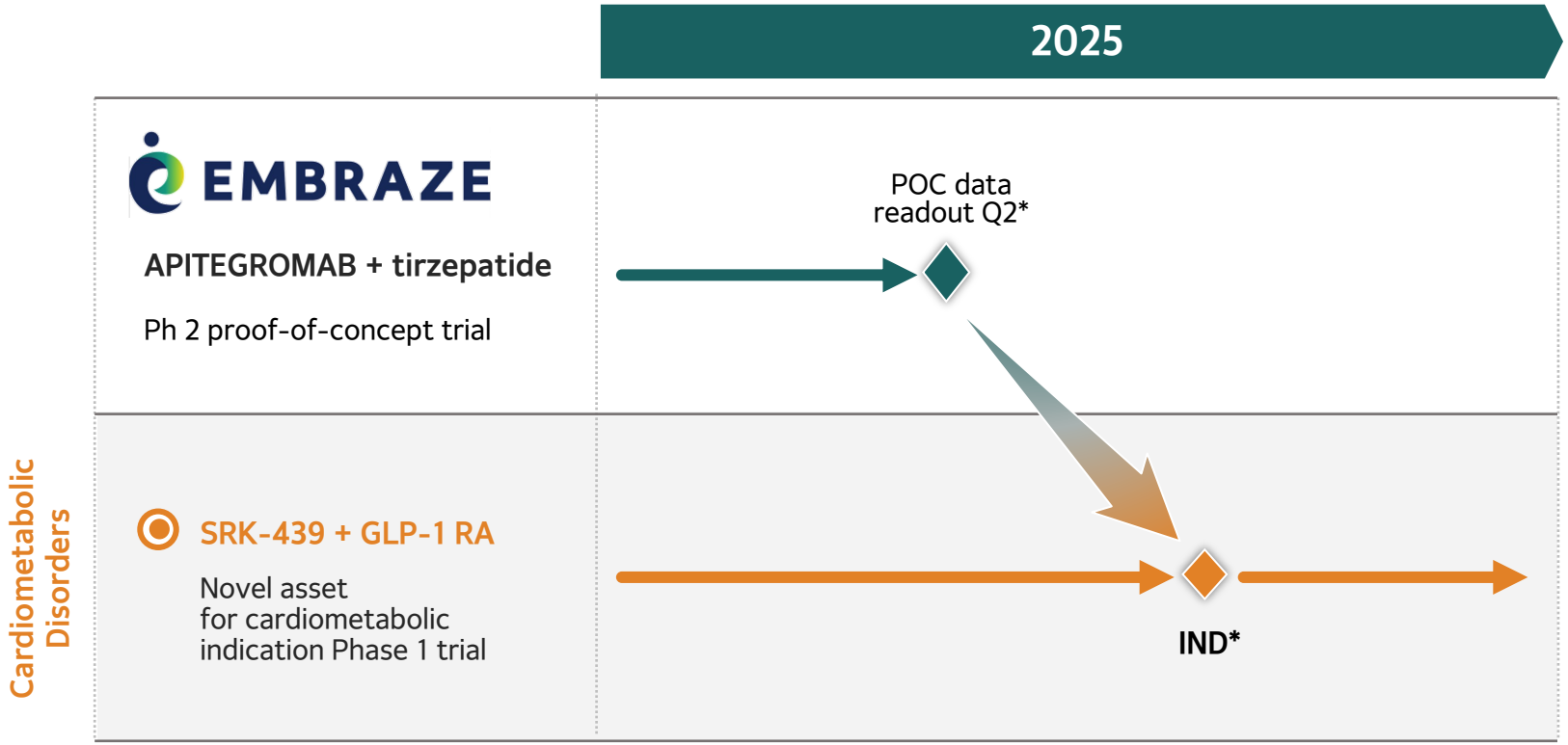
SRK-439: Best in Class Potential

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

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.

Industry-Leading Anti-Myostatin Platform: Leveraging Apitegromab's Success to Advance the Obesity Program



Testing hypothesis of selective anti-myostatin antibody in obese population

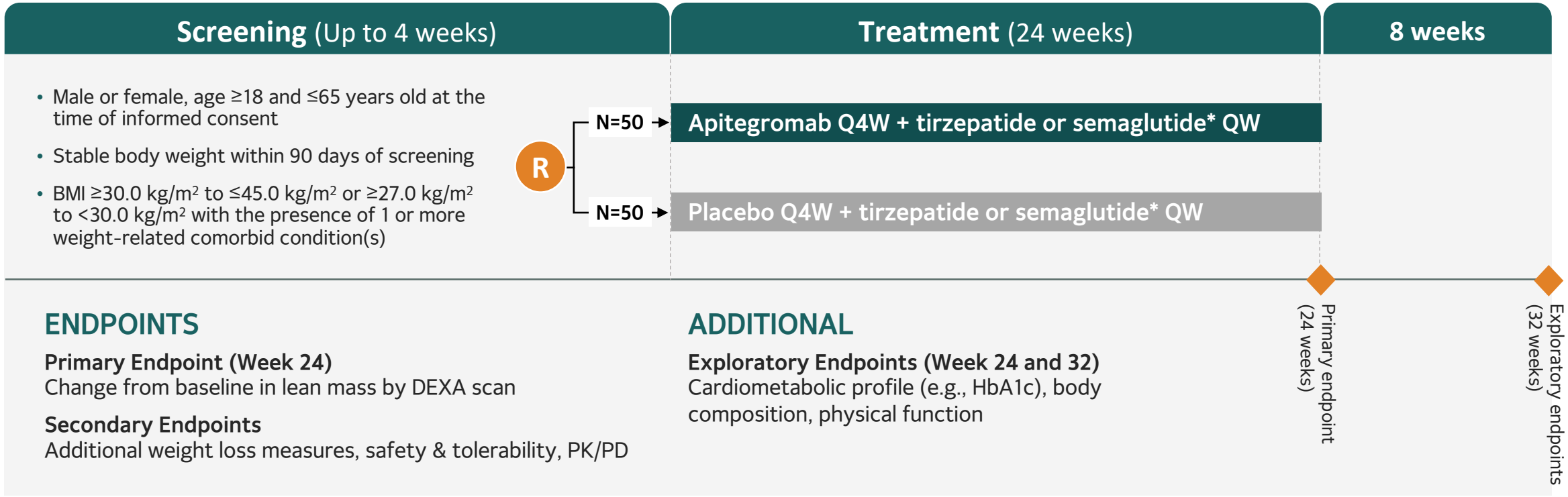
- EMBRAZE POC readout in Q2 2025
- SRK-439 IND submission in Q3 2025

*Expected timelines
POC=Proof of Concept; GLP-1 RA=GLP-1 receptor agonist.

Data from Phase 2 Proof-of-Concept Study of Apitegromab in Obesity Expected Q2 2025

EMBRAZE

Randomized, double-blind, placebo-controlled (n=102 enrolled)
Enrolled patients who are overweight or obese
Enrollment completed 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

*Due to expedited enrollment and timing of semaglutide clinical supply, all enrolled patients received tirzepatide.
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.

Goals of the EMBRAZE Proof-of-Concept Study

EMBRAZE

Study Aims to Demonstrate

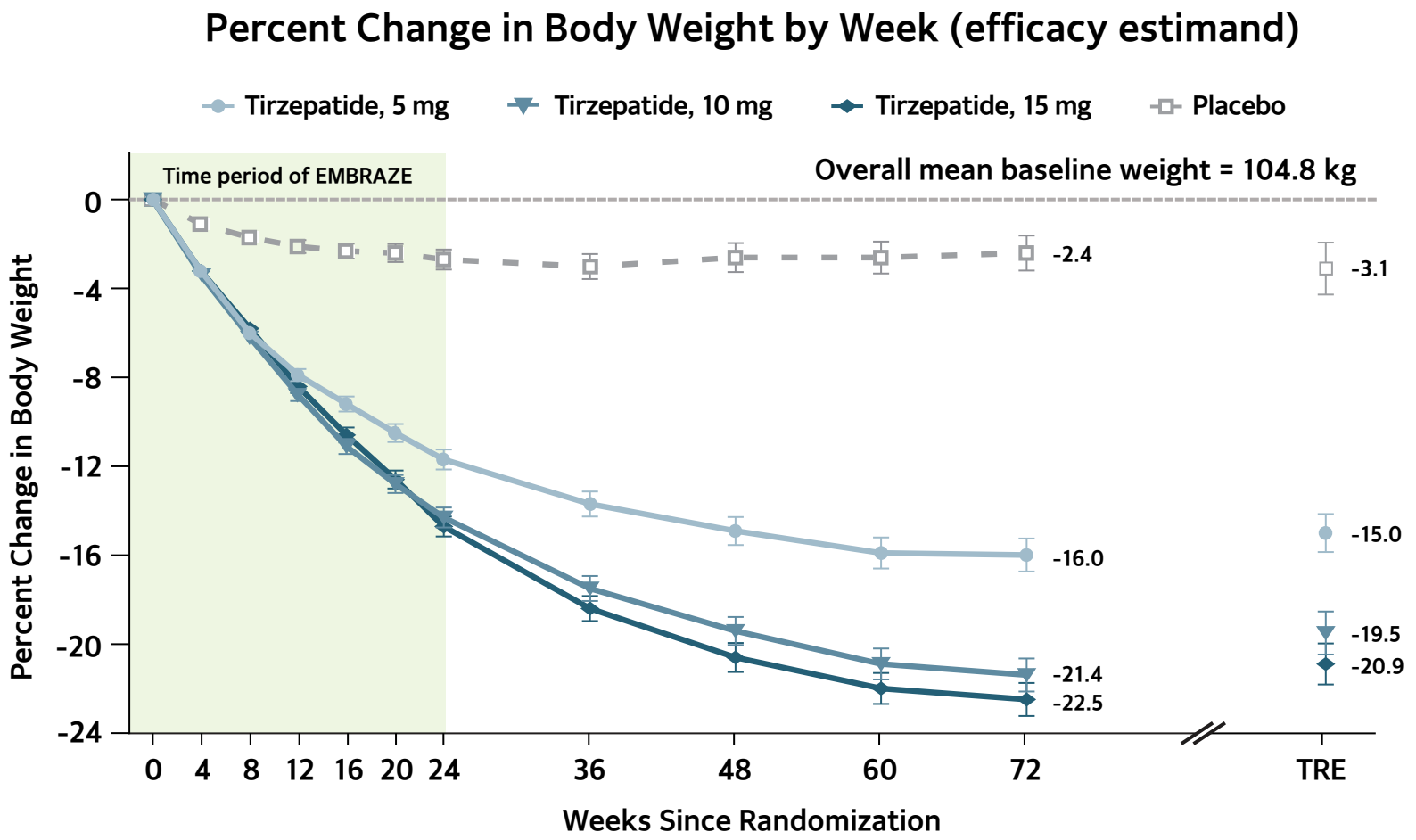
- Preservation of lean mass in obese or overweight patients
- Safety and tolerability
- Potential to improve metabolic profile and physical function

INSIGHTS GAINED FROM EMBRAZE STUDY

to inform SRK-439 development

Initiated trial in May 2024, ahead of target timeline	Enrollment completed in September 2024	Topline data expected in Q2 2025

Tirzepatide-Induced Weight Loss Accompanies Significant Muscle Loss



Tirzepatide

DECREASE in **lean mass of 10.9%** accompanies DECREASE in **body weight**

Figure from Jastreboff, A.M. et al. *N Engl J Med.* 2022;387(3):205-216.
* Data from Phase 3 clinical trial of tirzepatide in adults with obesity.

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

ScholarRock™

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

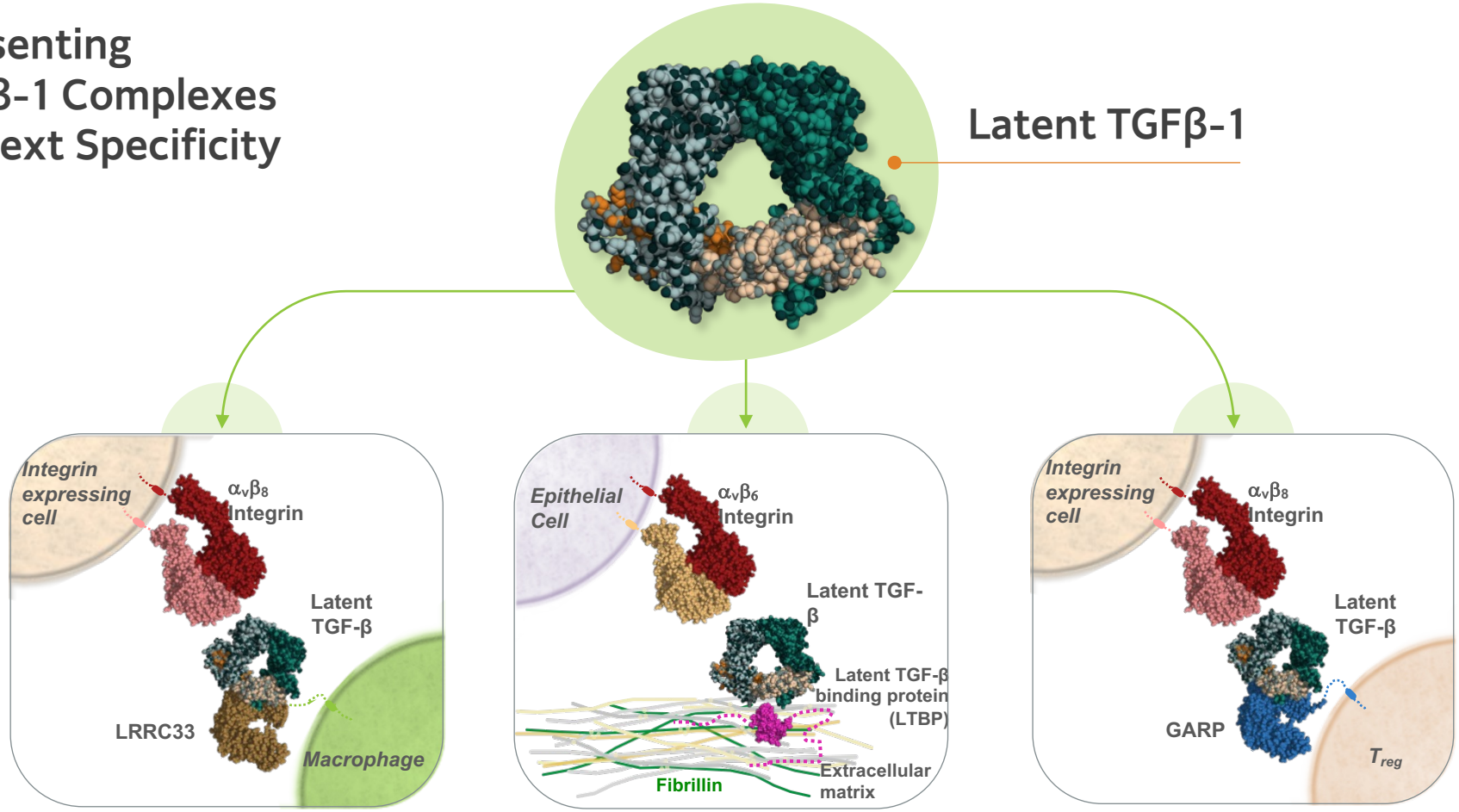
PNAS, February 24, 1986 PNAS

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



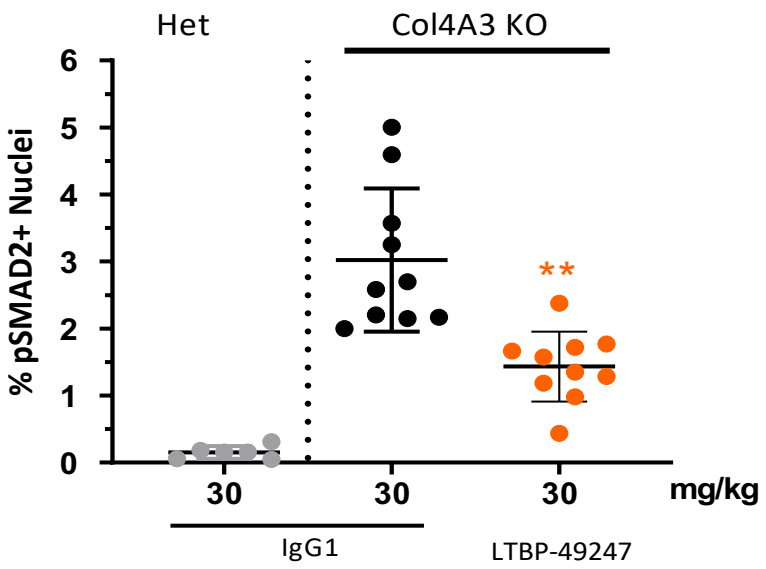
LRRC33 Presents TGFβ on Macrophages

LTBP1 & 3 Present TGFβ in Connective Tissue

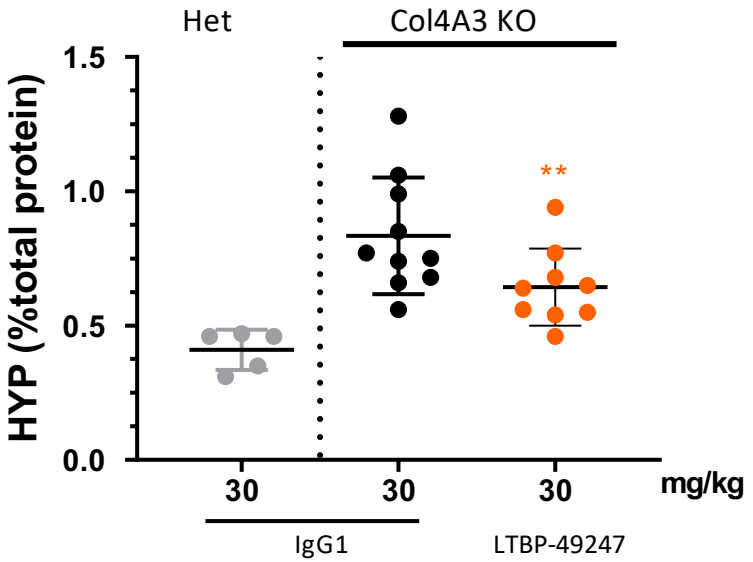
GARP Presents TGFβ on Tregs

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)



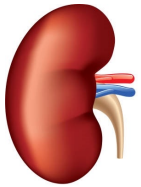
LTBP-49247 reduced fibrosis in kidneys of Alport model



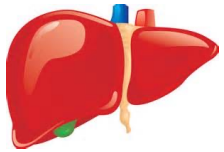
** p < 0.01
One way ANOVA vs. IgG
HYP=hydroxyproline

- 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

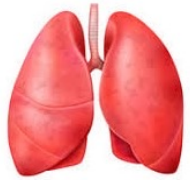
Significant Opportunities to Address High Unmet Need Across Multiple Fibrotic Indications



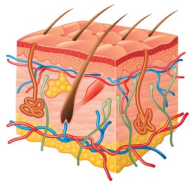
Alport Syndrome (AS)
Focal Segmental Glomerulosclerosis (FSGS)
IgA Nephropathy (IgAN)



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

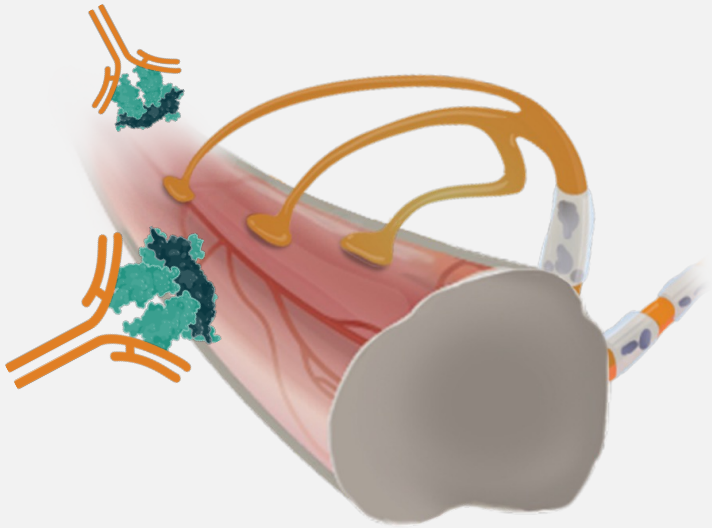
* If approved by relevant health authorities

Appendix

ScholarRock™

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

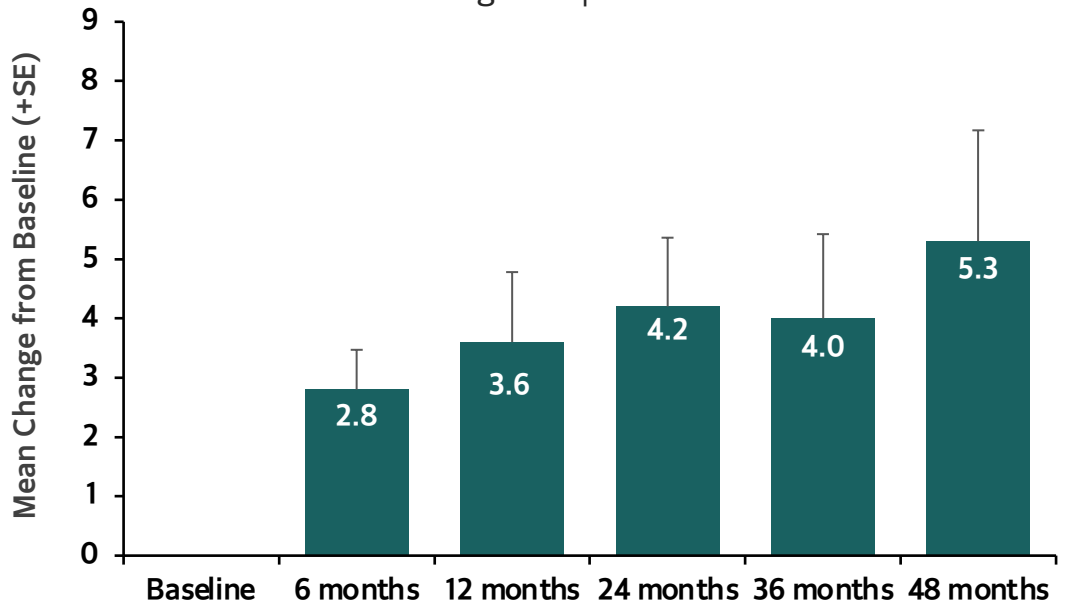
Apitegromab TOPAZ Clinical Trial: Motor Function Outcomes by HFMSE Over 48 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients[1]

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

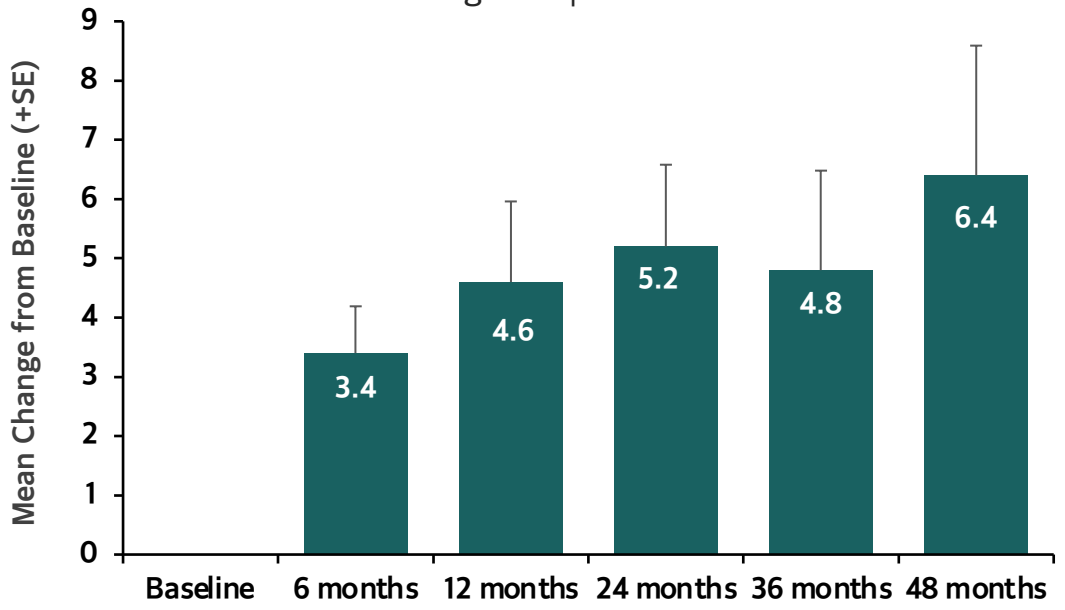
Baseline mean age=7.3 | **Time on SMN Rx=24.1m**



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.

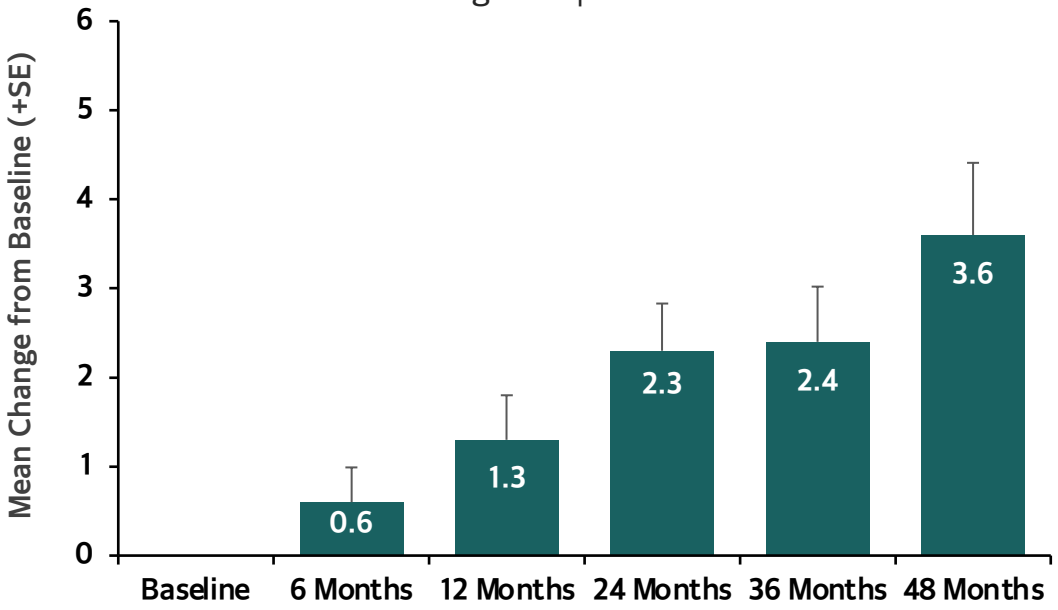
Apitegromab TOPAZ Clinical Trial: Motor Function Outcomes by RULM Over 48 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients[1]

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

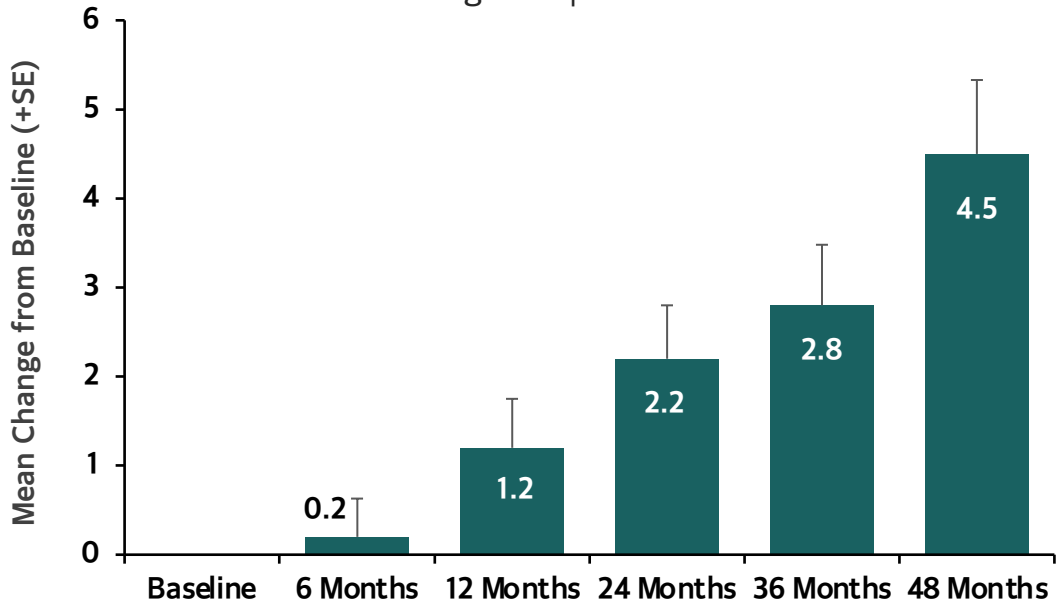
Baseline mean age=7.3 | Time on SMN Rx=24.1m



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.

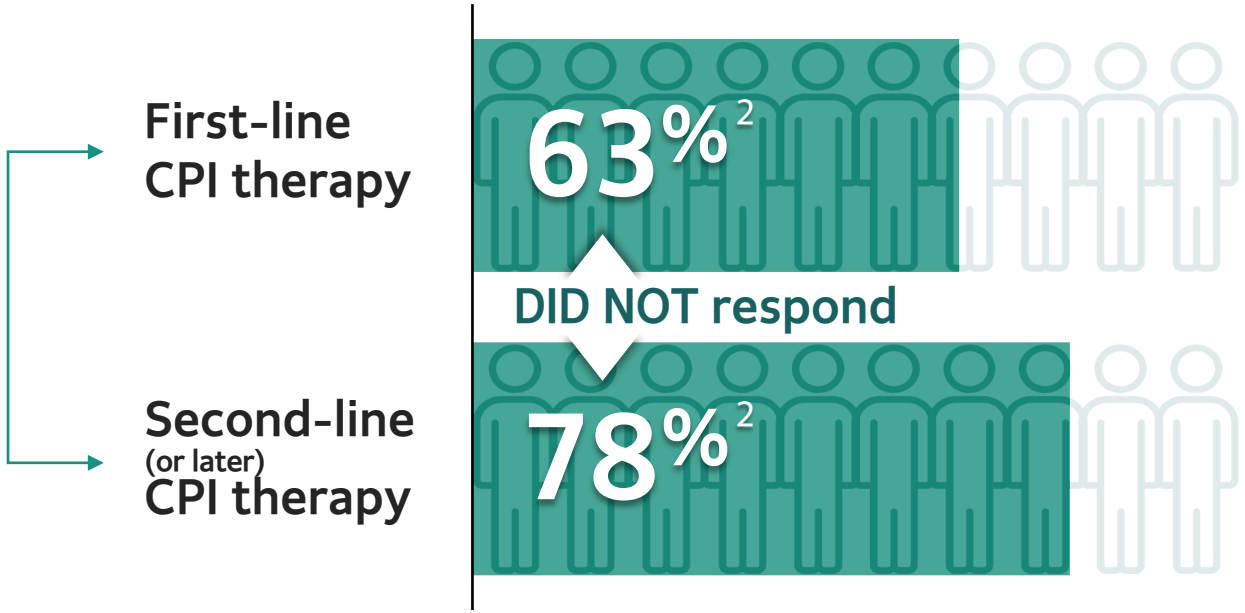
DRAGON

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

ScholarRock™

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

7.9–10.4[1]
MILLION
US patients
on CPI therapies



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 Castiglioni[1], Kobe Yuen[1], Yulei Wang[1], Edward E. Kadel III[1], Hartmut Koeppen[1], Jillian L. Astarita[1], Rafael Cubas[1], Suchit Jhunjhunwala[1], Romain Banchereau[1], Yagai Yang[1], Yinghui Guan[1], Cecile Chalouni[1], James Ziai[1], Yasin Şenbabaoğlu[1], Stephen Santoro[1], Daniel Sheinson[1], Jeffrey Hung[1], Jennifer M. Giltnane[1], Andrew A. Pierce[1], Kathryn Mesh[1], Steve Lianoglou[1], Johannes Riegler[1], Richard A. D. Carano[1], Pontus Eriksson[2], Mattias Höglund[2], Loan Somarriba[3], Daniel L. Halligan[3], Michiel S. van der Heijden[4], Yohann Loriot[5], Jonathan E. Rosenberg[6], Lawrence Fong[7], Ira Mellman[1], Daniel S. Chen[1], Marjorie Green[1], Christina Derleth[1], Gregg D. Fine[1], Priti S. Hegde[1], Richard Bourgon[1] & Thomas Powles[8]

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

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

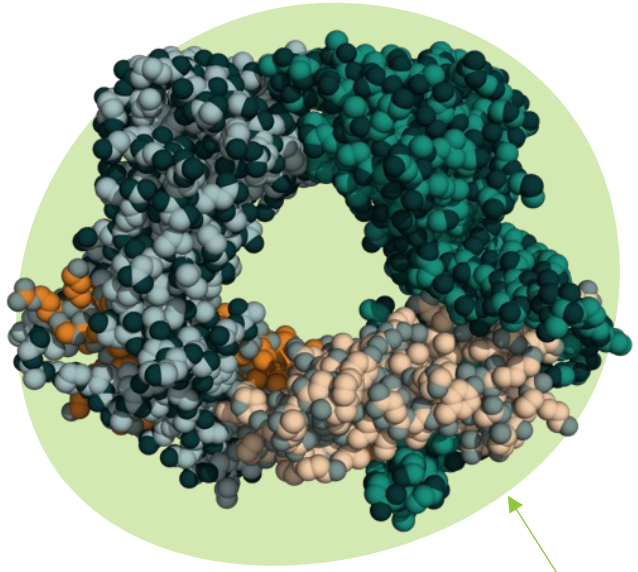
Rik Derynck[1,2,3], Shannon J. Turley[4] and Rosemary J. Akhurst[2,3]

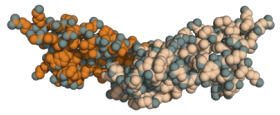
July 24, 2020: https://doi.org/10.1038/ s41571-020-0403-1

August 2022.

"Bristol Myers Squibb Enters Agreement to Acquire Forbius TGF-beta Program"

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





Traditional Target
"Mature" growth factor

SRK-181: Latent TGFβ-1 Inhibitor

Targets TGFβ-1	**Potential to overcome CPI resistance**	SRK-181 inhibits the TGFβ-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 TGFβ inhibition	Other programs target multiple isoforms of TGFβ
Targets the latent form of TGFβ-1	**Increases opportunity to inhibit TGFβ-1**	Selectively targeting the latent form shuts off the growth factor before activation	Most other programs target the mature form of TGFβ-1
Context-independent	**Inhibits all sources of TGFβ-1**	SRK-181 targets all TGFβ-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.

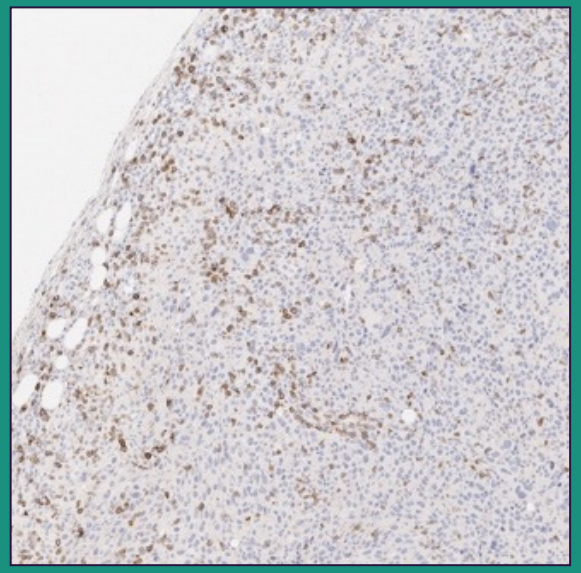
SRK-181-mIgG1 + Anti-PD1 Overcomes Immune Exclusion

Overcoming immune exclusion

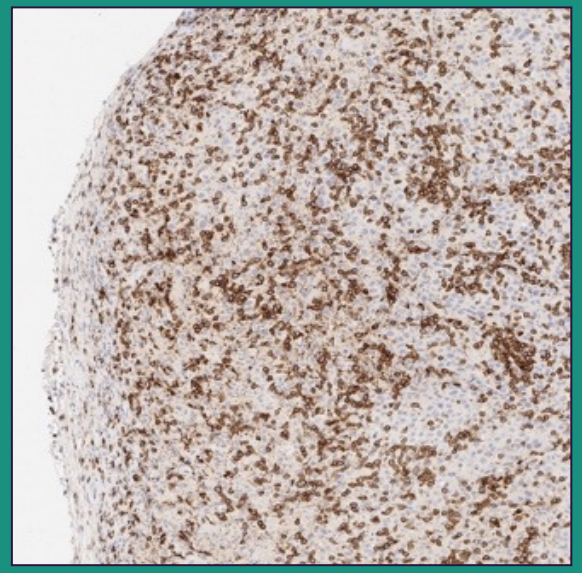
Tumor micro-environment

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

Preclinical data published in *Science Translational Medicine*. Martin CJ, et al. *Sci Transl Med.* 2020 Mar 25;12(536):eaay8456. https://scholarrock.com/platform/publications.
Data from MBT-2 syngeneic tumor model. Dose 10mg/kg QW for 4 weeks.

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.

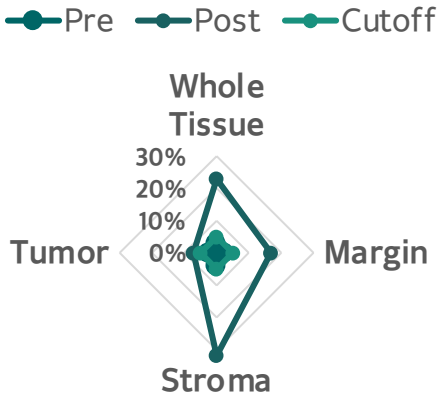
ADA, anti drug antibody; BOR, best overall response; ccRCC, clear cell renal cell carcinoma; DCR, disease control rate; DoR, duration of response; ECOG, eastern cooperative oncology group; HNSCC, head and neck squamous cell carcinoma; MEL, melanoma; NSCLC, non-small cell lung cancer; ORR, objective response 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.

ScholarRock

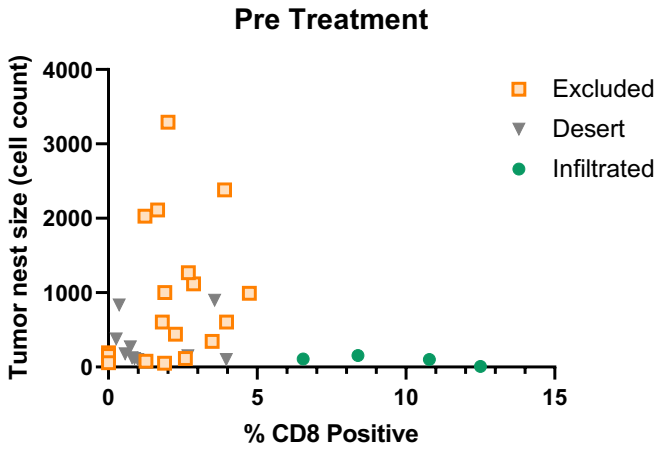
SRK-181 in Combination with Anti-PD1 Increases Infiltration of CD8+ T Cells in Melanoma

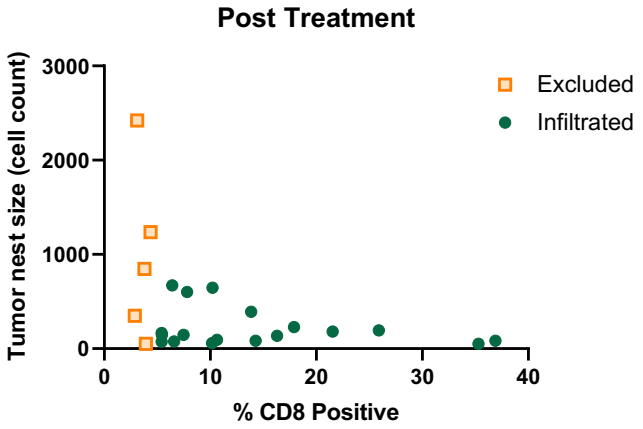
- Paired biopsies from 2 melanoma patients were analyzed for CD8 content.
- An increase in CD8+ T cell infiltration was observed in both biopsy pairs, overcoming an initially excluded or desert phenotype and resulting in more infiltrated tumor nests.
- Shown here is the representative quantification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

Primary Compartmental Analysis % CD8+ T cells per compartment

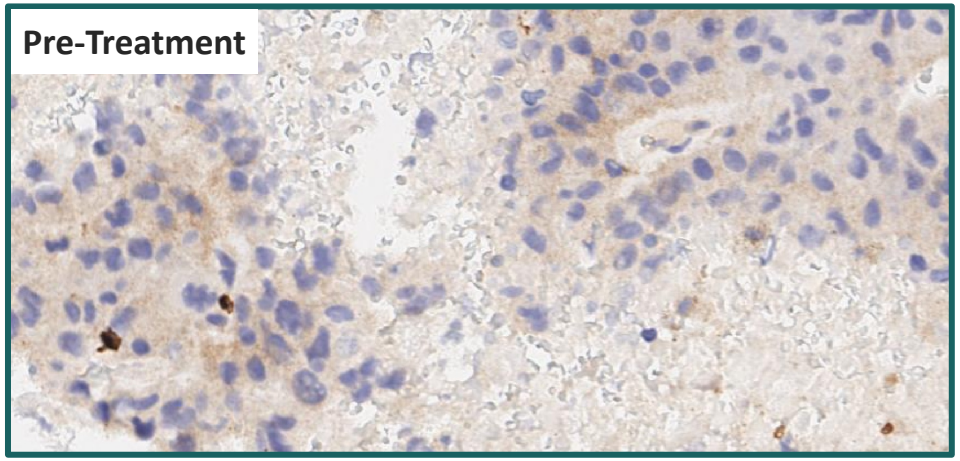


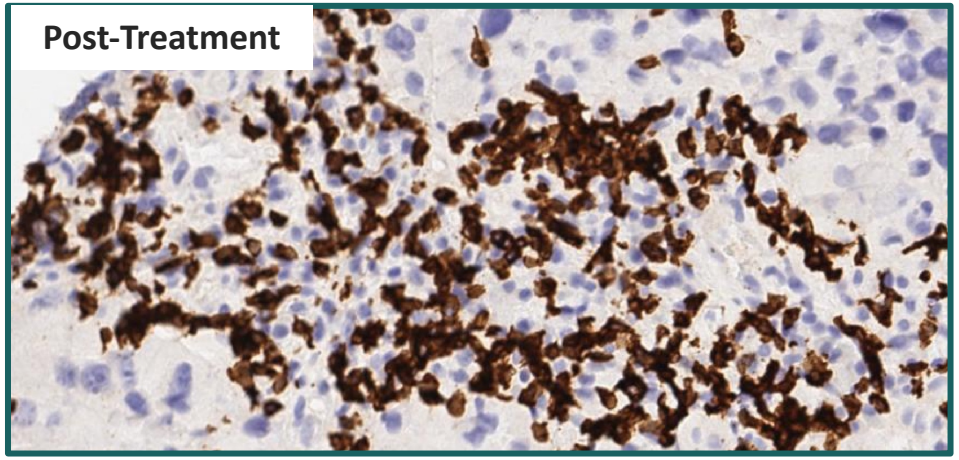
Tumor Nest Analysis





CD8 Stain – Melanoma, Pre and Post Treatment





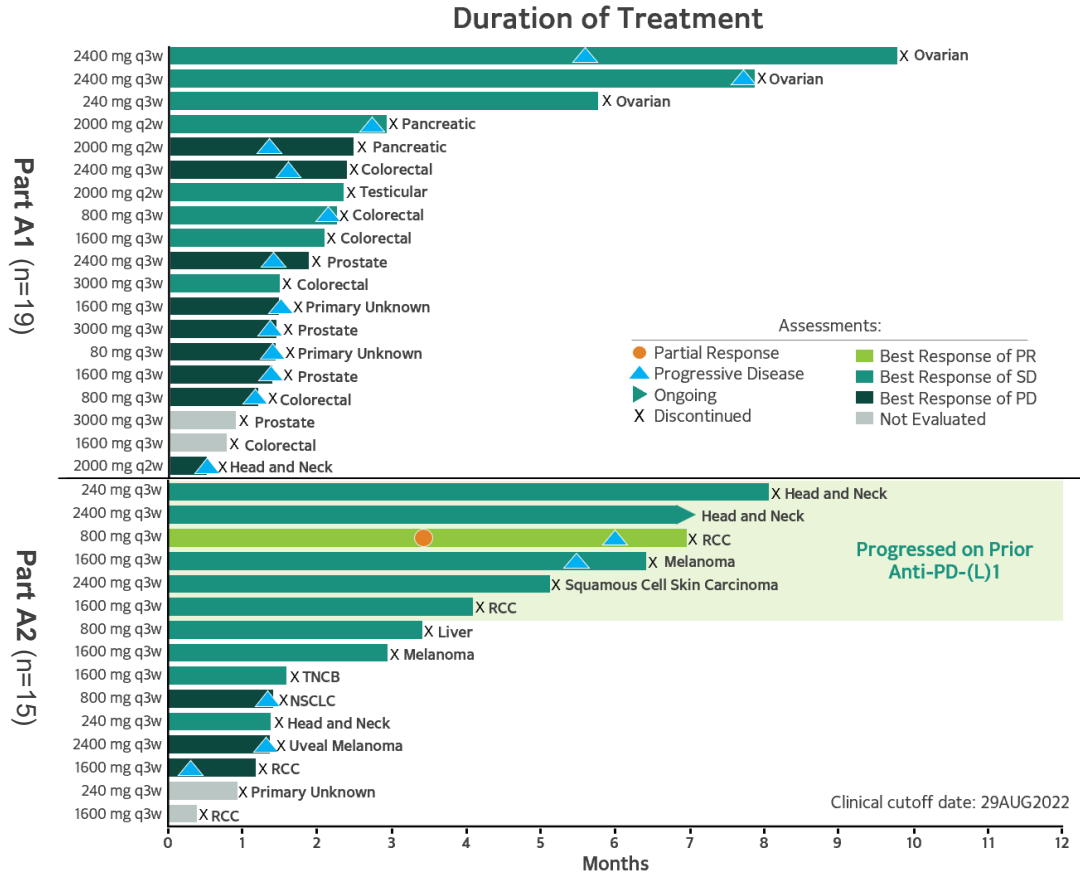
Preliminary Safety and Efficacy
Phase 1 *Dose Escalation Phase*

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 does; 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

ScholarRock

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)*

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 maculo-popular and pneumonitis (2 patients), bullous pemphigoid, colitis, erythroderma, generalized erythematous rash, invasive squamous cell carcinoma, mucositis oral (1 patient each).

[#]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

ScholarRock

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.

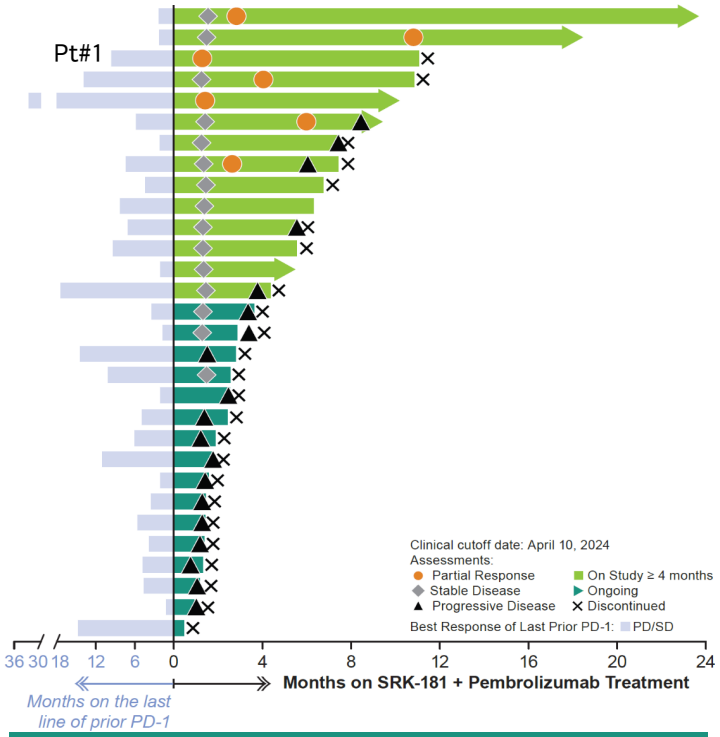
- There was 1 treatment-related Grade 4 AE (Dermatitis exfoliative generalised)
- There was no treatment-related Grade 5 AE
- Treatment-related SAE >2% (2 patients) were Pemphigoid (irAE)

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

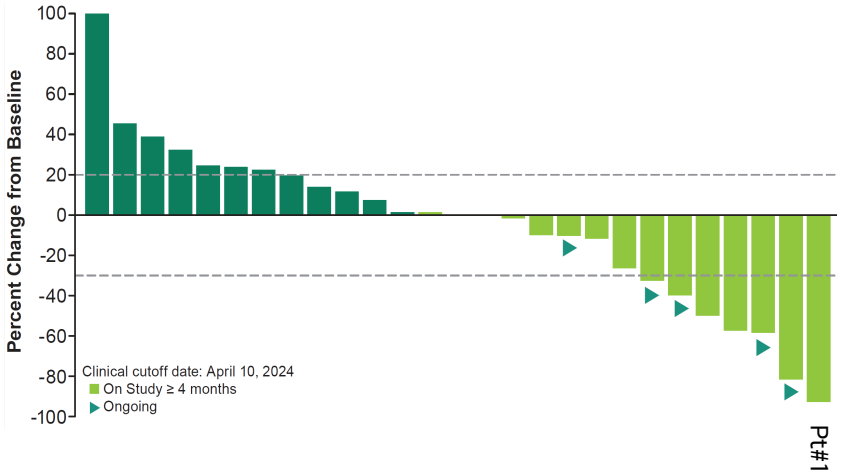
ScholarRock

Efficacy in Cohort ccRCC

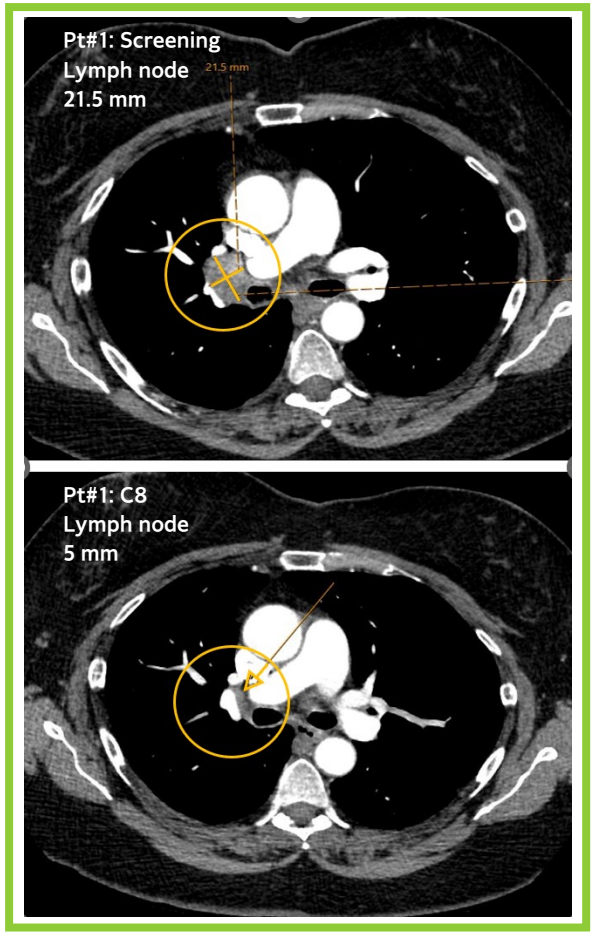
Clinical Responses in Heavily Pre-treated and Anti-PD-1 Resistant Patients



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

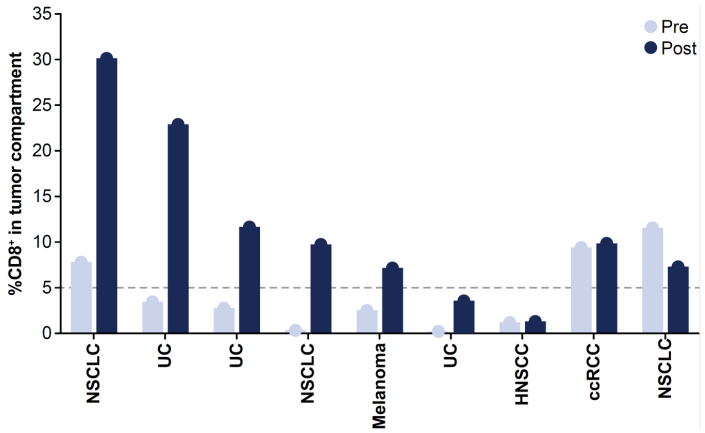
ScholarRock

Proof of Mechanism

SRK-181 and Pembrolizumab Treatment Creates a Proinflammatory Microenvironment

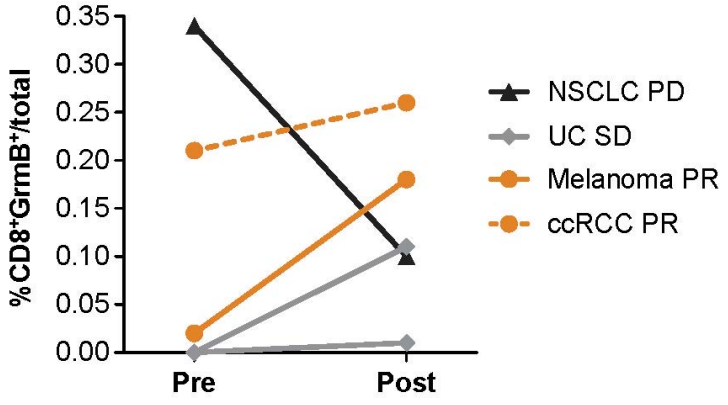
- SRK-181 and pembrolizumab increase CD8+ T-cells infiltration into tumors across multiple tumor types
- CD8+ T-cell were activated (CD8+GrmB+) in responding patients across multiple cohorts
- The number of CD8+GrmB+ cells correlates with tumor shrinkage

SRK-181 and Pembrolizumab Increased CD8+ Infiltration

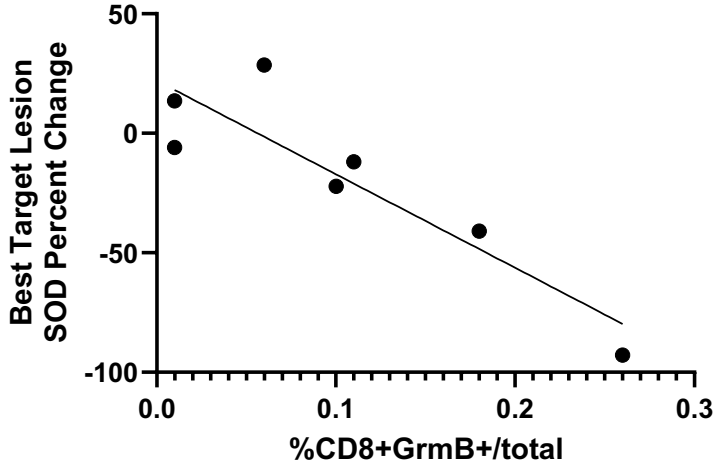


Line indicates cutoff that defines infiltrated status.
Data generated from available paired biopsies that were evaluated using a chromogenic assay.

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.

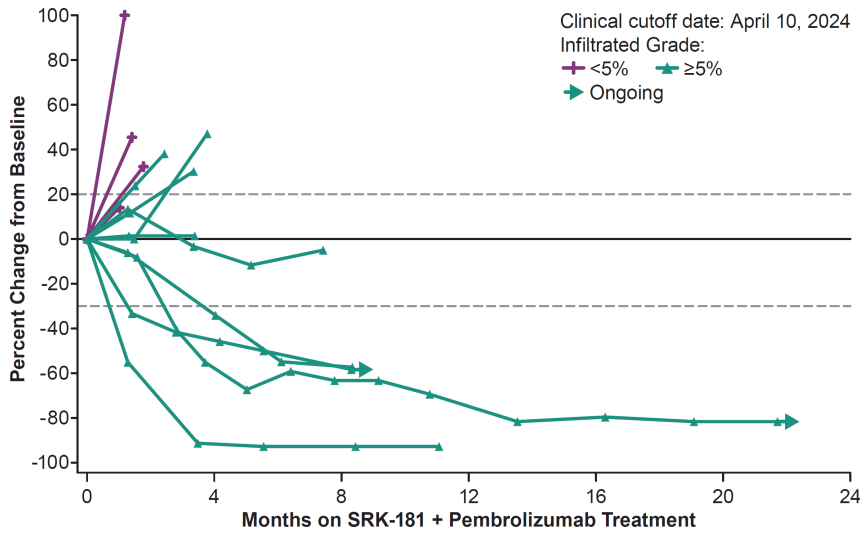
ccRCC, clear cell renal cell carcinoma; CD, cluster of differentiation; GrmB, Granzyme B; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; UC, urothelial carcinoma.
Data cut date: Apr 10, 2024

ScholarRock

Biomarker Data May Inform Patient Selection Strategy

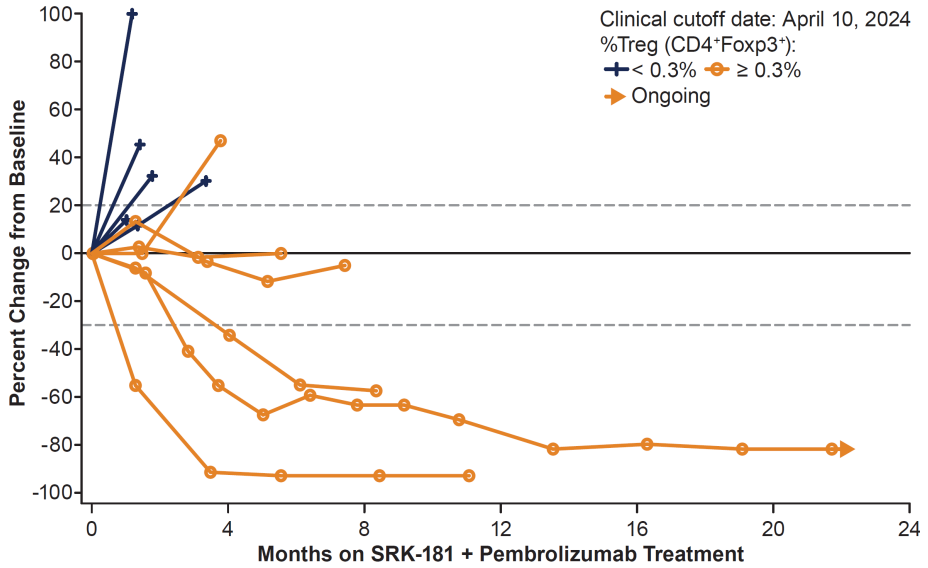
Baseline CD8+ T-cell Infiltration Status and Baseline Treg Levels Suggest a Higher Chance of Clinical Response

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

ScholarRock

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 alone[1]**
- **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

PD-1/PD-L1)

DRAGON Phase 1 POC Trial to Evaluate SRK-181's Ability to Overcome Primary Resistance to Checkpoint Inhibitors

DRAGON

PART A

A1

SRK-181
all-comers

- SRK-181 80 mg (n=1)
- SRK-181 240 mg (n=1)
- SRK-181 800 mg (n=3)
- SRK-181 1600 mg (n=3)
- SRK-181 2400 mg (n=3)
- SRK-181 3000 mg (n=3)*

A2

SRK-181+anti-PD-(L)1;
non-responders to prior anti-PD-(L)1

- SRK-181 240 mg (n=3)
- SRK-181 800 mg (n=3)
- SRK-181 1600 mg (n=3)
- SRK-181 2400 mg (n=3)

PART B

SRK-181 + pembrolizumab;
non-responders to prior anti-PD-1

COHORT	TREATMENT
Non-small cell lung cancer	SRK-181 + pembrolizumab
Urothelial carcinoma	SRK-181 + pembrolizumab
Cutaneous melanoma	SRK-181 + pembrolizumab
Clear cell renal cell carcinoma**	SRK-181 + pembrolizumab
Head and neck squamous cell** carcinoma	SRK-181 + pembrolizumab

* A cohort of 2000 mg Q2W (n=3) was also evaluated.
**The clear cell RCC and HNSCC cohorts will also explore the effects of SRK-181 in patients with relapsed response after anti-PD-1 treatment.

1. NCT04291079 on www.clinicaltrials.gov.

DRAGON Part A: Safety

PART A1 Monotherapy

Treatment-Emergent AEs Related to SRK-181, All Grades >10%

Dose (MG)	80 N=1	240 N=1	800 N=3	1600 N=4	2400 N=3	3000 N=3	2000 N=4	All N=19
Fatigue	0	1	0	0	1	0	1	3 (15.8%)
Decreased Appetite	1	0	1	0	0	0	0	2 (10.5%)
Nausea	1	0	0	0	0	0	1	2 (10.5%)

No DLTs were observed up to 3000 mg q3w and 2000 mg q2w

No Grade 4 or 5 treatment-related AEs occurred

Treatment-related Grade 3 AEs:

- Alanine aminotransferase increased (1 patient)

Treatment-related SAEs:

- None

PART A2 Combination Treatment

Treatment-Emergent AEs Related to SRK-181 or Anti-PD(L)1, All Grades >10%

Dose (MG)	240 N=3	800 N=3	1600 N=6	2400 N=3	All N=15
Rash maculo-papular	1	1	1	2	5 (33.3%)
Pruritus	1	1	1	1	4 (26.7%)
Rash	0	1	0	2	3 (20.0%)
Diarrhea	0	0	2	0	2 (13.3%)
Pemphigoid	0	0	0	2	2 (13.3%)

No DLTs were observed up to 2400 mg q3w

No Grade 4 or 5 treatment-related AEs occurred

Treatment-related Grade 3 AEs:

- Pruritus (2 patients), blister, immune-mediated lung disease, pemphigoid, rash, rash maculo-popular and rash vesicular (1 patient each)

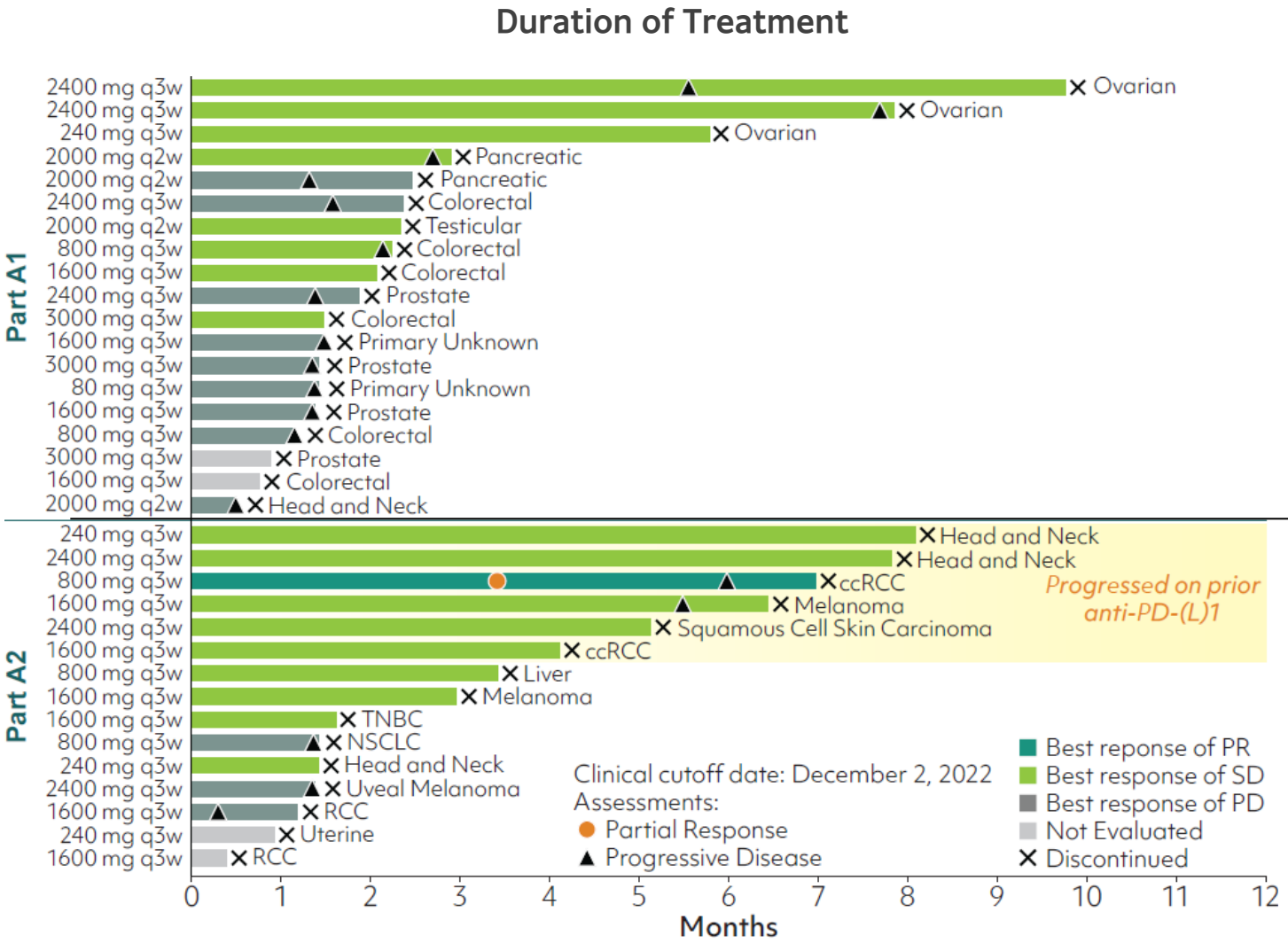
Treatment-related SAEs:

- Blister, pruritus, and rash (all in 1 patient) and immune-mediated lung disease (1 patient)

All dose levels were administered q3w except 2000 mg, which was administered q2w.

Yap T et al. Safety and Efficacy Results of SRK-181, a latent TGFβ1 inhibitor, from a Phase 1 trial (DRAGON Trial); Presented at ESMO-TAT; March 7, 2023. *Clinical cutoff date: December 2, 2022. Response is assessed using RECIST v1.1 by PI; the scan is performed during screening, 6 weeks after first dose, every 9 weeks for the next 6 months of treatment, and every 12 weeks thereafter. SRK-181 is an investigational drug candidate that is being evaluated for the treatment of cancer. SRK-181 has not been approved by the US FDA or any other health authority, and its safety and efficacy have not been established.

DRAGON Part A: Preliminary Efficacy Data*



Part A1 (n=19)

- 8 patients had a best response of stable disease (SD)

All 3 patients with ovarian cancer were stable for 6-10 months

Part A2 (n=15)

- At 800 mg q3w, 1 partial response (PR) was observed in patient with anti-PD-1-resistant clear cell renal cell carcinoma (ccRCC)
- 9 patients had best response of SD
- 6 patients (green highlight) were stable beyond the 16-week cutoff
  - 1 ongoing patient with head and neck cancer had a 29.4% tumor reduction

Yap T et al. Safety and Efficacy Results of SRK-181, a latent TGFβ1 inhibitor, from a Phase 1 trial (DRAGON Trial); Presented at ESMO-TAT; March 7, 2023. *Clinical cutoff date: December 2, 2022. Response is assessed using RECIST v1.1 by PI; the scan is performed during screening, 6 weeks after first dose, every 9 weeks for the next 6 months of treatment, and every 12 weeks thereafter. SRK-181 is an investigational drug candidate that is being evaluated for the treatment of cancer. SRK-181 has not been approved by the US FDA or any other health authority, and its safety and efficacy have not been established.

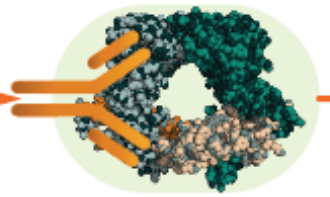
Mechanism of Action

SRK-181, a Selective Anti-TGFβ1 Antibody, Overcomes CPIs Resistance

TGFβ1 → Drives tumor immune escape that enables tumor survival[1] → Key driver of tumor resistance to CPIs[1] → Present in multiple compartments of the tumor microenvironment[1]

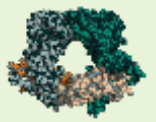
SRK-181 overcomes immune suppression and enhances tumor cell killing

Fully human IgG4 monoclonal antibody



Complete inhibition of TGFβ1

Inhibits activation of latent TGFβ-1 across ALL tumor compartments



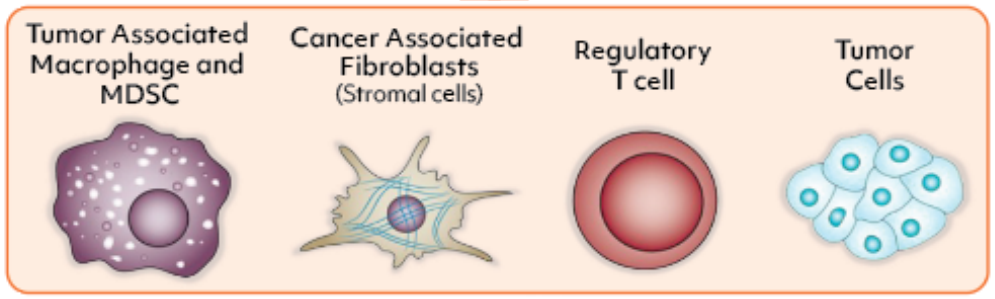
Latent TGFβ1

Mature TGFβ1

SRK-181 Targets latent TGFβ1 inhibiting growth factor before it gets activated

High selectivity to TGFβ1 vs TGFβ2/3

Increases therapeutic window and demonstrates an improved safety profile in GLP nonclinical toxicology studies, with no cardiotoxicities

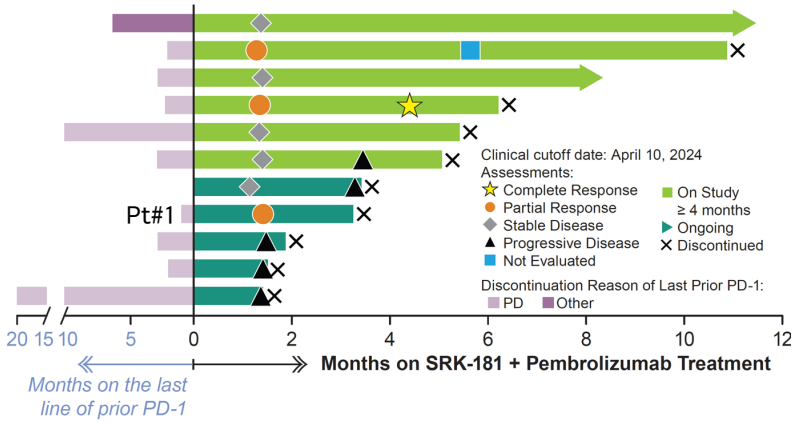


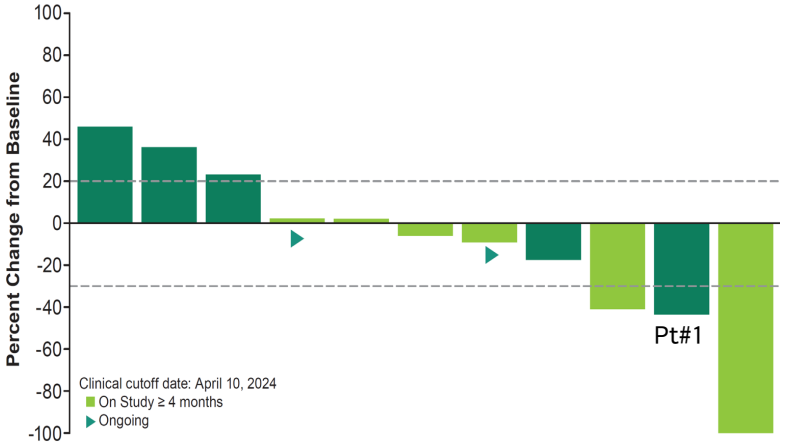
Overcome immune suppression and enhance tumor cell killing

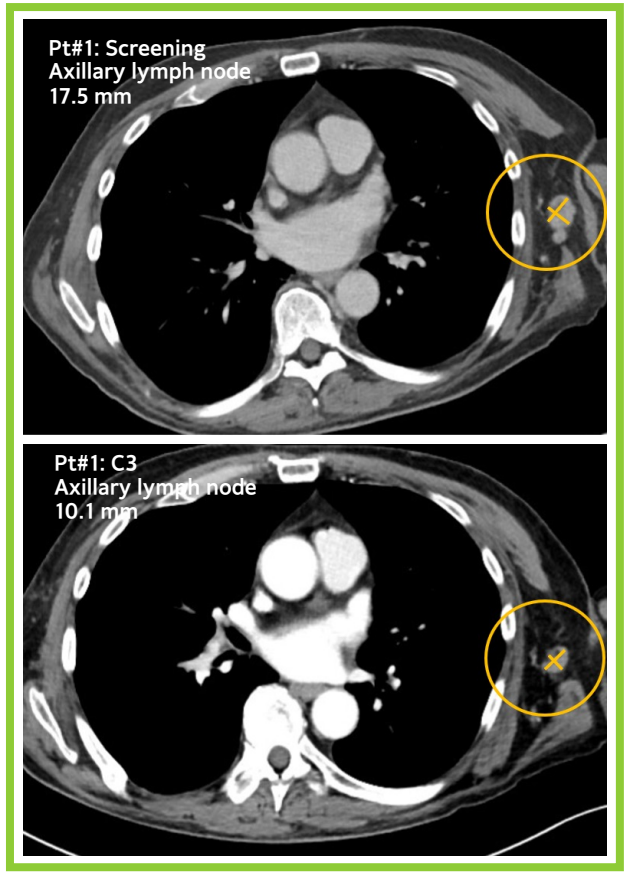
1.Batlle E, et al. *Immunity.* 2019; 50(4):924-940.
CPI, checkpoint inhibitor; GLP, good laboratory practice; MDSC, myeloid derived suppressor cells; TGFβ1, transforming growth factor beta-1.

Efficacy in Cohort MEL

Clinical Responses in Anti-PD-1 Non-responders







Efficacy	Intent To Treat N=11
ORR	3 (27.3%)
Confirmed CR	1 (9.1%)
Confirmed PR	1 (9.1%)
mDoR (Months)	4.9 (1.8, 7.1)
DCR	8 (72.7%)

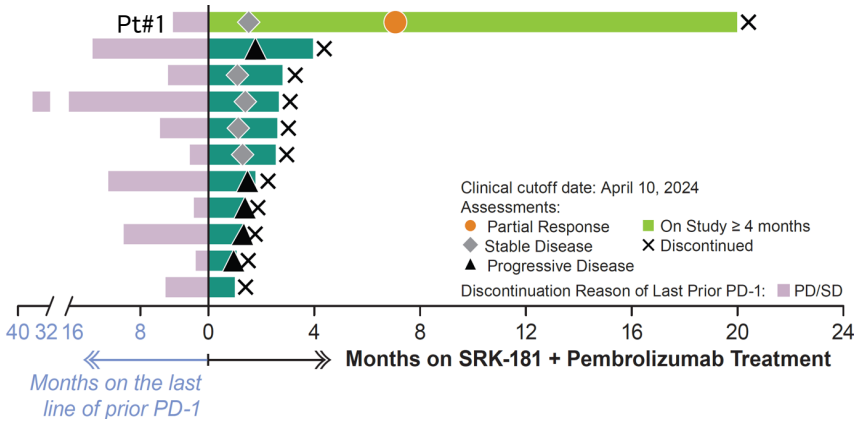
- **Median lines of prior cancer therapy: 3 (range 1 – 7)**
  - All have SD or PD as BOR to the last prior anti-PD-1
  - 9 (82%) had PD from the last prior anti-PD-1

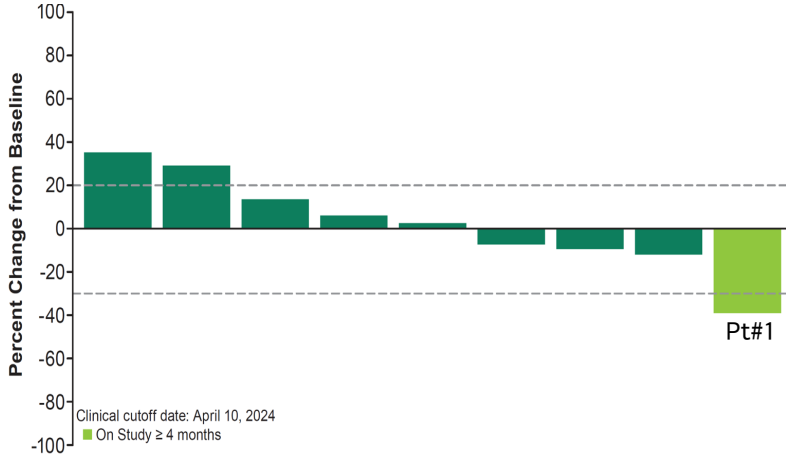
BOR, best overall response; CR, complete response; DCR, disease control rate; mDoR, median duration of response; MEL, melanoma; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response.
Data cut date: Apr 10, 2024

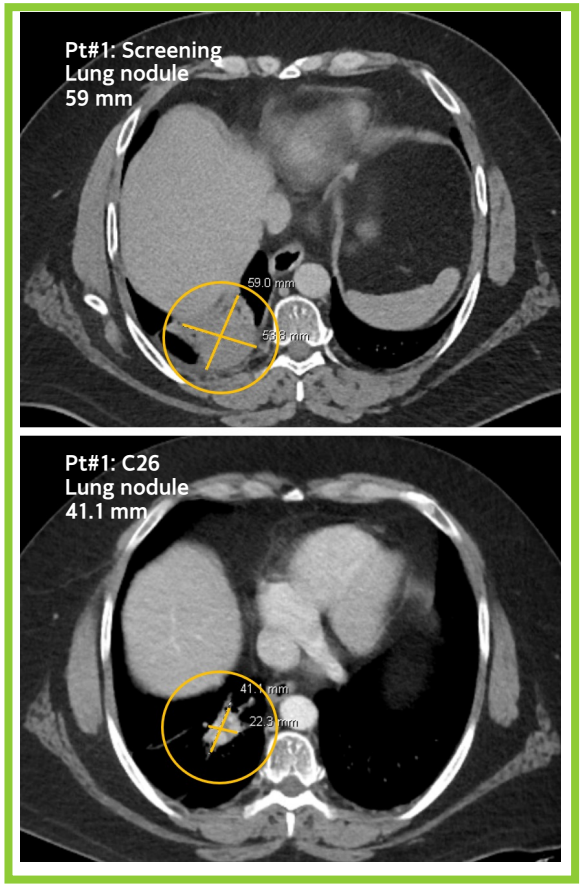
ScholarRock

Efficacy in Cohort UC

Clinical Responses in Anti-PD-1 Non-responders







Efficacy	Intent To Treat N=11
ORR	1 (9.1%)
Confirmed PR	1 (9.1%)
mDoR (Months)	12.9 (12.9, 12.9)
DCR	5 (45.5%)

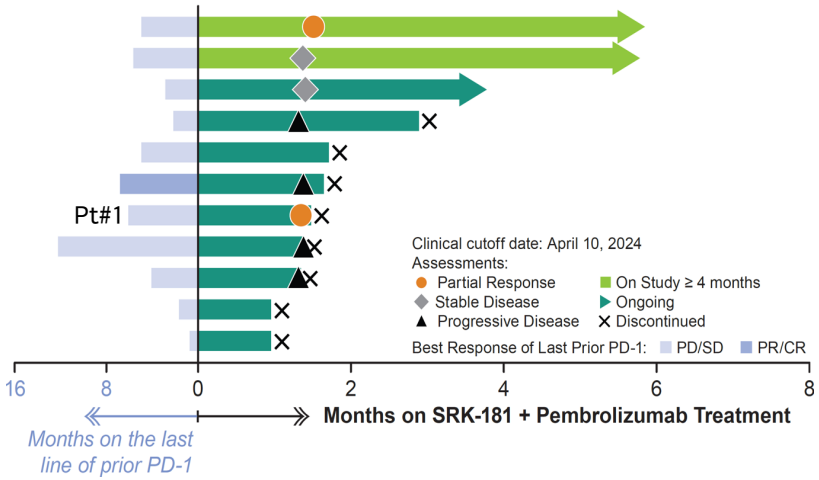
- **Median lines of prior cancer therapy: 4 (range 2 – 5)**
  - All have SD or PD as BOR to the last prior anti-PD-1
  - All had PD from the last prior anti-PD-1

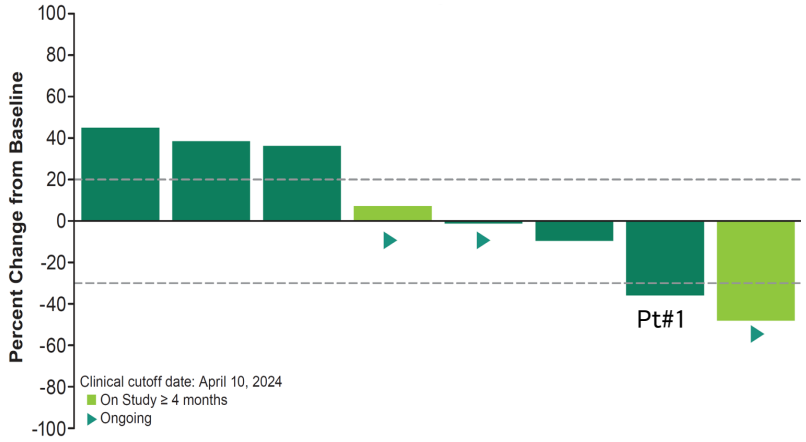
BOR, best overall response; DCR, disease control rate; mDoR, median duration of response; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease; UC, urothelial carcinoma.
Data cut date: Apr 10, 2024

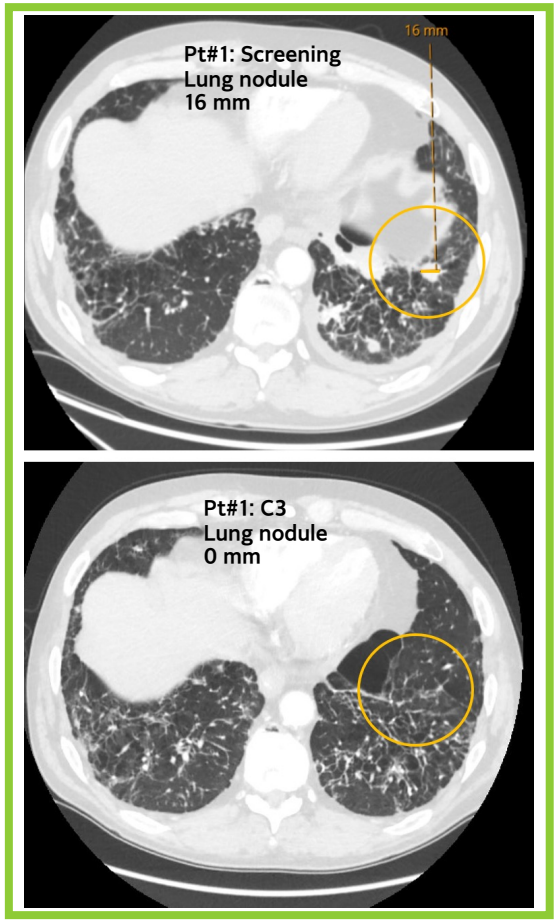
ScholarRock

Efficacy in Cohort HNSCC

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







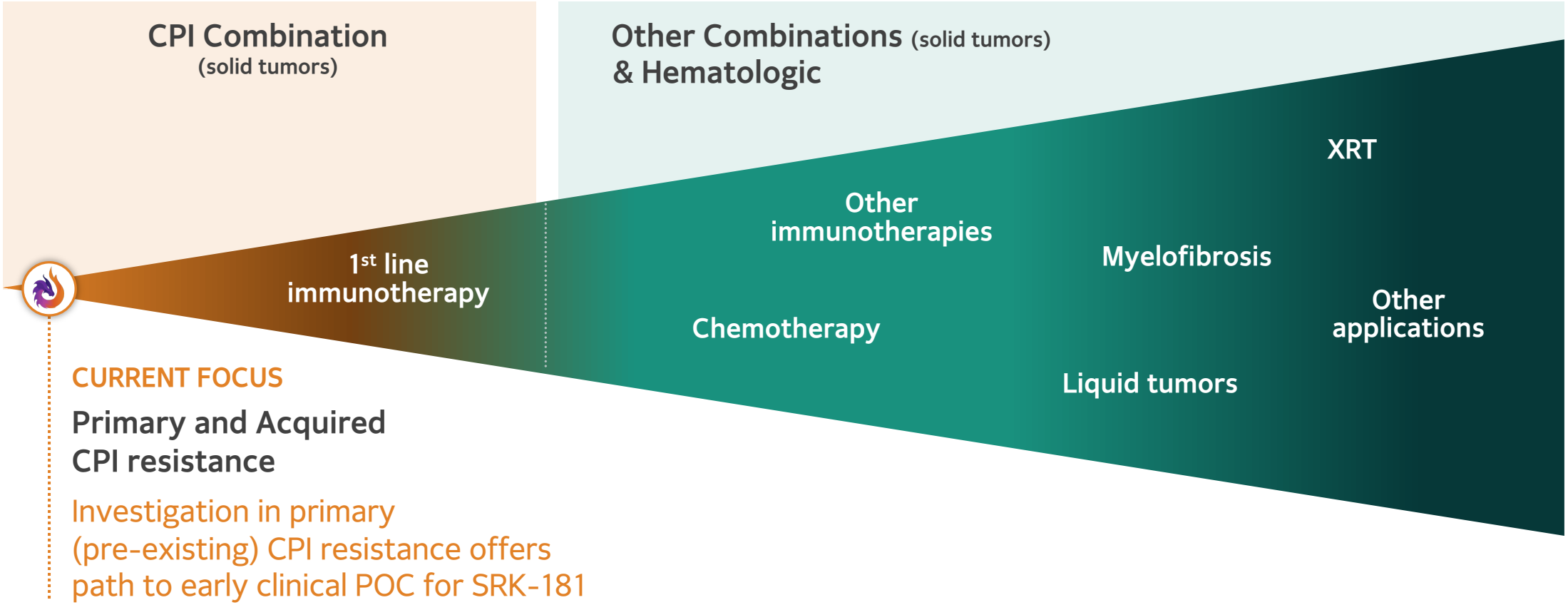
Efficacy	Intent To Treat N=11
ORR	2 (18.2%)
Confirmed PR	1 (9.1%)
mDoR (Months)	2.2+ (0.1, 4.3+)
DCR	4 (36.4%)

- **Median lines of prior cancer therapy: 3 (range 1 – 7)**
  - 10 (91%) have 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; HNSCC, head and neck squamous cell carcinoma; 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.
Data cut date: Apr 10, 2024

ScholarRock

SRK-181: Transformative Potential as the Backbone For Next Era of Cancer Therapy



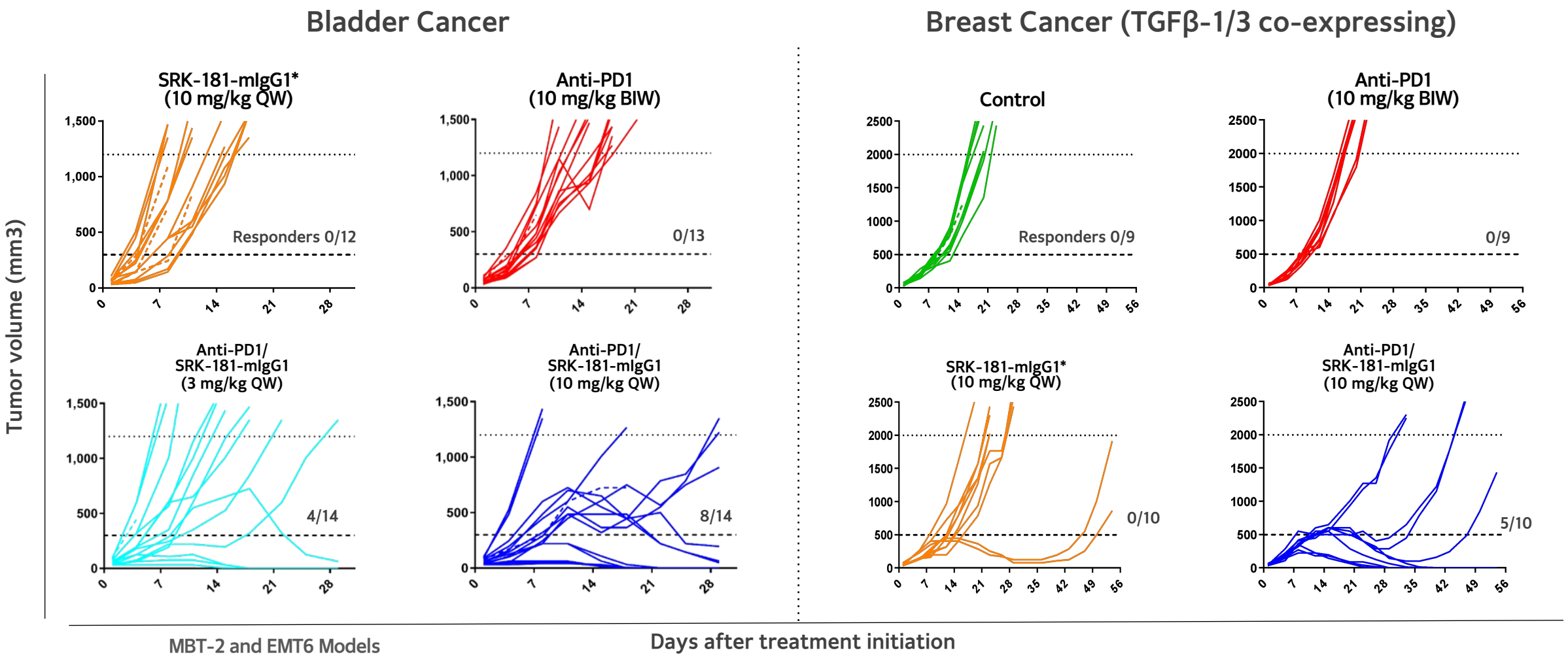
First in class monoclonal antibody targeting latent and context-independent binding to TGFB-1

SRK-181 Therapeutic Hypothesis: Potential Advantages of Latent TGFβ-1 Inhibitor

	SRK-181*	Bifunctional TGFβ/CPI	ALK5 Inhibitor	Nonselective TGFβ antibody
Selectivity for TGFβ-1: potential for wider therapeutic window and improved safety	✓	✗	✗	✗
Ability to combine with any anti-PD-(L)1	✓	✗	✓	✓
Ability to optimize dosing of each component of combination therapy	✓	✗	✓	✓
Activity spatially distinct from anti-PD-(L)1 in tissue	✓	✗	✓	✓
Inhibits all sources of TGFβ-1 contributing to CPI resistance (Context independent)	✓	✗	✓	✓
Target latent form (Blocks TGFβ-1 activation)	✓	✗	✗	✗

*SRK-181 is an investigational product candidate currently being evaluated in DRAGON phase 1 clinical trial. The efficacy and safety of SRK-181 have not been established.

TGFβ-1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

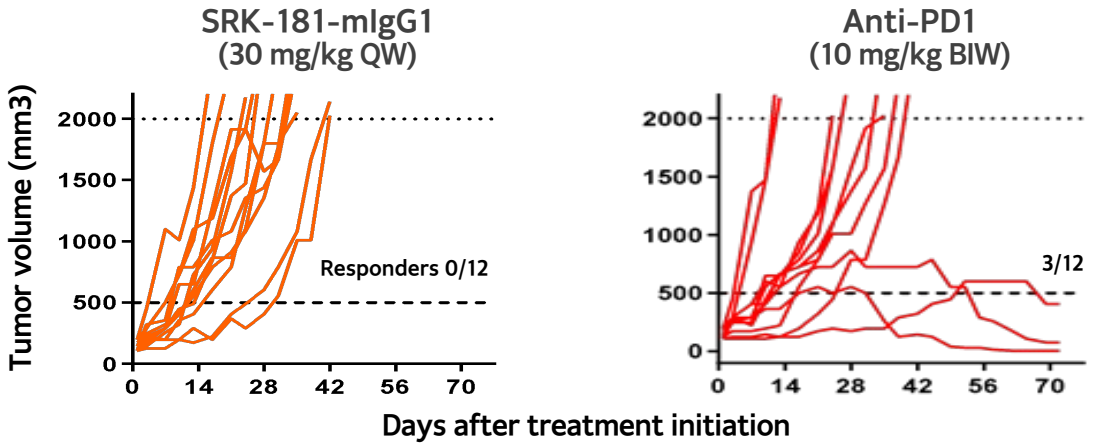


Preclinical data published in Science Translational Medicine. Martin CJ, et al. Sci Transl Med. 2020 Mar 25;12(536):eaay8456. https://scholarrock.com/platform/publications/.
*SRK-181-mIgG1 is the murine version of SRK-181; responder defined as tumor size <25% endpoint volume at study end.

SRK-181-mIgG1 Combination Treatment Led to Melanoma Tumor Regression and Survival Benefit

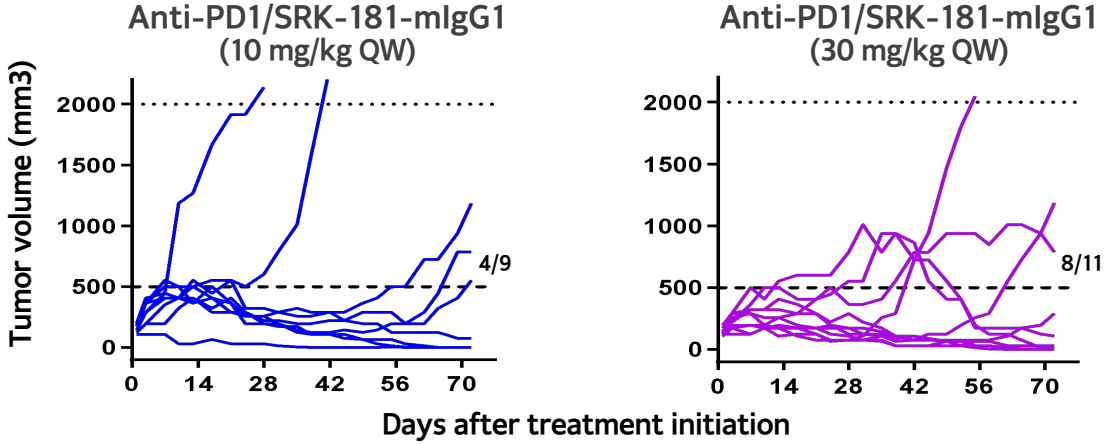
Tumor Regression

Monotherapy

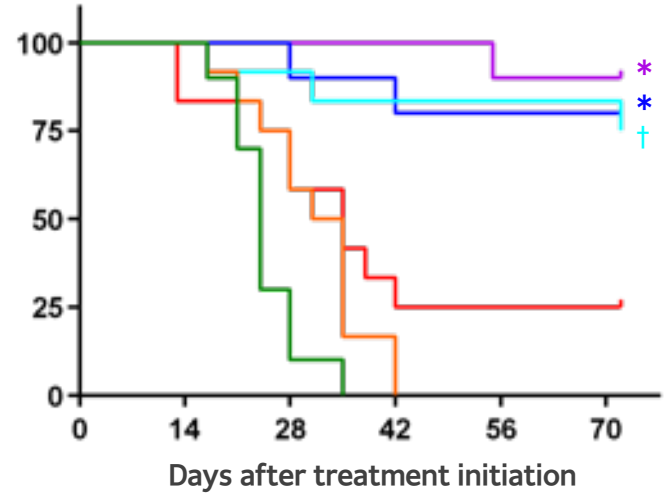


Combination Therapy

Led to tumor regression and survival benefit



Survival Benefit



*P<0.01.
†P<0.05 Log-rank (Mantel-Cox test) vs anti-PD1.

Melanoma (Cloudman S91) model

Preclinical data published in Science Translational Medicine. Martin CJ, et al. Sci Transl Med. 2020 Mar 25;12(536):eaay8456. https://scholarrock.com/platform/publications.

Selectivity of SRK-181 Offers Potential to Overcome Toxicity and Dose-limiting Challenges of Non-selective TGFβ Pathway Approaches

Toxicology:

- Unremarkable
- Minimal
- Slight
- Moderate

Non-selective TGFβ

Toxicity: Minimal, slight and moderate

Selective TGFβ-1

Toxicity: Minimal

Microscopic Observations in Heart	CONTROL Vehicle iv, qwk x 4	LY2109761 300 mg/kg po, qd x 8	PanTGFβAb 30 mg/kg Iv, 1 dose	SRK-181 10 mg/kg iv, qwk x 4	SRK-181 30 mg/kg iv, qwk x 4	SRK-181 100 mg/kg iv, qwk x 4
Valvulopathy						
Atrium—Mixed cell infiltrate						
Myocardium—Degeneration/necrosis						
Myocardium—Hemorrhage				*		
Myocardium—Mixed cell infiltrate, base						
Coronary artery—Necrosis with inflammation						
Cardiomyocyte—Necrosis/inflammatory cell infiltrate				*		

* Not test article related

Repeat Dose Pilot Toxicology Study

Adult female Sprague Dawley rats

Cardiac findings were exhibited
in animals dosed with pan-TGFβ antibody or LY2109761 (inhibitor of ALK5, common TGFβ receptor kinase) **as expected based on published data†**

NO CARDIOTOXICITIES (valvulopathy) were noted with SRK-181
NOAEL for SRK-181: 100 mg/kg QW
(highest dose evaluated)

4-week GLP toxicology studies

RATS
NOAEL for SRK-181: 200 mg/kg QW
(highest dose evaluated)

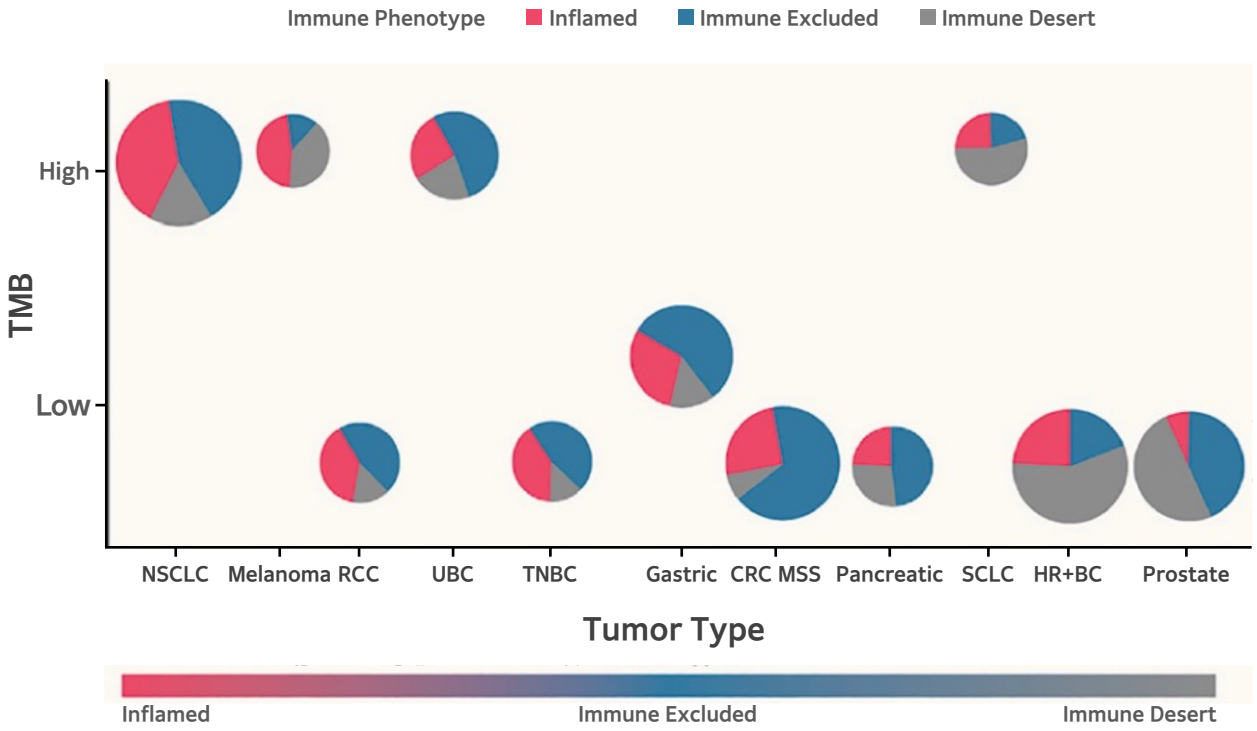
NON-HUMAN PRIMATES
NOAEL for SRK-181: 300 mg/kg
(highest dose evaluated)

Preclinical data published in *Science Translational Medicine*. Martin CJ, et al. *Sci Transl Med* 2020 Mar 25;12(536): eaay8456.

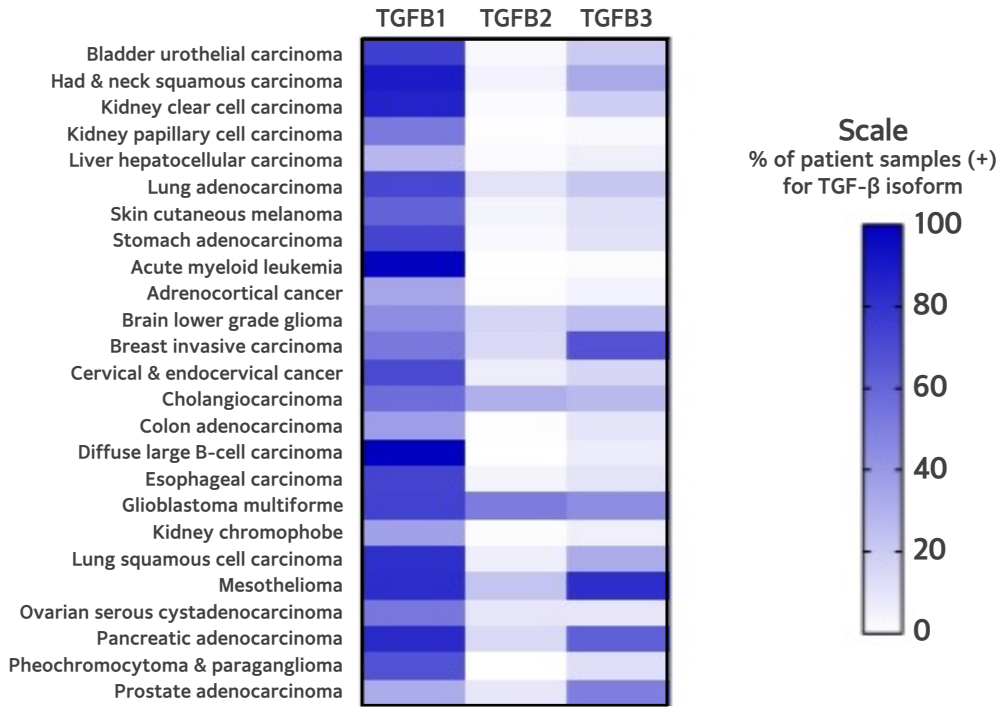
*Source: Anderton MJ, et al. Induction of heart valve lesions by small-molecule ALK5 inhibitors. *Toxicol Pathol*. 2011;39: 916-924.; and Stauber AJ, et al. Nonclinical safety evaluation of a transforming growth factor β Receptor I kinase inhibitor in Fischer 344 rats and beagle dogs. *J Clin Pract*. 2014: 4:3.

Emerging Evidence Implicates TGFβ-1 as Driving Primary Resistance to Checkpoint Inhibitors

Substantial % of Solid Tumors Exhibit Immune Exclusion



Cancer Genome Atlas RNAseq Analysis of >10,000 Samples Spanning 33 Tumor Types*



Human Tumor Analyses Reveal TGFβ-1 as Most Likely Driver of TGFβ Signaling Pathway in Cancers

†Priti H, et al. Top 10 challenges in cancer immunotherapy. *Immunity*. 2020 Jan 14:52(1):17-35. https://doi.org/10.1016/j.immuni.2019.12.011.
*Source: National Cancer Institute - Cancer Genome Atlas Program.

Biomarker Strategies Employed in DRAGON Trial

Multiple tissue-based and circulating biomarker analyses to be evaluated in DRAGON study

Immunophenotyping
Assessment of immune landscape

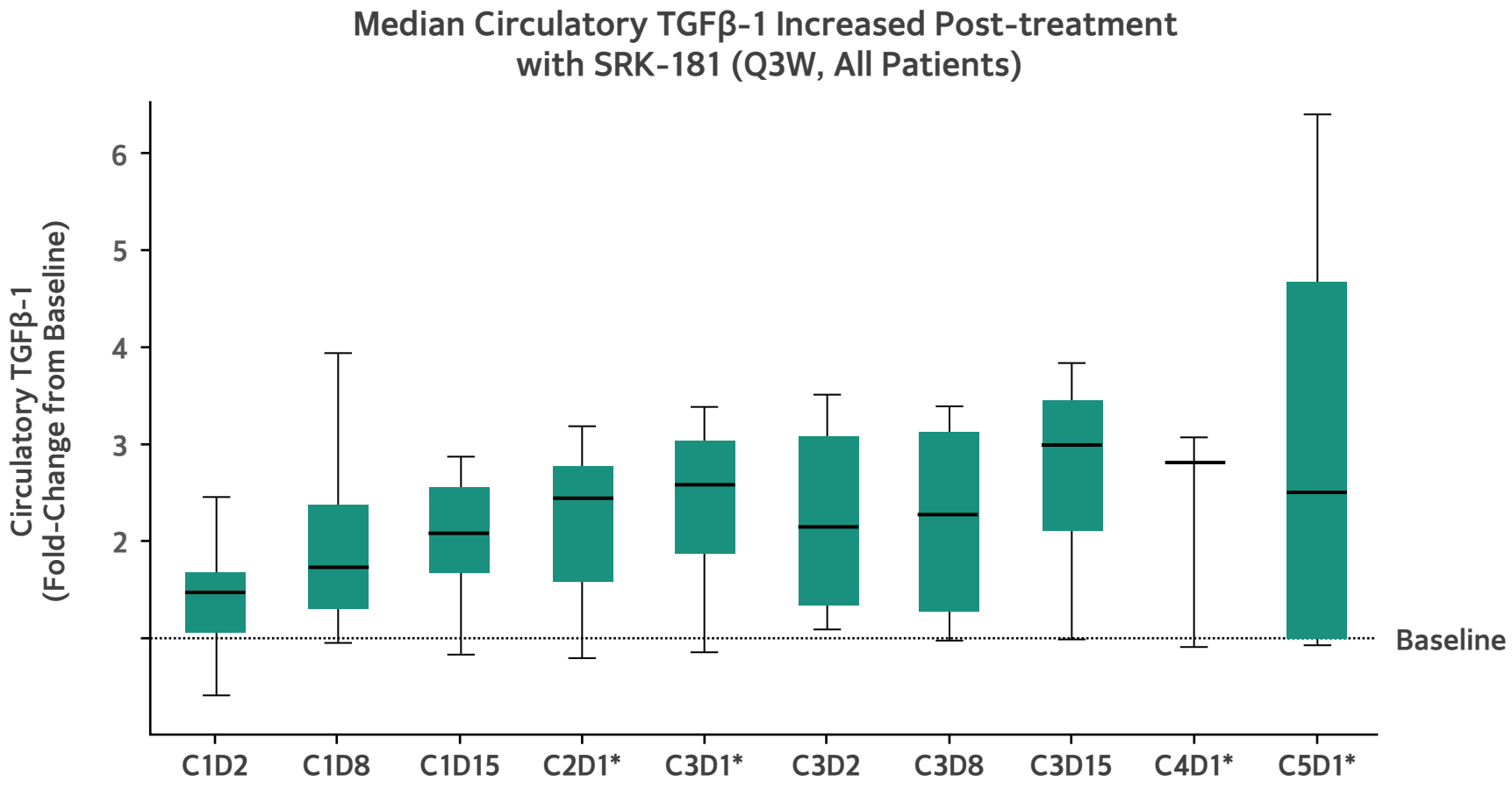
- Higher resolution histochemical characterization of tumor immune contexture (e.g. CD8+)
  - Classification of inflamed, excluded or immune desert tumors and tumor nests
  - Ability of SRK-181 to overcome tumor immune exclusion
- Analysis of immune response markers (e.g. PD-L1)
- Changes to intra-tumoral and/or circulating immune cell contexture (MDSC)

TGFβ-1 pathway evaluation
Assessment of signaling pathway

- Show evidence of the SRK-181 target engagement
  - e.g. circulating TGFβ-1 levels
- TGFβ pathway modulation:
  - e.g. Histochemical analysis of pSMAD
  - e.g. RNA-based TGFβ gene signatures and pathway analyses
- Paired biopsies from the head and neck cohort allow for a potential to accelerate the development path

Clear Evidence of Target Engagement

Pharmacodynamic Biomarker Results for Part A: Circulatory TGFβ-1



Binding to latent TGFβ-1 delays maturity state allowing TGFβ-1 to accumulate in system

Combination treatment with pembrolizumab did not appear to impact circulatory TGFβ-1 levels

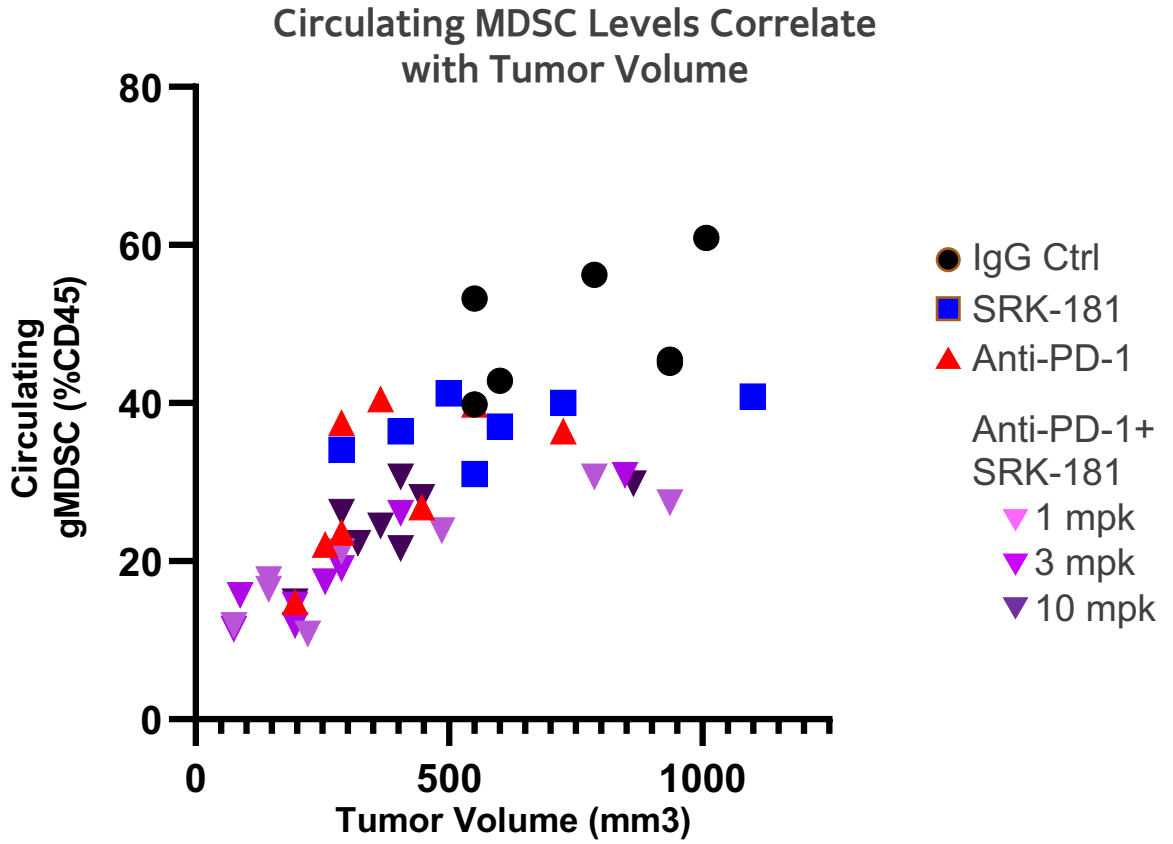
Yap T et al. SRK-181, a latent TGFβ1 inhibitor: safety, efficacy, and biomarker results from the dose escalation portion of a phase I trial (DRAGON trial) in patients with advanced solid tumors (Poster 780); Presented at SITC; Nov. 10-11, 2022. Circulatory TGFβ-1 and PF4 levels were quantitated by using validated ELISA kits from R&D System.12 Because platelet activation during sample processing can lead to elevated TGFβ-1 levels, samples with elevated PF4, a platelet activation biomarker, were excluded from the analysis based on a preliminary cutoff value.
Pre-infusion.
SRK-181 is an investigational drug candidate that is being evaluated for the treatment of cancer. SRK-181 has not been approved by the US FDA or any other health authority, and its safety and efficacy have not been established.

Preclinical Data Provide Scientific Rationale to Evaluate Peripheral Samples for Evidence of SRK-181 Activity

Immunophenotyping
Assessment of immune landscape

Measurement of MDSCs in circulation may provide indirect evidence of drug action on the tumor

- Myeloid-derived suppressor cells (MDSCs) have immune suppressive functions
- SRK-181 plus anti-PD1 combination drive MDSC levels down significantly in the tumor microenvironment
- Reductions in circulating MDSC levels correlate with reduced tumor volume following SRK-181 and anti-PD1 treatment in MBT-2 tumor model



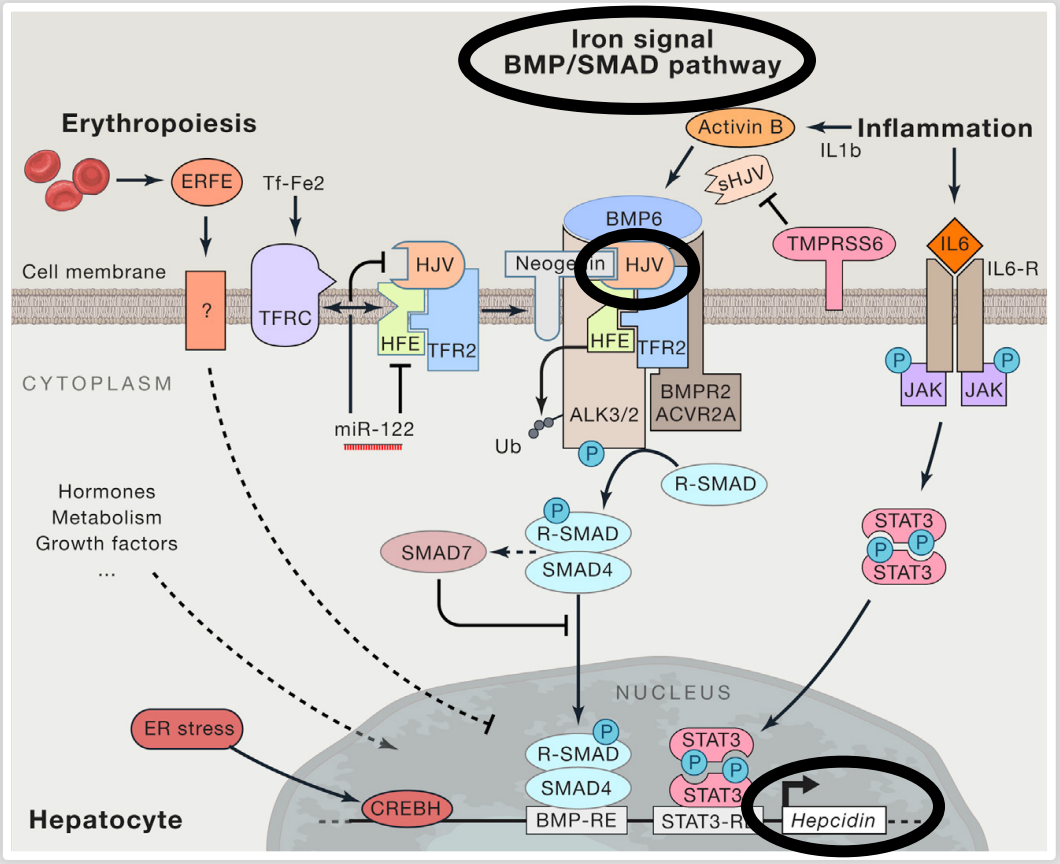
Both tumoral and circulatory MDSC are being evaluated in the DRAGON study

MBT-2 bladder tumor model IgG, anti-PD-1 and SRK-181-mIgG1 dosed d1, d7
Analysis on day 10

Iron-Restricted Anemia

ScholarRock

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 regulation[1]
- Knockout phenotypes and tissue-specific expression pattern demonstrate that its predominant role is in iron homeostasis[2]
- Member of repulsive guidance molecule (RGM) family (RGMa, RGMb, RGMc/HJV) that act as BMP co-receptors to modulate BMP signaling[3]

Anemia of Inflammation/ Chronic Disease

- Elevation of proinflammatory cytokines drives increased hepcidin expression and results in anemia due to functional iron deficiency[4]

Untreated	Ab treated
↑ Hepcidin	↓ Hepcidin
↓ Serum iron	↑ 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

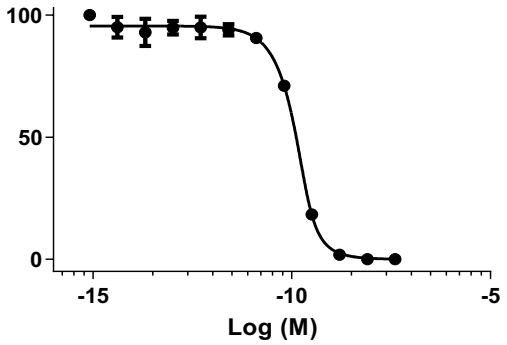
1: *Kuns-Hashimoto R, et al.* (2008) Selective binding of RGMc/hemojuvelin, a key protein in systemic iron metabolism, to BMP-2 and neogenin. *Am J Physiol Cell Physiol* 294(4):C994-C1003
2: *Constante M, et al.. (2007)* Repression of repulsive guidance molecule C during inflammation is independent of Hfe and involves tumor necrosis factor-alpha. *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

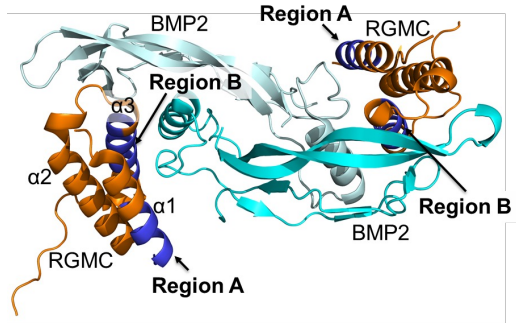
Key Attributes of HJV-35202:[1,2]

- 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)

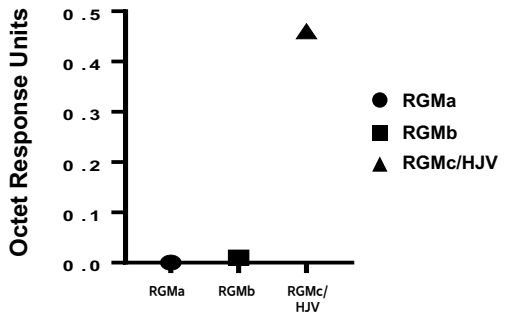
Potent in vitro binding affinity (KD=3.9E-11)



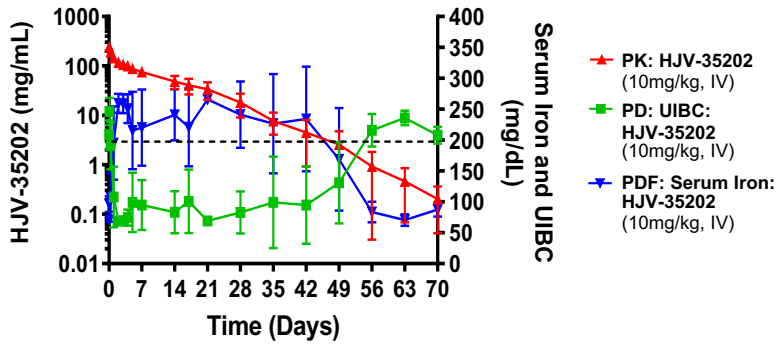
Highly specific to RGMc/HJV with well understood mechanism



Specific to RGMc over other RGM family members

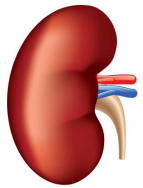


Sustained PD effect in single dose Cyno study



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