Deep Insights Advancing Impactful Medicines

May 2023

ScholarRock™

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Various statements in this presentation concerning the future expectations, plans and prospects of Scholar Rock, Inc. (“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 clinical trials for apitegromab, SRK-181, and other product candidates and indication selection and development timing, its cash runway, the ability of any product candidate to perform in humans in a manner consistent with earlier nonclinical, preclinical or clinical trial data, and the potential of its product candidates and proprietary platform. The use of words such as “may,” “could,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify such forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. All such forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, without limitation, that preclinical and clinical data, including the results from the Phase 2 trial of apitegromab or Part A of the Phase 1 trial of SRK-181, are not predictive of, may be inconsistent with, or more favorable than, data generated from future clinical trials of the same product candidate, including the Phase 3 clinical trial of apitegromab in SMA and Part B of the Phase 1 clinical trial of SRK-181, respectively, Scholar Rock’s ability to provide the financial support, resources and expertise necessary to identify and develop product candidates on the expected timeline, the data generated from Scholar Rock’s nonclinical and preclinical studies and clinical trials, information provided or decisions made by regulatory authorities, competition from third parties that are developing products for similar uses, Scholar Rock’s ability to obtain, maintain and protect its intellectual property, the success of Scholar Rock’s current and potential future collaborations, Scholar Rock’s dependence on third parties for development and manufacture of product candidates including, without limitation, to supply any clinical trials, Scholar Rock’s ability to manage expenses and to obtain additional funding when needed to support its business activities and establish and maintain strategic business alliances and new business initiatives, and the impacts of current macroeconomic and geopolitical events, including changing conditions from the COVID-19 pandemic, hostilities in Ukraine, increasing rates of inflation and rising interest rates, on business operations and expectations, as well as those risks more fully discussed in the section entitled "Risk Factors" in Scholar Rock’s Annual Report on Form 10-K for the quarter ended December 31, 2022, 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.

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

ScholarRock™

Scholar Rock:

Transforming Patient Lives, Targeting High Unmet Medical Need

Revolutionary Platform

- Global leader in TGFβ superfamily biology
- Targeting the latent forms of growth factors
- Exquisite selectivity to deliver differentiated therapeutic profiles

Neuromuscular and Beyond

- Rich preclinical pipeline focused on high unmet patient needs
- Phase 3 SAPPHIRE study underway, data readout expected in 2024
- Phase 1 POC DRAGON study underway in immuno-oncology

Positioned for Success

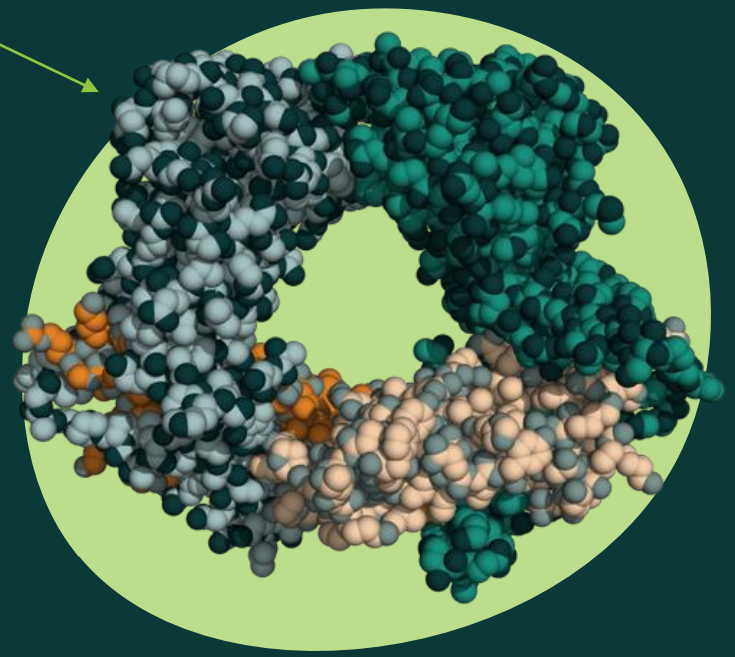
- Compelling proof-of-concept TOPAZ data informed Phase 3 SAPPHIRE study design
- Seasoned leadership team with track record of clinical and commercial success
- Anticipated cash runway into 2025

Strategic Optionality

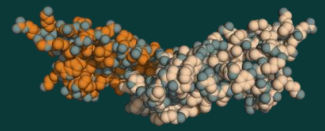
- Commercial planning underway for apitegromab (SMA) in US and Europe
- Broad platform, including promising early-stage assets, provides opportunities to advance alone or in partnership

Revolutionary Approach to Regulating TGFβ Superfamily Implicated in Devastating Diseases

Scholar Rock's Target
Latent Growth Factor



Traditional Target
"mature" growth factor



TGFβ Superfamily: Highly Sought-After Targets

Recognized by the industry as important targets given their fundamental roles in regulating a variety of cellular processes

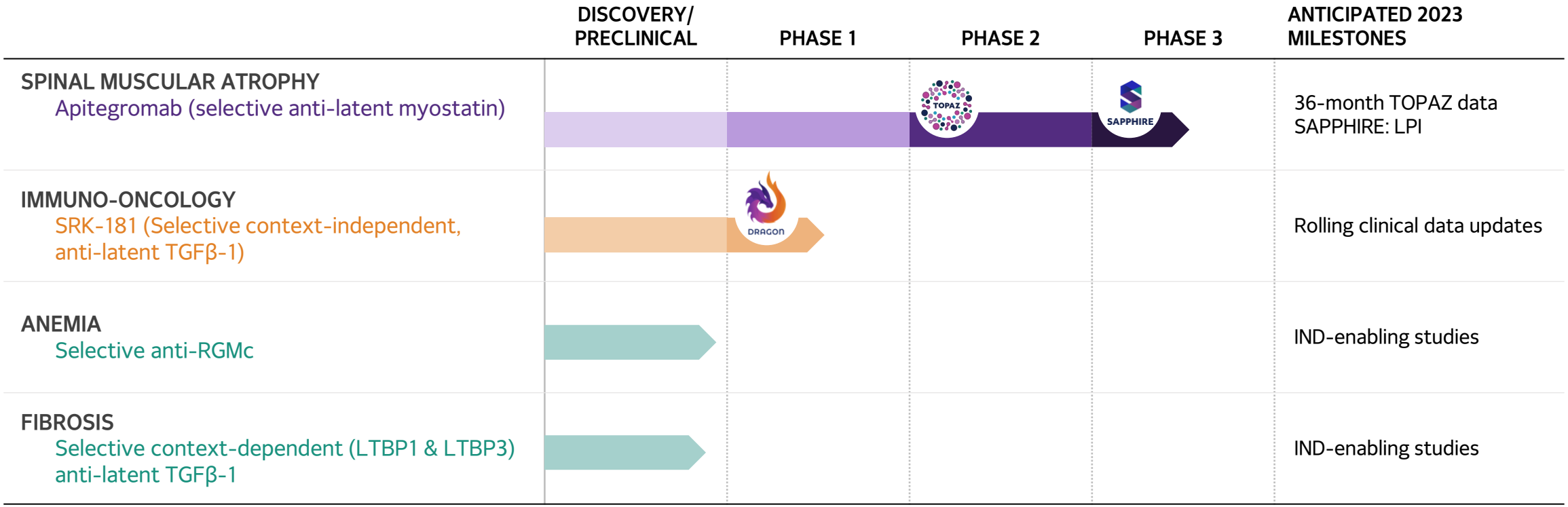
Dysregulation plays a role in devastating diseases that have a high unmet need, including:

- Neuromuscular disorders
- Fibrosis
- Oncology

Scholar Rock's R&D Platform
Transforming Medical Practice

- Selectively target the latent form of growth factors in the microenvironment of cells and tissues with uniquely designed antibodies
- Overcome the challenges that plague traditional approaches that target the "mature" growth factor, which are difficult to differentiate and lead to unintended negative effects

Robust Pipeline of Novel Product Candidates



Potential to transform the lives of patients with a wide range of serious diseases, including neuromuscular disorders, oncology, and fibrosis

Leadership Team: Experienced in Drug Development and Commercialization

Jay Backstrom, MD, MPH
President & CEO

30 years of clinical R&D experience, leading multiple successful regulatory approvals

Ted Myles, MBA
Chief Operating Officer & CFO

25 years of progressive experience in clinical and commercial-stage companies

Jing Marantz, MD, PhD
Chief Medical Officer

20 years of development and medical leadership experience across neurology, hematology/oncology, and rare diseases

Tracey Sacco
Chief Commercial Officer

20 years of commercial leadership experience, including product launch and global commercial strategy

Mo Qatanani, PhD
SVP, Research

15 years of industry experience on the strategic and operational sides of research & development

Caryn Parlavecchio
Chief Human Resources Officer

25 years of experience leading HR, culture transformation, leadership development, DEI, and talent management

Junlin Ho, JD
General Counsel & Corporate Secretary

15 years of experience leading and advising life sciences companies in areas of legal and compliance

TOPAZ

SAPPHIRE

Apitegromab: The Next Potential Transformative Therapy for Patients with Spinal Muscular Atrophy (SMA)

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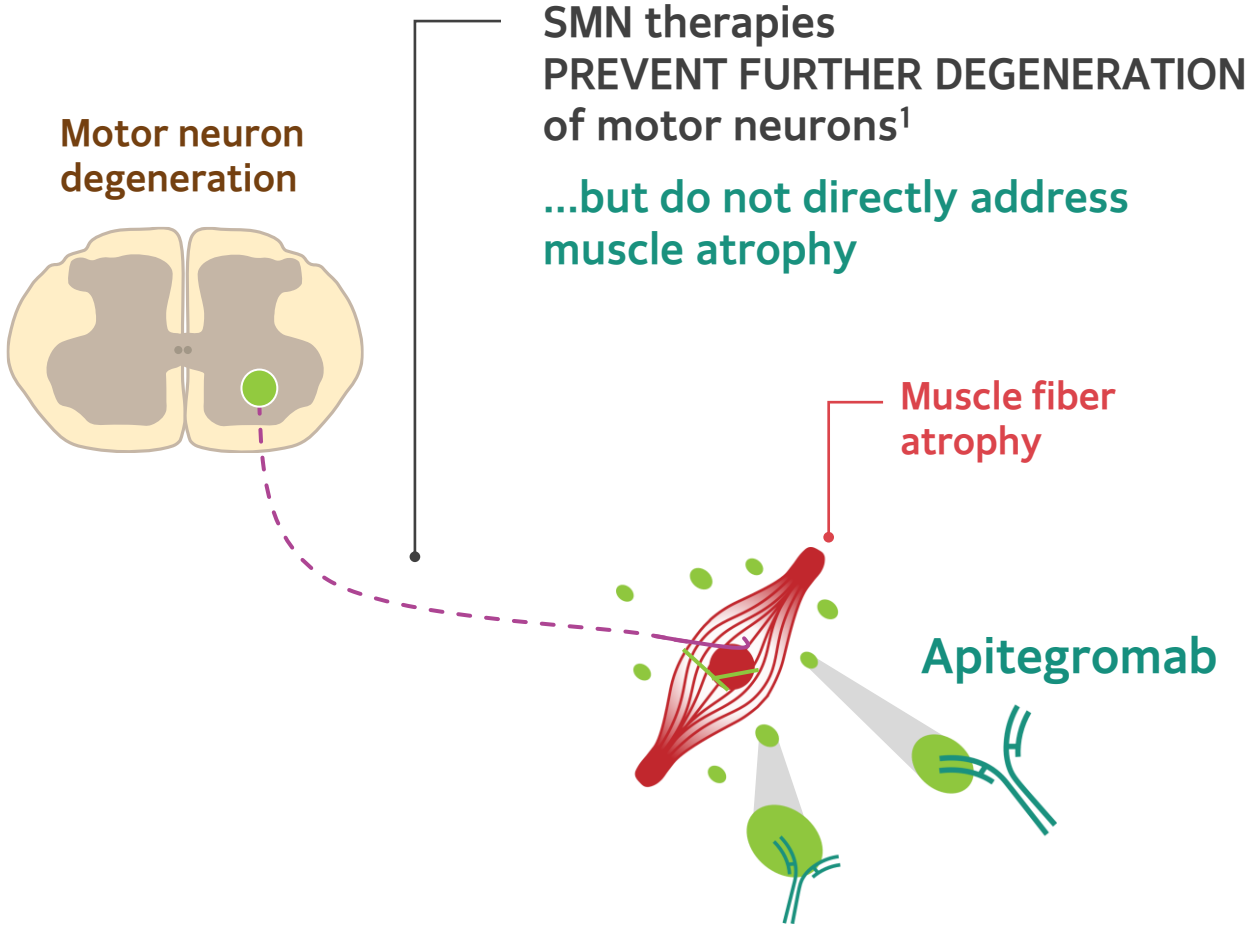
Apitegromab: Potential Muscle-Targeted Therapy for SMA



Apitegromab is a MUSCLE-TARGETED APPROACH aimed at improving motor function*[2,3]

Myostatin is a negative regulator of skeletal muscle growth

Apitegromab is a fully human, mAb that specifically binds to proforms of myostatin and inhibits myostatin activation, leading to increased muscle mass and muscle function

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

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

Spinal Muscular Atrophy

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

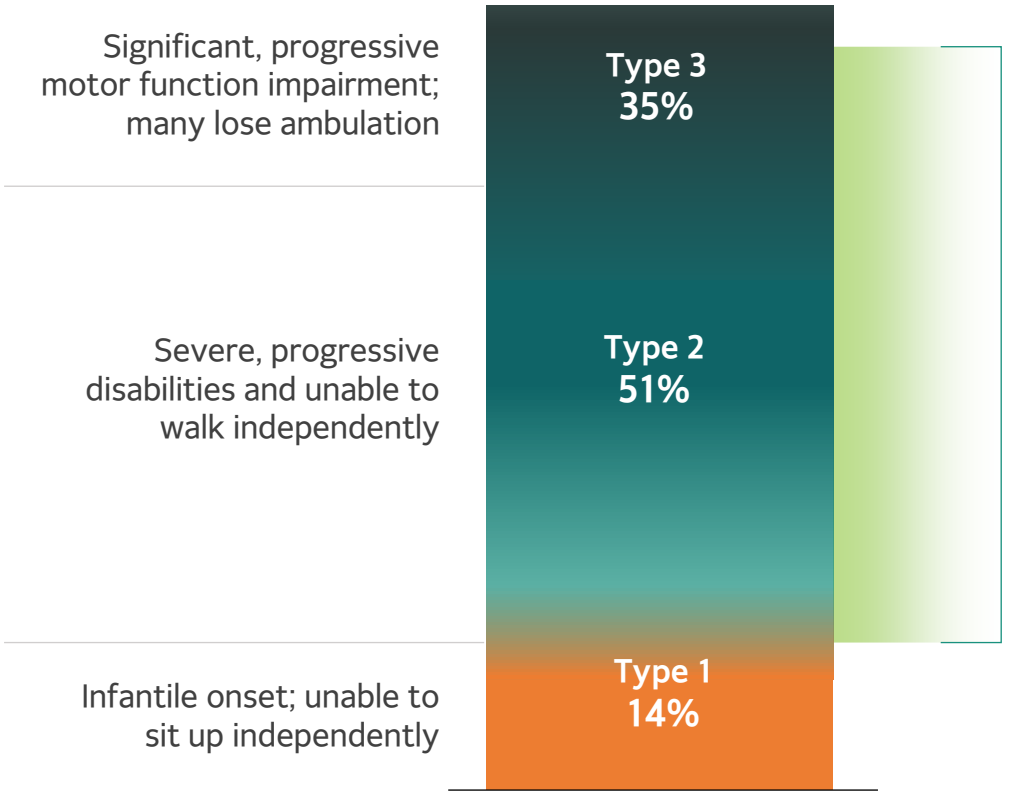
GLOBAL DISEASE:

30,000-35,000 affected

in US and Europe alone[1, 2, 3,4]

ALMOST 70% OF INDIVIDUALS WITH SMA IN THE U.S. HAVE RECEIVED AN FDA-APPROVED TREATMENT

Cure SMA. State of SMA. May 31, 2022, p. 20



TOPAZ* 12-month results showed transformative potential in non-ambulatory Types 2 and 3 patients

>2/3 of overall patient population

*TOPAZ Phase 2 trial evaluated patients with Type 2 and 3 SMA (did not include Type 1)

1. Lally et al, Orphanet Journal of Rare Diseases, 2017; 2. SMA Europe. SMATracker. About SMA. Accessed January 24, 2022. https://smatracker.eu/what-is-spinal-muscular-atrophy; 3. National Organization for Rare Disorders. Spinal muscular atrophy. Accessed January 24, 2022. https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/. 4. Cure SMA. Care Series Booklet. Accessed September 19, 2021. 2020. https://www.curesma.org/wpcontent/uploads/2020/08/08262020_Understanding_SMA_vWeb.pdf.

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.

Potential to Pioneer a New Treatment Era: Opportunity for Muscle-Targeted Therapy to Be Used With SMN Therapies

	SPINRAZA® (nusinersen) injection 12 mg/5 mL	Evrysdi™ risdiplam 60 mg powder for oral solution	zolgensma® (onasemnogene abeparvovec-xioi) suspension for intravenous infusion
PHASE 3 TRIAL DESIGN	**Type 1, 2 ,3** **1 day – 12 years of age** (Non-ambulatory recruited)	**Type 1, 2, 3** **1 month – 25 years of age** (Ambulatory and Non-ambulatory recruited)	**Type 1** **up to 6 months of age** (Non-ambulatory recruited)
PRIMARY ENDPOINT	Mean change from baseline in HFMSE at 15 months	Mean change from baseline in MFM-32 at 12 months	Ability to sit independently and event-free survival
INITIAL INDICATION†	Spinal Muscular Atrophy (SMA) in pediatric and adult patients	Spinal Muscular Atrophy (SMA) in pediatric and adult patients	Spinal Muscular Atrophy (SMA) in pediatric patients less than 2 years
CURRENT MARKET PENETRATION	Patients treated WW: >11,000* Revenues (LTM): $1.7+ billion	Patients treated WW: >7000** Revenues (YTD'0922): ~CHF 793 million	Patients treated WW: >2500*** Revenues (LTM): $ 1.4+ billion

Patients continue to experience major functional impairments despite utilization of SMN therapies

*As of Biogen SPINRAZA website and 3Q22 financial update on 10/25/22; includes patients treated worldwide in post-marketing setting, expanded access program, and clinical trials.
**As of Roche YTD Sep'2022 financial update on 10/18/22; includes patients treated worldwide between clinical trials, commercial, and compassionate use program.
***As of Novartis 3Q22 financial update on 10/25/22; commercially, via managed access programs and in clinical trials
HFMSE = Hammersmith Functional Motor Scale Expanded; MFM-32 = Motor Function Measure – 32 items

†Refer to most current USPI

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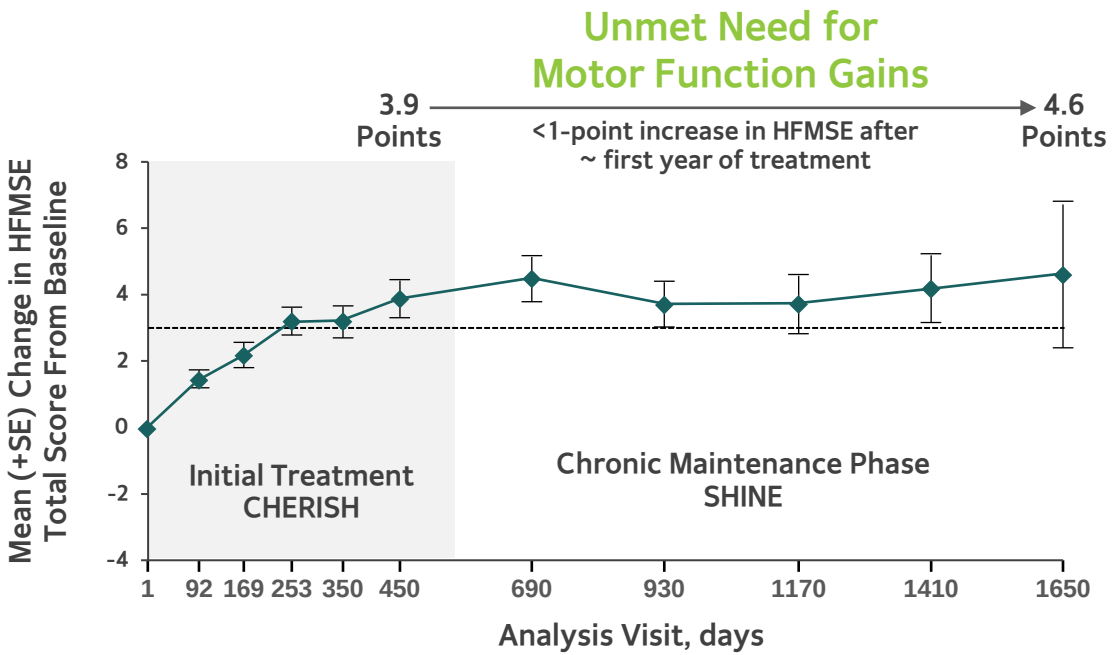
Motor Gains in Patients with Types 2 and 3 SMA on SMN Therapies Appear to Plateau After Initial Gains

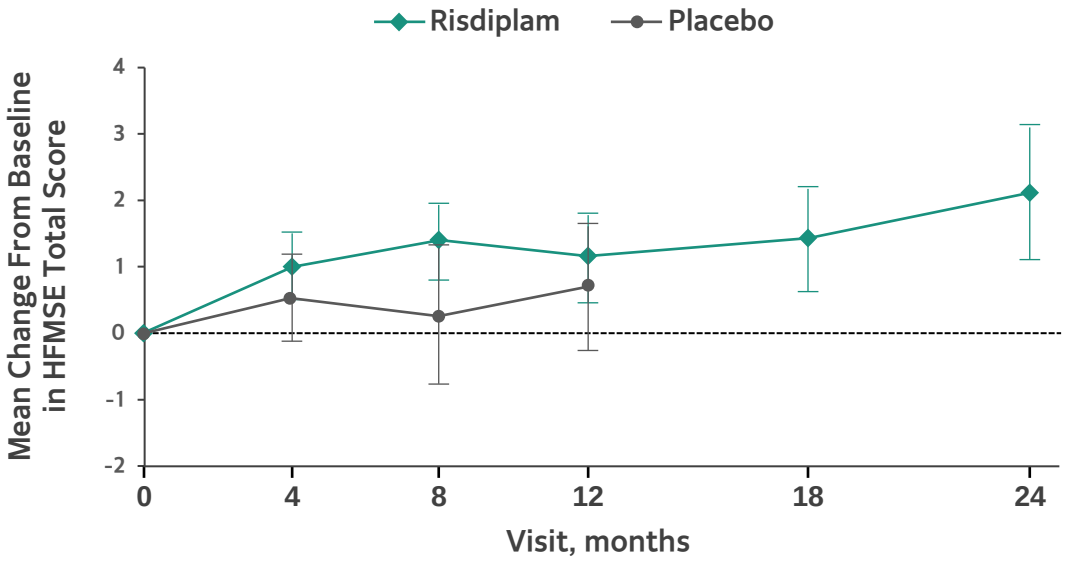
NUSINERSEN[1]

Plateauing of HFMSE increases observed following initial treatment effects for nusinersen



RISDIPLAM[2*]

Plateau of HFMSE increases observed following initial treatment effect of risdiplam, although longer timeframes currently under investigation



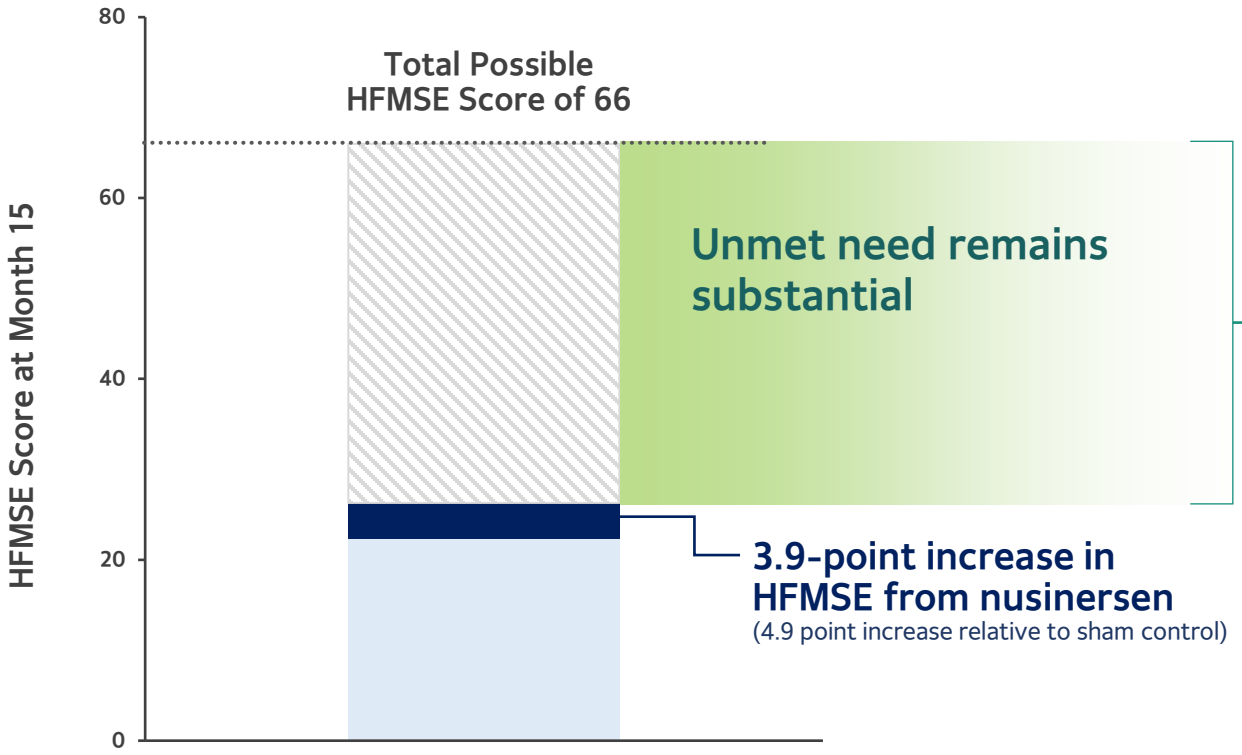
HFMSE=Hammersmith Functional Motor Scale-Expanded.

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.

* Overall population 2-25 years old.

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

Apitegromab Offers Potential to Address Unmet Patient Need



Mean improvement in HFMSE experienced by patients with non-ambulatory Types 2/3 SMA in nusinersen Phase 3 CHERISH trial

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

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

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TOPAZ Age 2-12 Analysis* in Pooled Non-Ambulatory Cohorts (20mg/kg)

Transformative Potential as Add-On for Apitegromab[1,2]

Mean HFMSE Increase OF 4.4 POINTS

with majority experiencing ≥ 3-point increases on top of background SMN therapy

HFMSE Gains Also Notable
in subset of individuals in this analysis who had started background nusinersen at age ≥ 5:

- 75% (6/8) with ≥ 1-point increase
- 50% (4/8) with ≥ 3-point increase

TOPAZ results showed HFMSE improvement from baseline or RHS stabilization across all three pre-specified cohorts.[1]

Non-Ambulatory Types 2/3 SMA (Apitegromab 20 mg/kg; Intent-to-Treat Population)	**Age 2-12 years** (n=16†)
Mean HFMSE change from baseline, (95% CI)	**+4.4 (1.3, 7.4)**
Patients with ≥ 1-pt increase in HFMSE, n (%)	**13 (81%)**
Patients with ≥ 3-pt increase in HFMSE, n (%)	**9 (56%)**

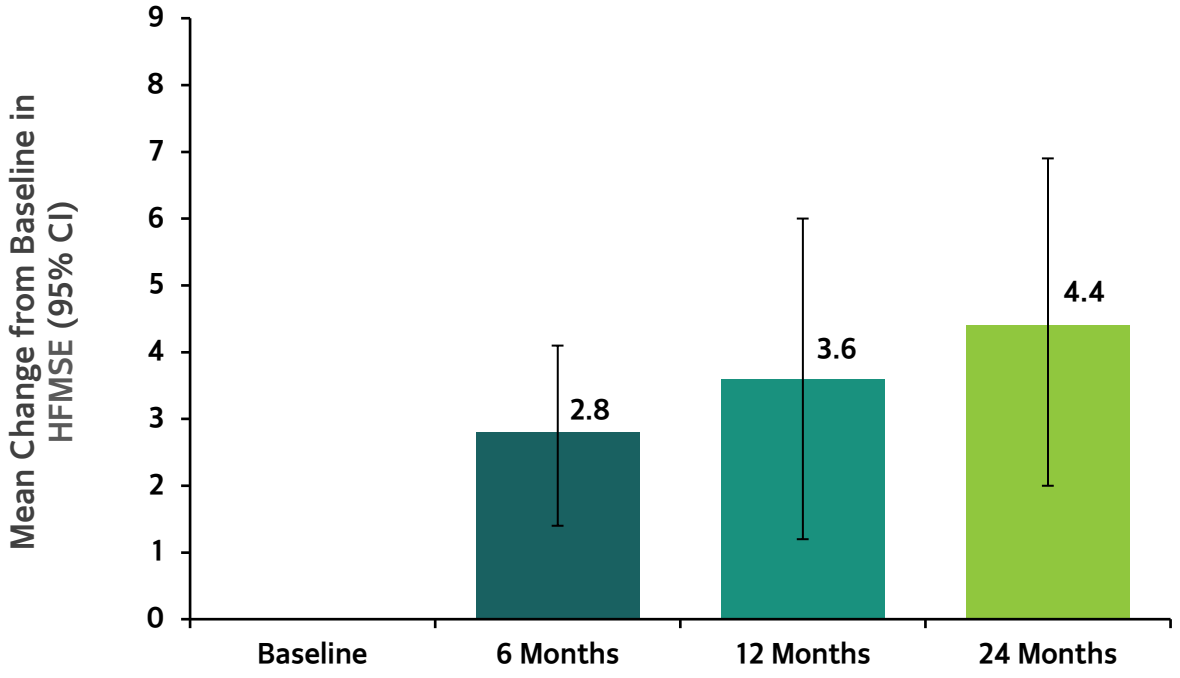
No safety signals for apitegromab were identified to date; the five most frequently reported treatment-emergent adverse events were headache, pyrexia, upper respiratory tract infection, cough, and nasopharyngitis

*Exploratory, post hoc analysis; †For 12-month endpoint, if patients skipped three consecutive doses due to site restrictions caused by COVID-19, records after dose skipping were excluded from analysis. The last observation carry forward was used for other missing data; 1.Crawford T et al. TOPAZ topline results; Presented at CureSMA, 2021 Virtual SMA Research & Clinical Care Meeting; June 9-11, 2021. 2. Scholar Rock Inc. Corporate Presentations, August 2022 at Deep Insights, Impactful Medicines (scholarrock.com)
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.

Sustained Increases in HFMSE Observed Over 24 Months of Apitegromab

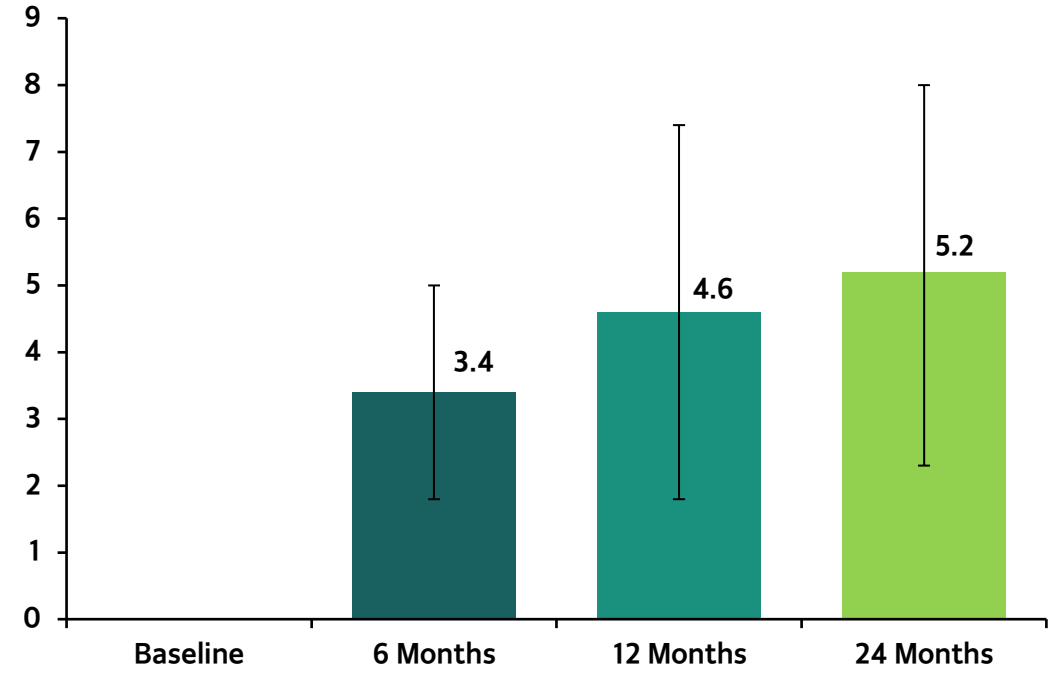
Pooled Non-Ambulatory Patients Excluding Data Post Scoliosis Surgery (all dose groups)

Age 2-21 Years



	Baseline	6 Months	12 Months	24 Months
n=	35	29	32	28

Age 2-12 Years



	Baseline	6 Months	12 Months	24 Months
n=	29	23	26	23

For the 24-month evaluation, an observed case analysis was conducted, which pooled all the non-ambulatory patients (Cohorts 2 and 3) and was based upon the available data for given timepoints. This analysis population 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). This analysis excludes from the observed case analysis any HFMSE data following scoliosis surgery in TOPAZ. Of the three non-ambulatory patients who had scoliosis surgery, data from one was excluded and the other two did not have valid HFMSE assessments. Error bars represent SEM. Values in parentheticals represent 95% confidence interval. Crawford T et al. TOPAZ EXTENSION: 24-MONTH EFFICACY AND SAFETY OF APITEGROMAB IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TYPE 2 AND TYPE 3 SMA) Podium Presentation Presented at CureSMA; June 2022. Data on File. Scholar Rock, Inc. Cambridge, MA. 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.

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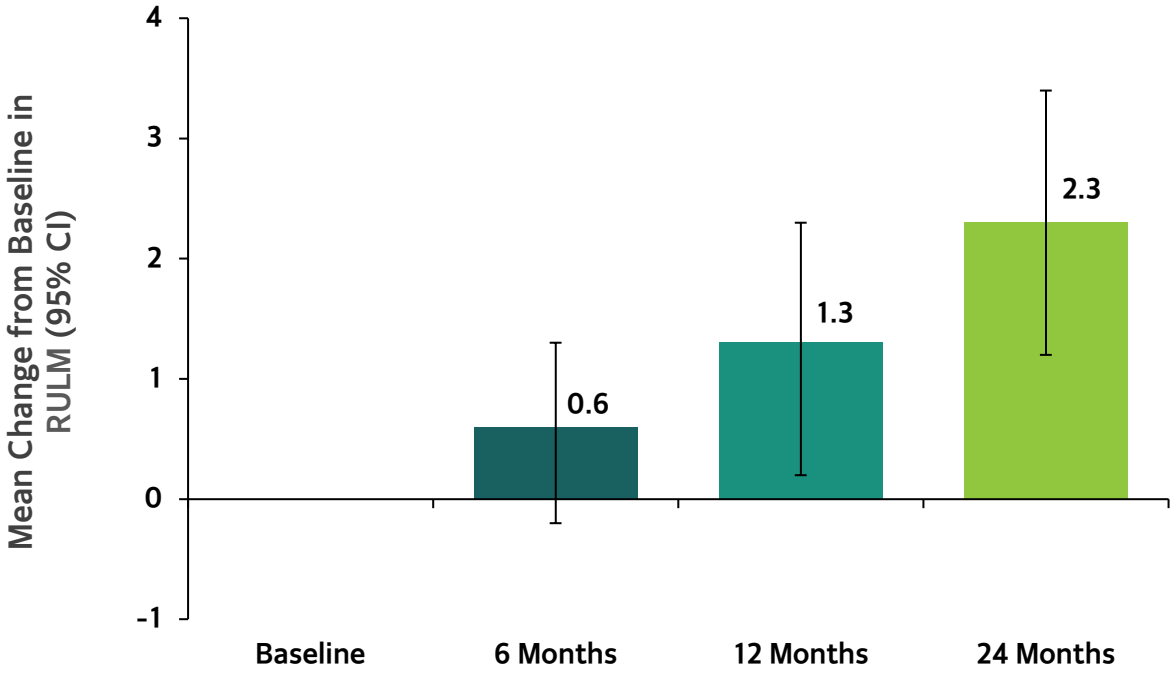
Continued Increase in RULM Observed at 24 Months of Apitegromab

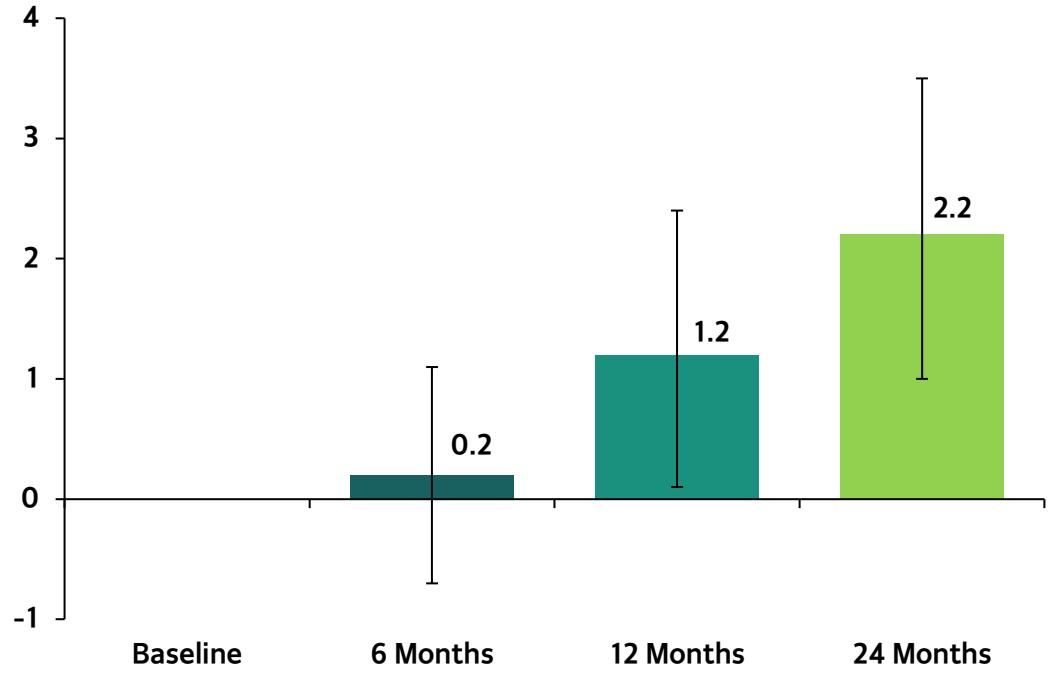
Pooled Non-Ambulatory Patients Excluding Data Post Scoliosis Surgery (all dose groups)

Age 2-21 Years



	Baseline	6 Months	12 Months	24 Months
n=	34	28	31	30

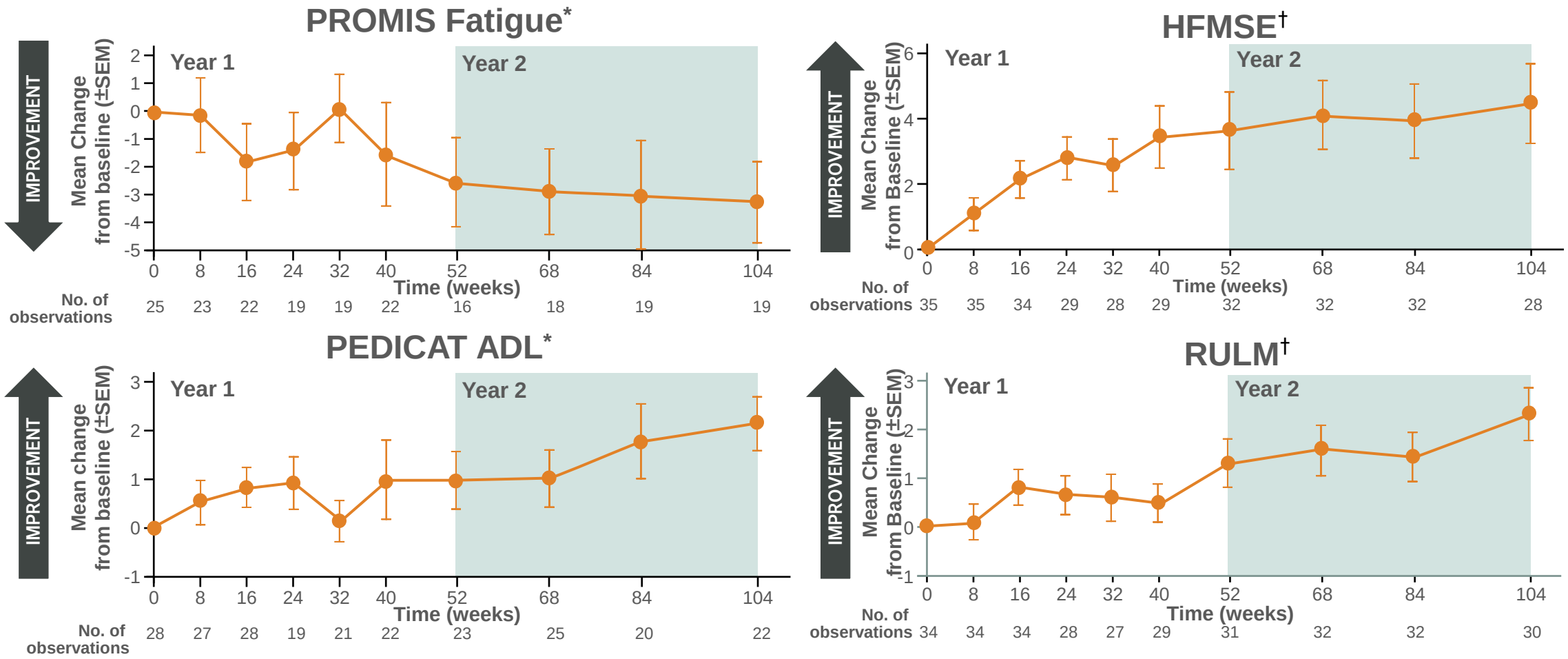
Age 2-12 Years



	Baseline	6 Months	12 Months	24 Months
n=	28	22	25	25

For the 24-month evaluation, an observed case analysis was conducted, which pooled all the non-ambulatory patients (Cohorts 2 and 3) and was based upon the available data for given timepoints. This analysis population 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). This analysis excludes data from 3 non-ambulatory patients after their scoliosis surgery during TOPAZ from the Observed Case Analysis. Error bars represent SEM. Values in parentheticals represent 95% confidence interval. Crawford T et al. TOPAZ EXTENSION: 24-MONTH EFFICACY AND SAFETY OF APITEGROMAB IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TYPE 2 AND TYPE 3 SMA) Podium Presentation Presented at CureSMA; June 2022. Data on File. Scholar Rock, Inc. Cambridge, MA. 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.

Improvements in PRO Measures Consistent With Motor Function Over 24 Months



*Observed Case Analysis includes all participants who had a valid measurement at Day 728.; OC analysis included participants treated with 2 mg/kg as well as 20 mg/kg of apitegromab. This analysis does not exclude any participants who missed doses due to COVID-19 related site access restrictions. †24-month Sensitivity Analysis excludes from the OC Analysis any HFMSE data following scoliosis surgery in TOPAZ. Of the three nonambulatory participants who had scoliosis surgery, data from one was excluded and the other two did not have valid HFMSE assessments. **ADL**, activities of daily living; **HFMSE**, Hammersmith Functional Motor Scale Expanded; **OC**, observed case; **PRO**, participants reported outcomes; **RULM**, Revised upper limb module; **SEM**, standard error of the mean. Crawford T et al. Apitegromab in SMA (TOPAZ Trial): Covariates of Multiple Efficacy Endpoints From 24 Month Data. Presented at MDA Annual Conference; March 22, 2023.

No Serious Safety Risks Identified Over 24 Months of Apitegromab Treatment

Treatment-Emergent Adverse Events (TEAEs)*	2 mg/kg dose (N=10) n (%)	20 mg/kg dose (N=48) n (%)	Total (N=58) n (%)
Any TEAE	10 (100)	45 (93.8)	55 (94.8)
Any Serious TEAE	3 (30)	11 (22.9)	14 (24.1)
Any TEAE leading to study drug discontinuation	0 (0.0)	1 (2.1)	1 (1.7)
Any Grade 3 (severe) or higher TEAE	2 (20)	9 (18.8)	11 (19)

Incidence and types of TEAEs were consistent with the underlying disease or nusinersen therapy

Five most frequently reported TEAEs were headache, pyrexia, upper respiratory tract infection, cough, and nasopharyngitis

No deaths or Suspected Unexpected Serious Adverse Reactions (SUSARs) reported

Adverse events reported as mostly mild to moderate in severity

No identified serious risks as of 4/7/2022

approximately 90% remain on apitegromab as of 12/31/2022**

Crawford T et al. TOPAZ EXTENSION: 24-MONTH EFFICACY AND SAFETY OF APITEGROMAB IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TYPE 2 AND TYPE 3 SMA) Podium Presentation Presented at CureSMA; June 2022

*Notes: % = 100 x n/N (n=incidence)

**51/57 patients

Treatment-emergent adverse events (TEAEs) are defined as adverse events (AEs) that start after the first dose of study drug or start prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug. Data is for safety events collected over the 24-month period and includes patients who switched from 2 mg/kg to 20 mg/kg. Data on file, extracted on April 7, 2022. Scholar Rock, Inc. Cambridge, MA. 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

Sapphire Phase 3 Pivotal Trial

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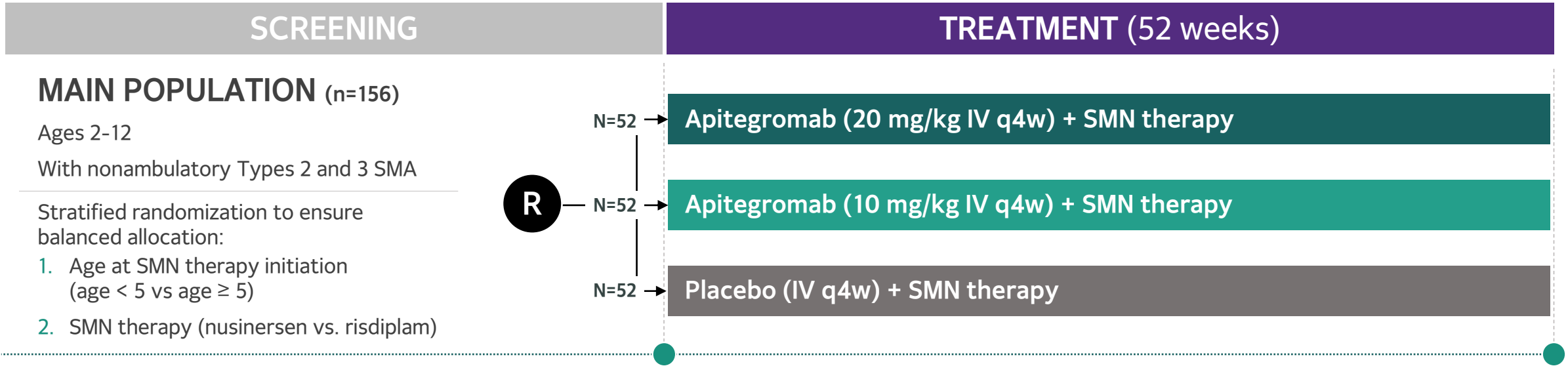
Ongoing SAPPHIRE Phase 3 Trial Overview

SAPPHIRE

Randomized, double-blind, placebo-controlled, parallel arm design (n=204)
Enrolling patients on SMN therapy (nusinersen or risdiplam)
Anticipate completing enrollment in 2023



ENDPOINTS

Primary Efficacy:
Mean HFMSE change from baseline at 12 months

Additional Efficacy Measures:
RULM, WHO, other outcome measures

Safety, PK/PD, ADA

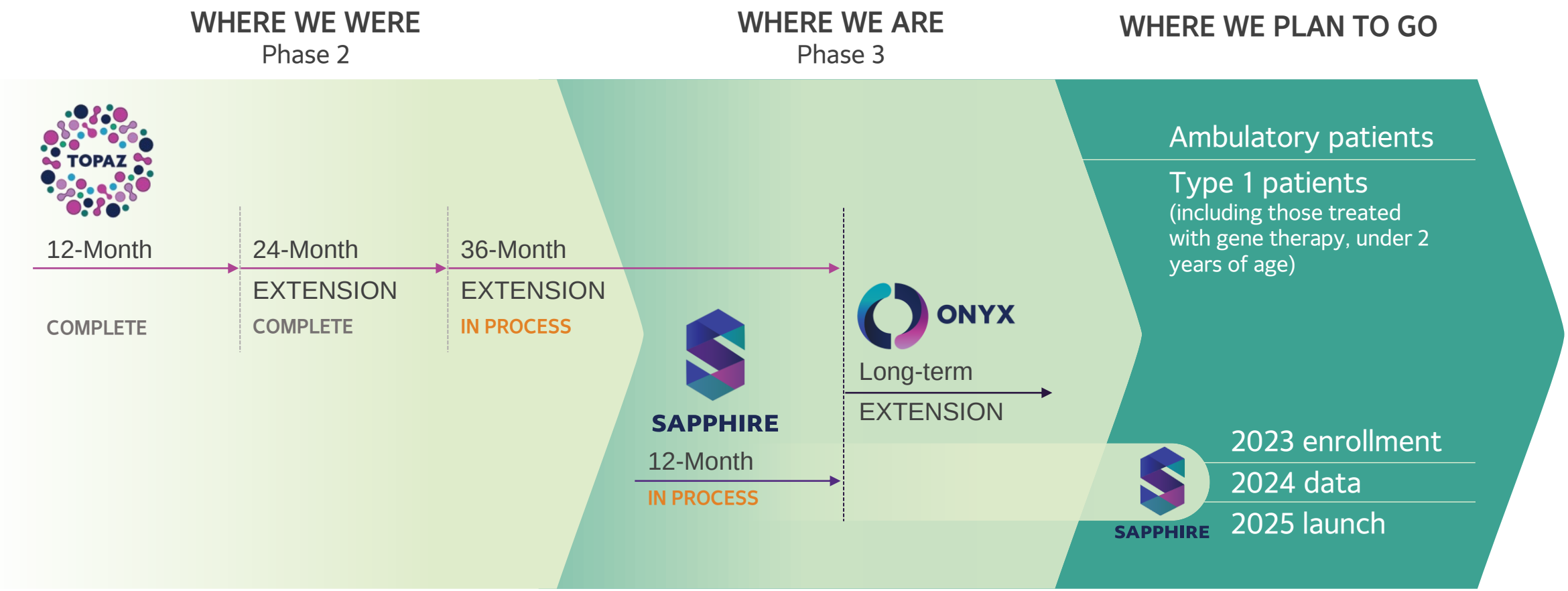
Additional Data Opportunities

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

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

ClinicalTrials.gov Identifier: NCT05156320
R=Randomization

Executing on the Promise: Apitegromab SMA Trials



Apitegromab Summary

Differentiation

- Potential first muscle-targeted therapy in SMA
- Robust body of data supports therapeutic potential

Strong Scientific Rationale

- Strong pre-clinical evidence indicates upstream targeting of structurally differentiated latent myostatin avoids undesirable off-target effects
- Phase 2 TOPAZ trial demonstrated the therapeutic potential of inhibiting the latent forms of growth factors

Clear Clinical Pathway

- TOPAZ has demonstrated sustained motor function gains to date in patients with nonambulatory Types 2 and 3 SMA
- Pivotal Phase 3 SAPPHIRE trial: last patient in expected in 2023
- FDA has granted Fast Track, Orphan Drug, and Rare Pediatric Disease designations
- European Medicines Agency (EMA) has granted Priority Medicines (PRIME) and Orphan designations

High Unmet Medical Need & Significant Commercial Opportunity

- SMN therapies prevent further degeneration of motor neurons but do not directly address muscle atrophy
- Apitegromab is a muscle-targeted approach and has the potential to address this unmet medical need
- Global SMA treatment market expected to grow in the next five years

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DRAGON

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

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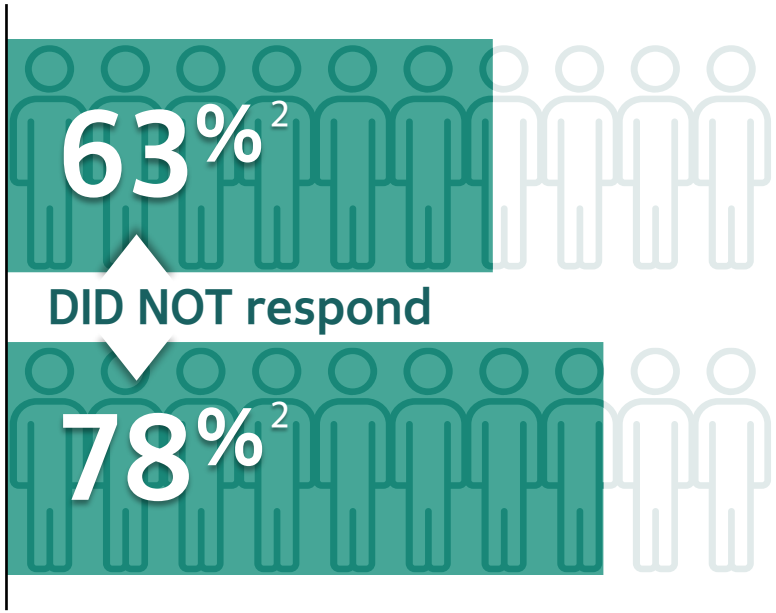
Resistance to Checkpoint Inhibitor (CPI) Therapies Remains a Significant Clinical Challenge

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

→ First-line CPI therapy

→ Second-line (or later) CPI therapy



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]

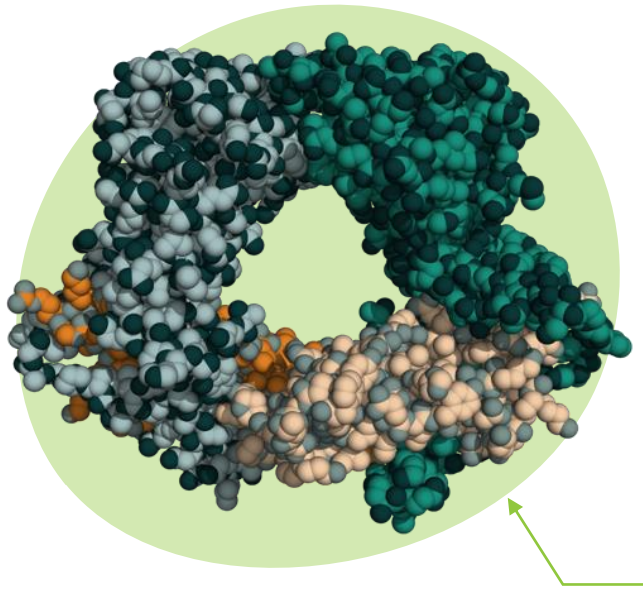
July 24, 2020: https://doi.org/10.1038/ s41571-020-0403-1

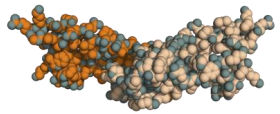
August 2022.

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

ScholarRock

SRK-181: Unique Latent TGFβ-1 Selective Approach to Overcoming 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.

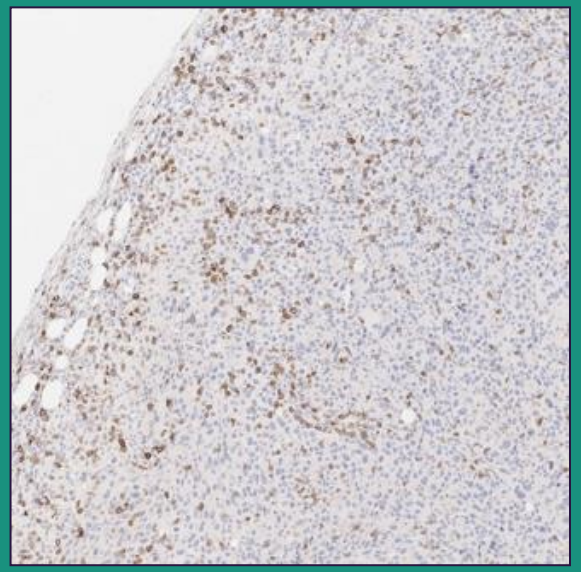
SRK-181-mIgG1 + Anti-PD1 Overcomes Immune Exclusion

Overcoming immune exclusion

Tumor micro-environment

Anti-PD1

Immune Exclusion



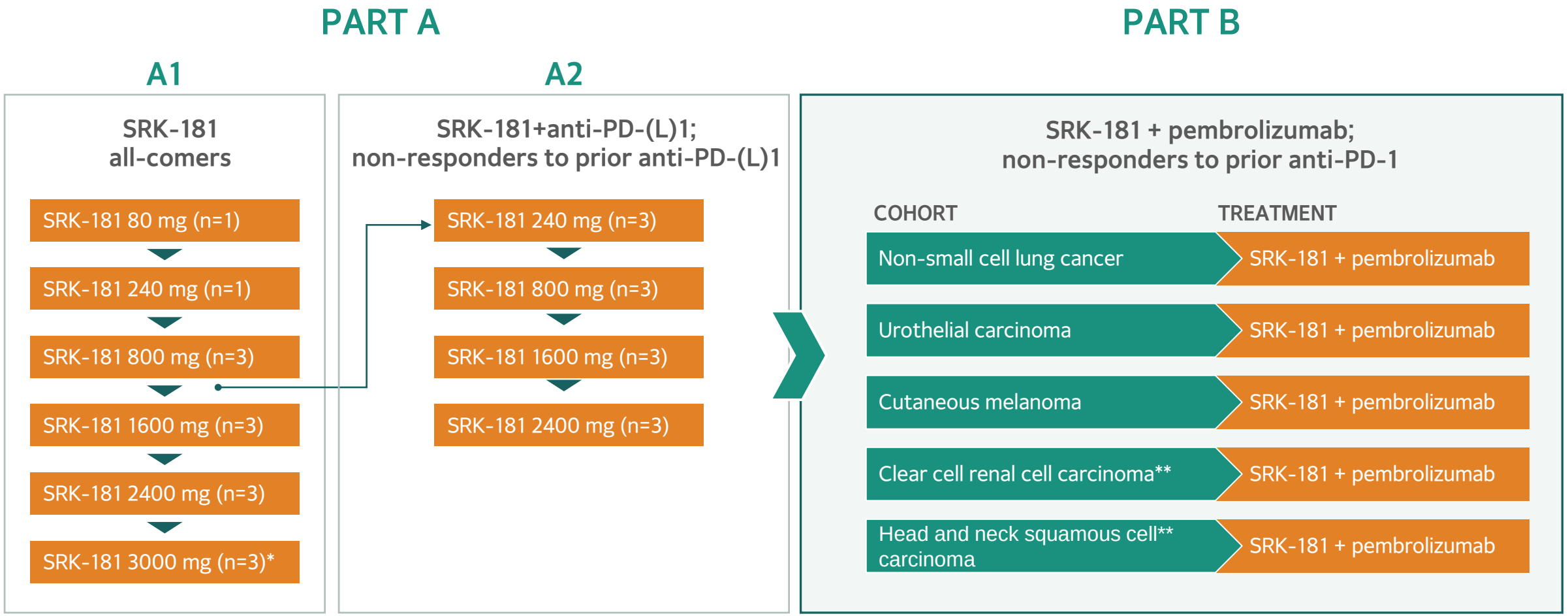
Anti-PD1/ SRK-181-mIgG1

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.

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



* 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)

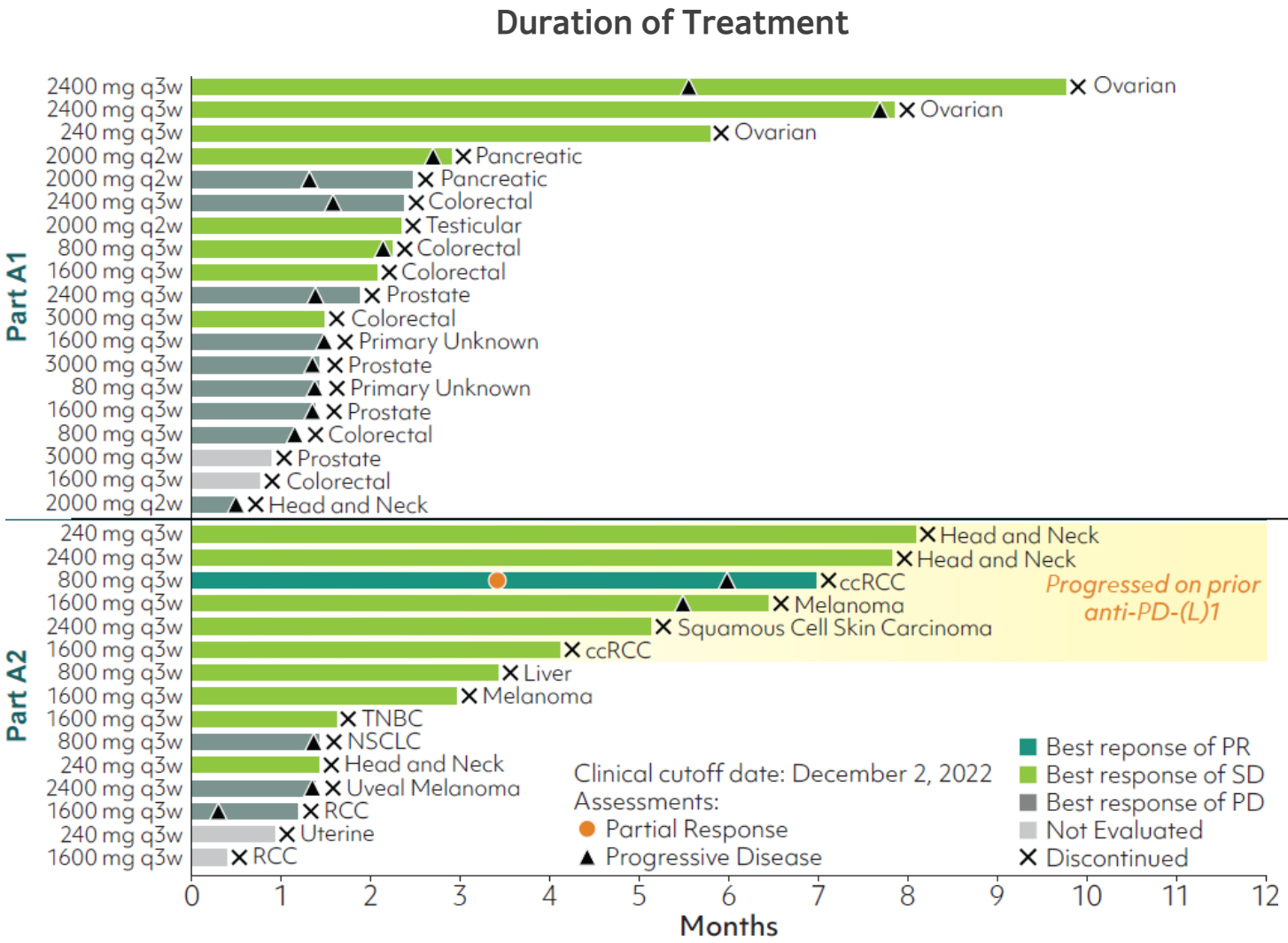
Treatment-related SAEs:

- 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)

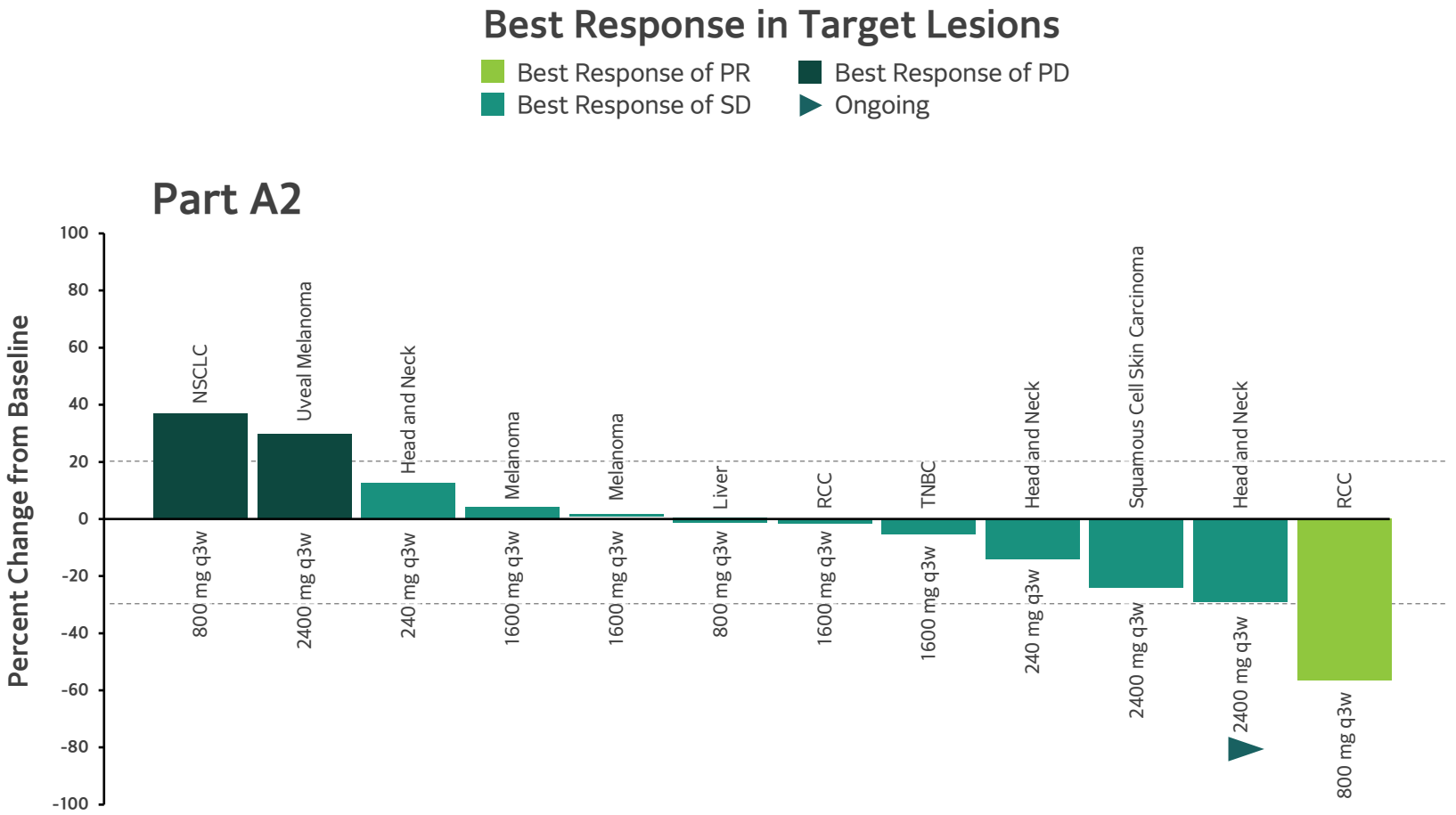
All 3 patients with ovarian cancer were stable for 6-10 months

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.

Preliminary Efficacy Data in Combination with Pembrolizumab: Best Response in Target Lesions



Part B (as of 12/2/22)

- **20 patients dosed across multiple cohorts**
- **Two confirmed PRs**
  ongoing patients with anti-PD-1 resistant clear cell renal cell carcinoma
- **All dose levels were generally well tolerated**
  SRK-181 dose of 1500 mg q3w or 1000 mg q2w in combination with anti-PD-(L)1 for Part B

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.

Summary of ccRCC Patients on Combination Treatment (Part A2 and Part B)

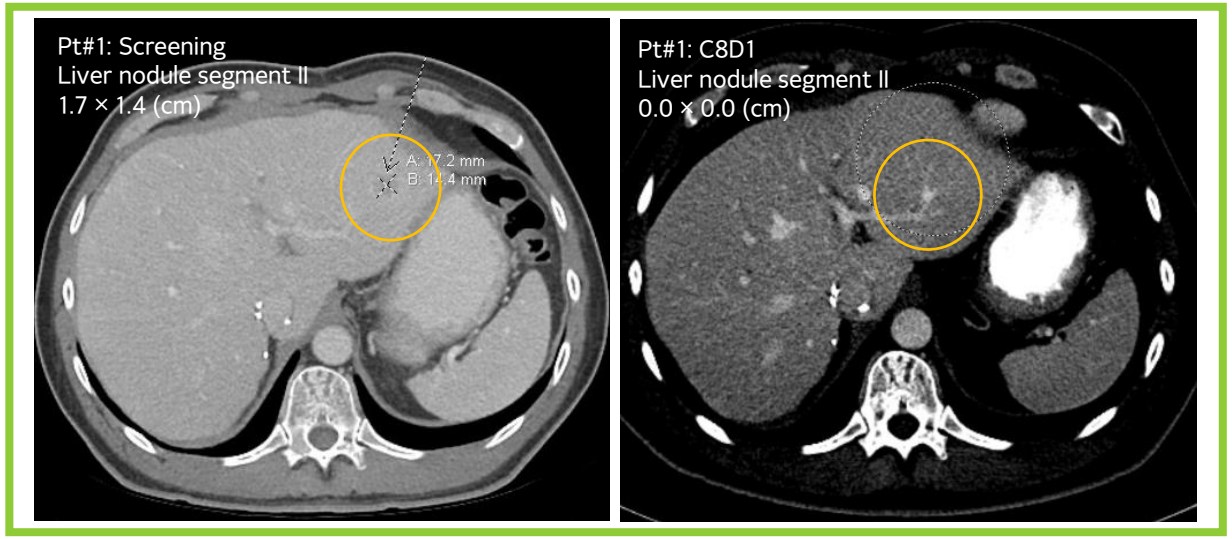
As of clinical cutoff date of Dec 2, 2022:

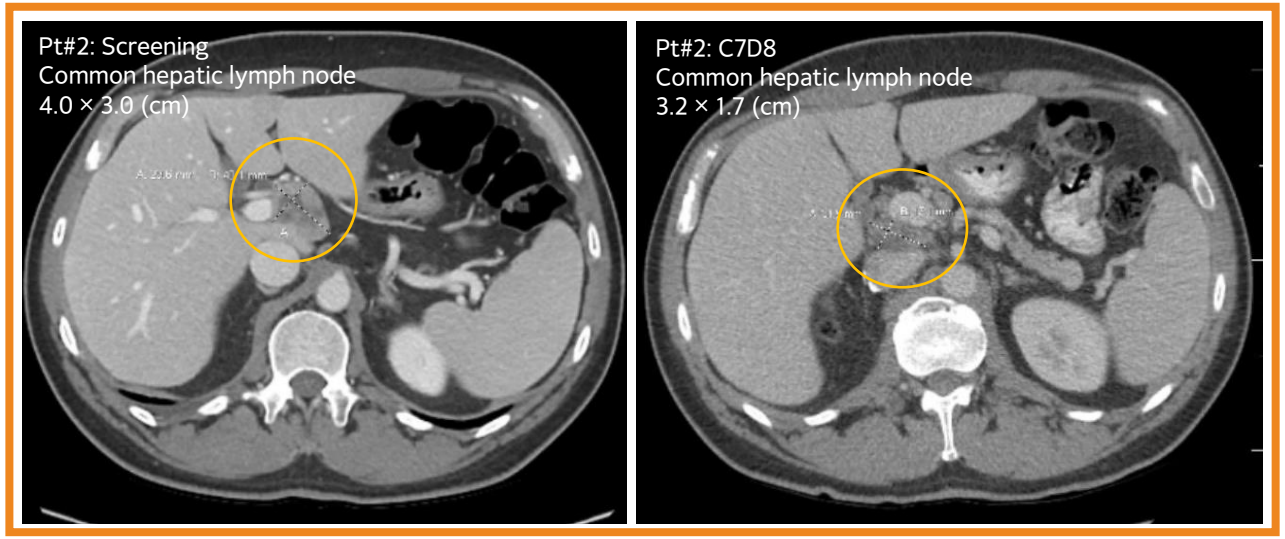
- 11 ccRCC patients enrolled
  - n=2 in Part A2 (all discontinued from study) and n=9 in Part B (5 pts remain on study)
  - enrollment in Part B continues
- 3 confirmed PRs observed in ccRCC patients based on investigator assessment
  - Patients are anti-PD-1 resistant patient (no response on prior anti-PD-1 therapy and disease progress on the most recent prior anti-PD-1 therapy)
  - ORR: 27% (3/11)

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.

Summary of ccRCC Patients with PR in Dragon (Part A2 and Part B, Combination Treatment)

Responded Pts	SRK-181 Dose (mg, Q3W)	Age (Year)/ Gender	Lines of Prior Therapy	IMDC Score at Screening	Metastatic Sites at Screening	Pt Status	Duration of Treatment (wks)	Best % Change in SOD* from Baseline
Pt #1	Part A2, 800	56/M	1. Sunitinib **2. Nivolumab/Ipilimumab** 3. Cabozantinib 4. Lenvatinib/Everolimus **5. Pembrolizumab/Axitinib**	3 (Poor risk)	Lung/ Lymph Nodes/ Pleural/ Pancreas/ Bone	Off study	30	-57%
Pt #2	Part B, 1500	58/M	**1. Nivolumab/Ipilimumab** 2. Cabozantinib	3 (Poor risk)	Lung/ Lymph Nodes/Liver	Ongoing	32+ (by Dec 2, 2022)	-67%
Pt #3	Part B, 1500	63/M	**1. Nivolumab/Ipilimumab** **2. Nivolumab** 3. Cabozantinib	2 (Intermediate risk)	Lung/ Lymph Nodes	Ongoing	16+ (by Dec 2, 2022)	-50%





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. *SOD: sum of diameters in target lesions. 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.

SRK-181: Encouraging Early Clinical Data Consistent with Hypothesis

Preclinical Data

TGFβ pathway evaluation (PD)
- ✓ Target engagement (blood)
- ✓ TGFβ-1 signaling (tumor p-SMAD2 & RNAseq)

Immunophenotyping, including immune exclusion status
- ✓ Tumor immune contexture (e.g., tumor CD8+ T cells)
- ✓ Immune cell contexture (tumor & blood MDSCs)
- ✓ Immune response markers (e.g., IO gene signature)

Therapeutically relevant dose
- ✓ Drug exposure needed for efficacy

Objective response
- ✓ Anti-tumor response and survival benefits

Phase 1 DRAGON proof-of-concept trial

TGFβ pathway evaluation (PD)
- ✓ Target engagement (blood)
- ⧗ TGFβ-1 signaling (tumor p-SMAD2 & RNAseq)

Immunophenotyping, including immune exclusion status
- ⧗ Tumor immune contexture (e.g., tumor CD8+ T cells)
- ⧗ Immune cell contexture (tumor & blood MDSC's)
- ⧗ Immune response markers (e.g., IO gene signature)

Therapeutically relevant dose
- ✓ Dosing regimens achieved target steady state levels

Objective response
- ✓ Anti-tumor response observed (partial responses)

SRK-181 Summary

Differentiation

- First in class monoclonal antibody targeting latent and context-independent binding to TGFβ1
- Differentiated from other TGFβ inhibitors by its novel selectivity
- Offers potential to avoid toxicity and dose-limiting challenges of non-selective TGFβ inhibition approaches

Strong Scientific Rationale

- Emerging evidence implicates TGFβ1 as driving resistance to checkpoint inhibitor therapies
- Potent and selective inhibitor of latent TGFβ1 activation in preclinical studies
- Strong safety and preclinical efficacy data

Clear Clinical Pathway

- DRAGON Part A demonstrated ability to escalate to high doses of SRK-181 at levels exceeding the anticipated efficacious drug exposure level
- Advanced to DRAGON Part B: Evaluating SRK-181 in 5 parallel tumor-specific cohorts, with efficient path towards early POC for each
- Early efficacy signals have been observed

High Unmet Medical Need & Large Commercial Opportunity

- PD-(L)1* becoming a standard of care therapy in many tumor types; the market for synergistic combination product would be vast
- SRK-181 could potentially be used in many tumor types, potentially both in patients resistant to PD-(L)1 and in CPI naïve patients, as well as other therapeutic applications

*(PD-1/PD-L1)

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Next Horizon: 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

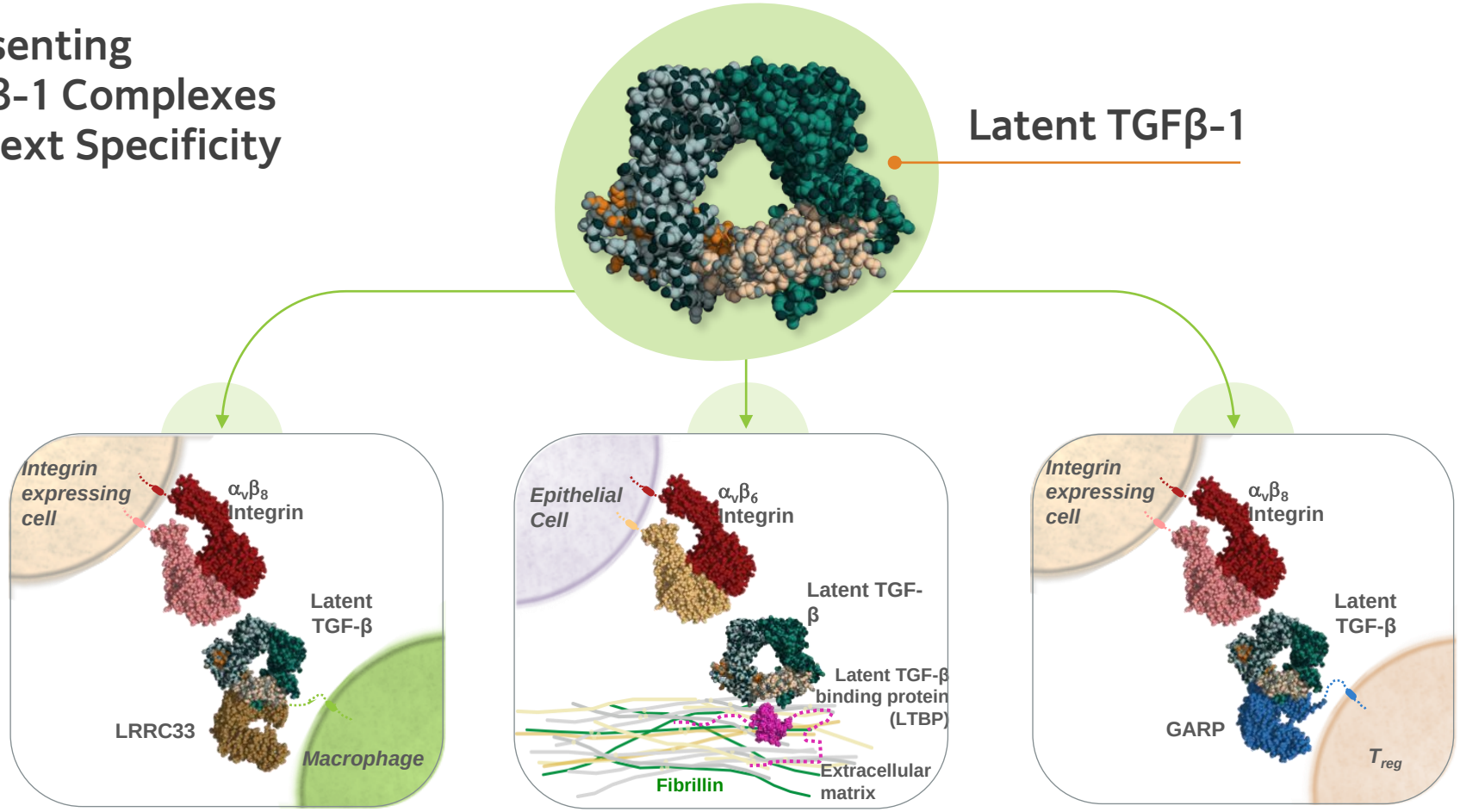
PNAS, February 24, 1986 PNAS

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



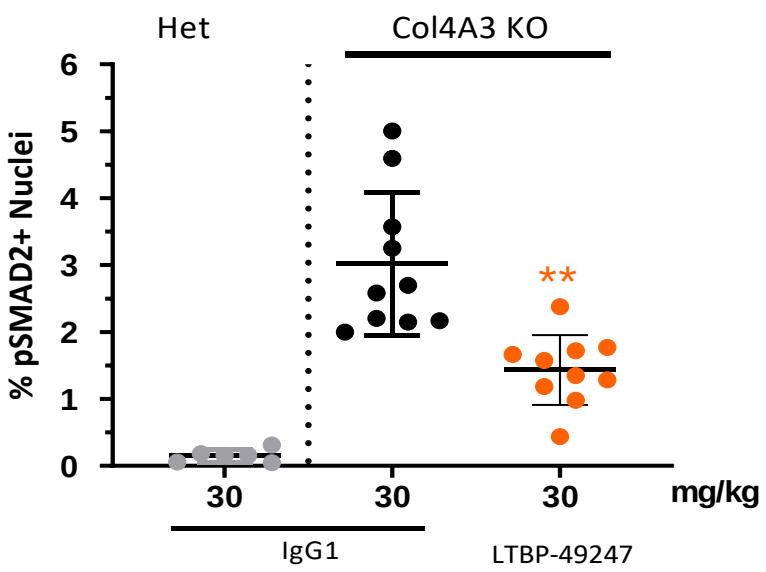
LRRC33 Presents TGFβ on Macrophages

LTBP1 & 3 Present TGFβ in Connective Tissue

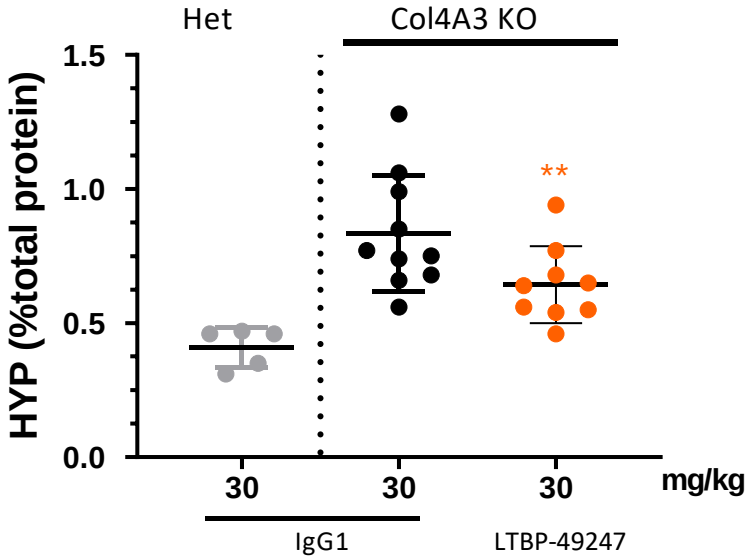
GARP Presents TGFβ on Tregs

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

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



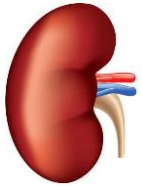
LTBP-49247 reduces fibrosis in kidneys of Alport model



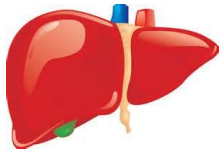
** p < 0.01
One way ANOVA vs. IgG
HYP=hydroxyproline

- 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

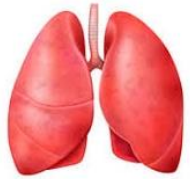
Significant Opportunities to Address High Unmet Need Across Multiple Fibrotic Indications



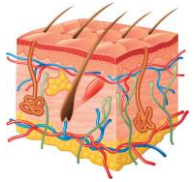
Alport Syndrome (AS)
Focal Segmental Glomerulosclerosis (FSGS)
IgA Nephropathy (IgAN)



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

Next Horizon: Iron-Restricted Anemia

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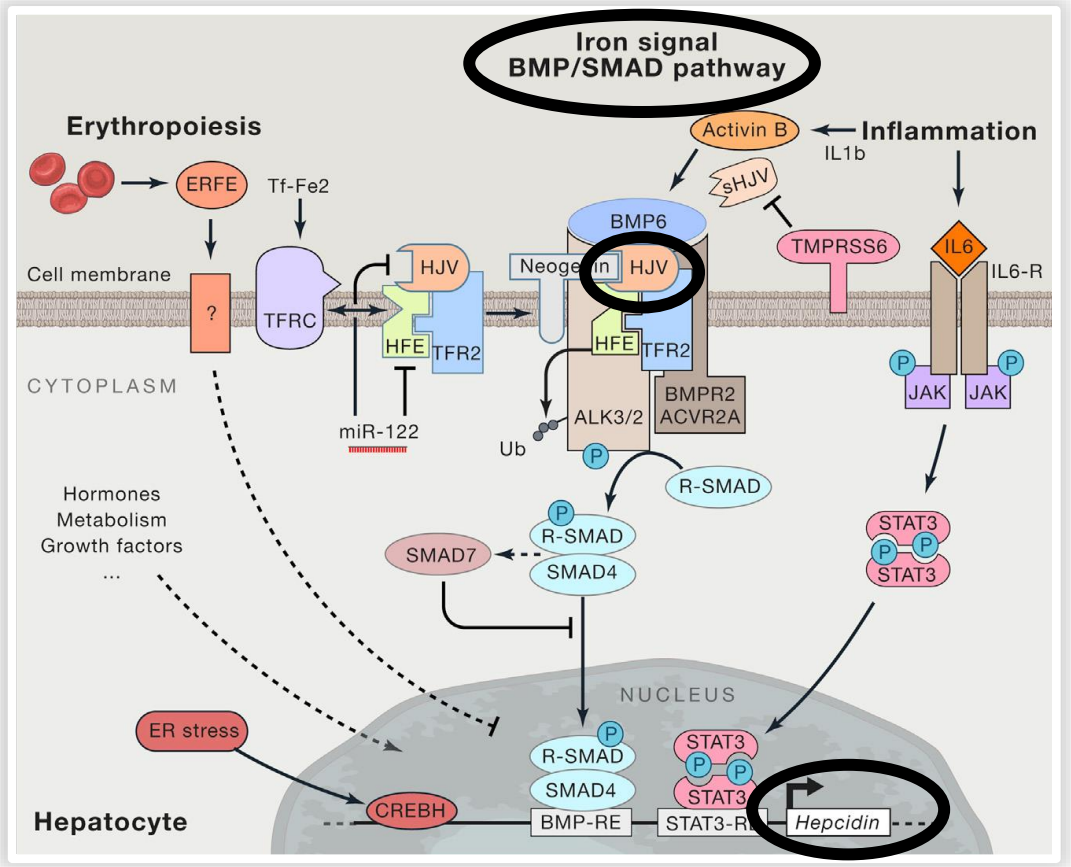
BMP6/RGMc Pathway is a Well Validated Regulator of Systemic Iron Homeostasis



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

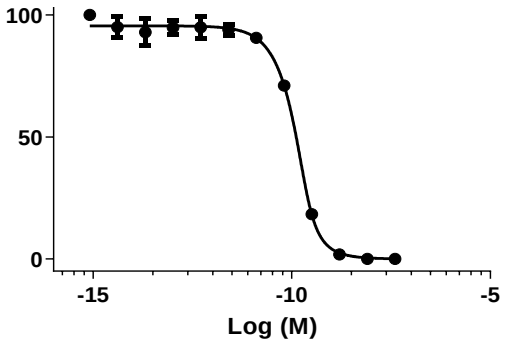
Fig: Muckenthaler, M.U., Rivella, S., Hentze, M.W. and Galy, B. (2017) A Red Carpet for Iron Metaboism. *Cell*, 168(3): 344-361
1: *Kuns-Hashimoto R, et al.* (2008) Selective binding of RGMc/hemojuvelin, a key protein in systemic iron metabolism, to BMP-2 and neogenin. *Am J Physiol Cell Physiol* 294(4):C994-C1003
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: A High-Affinity Antibody Demonstrating Selective Inhibition of HJV/RGMc and Robust PK/PD in Cynos

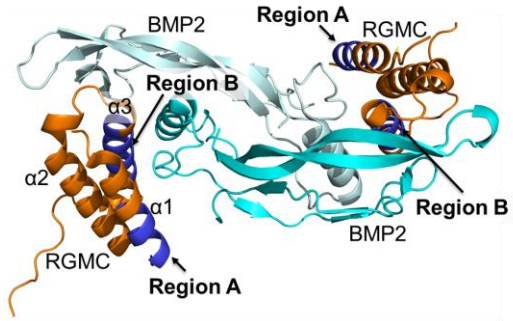
Key Attributes of HJV-35202:[1,2]

- 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)

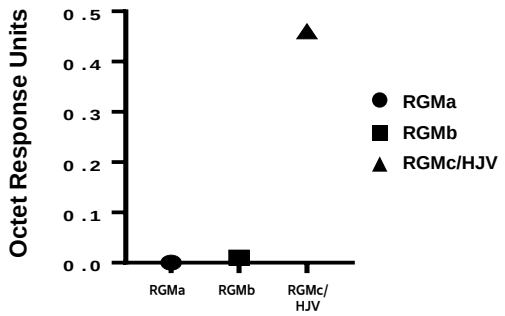
Potent in vitro binding affinity (KD=3.9E-11)



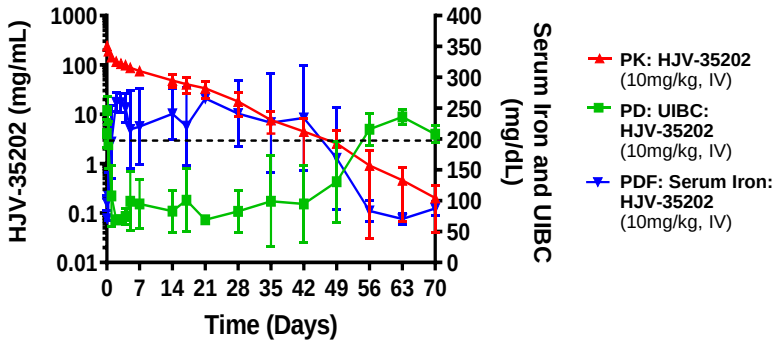
Highly specific to RGMc/HJV with well understood mechanism



Specific to RGMc over other RGM family members

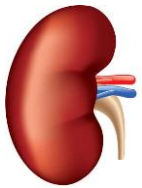


Sustained PD effect in single dose Cyno study



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

Scholar Rock Summary

Key Investment Highlights

Revolutionary Platform

Discover and Develop
monoclonal antibodies with extraordinary selectivity

Overcome the Challenges
targeting the latent forms of growth factors

Robust Clinical Pipeline

Apitegromab (Phase 3)
- Potential first-in-class
- Significant market opportunity
- Program on track
- Clear path to approval

SRK-181 (Phase 1)
- Potential to shift current treatment landscape for cancer patients with CPI resistance

Upcoming Data Readouts
for both clinical programs

Positioned For Success

Discovery-stage Pipeline
- Fibrosis and iron-restricted anemia
- Strategic optionality

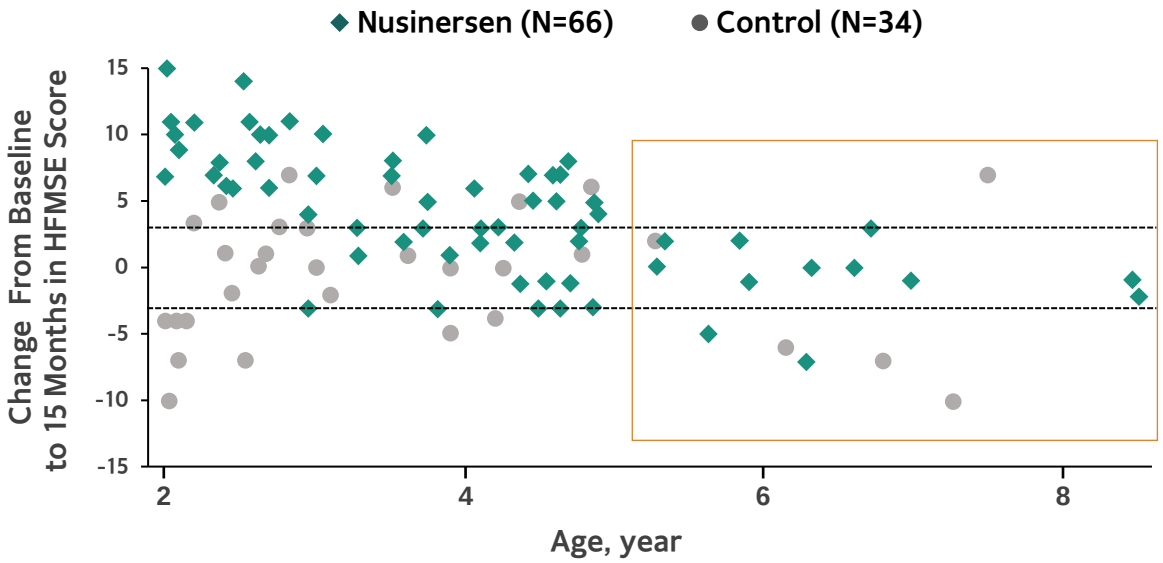
$205M financing in June 2022
- Cash balance of $275M as of March 31, 2023; anticipated runway into 2025

Appendix

ScholarRock™

Non-Ambulatory Type 2/3 SMA:
Majority of Patients Started on SMN Therapy After Age 5 Do Not Experience Motor Function Increases

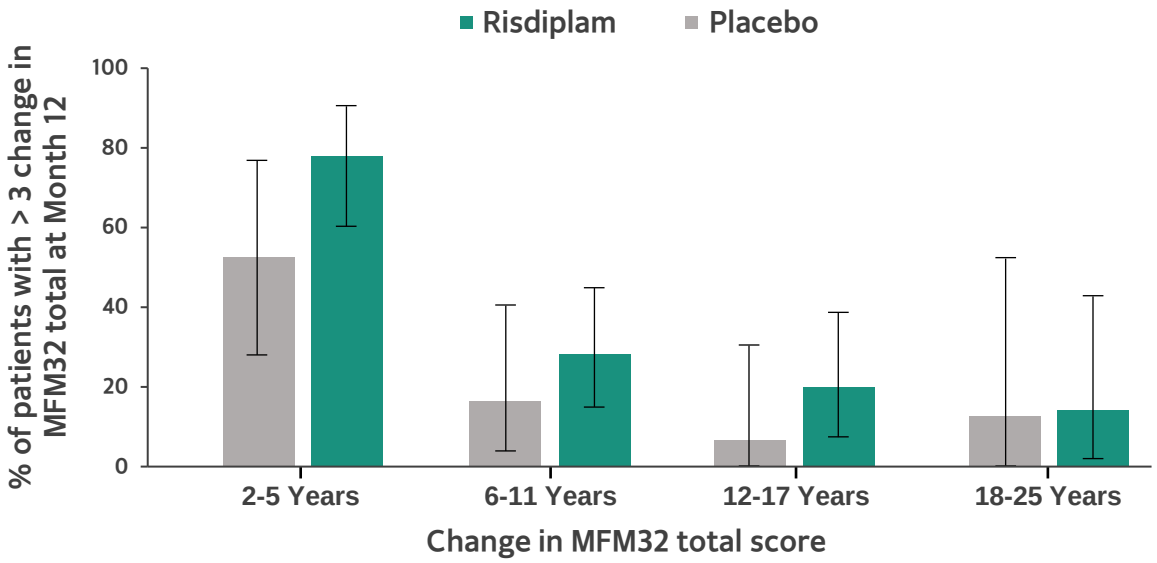
Nusinersen CHERISH Trial in Later-Onset SMA[1]



In patients with later-onset SMA who were age ≥5 at screening:

- Primary benefit of nusinersen: stabilization of motor function
- Majority of patients do not experience HFMSE increases

Risdiplam SUNFISH Trial in Later-Onset SMA[2]



- Low percentage of patients over the age of 5 achieved ≥3-point increase on MFM32 scale, even with risdiplam treatment
- HFMSE secondary endpoint showed a mean 0.58-point improvement over placebo (not statistically significant)

1. Mercuri E, et.al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med.* 2018;378:625-635.
2. Efficacy and safety of risdiplam (RG7916) in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA) Roche/PTC Therapeutics
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

SAPPHIRE Phase 3 Design is Optimized by Insights from TOPAZ

TOPAZ Learnings	SAPPHIRE Design Elements
Largest HFMSE gains observed in the non-ambulatory Type 2/3 SMA cohorts	• Study population: Non-ambulatory Type 2/3 SMA • Primary efficacy endpoint: HFMSE
Exploratory age 2-12 analysis in non-ambulatory Type 2/3 showed transformative potential	Age 2-12 main efficacy population
HFMSE gains evident by 12 months of treatment	12-month treatment duration
Dose response seen (greater effect observed with 20 mg/kg over 2 mg/kg)	• 20 mg/kg apitegromab dose • Also evaluating 10 mg/kg arm (to explore potential that dose between 2 and 20 mg/kg may be comparable to 20 mg/kg)

TOPAZ Subject Disposition, Demographics and Baseline Characteristics[1,2]

	AMBULATORY PATIENTS		NON-AMBULATORY PATIENTS		
	COHORT 1		COHORT 2	COHORT 3	
	20 mg/kg monotherapy	20 mg/kg + nusinersen	20 mg/kg + nusinersen	2 mg/kg + nusinersen	20 mg/kg + nusinersen
N (dosed)	11	12	15	10	10
Mean age at screening (min, max)	12.1 (7, 19)	13.1 (7, 21)	11.7 (8, 19)	4.1 (2, 6)	3.8 (2, 6)
Mean age at SMA diagnosis (min, max)	5.9 (2, 15)	4.5 (2, 15)	3.1 (1, 16)	1.2 (1, 2)	1.2 (1, 3)
Female (%)	73%	58%	53%	30%	50%
SMN2 Gene Copy* (#, %)					
2	1 (9%)	0 (0%)		1 (10%)	1 (10%)
3	4 (36%)	9 (75%)	11 (73%)	8 (80%)	8 (80%)
4	4 (36%)	1 (8%)	2 (13%)	1 (10%)	0 (0%)
# of maintenance doses of nusinersen at baseline (min, max)	N/A	5.6 (2, 8)	5.1 (2, 9)	5.5 (2, 9)	5.4 (3, 8)
Discontinuation(s)	0	2†	1†	0	0
Scoliosis (#, %)	7 (63.6)	4 (33.3)	11 (73.3)	4 (40%)	3 (30%)
Contracture(s) (#, %)	6 (54.5)	7 (58.3)	13 (86.7)	8 (80%)	4 (40%)
Mean RHS score (min, max)	47.6 (26, 63)	51.3 (43, 62)			
Mean HFMSE score (min, max)			22.7 (13, 39)	26.1 (12, 44)	23.5 (14, 42)

*1 patient answered 3-4, 1 patient answered >4 , both patients are in Cohort 1 treated with 20 mg/kg + nusinersen; data not available for all patients.
†1 cohort 1 patient discontinued study in 12M Treatment Period, 1 cohort 1 patient and 1 cohort 2 patient discontinued during 24M Extension Period A. All discontinuations were for reasons unrelated to study drug.
HFMSE=Hammersmith Functional Motor Scale Expanded; RHS=Revised Hammersmith Scale.

1. Crawford T et al. Presented at: 2022 Annual SMA Conference; June 16-19, 2022; Anaheim, CA. 2. Data on file; Scholar Rock. 2022.

Non-Ambulatory Type 2 High Dose Cohort: Initiated nusinersen age <5[1,2]

Increases in HFMSE observed in patients already treated with chronic maintenance nusinersen

- Improved: 88% (7/8)
- ≥ 5-point increase: 63% (5/8)
- > 10-point increase: 38% (3/8)

Continuous and durable improvements observed through 12-months of treatment

Apitegromab (20 mg/kg) + nusinersen	n=8*
Mean change from baseline in HFMSE (95% CI)	**+7.1 (1.8, 12.5)**
# (%) patients achieving:	
≥ 1-pt increase in HFMSE	7/8 (88%)
≥ 3-pt increase in HFMSE	5/8 (63%)
≥ 5-pt increase in HFMSE	5/8 (63%)
Baseline characteristics: mean (min, max)	n=10
Age	3.8 (2, 6)
HFMSE score	23.5 (14, 42)
# of nusinersen maintenance doses	5.4 (3, 8)

*This was a primary intent-to-treat (ITT) analysis that, as prespecified, excluded 2 patients who missed 3 doses due to COVID-19 related site access restrictions. An all-patients sensitivity analysis that included those 2 patients had similar results as this primary ITT analysis.

1. Crawford T et al. TOPAZ topline results; Presented at CureSMA, 2021 Virtual SMA Research & Clinical Care Meeting; June 9-11, 2021. 2. Data on file; Scholar Rock. 2022.

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.

Non-Ambulatory Type 2/3 Cohort: Initiated nusinersen age ≥5[1,2]

Majority of patients improved in HFMSE (despite initiating background nusinersen age ≥ 5)

- ≥ 1-point increase: **~67%**
- ≥ 3-point increase: **~30%**

Durability of effect observed through 12-months of treatment

Apitegromab (20 mg/kg) + nusinersen	Per Protocol Population* (n=13)	Intent-to-Treat Population (n=14)
Mean change from baseline in HFMSE (95% CI)	**+1.2 (-0.5, 2.9)**	**+0.6 (-1.4, 2.7)**
# (%) patients achieving:		
≥ 1-pt increase in HFMSE	**9/13 (69%)**	9/14 (64%)
≥ 3-pt increase in HFMSE	**4/13 (31%)**	4/14 (29%)
≥ 5-pt increase in HFMSE	**2/13 (15%)**	2/14 (14%)
Baseline characteristics: mean (min, max)	n=15	
Age	11.7 (8, 19)	
HFMSE score	22.7 (13, 39)	
# of nusinersen maintenance doses	5.1 (2, 9)	

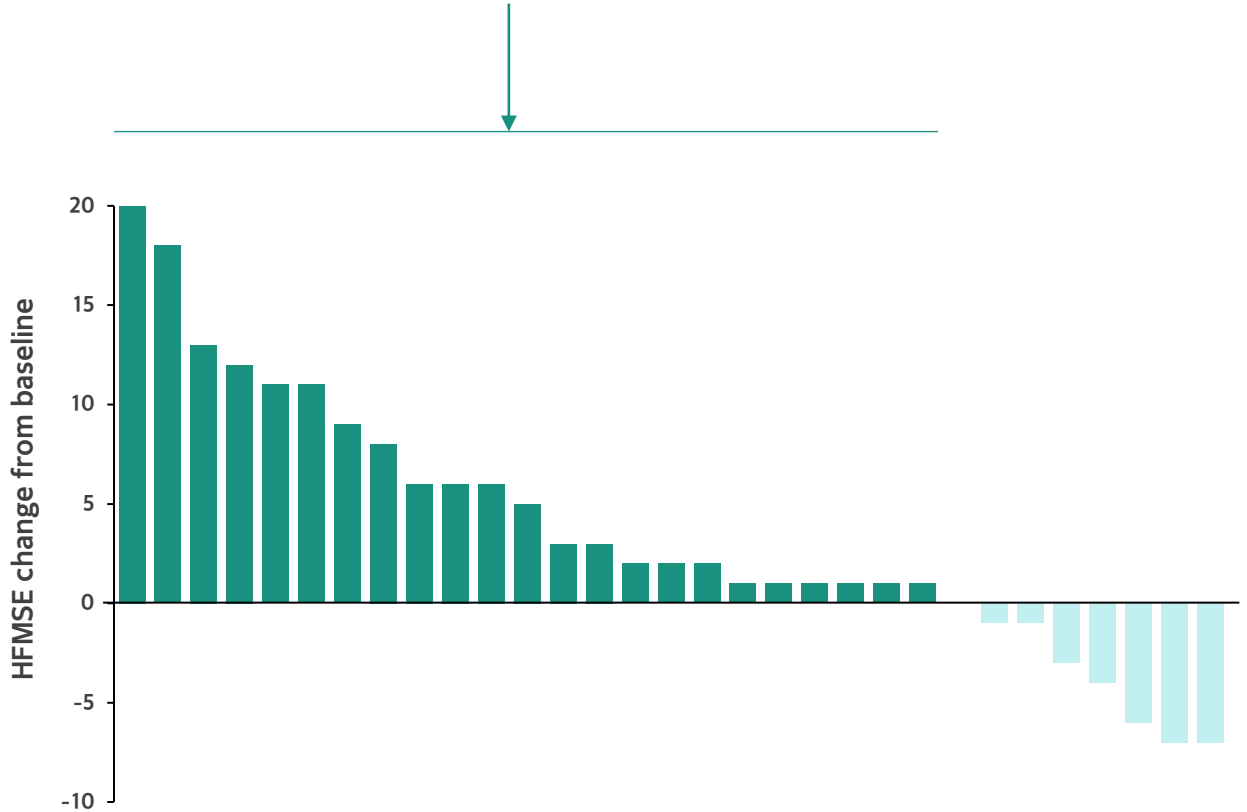
*Intent-to-treat analysis excluded 1 patient (per prespecified approach) who missed 3 doses due to COVID-19 related site access restrictions; 1 patient who had inadvertently been enrolled who was receiving (and continued to receive) an acetylcholinesterase inhibitor was removed, which is not permitted per the trial protocol; 1. Crawford T et al. TOPAZ topline results; Presented at CureSMA, 2021 Virtual SMA Research & Clinical Care Meeting; June 9-11, 2021. 2. Data on file. Scholar Rock, Inc. Apitegromab is an investigational drug candidate being evaluated for the treatment of spinal muscular atrophy. Apitegromab has not been approved for any use by the US FDA or any other health authority, and its safety and efficacy have not been established.

TOPAZ Topline 12-Month Data Showed Apitegromab's

Transformative Potential in Patients with Type 2/3 SMA

Majority of non-ambulatory patients* experienced HFMSE increases from apitegromab

during chronic maintenance phase of SMN therapy



Apitegromab led to HFMSE improvements in both non-ambulatory cohorts

including patients started on nusinersen at age ≥ 5

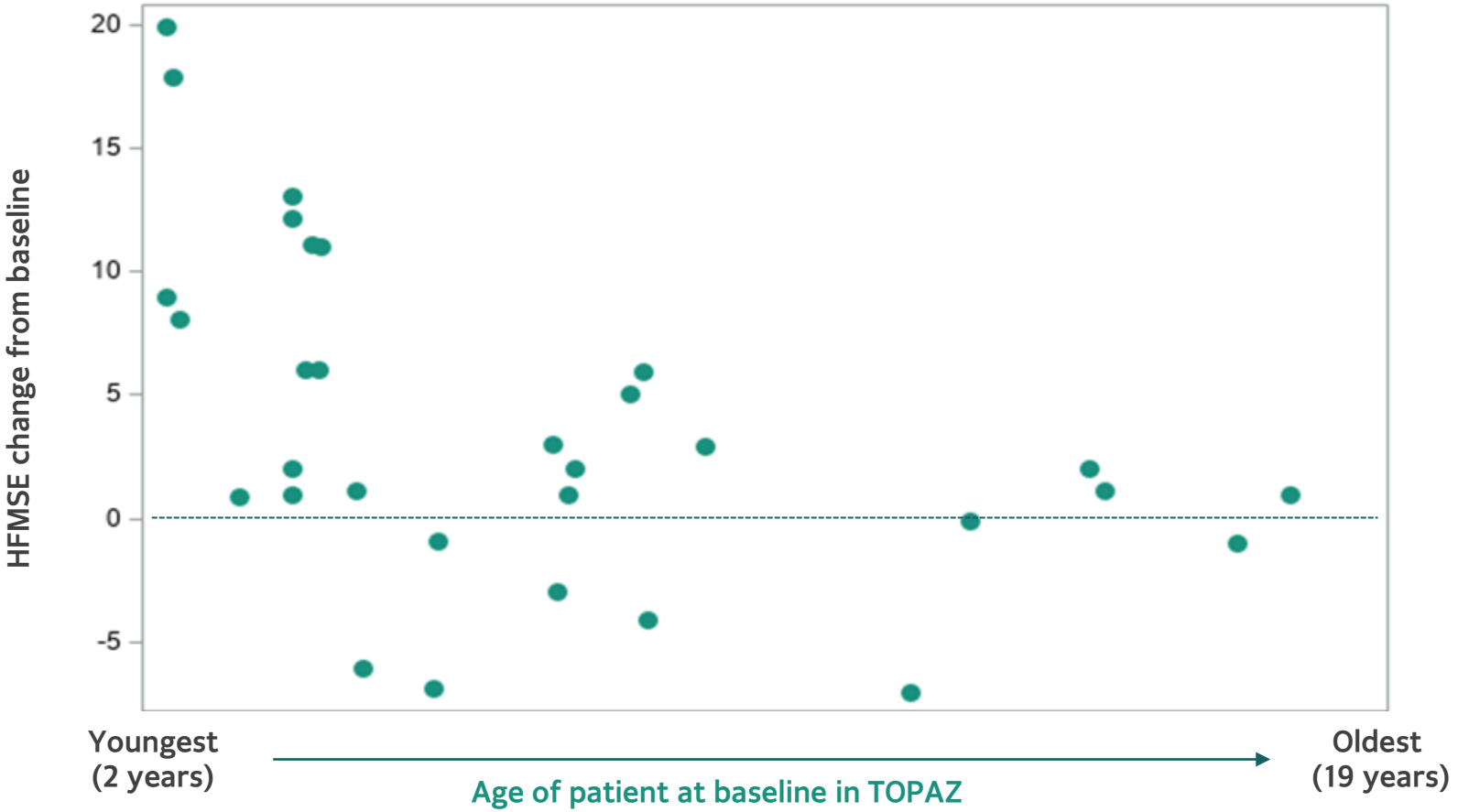
	Initiated background nusinersen	
	Age < 5**	Age ≥ 5
Mean HFMSE Increase	+7.1 points	+0.6 points
≥ 1-point Increase % (n/N)	88% (7/8)	64% (9/14)
≥ 3-point Increase % (n/N)	63% (5/8)	29% (4/14)

Crawford T et al. TOPAZ topline results; Presented at CureSMA, 2021 Virtual SMA Research & Clinical Care Meeting; June 9-11, 2021

* Pooled cohorts of non-ambulatory patients treated with apitegromab 20 mg/kg and 2 mg/kg

**Non-ambulatory patients who initiated background nusinersen at a young age of <5 years and treated with apitegromab 20 mg/kg dose. 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.

HFMSE Improvements Observed Across Age Range of Non-Ambulatory Patients with Relatively Larger Gains from Earlier Treatment

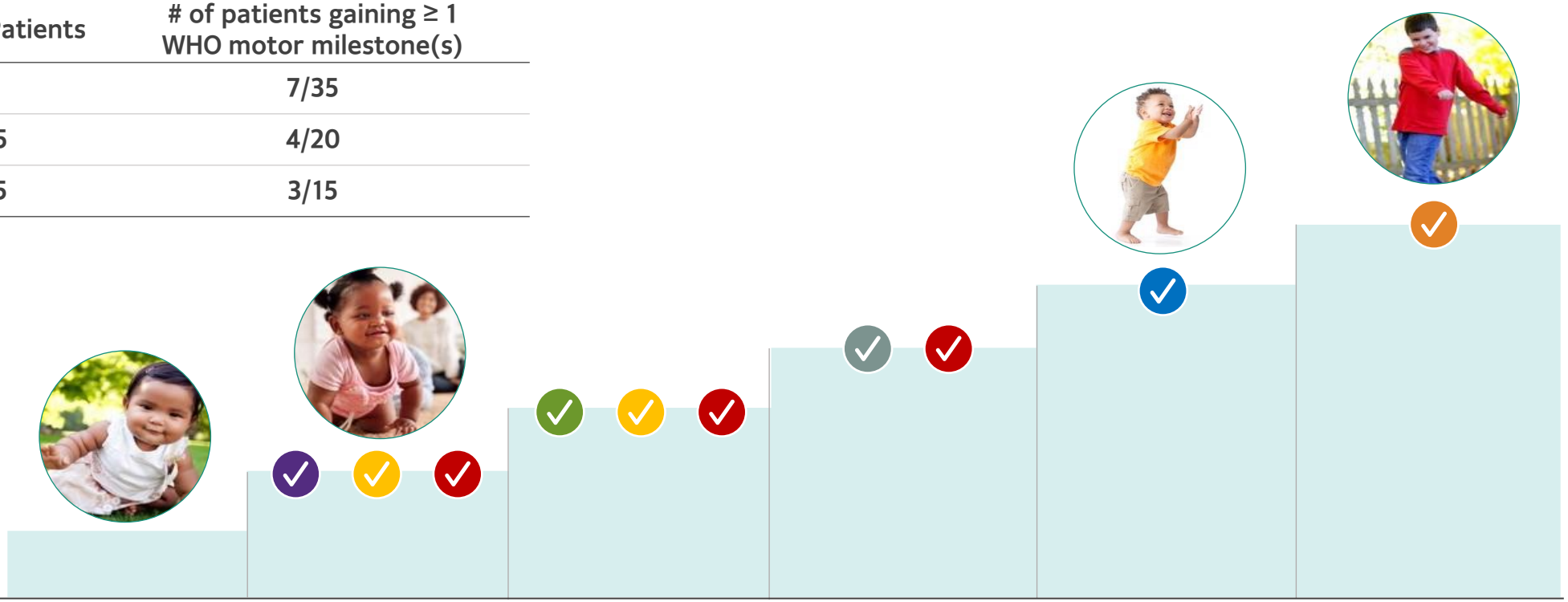


*Pooled cohorts of non-ambulatory patients treated with apitegromab 20 mg/kg and 2 mg/kg; excludes 4 patients who each missed 3 doses of apitegromab due to COVID-19-related site access restrictions and were not included in the primary (intent-to-treat) analysis.
Data on file. Scholar Rock, Inc. Cambridge, MA. 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.

WHO Motor Development Milestone Achievements Further Support Apitegromab's Potential to Improve Motor Function[1]

Non-ambulatory Type 2/3 Patients	# of patients gaining ≥ 1 WHO motor milestone(s)
Pooled	7/35
Initiated nusinersen age < 5	4/20
Initiated nusinersen age ≥ 5	3/15

Following 12 months of apitegromab treatment...



WHO motor milestone analysis included all patients who completed the 12-month treatment period, including 4 patients who missed 3 doses of apitegromab due to COVID-19-related site access restrictions. Median baseline score for both non-ambulatory cohorts was 1.0.

✓ 1 patient (initiated nusinersen age ≥5) **gained 2 new motor milestones** ✓ 1 patient (initiated nusinersen age <5, 20 mg/kg) **gained 3 new motor milestones**

Pictures are not of patients with SMA and are not meant to be representative of patients with SMA. 1. Crawford T et al. TOPAZ topline results; Presented at CureSMA, 2021 Virtual SMA Research & Clinical Care Meeting; June 9-11, 2021

Significance of Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM)

HFMSE

Assesses the physical abilities of patients with Types 2/3 SMA

ABLE TO:

Touch Head Above Ear Level
whilst maintaining stable trunk and head

Roll From Supine to Prone
over the right side without pulling/ pushing on hands

33 Items
Graded on scale 0 to 2

0 = unable
1 = performed with modification or adaptation
2 = without modification or adaptation

Item scores are summed to give a total score

The higher the total score, the greater the patient's motor function

Maximum score: 66

Examples of items:

- One hand to head in sitting
- Rolls supine to prone
- Lying to sitting
- Four-point kneeling
- Supported standing
- Stepping
- Ascends 4 stairs with railing

RULM

Evaluates Motor Performance in Upper Limbs

ABLE TO:

Bring Token to Cup
placed vertically at shoulder height

Bring Weight at Eye Level
using two hands

19 Items
Graded on scale 0 to 2
(Except for 1 activity with a binary score)

0 = unable
1 = able with modification
2 = able with no difficulty

Evaluated upper limb tasks correspond to ability to perform everyday activities

Maximum score: 37

Examples of items:

- Putting a coin into a cup
- Elevating a cup to mouth
- Picking up a coin
- Bringing hand to shoulder
- Lifting up weighted objects
- Opening a zip lock bag
- Drawing a line on paper

O'Hagen et al. 2007; Glanzman et al. 2011; Hammersmith Functional Motor Scale Expanded for SMA (HFMSE) Manual, 2019
Mazzone et al. 2017; Pierzchlewicz et al. 2021; Revised Upper Limb Module for SMA Manual, 2014

TOPAZ Extension Period: 24-Month Patient Disposition

	Cohort 1 Ambulatory	Non-Ambulatory		
		Cohort 2	Cohort 3	Total
# Non-Ambulatory Patients (2-21)		15	20	35
# Non-Ambulatory Patients (2-12)		9	20	29
Dropped Out (0-12 M)	1	0	0	0
Dropped Out (12-24 M)	1	1	0	1
Not Having Valid HFMSE testing at Month 24	Not applicable	5*	1**	6
Not Having RULM at Month 24	Not applicable	2***	1****	3
# of patients who received scoliosis surgery	1	2*****	1	3

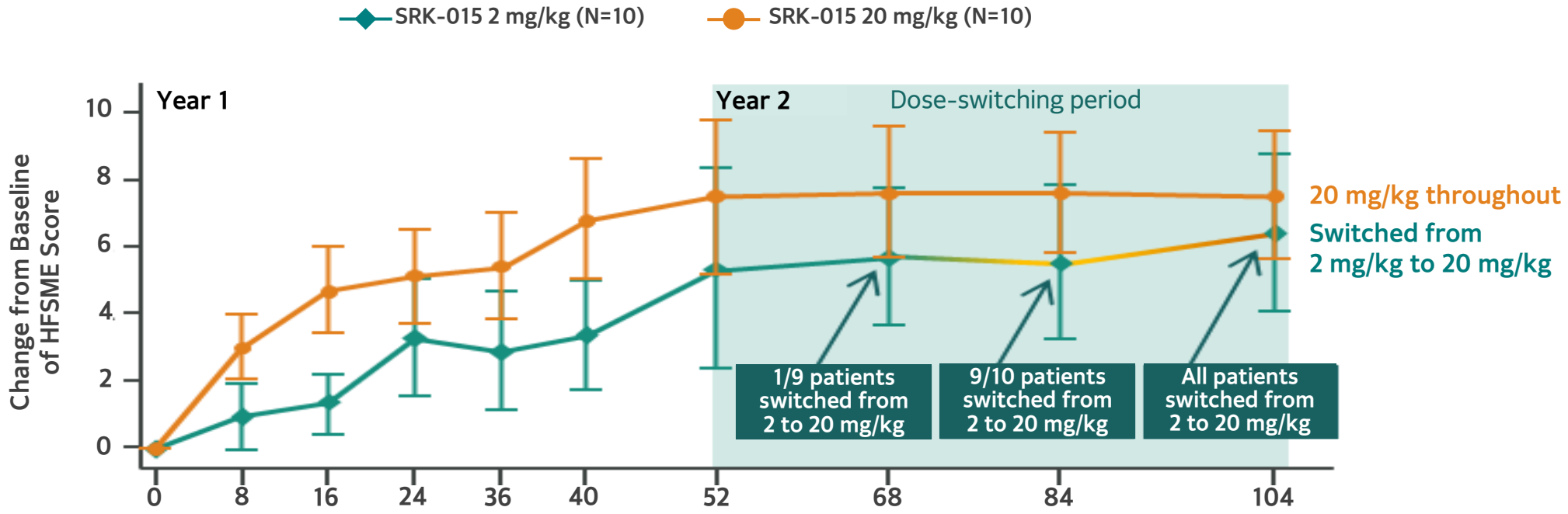
* Includes 1 patient who withdrew from study; 1 patient off schedule due to scheduled surgery; 1 patient who had hip pain; 1 patient with femur fracture; and 1 patient who refused to be in supine position.
** Patient with bilateral lower extremity cast
*** Includes 1 patient withdrew from study, and 1 patient off schedule due to planned surgery.
**** Patient was too young for RULM at baseline and RULM was not conducted at following visit.
***** Patients did not have valid HFMSE test at 24 months.

Strong Evidence of Dose Response Observed Over 24 Months

Further Supported by Data from Low Dose to High Dose Switch in Non-Ambulatory Patients

Mean Change from Baseline in HFSME Scores Over Time (Cohort 3)

Excludes data after scoliosis surgery



Sample Size at Each Visit

Cohort 3 SRK 2 mg/kg	10	10	10	7	8	9	9	9	10	10
Cohort 3 SRK 20 mg/kg	10	10	10	8	8	10	8	10	10	8

Crawford T et al. TOPAZ EXTENSION: 24-MONTH EFFICACY AND SAFETY OF APITEGROMAB IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TYPE 2 AND TYPE 3 SMA) Podium Presentation Presented at CureSMA; June 2022

This analysis excludes from the Observed Case Analysis the HFMSE data attained post-scoliosis surgery during TOPAZ. Error bars represent SEM.

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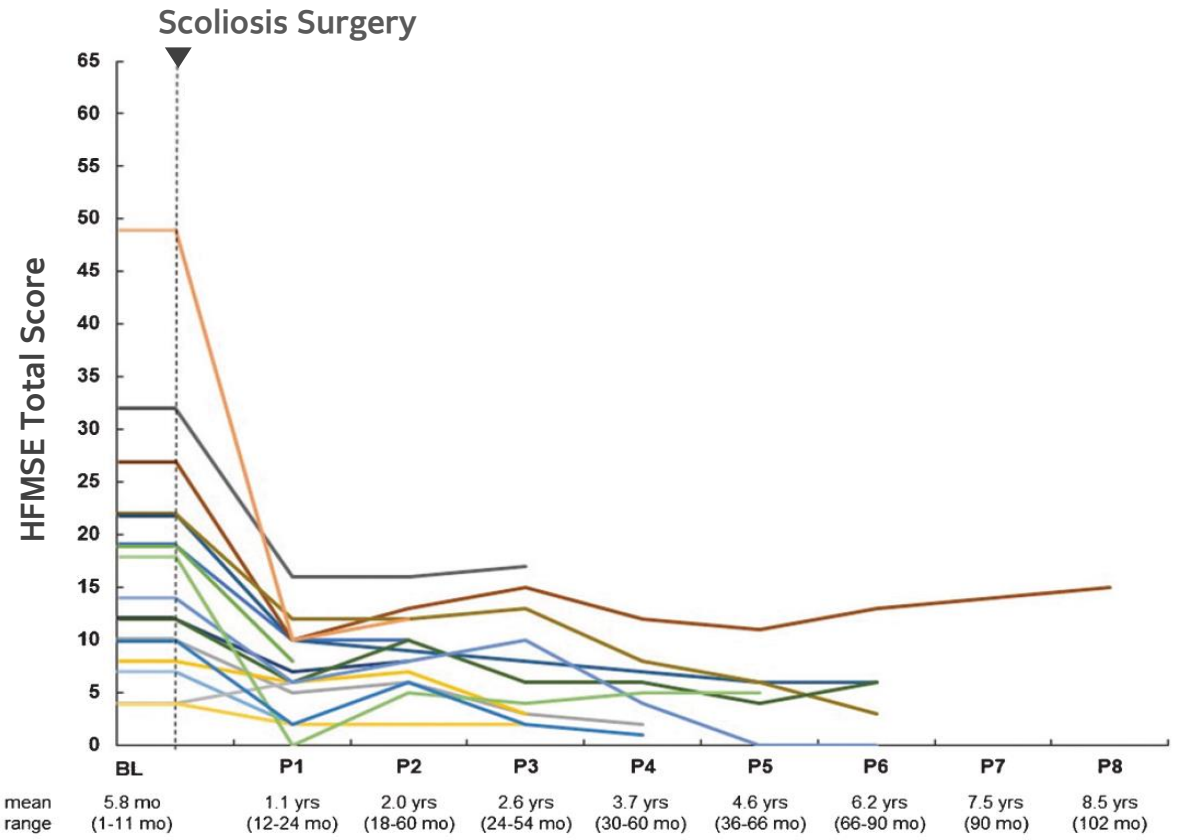
Reported Impact of Scoliosis Surgery on Motor Abilities in SMA

Post-Surgery HFMSE scores Type 2/3 SMA

peer-reviewed study



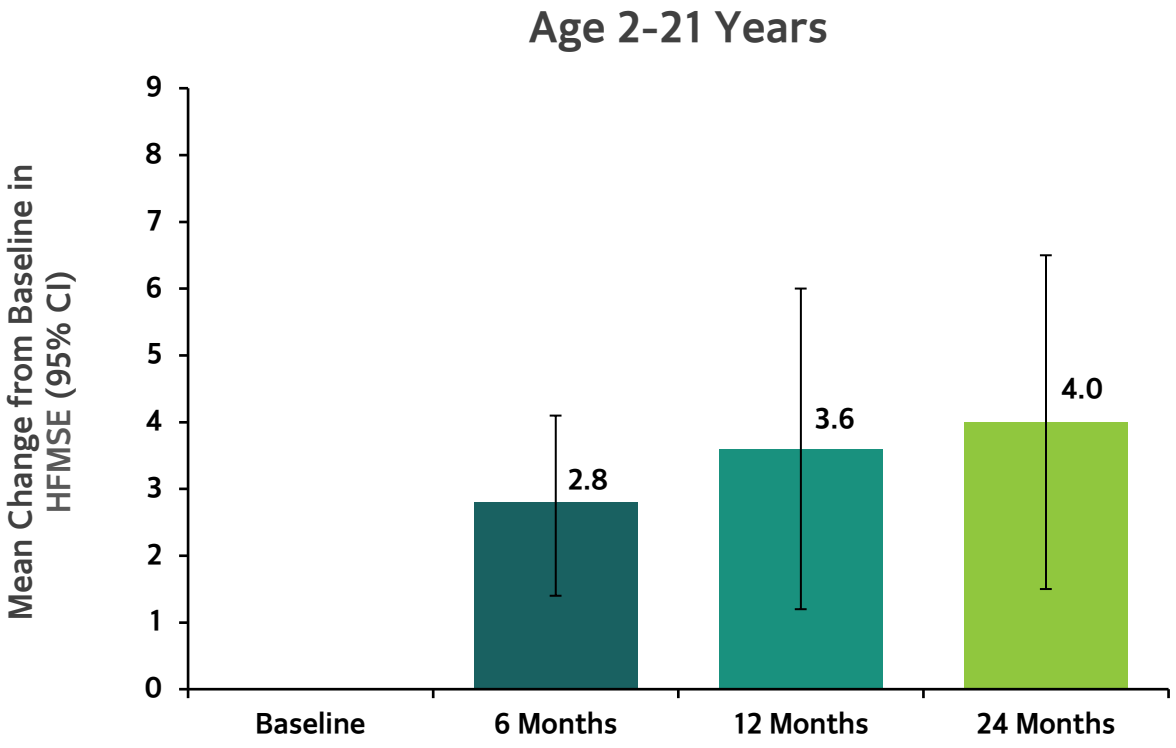
3-month post-surgery assessment

14/17	**Lost >3 points on the HFMSE** (mean change = - 12.1, SD = 8.9)	**Functionally meaningful change**
13/17	Minimal HFMSE changes within ± 2 points (mean change = - 0.7)	No change or stability
0/17	Improvement > 2 points post-surgery	

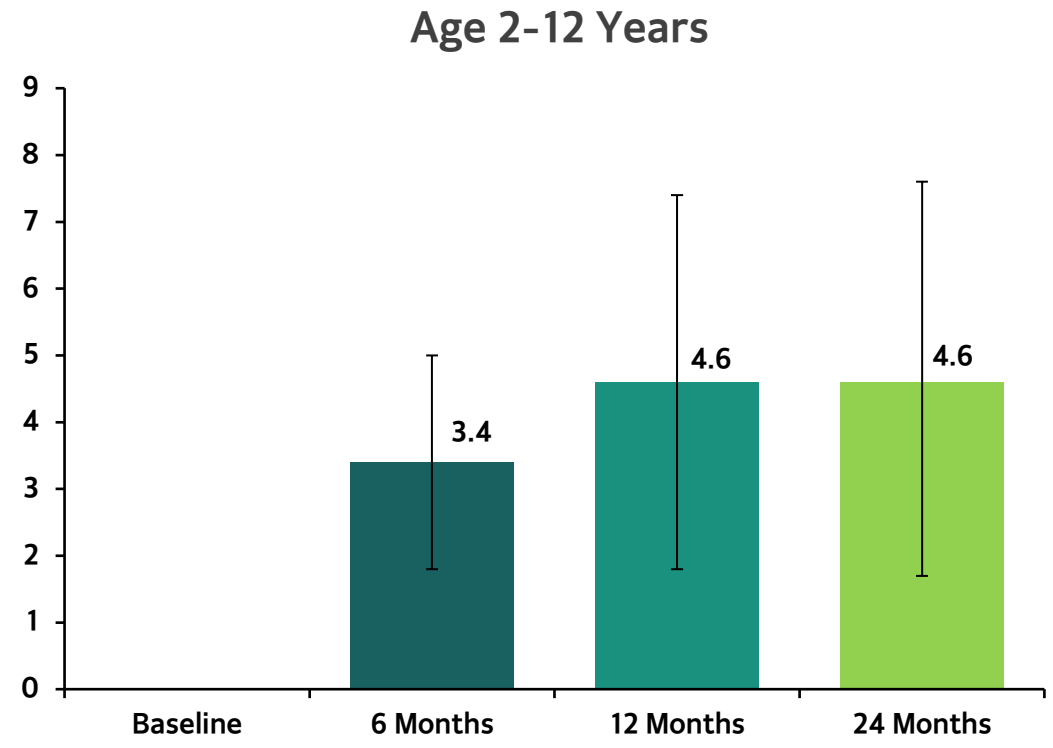
Dunaway Young et al. 2020

Sustained Increases in HFMSE Observed Over 24 Months of Apitegromab

Pooled Non-Ambulatory Patients



	Baseline	6 Months	12 Months	24 Months
n=	35	29	32	29



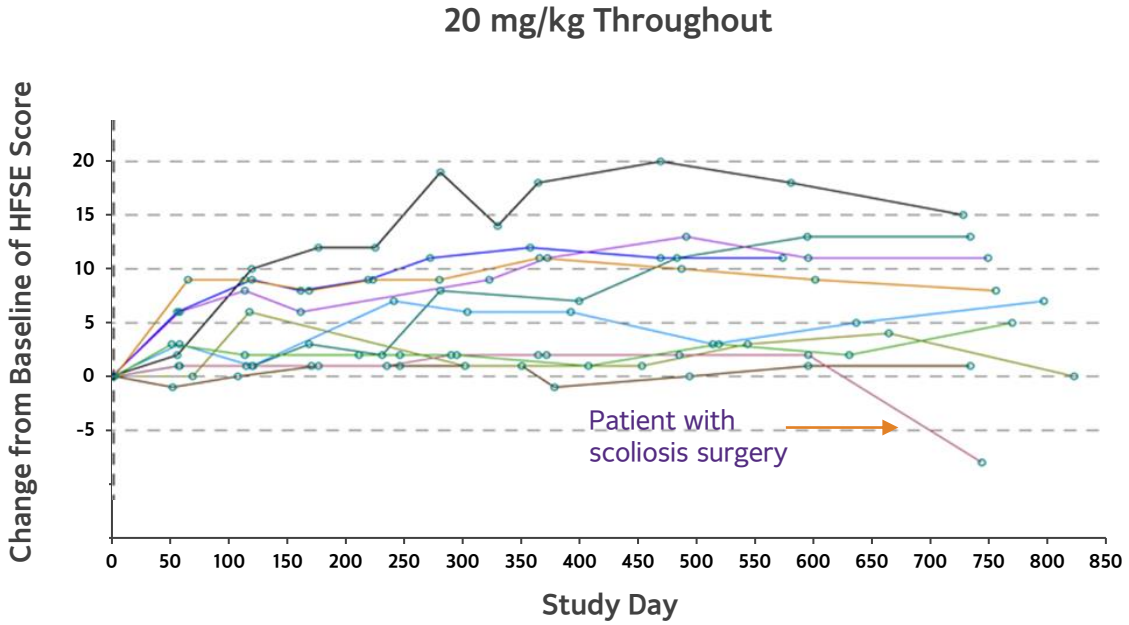
	Baseline	6 Months	12 Months	24 Months
n=	29	23	26	24

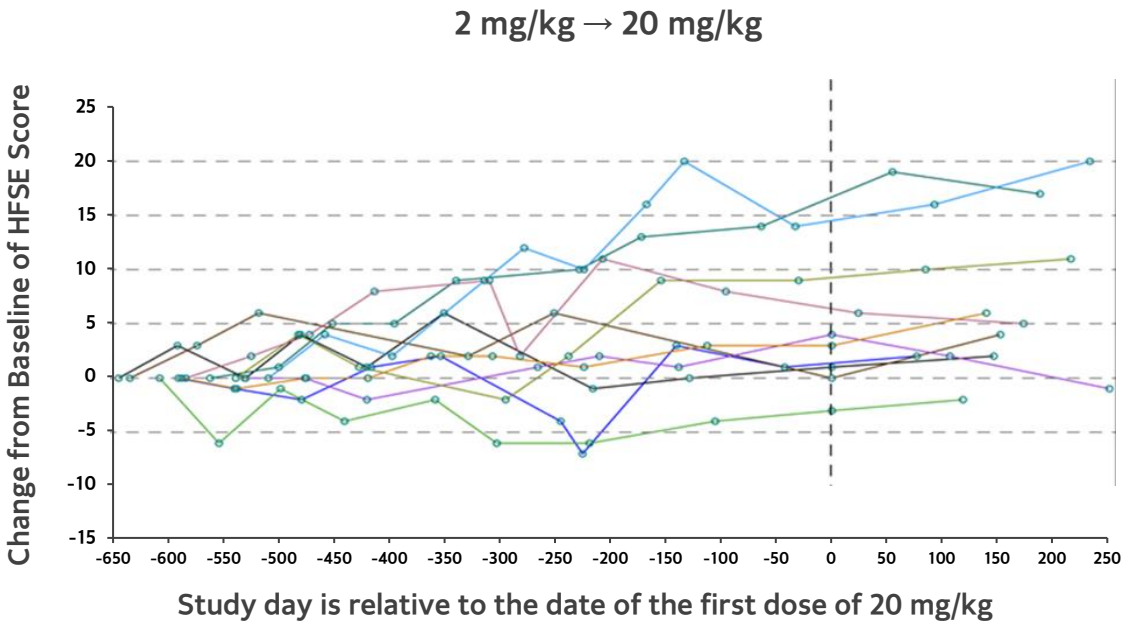
Observed Case Analysis is based upon data available for a given timepoint, and this analysis population includes patients treated with the lower dose 2 mg/kg and does not exclude any patients who missed apitegromab doses due to COVID-19 site access restrictions. Error bars represent standard error of the mean (SEM). Values in parentheticals represent 95% confidence interval. Data on File. Scholar Rock, Inc. Cambridge, MA. 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.

Strong Evidence of Dose Response Observed Over 24 Months

Further Supported by Data from Low Dose to High Dose Switch in Non-Ambulatory Patients

Most patients in Cohort 3 who switched from 2 mg/kg to 20 mg/kg continued to show HFMSE improvement





Rapid Increase

Benefit maintained through 24-month timepoint

Gradual increases of HFMSE at 2 mg/kg

Continued improvement after switch

Switch to 20 mg/kg

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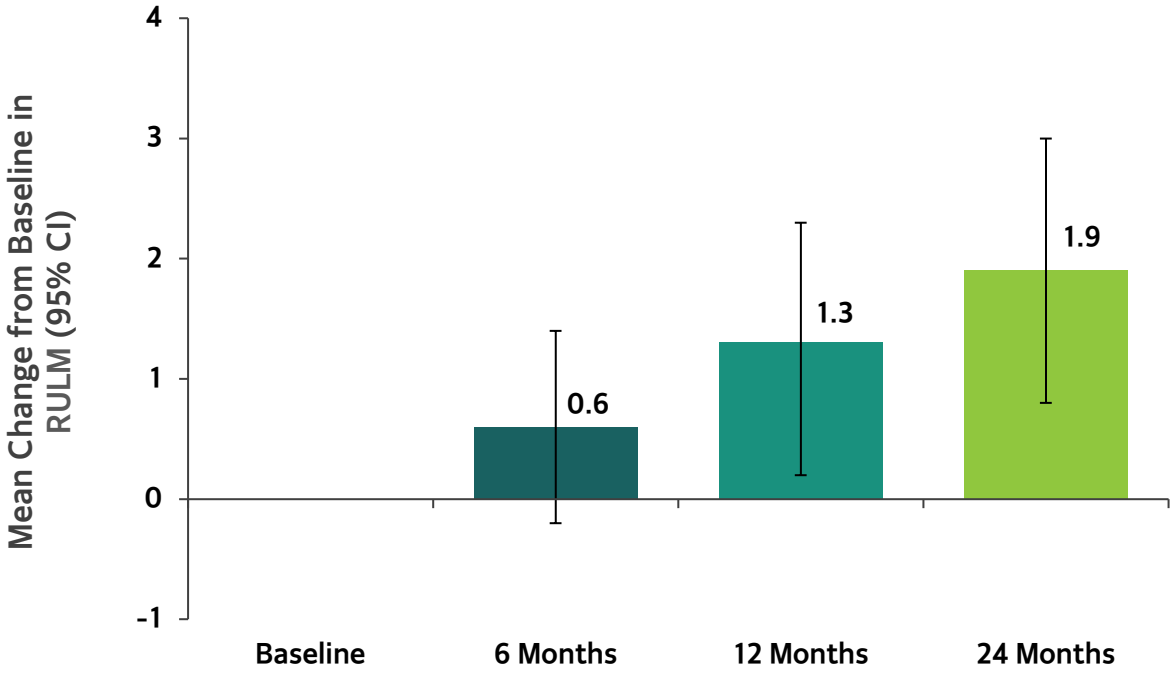
Continued Increase in RULM Observed at 24 Months of Apitegromab

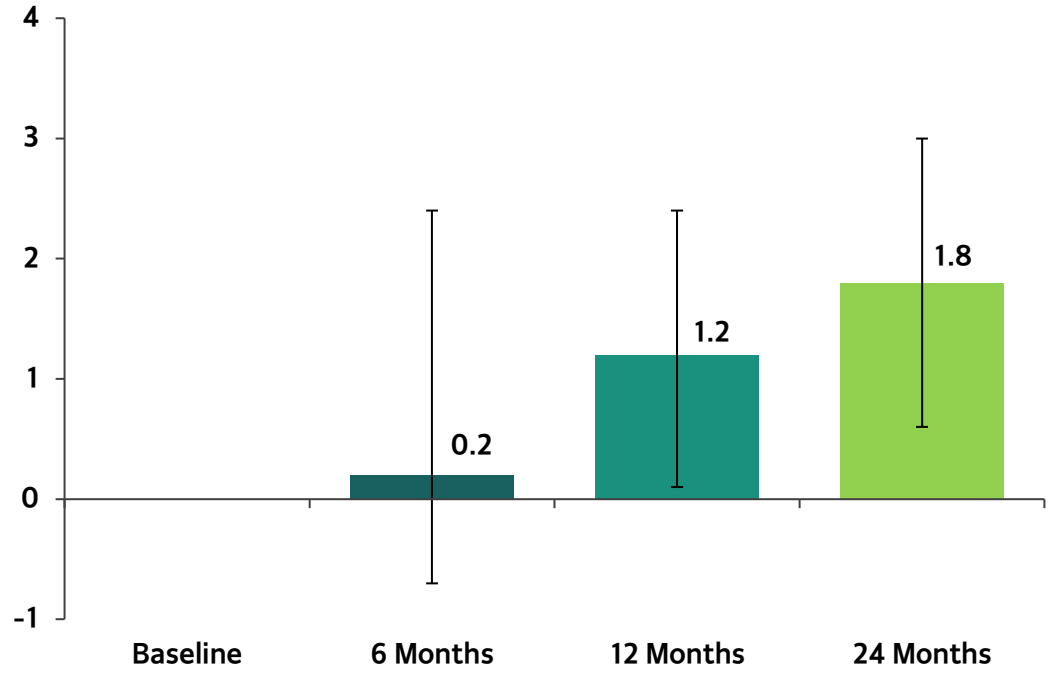
Pooled Non-Ambulatory Patients

Age 2-21 Years



	Baseline	6 Months	12 Months	24 Months
n=	34	28	31	33

Age 2-12 Years



	Baseline	6 Months	12 Months	24 Months
n=	28	22	25	28

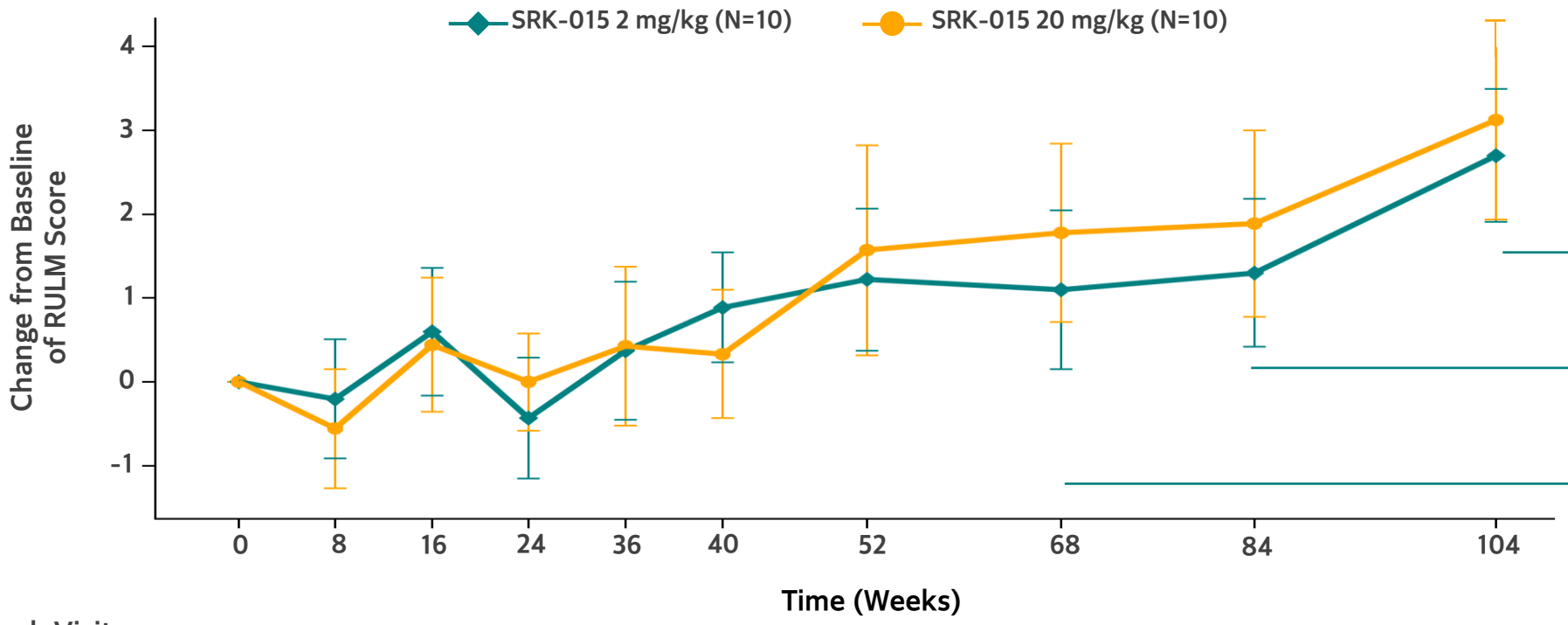
Observed Case Analysis is based upon data available for a given timepoint, and this analysis population includes patients treated with the lower dose 2 mg/kg and does not exclude any patients who missed apitegromab doses due to COVID-19 site access restrictions. Data on File. Scholar Rock, Inc. Cambridge, MA. 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.

Cohort 3: Mean RULM Score Change Over Time

RULM Trended Up in Low Dose Arm Patients After Switch to High Dose

Mean Change from Baseline in RULM Scores Over Time (Cohort 3)

Excludes data after scoliosis surgery



All patients in Cohort 3 switched from 2 mg/kg to 20 mg/kg

9 of 10 patients in Cohort 3 switched from to 2 mg/kg to 20 mg/kg

1 of 9 patients in Cohort 3 switched from 2 mg/kg to 20 mg/kg

Sample Size at Each Visit

Cohort 3 SRK 2 mg/kg	10	10	10	7	8	9	9	9	10	10
Cohort 3 SRK 20 mg/kg	10	10	10	8	8	10	8	10	10	8

Observed Case Analysis is based upon data available for a given timepoint, and this analysis population includes patients treated with the lower dose 2 mg/kg and does not exclude any patients who missed apitegromab doses due to COVID-19 site access restrictions. Error bars represent standard error of the mean (SEM). Error bars represent SEM.

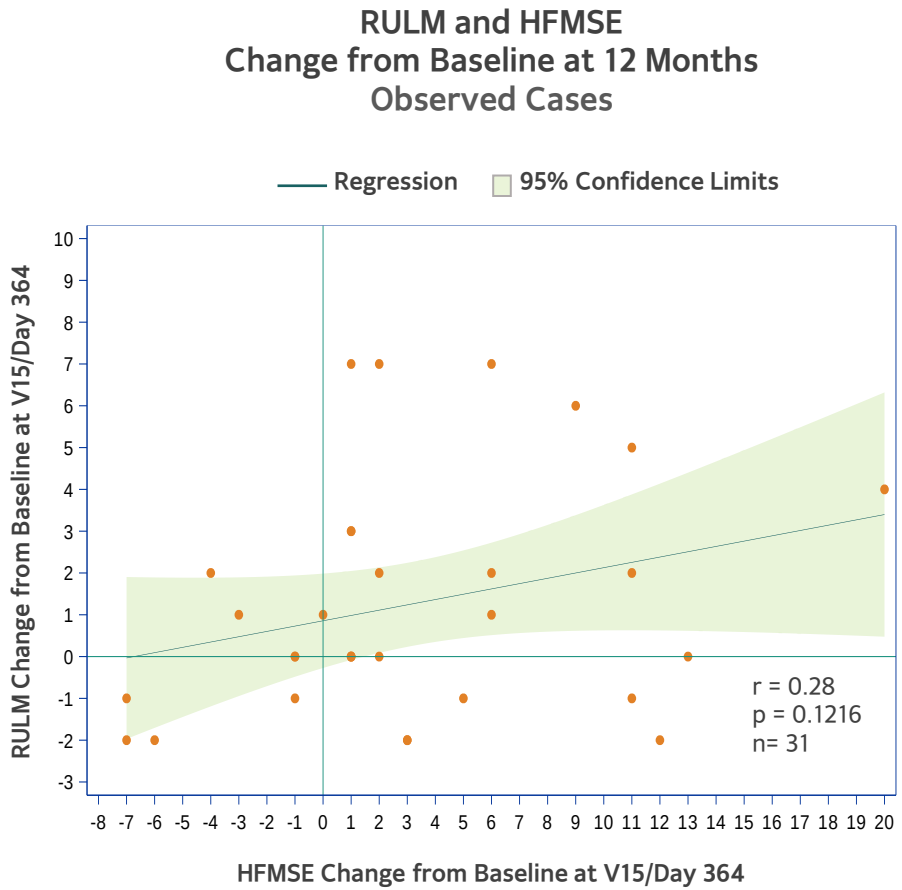
Crawford T et al. TOPAZ EXTENSION: 24-MONTH EFFICACY AND SAFETY OF APITEGROMAB IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TYPE 2 AND TYPE 3 SMA) Podium Presentation Presented at CureSMA; June 2022. Apitegromab is an investigational drug candidate being evaluated for the treatment of spinal 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.

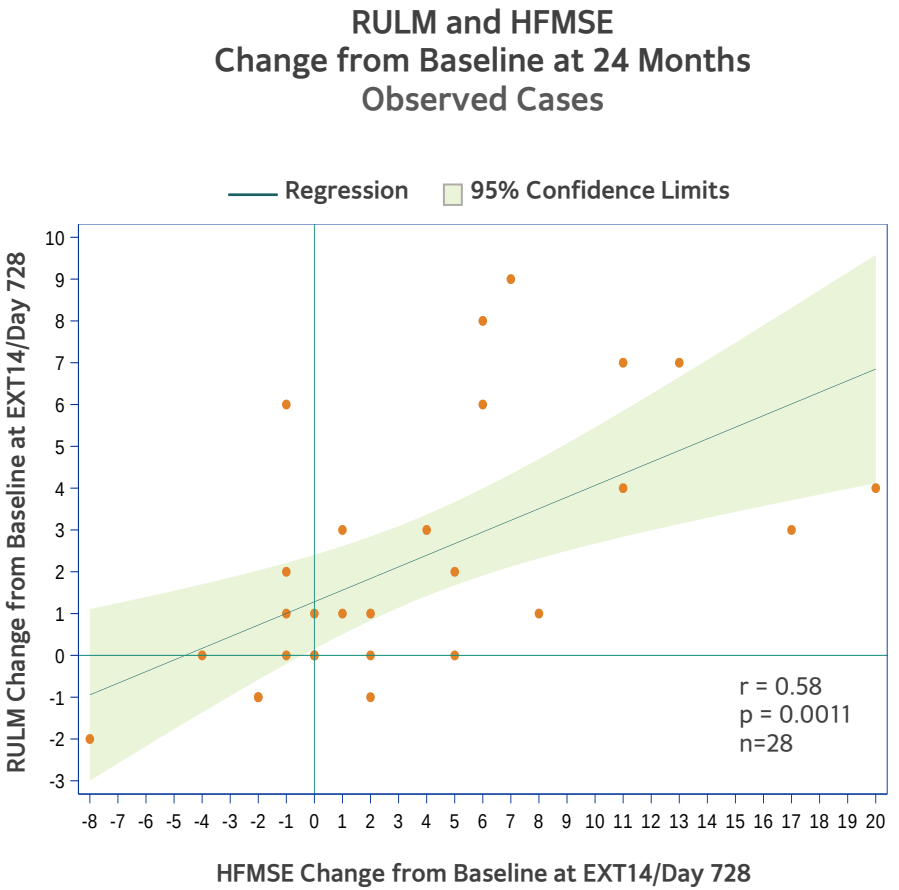
Correlation of HFMSE to RULM Increased Over 24 Months

Pooled Non-Ambulatory Patients

"The observation that the majority of patients in this analysis experienced gains in both the HFMSE and RULM over 24 months further supports the therapeutic potential of apitegromab."

- Basil Darras, MD
Associate Neurologist-in-Chief, Boston Children's Hospital;
Professor of Neurology, Harvard Medical School;
TOPAZ trial Investigator





Crawford T et al. TOPAZ EXTENSION: 24-MONTH EFFICACY AND SAFETY OF APITEGROMAB IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TYPE 2 AND TYPE 3 SMA) Podium Presentation Presented at CureSMA; June 2022.

This analysis is based on the Observed Case Analysis population. The 12-month graph displays all patients who had a valid measurement at visit 15 (Day 364) and the 24-month graph displays all patients who had a valid measurement at extension visit 14 (Day 728).; 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.

Activities of Daily Living and Fatigue: Assessed by Three Measures

PEDI-CAT, PROMIS, and ESBBT

Used to assess:

- **ADL**
- **Fatigue**
- **Muscle Endurance**

1 PEDI-CAT:

Measure of activities of daily living

Measures pediatric abilities through 3 functional domains, daily activities, mobility, and social cognitive[1]

- 4-point scale **(1=unable to 4=easy)** assessment of various activities, **higher scores reflect improved abilities**[1,2]
- PEDI-CAT has been validated in SMA, but alone cannot identify small changes in function across all types of SMA[3]

2 PROMIS (Fatigue):

Measure of Patient Fatigue

PRO measurement tool[4]

- Measures mild subjective feelings of tiredness to debilitating and sustained feelings of exhaustion**, with lower scores reflecting less fatigue**[4,5]
- Has been utilized to assess fatigue and fatigability in the Cure SMA database, but has not been fully validated in SMA[5]

3 ESBBT (Fatigability):

Measure of how fast a patient fatigues

Muscle endurance measurement tool[6]

- Part of a series of endurance shuttle tests that include: nine-hole peg test, box and block test, and walk test (ESNHPT, ESBBT, and ESWT)[6]
- Patients are asked to move blocks individually from one box to another in one minute, with **higher numbers of blocks suggesting higher muscle endurance**[6]
- The endurance shuttle tests have been validated for use in patients with SMA[7]

ADL, activities of daily living; ESBBT, endurance shuttle box and block test; ESNHPT, endurance shuttle nine-hole peg test; ESWT, endurance shuttle walk test; PEDI-CAT, pediatric evaluation of disability inventory computer adaptive test; PROMIS, patient-reported outcomes measurement information system; PRO(s), patient-reported outcome(s); SMA, spinal muscular atrophy.

1. Cre Care. PEDI-CAT. Accessed April 26, 2022. https://www.pedicat.com/. 2. Data on file; Scholar Rock. 2022. 3. Pasternak A, et al. *Muscle Nerve*. 2016;54(6):1097-1107. 4. NIH. PROMIS. Accessed April 26, 2022. https://commonfund.nih.gov/promis/index. 5. Belter L, et al. *Orphanet Journal of Rare Diseases*. 2020;15:217. 6. Cure SMA. Best Practices for Physical Therapists and Clinical Evaluators in Spinal Muscular Atrophy (SMA). 2021. Available at: https://www.curesma.org/wp-content/uploads/2021/09/Clinical-Evaluators-Best-Practices-13-August-2021.pdf. 7. Bartels B, et al. *Orphanet Journal of Rare Diseases*. 2020;15:75.

Therapeutic Potential of Apitegromab Observed in the Ambulatory Type 3 SMA Cohort at 24 Months[1-4]

Ambulatory Patients
(Revised Hammersmith Scale; RHS)

24-Month Analysis	COHORT 1		
	20 mg/kg pooled[1] (n=21)	20 mg/kg Monotherapy[4] (n=11)	20 mg/kg + nusinersen[2,3] (n=10)
Mean change from baseline, (95% CI)	-1.8 (-4.7, 1.1)	-2.8 (-8.4, 2.8)	-0.7 (-3.1, 1.7)
Patients achieving ≥ 1-pt increase, n (%)	9/21 (42.9%)	5/11 (45.5%)	4/10 (40%)
Patients achieving ≥ 3-pt increase, n (%)	5/21 (23.8%)	3/11 (27.3%)	2/10 (20%)

Observed Case Analysis includes all patients who had a valid measurement at E14 (Day 728). Inclusive of data from 3 patients in apitegromab monotherapy who lost ability to ambulate. 1. Crawford T et al. TOPAZ EXTENSION: 24-MONTH EFFICACY AND SAFETY OF APITEGROMAB IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TYPE 2 AND TYPE 3 SMA) Podium Presentation Presented at CureSMA; June 2022. 2. Crawford T et al. P.102. Apitegromab in SMA: An analysis of multiple efficacy endpoints in the TOPAZ extension study Neuromuscular Disorders.2022; 32 (SUPPLEMENT 1): S86-S87. 3. Crawford T et al. P.102. Apitegromab in SMA: An analysis of multiple efficacy endpoints in the TOPAZ extension study; Poster Presented and Poster Highlights Podium Presentation presented WMS October 2022. 4. Data on File, Scholar Rock Inc. 2022. 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.

Overall Safety and Tolerability Profile Over 24 Months of Treatment: Serious TEAEs

- Fourteen patients experienced a serious TEAE, all assessed by the respective trial investigator as unrelated to apitegromab:
  - One patient treated with 2 mg/kg dose (Cohort 3) was hospitalized due to adenoidal hypertrophy and tonsillar hypertrophy to perform scheduled adenotonsillectomy (Grade 2). Events resolved without sequelae.
  - Two patients treated with 20 mg/kg dose (both Cohort 1) presented with gait inability considered a significant disability (both Grade 3). Events remain ongoing.
  - One patient treated with 20 mg/kg dose (Cohort 1) was hospitalized with post lumbar puncture syndrome (Grade 2). Event resolved without sequelae.
  - One patient treated with 20 mg/kg dose (Cohort 1) was hospitalized due to viral upper respiratory tract infection (Grade 2). Event resolved without sequelae.
  - Five patients treated with 20 mg/kg dose (one from Cohort 1, three from Cohort 2, and one from Cohort 3) were hospitalized for spinal fusion surgery/ scoliosis/ scoliosis surgery (all Grade 3). All events resolved without sequelae.
  - One patient treated with 20 mg/kg dose (Cohort 1) was hospitalized due to bilateral developmental hip dysplasia and left hip dislocation (both Grade 3). Events resolved without sequelae.
  - One patient treated with 2 mg/kg dose (Cohort 3) was hospitalized due to hip dislocation (Grade 3). Event resolved with sequelae (anxiety and post-operative pain).
  - One patient treated with 20 mg/kg dose (Cohort 3) was hospitalized due to respiratory syncytial virus infection (Grade 2). Events resolved without sequelae.
  - One patient treated with 2 mg/kg dose (Cohort 3) was hospitalized due to vomiting and pneumonia (Grade 3). Events resolved without sequelae.

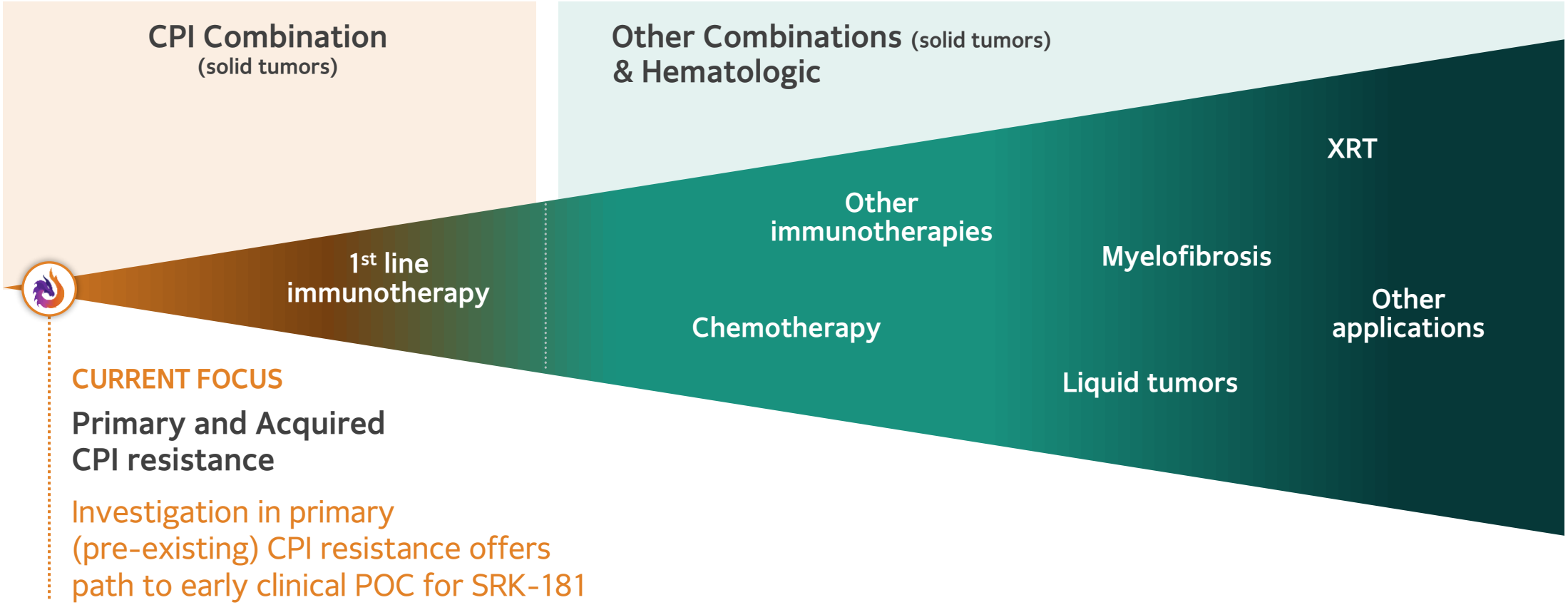
Apitegromab is an investigational drug candidate being evaluated for the treatment of spinal muscular atrophy. Apitegromab has not been approved for any use by the US FDA or any other health authority, and its safety and efficacy have not been established.

Overall Safety and Tolerability Profile Over 24 Months of Treatment: Non-Serious Grade 3 Events

- Four patients presented with non-serious Grade 3 events, all assessed by the respective trial investigator as unrelated to apitegromab:
  - One patient treated with 20 mg/kg dose (Cohort 1) presented with post lumbar puncture syndrome. Event resolved without sequelae.
  - One patient treated with 20 mg/kg dose (Cohort 2) presented with worsening of scoliosis. Event resolved (with surgery, reported as serious, above) without sequelae.
  - One patient treated with 20 mg/kg dose (Cohort 2) presented with osteopenia. Events remains ongoing.
  - One patient treated with 2 mg/kg (Cohort 3) presented with two instances of hypoglycemia and one instance of metabolic acidosis. All events resolved without sequelae.
  - One patient (Cohort 1) discontinued from the trial due to Grade 2 muscle fatigue that started prior to initiation of dosing with study drug; assessed by the trial investigator as unrelated to apitegromab.

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.

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

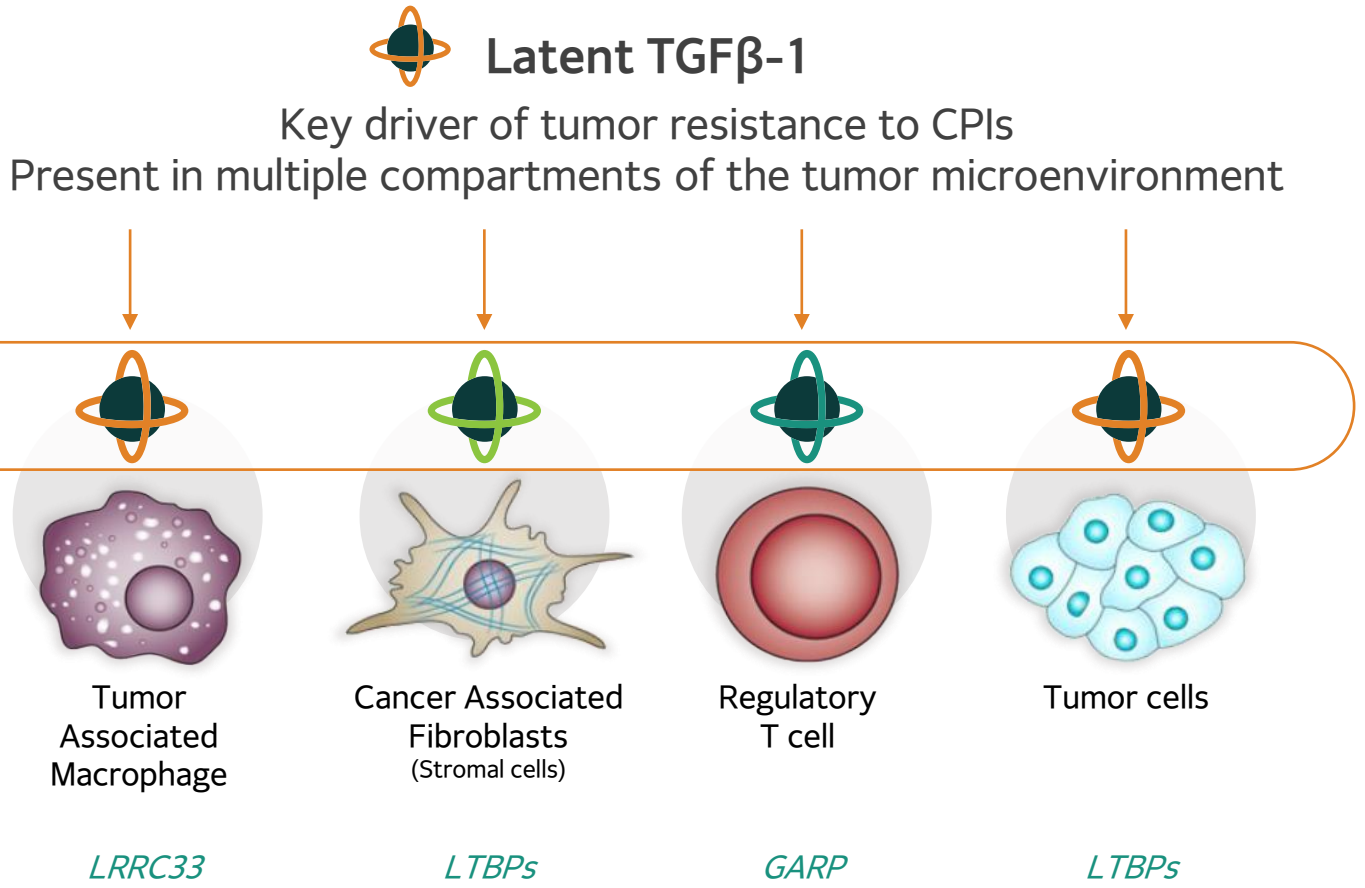
Context-Independent: SRK-181 Inhibits Latent TGFβ-1 Across All Compartments of the Tumor Microenvironment

SRK-181

Targets latent TGFβ-1

Inhibits activation of latent TGFβ-1 across **ALL** compartments

Turns it off at the source



TGFβ Latent growth factor

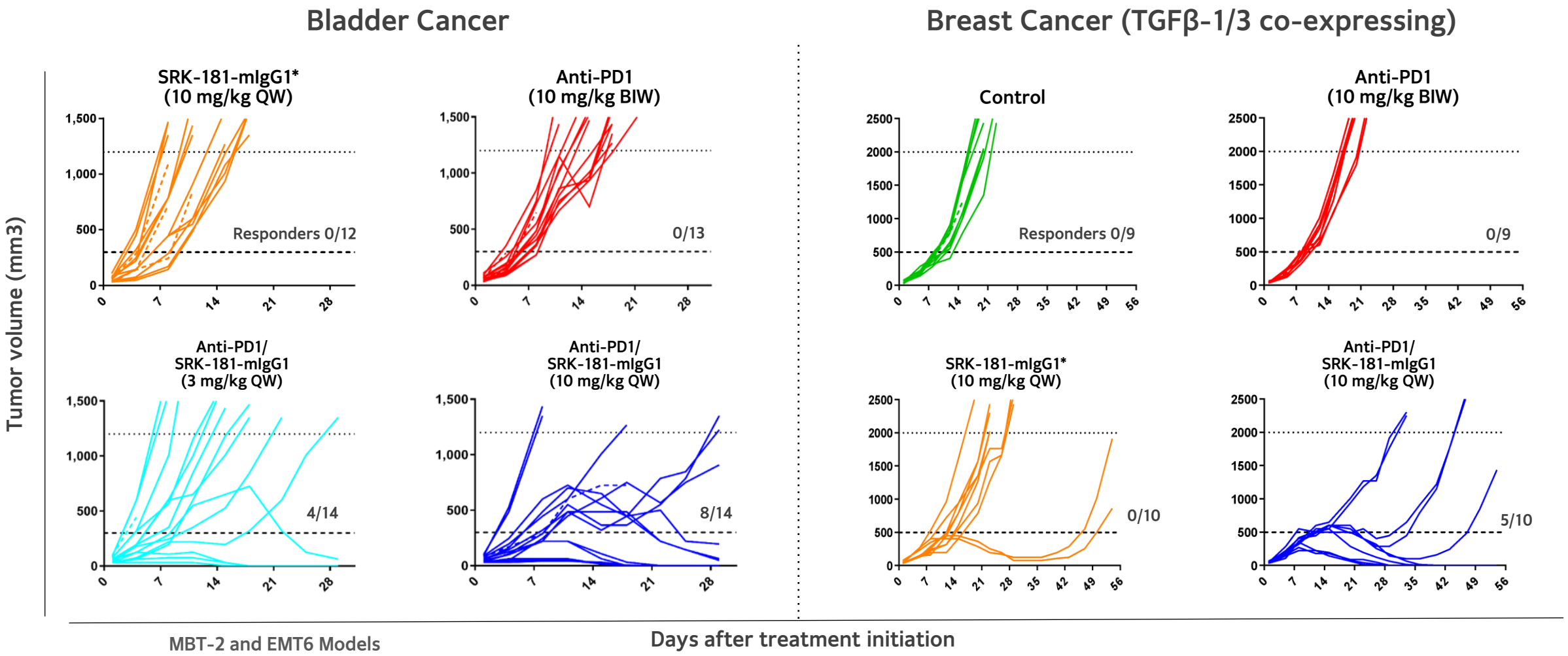
LRRC33: leucine-rich-repeat-containing protein family member 33 | LTBPs: latent transforming growth factor β binding proteins | GARP: glycoprotein A repetitions predominant

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

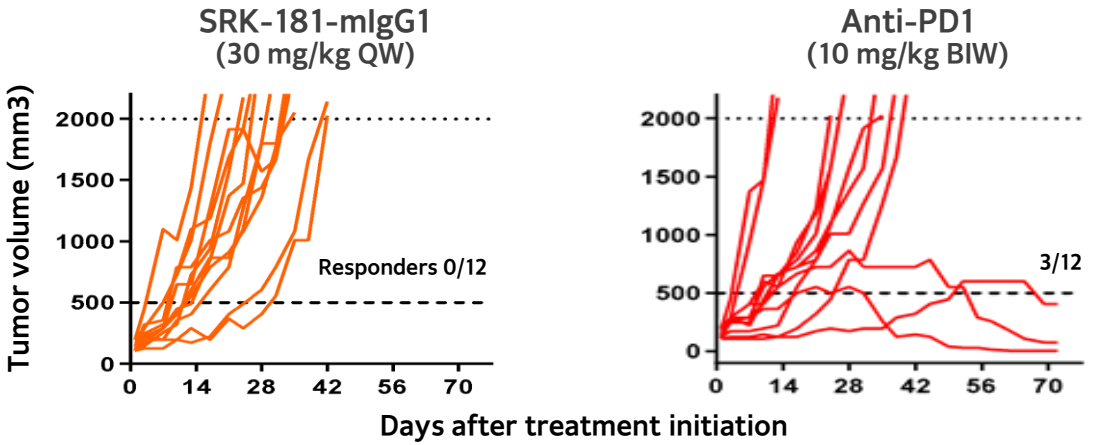


Preclinical data published in Science Translational Medicine. Martin CJ, et al. Sci Transl Med. 2020 Mar 25;12(536):eaay8456. https://scholarrock.com/platform/publications/.
*SRK-181-mIgG1 is the murine version of SRK-181; responder defined as tumor size <25% endpoint volume at study end.

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

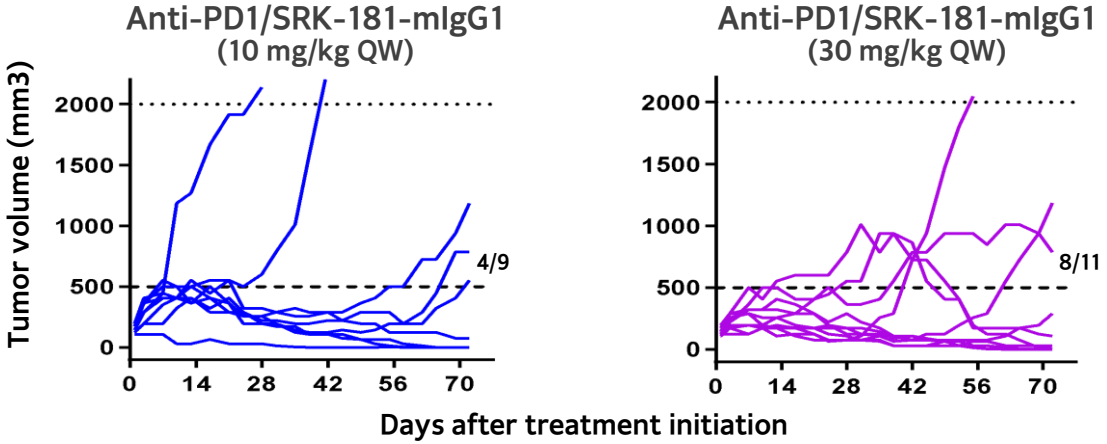
Tumor Regression

Monotherapy

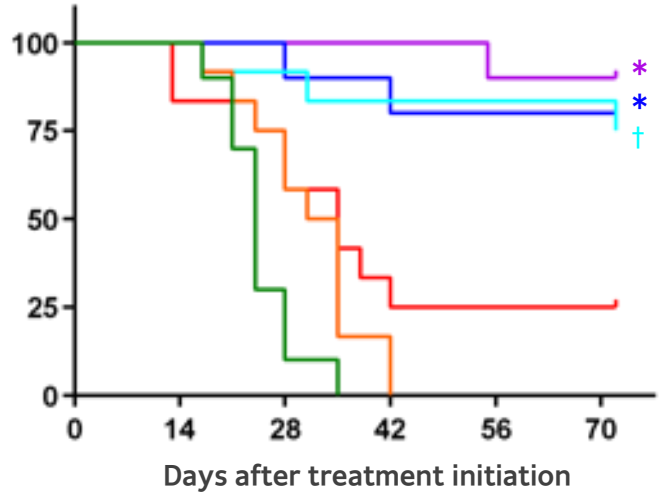


Combination Therapy

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

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				*		

Non-selective TGFβ

Toxicity: Minimal, slight and moderate

Selective TGFβ-1

Toxicity: Minimal

* 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

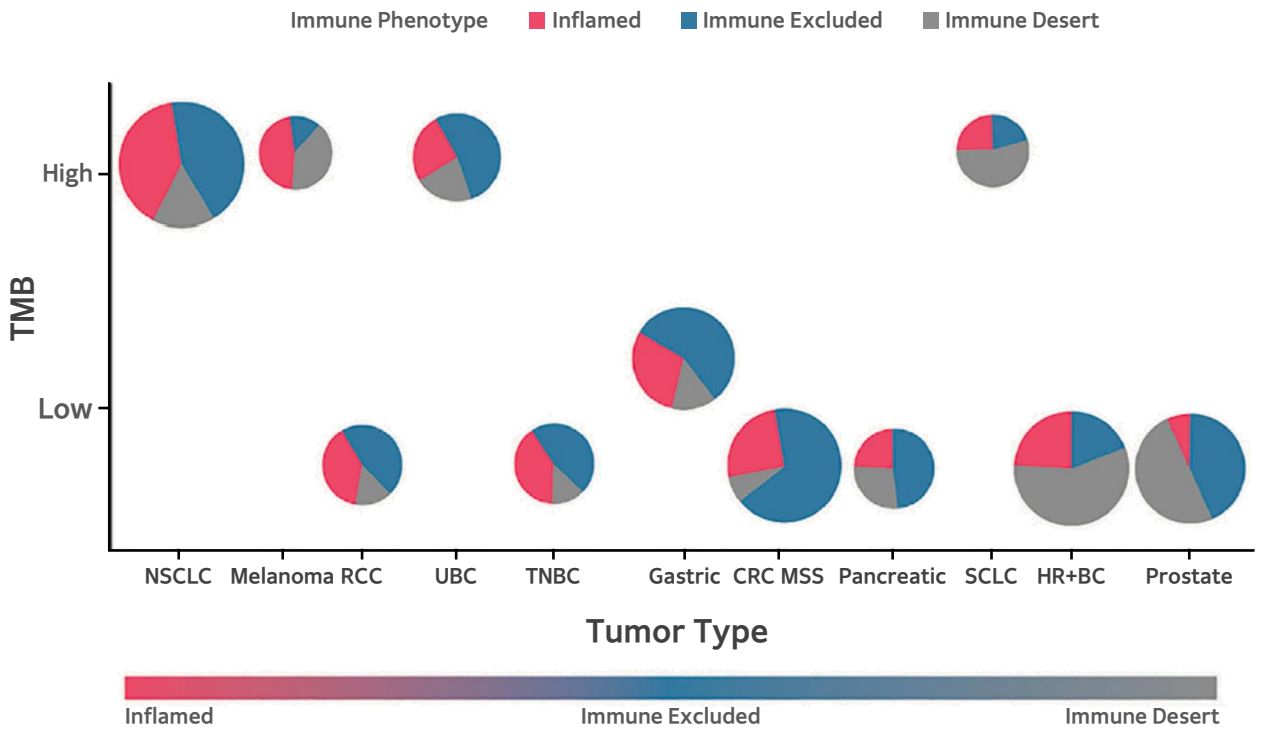
NOAEL for SRK-181: 300 mg/kg (highest dose evaluated)

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

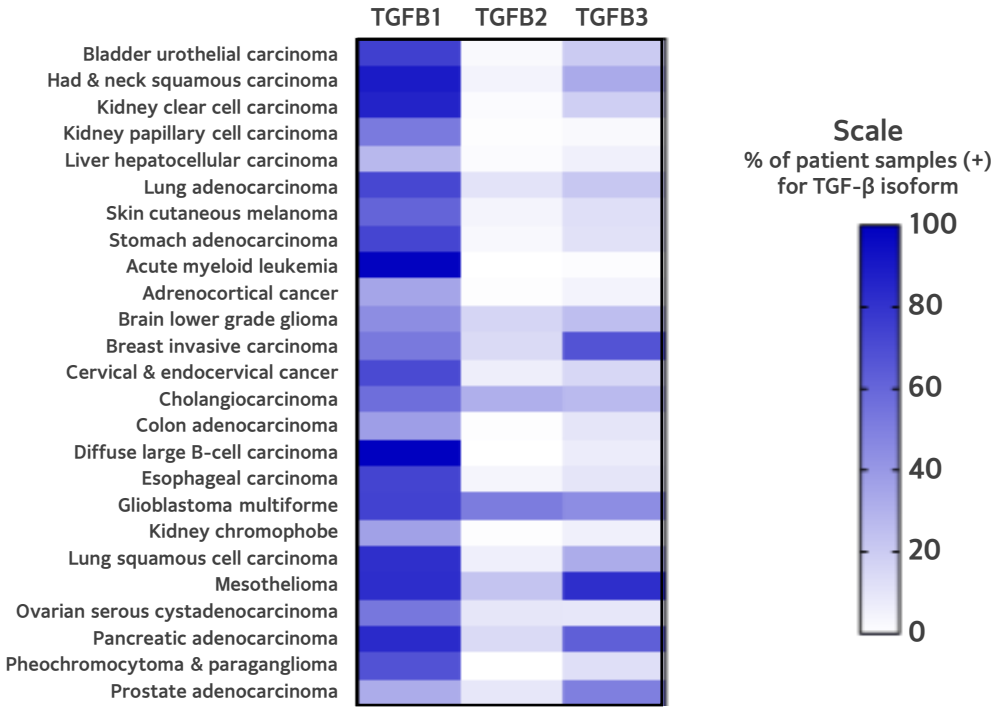
*Source: Anderton MJ, et al. Induction of heart valve lesions by small-molecule ALK5 inhibitors. *Toxicol Pathol*. 2011;39: 916-924.; and Stauber AJ, et al. Nonclinical safety evaluation of a transforming growth factor β Receptor I kinase inhibitor in Fischer 344 rats and beagle dogs. *J Clin Pract*.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

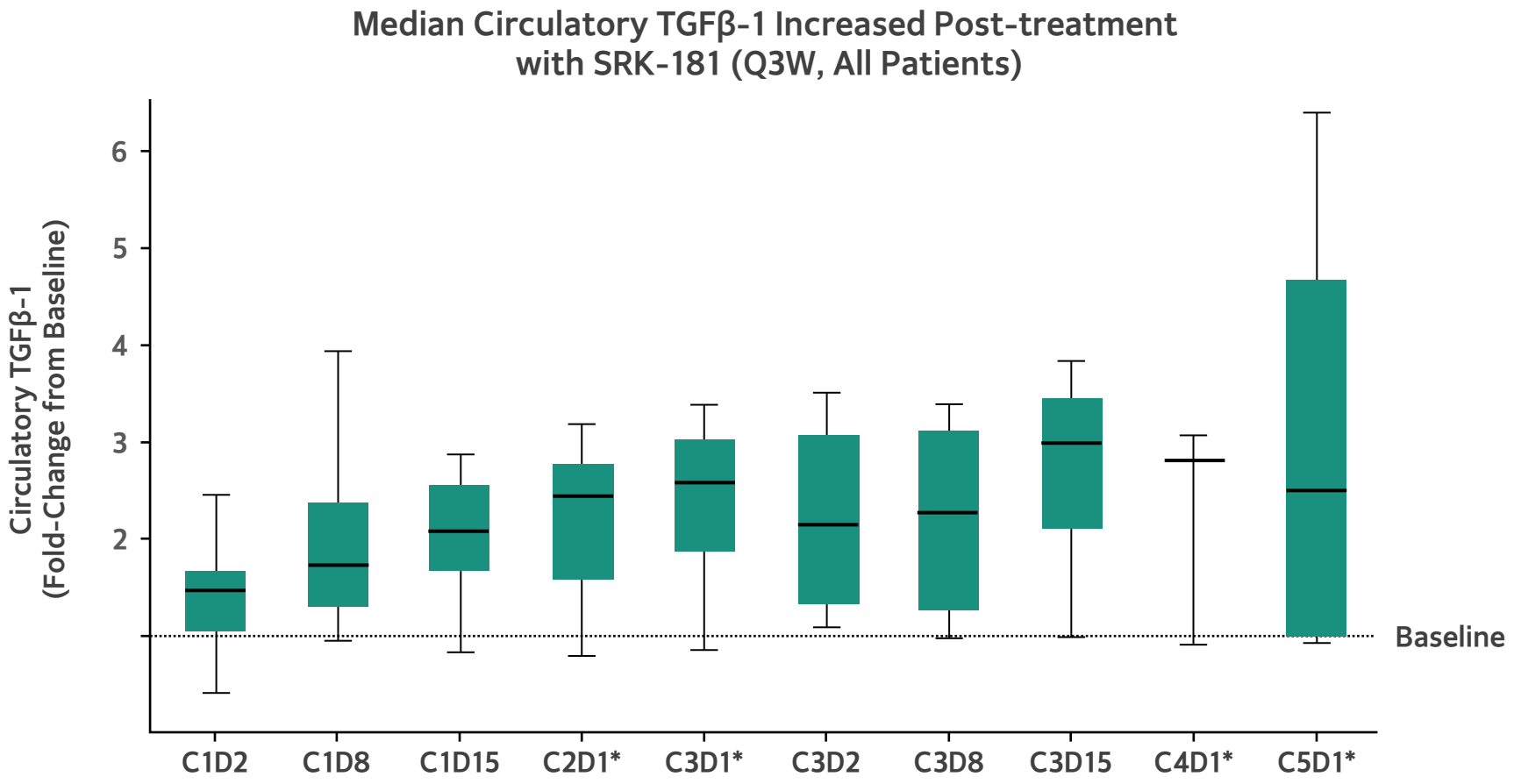
- Higher resolution histochemical characterization of tumor immune contexture (e.g. CD8+)
  - Classification of inflamed, excluded or immune desert tumors and tumor nests
  - Ability of SRK-181 to overcome tumor immune exclusion
- Analysis of immune response markers (e.g. PD-L1)
- Changes to intra-tumoral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

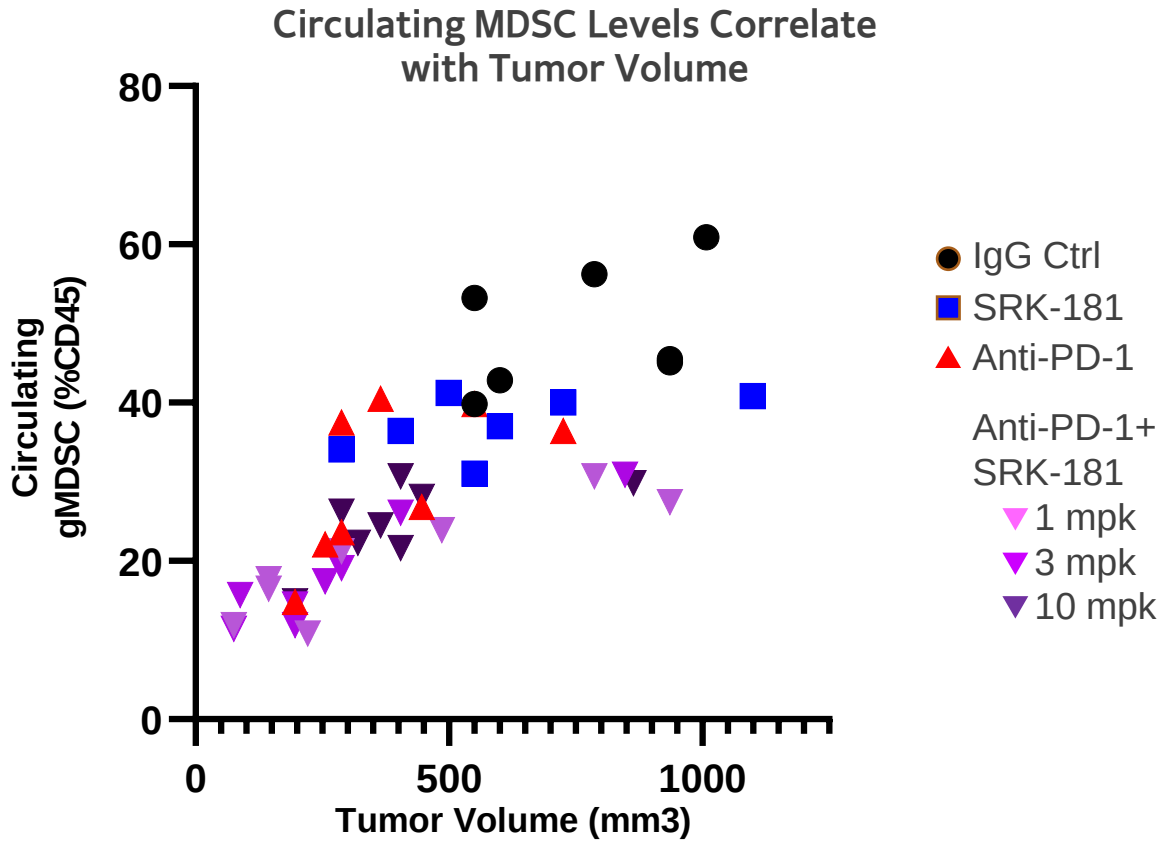
Yap T et al. SRK-181, a latent TGFβ1 inhibitor: safety, efficacy, and biomarker results from the dose escalation portion of a phase I trial (DRAGON trial) in patients with advanced solid tumors (Poster 780); Presented at SITC; Nov. 10-11, 2022. Circulatory TGFβ-1 and PF4 levels were quantitated by using 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