# Deep Insights Advancing Impactful Medicines

41st Annual J.P. Morgan Healthcare Conference | January 2023

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# Disclaimers

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 Quarterly Report on Form 10-Q for the quarter ended September 30, 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.



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# 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

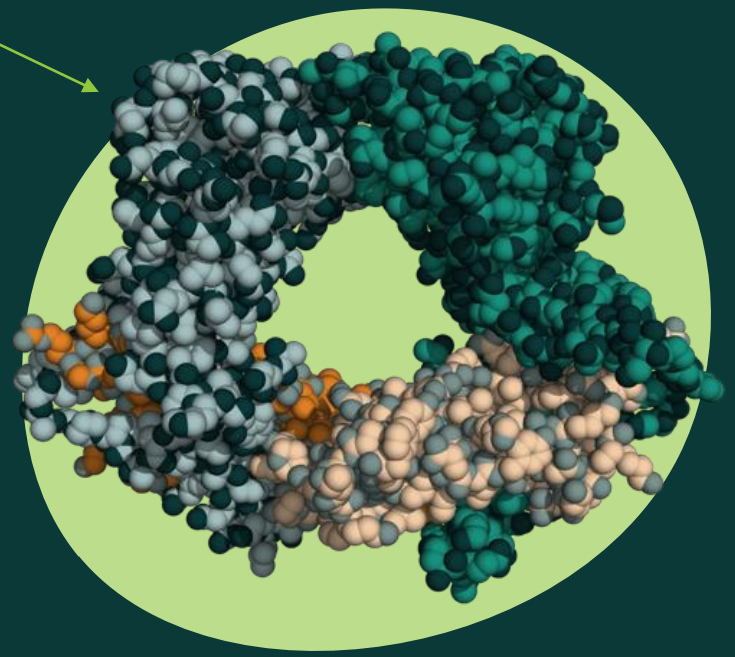
- Compelling proof-of-concept TOPAZ data informed Phase 3 SAPPHIRE study design
- Seasoned leadership team with track record of clinical and commercial success
- Anticipated cash runway into 2025

### Strategic Optionality

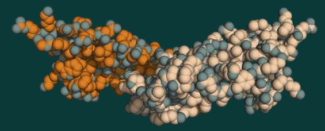
- Commercial planning underway for apitegromab (SMA) in US and Europe
- Broad platform, including promising early-stage assets, provides opportunities to advance alone or in partnership

# 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

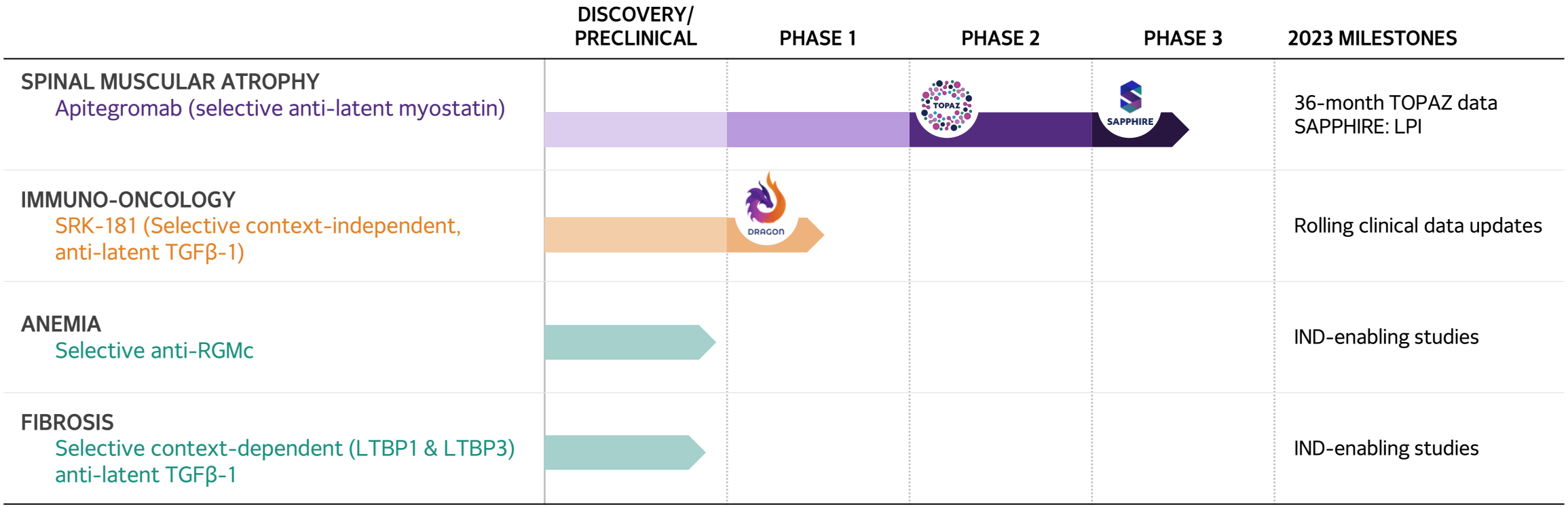
Dysregulation plays a role in devastating diseases that have a high unmet need, including:

- 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 suffering from 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

ACCELERON PHARMA · Celgene

**Ted Myles, MBA**
Chief Operating Officer & CFO

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

amag PHARMACEUTICALS · OCATA THERAPEUTICS™

**Junlin Ho, JD**
General Counsel & Corporate Secretary

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

FOUNDATION MEDICINE · Ziopharm ONCOLOGY

**Caryn Parlavecchio**
Chief Human Resources Officer

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

HolyName · NOVARTIS

**Jing Marantz, MD, PhD, MBA**
Chief Medical Officer

20 years of industry expertise across clinical pharmacology, neurology, hematology/oncology, and rare diseases

ACCELERON PHARMA · Alnylam PHARMACEUTICALS

**Mo Qatanani, PhD**
SVP, Research

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

Dyne THERAPEUTICS · ALEXION

TOPAZ

SAPPHIRE

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

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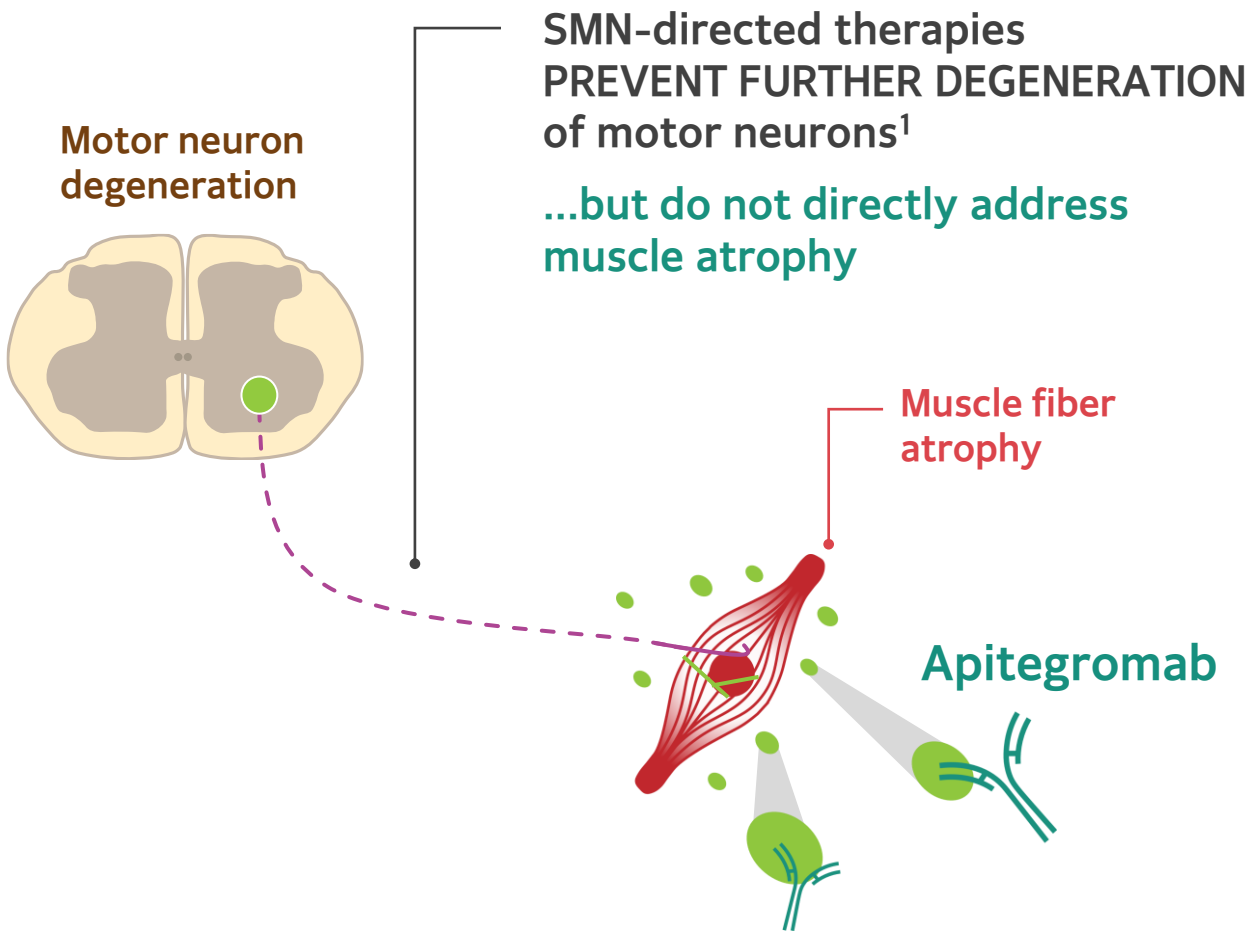
# Apitegromab: Potential Muscle-Directed Therapy for SMA




## Apitegromab is a MUSCLE-DIRECTED 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]

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

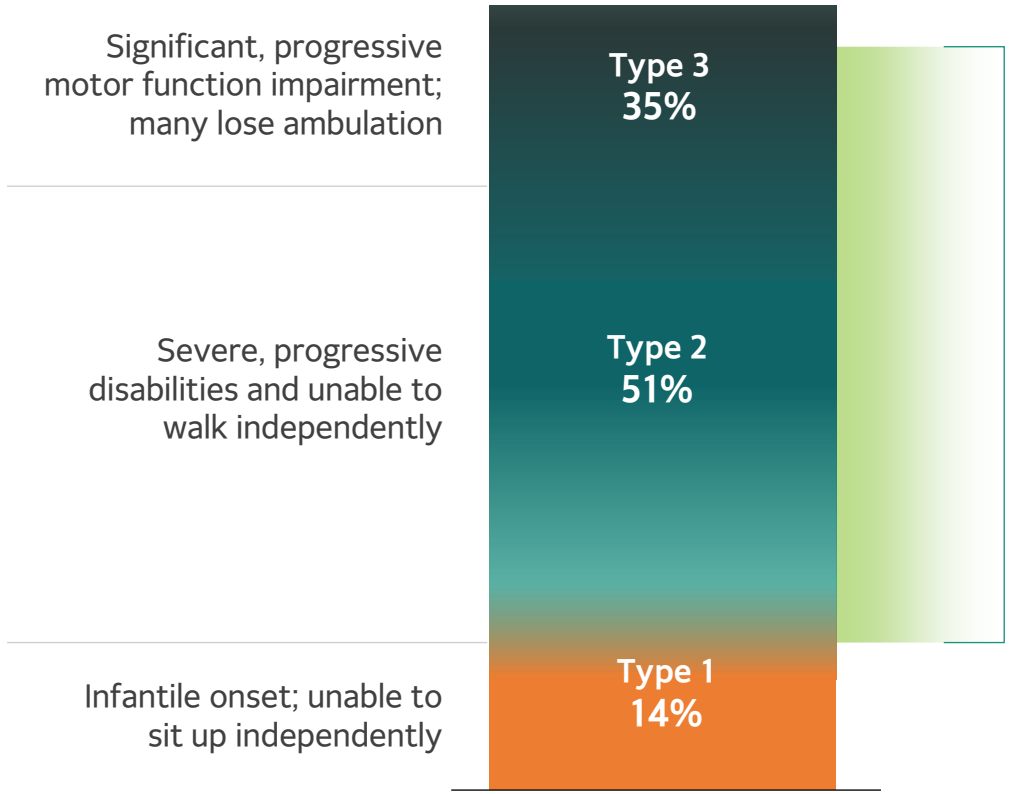
1. Lally et al, Orphanet Journal of Rare Diseases, 2017; 2. SMA Europe. SMATracker. About SMA. Accessed January 24, 2022. https://smatracker.eu/what-is-spinal-muscular-atrophy; 3. National Organization for Rare Disorders. Spinal muscular atrophy. Accessed January 24, 2022. https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/. 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.

kbv research
Knowledge Based Value

## Global SMA Treatment Market expected to reach $11.4B by 2028

KBV Research and secondary Research Analysis. Global Spinal Muscular Atrophy Market Analysis (2022-2028). November 2022, p. 42




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

**>2/3 of overall patient population**

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# Potential to Pioneer a New Treatment Era: Opportunity for Muscle-Directed Therapy to Complement SMN-Directed 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**<br>**1 day – 12 years of age**<br>(Non-ambulatory recruited) | **Type 1, 2, 3**<br>**1 month – 25 years of age**<br>(Ambulatory and Non-ambulatory recruited) | **Type 1**<br>**up to 6 months of age**<br>(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*<br>Revenues (LTM): $1.7+ billion | Patients treated WW: >7000**<br>Revenues (YTD'0922): ~CHF 793 million | Patients treated WW: >2500***<br>Revenues (LTM): $ 1.4+ billion |

**Patients continue to experience major functional impairments despite utilization of SMN-directed 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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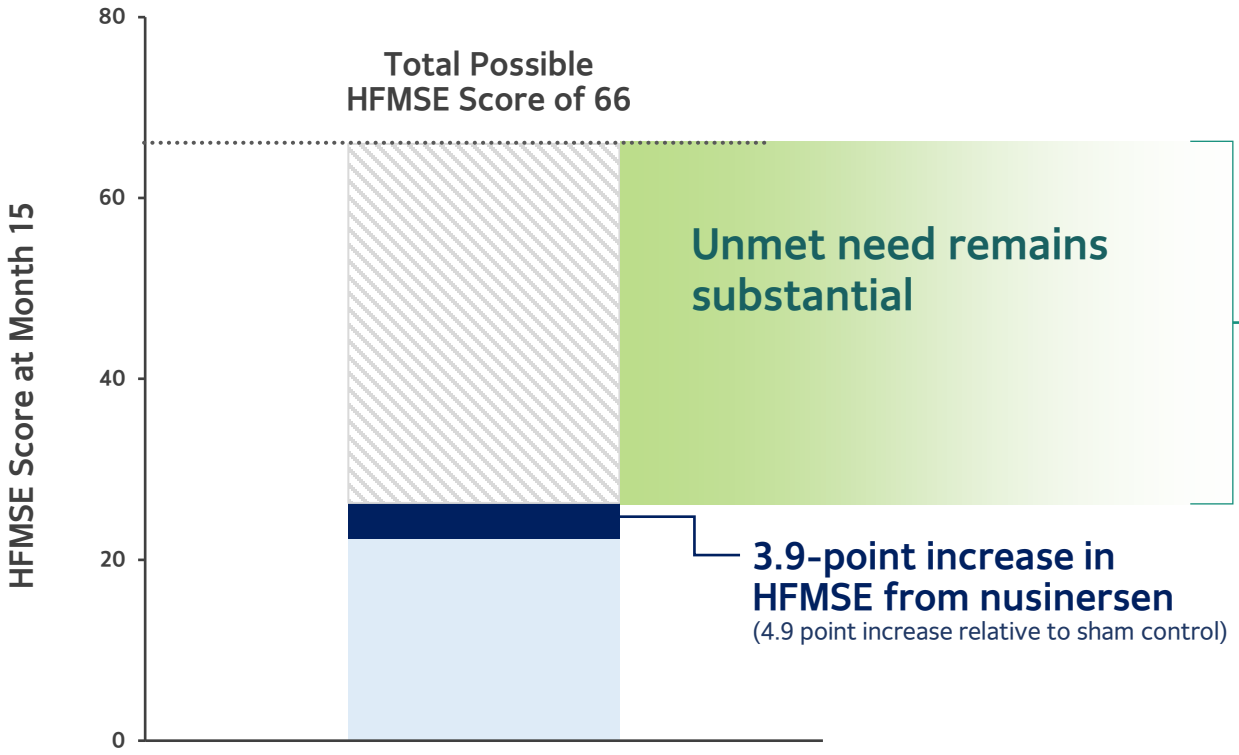
# Apitegromab Offers Potential to Address Unmet Patient Need




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-directed 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**<br>(Apitegromab 20 mg/kg; Intent-to-Treat Population) | **Age 2-12 years**<br>(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%)** |

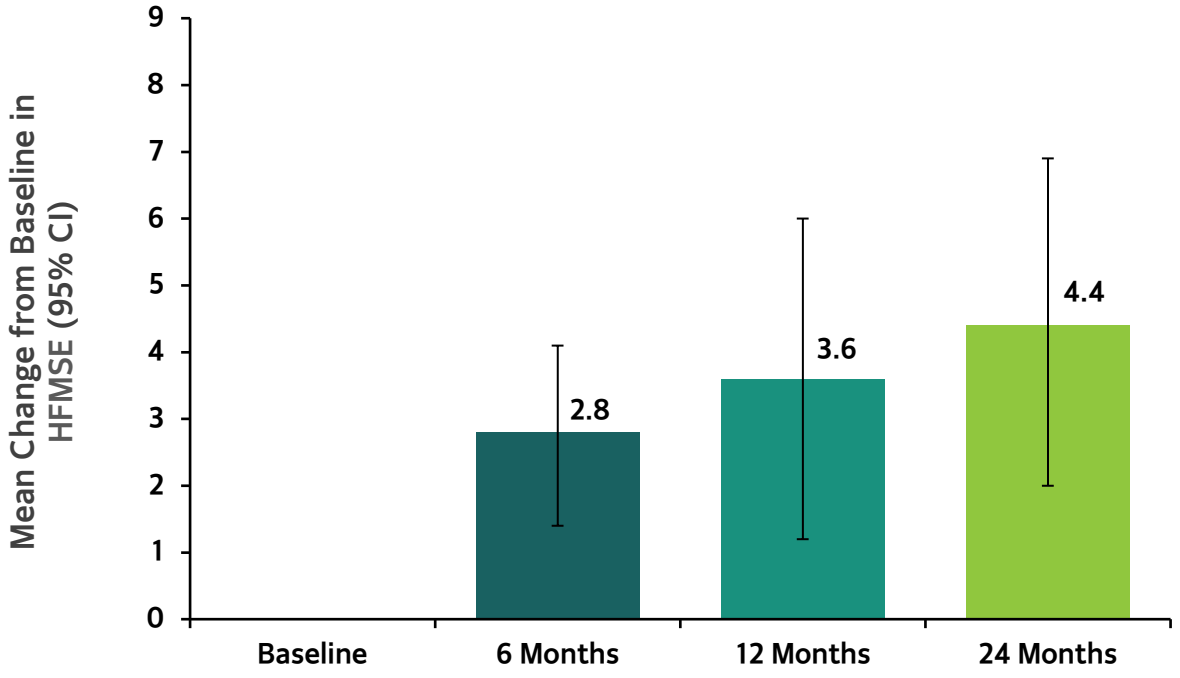
No safety signals for apitegromab were identified to date; the five most frequently reported treatment-emergent adverse events were headache, pyrexia, upper respiratory tract infection, cough, and nasopharyngitis

*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.

# Sizable, Sustained Increases in HFMSE Observed Over 24 Months of Apitegromab

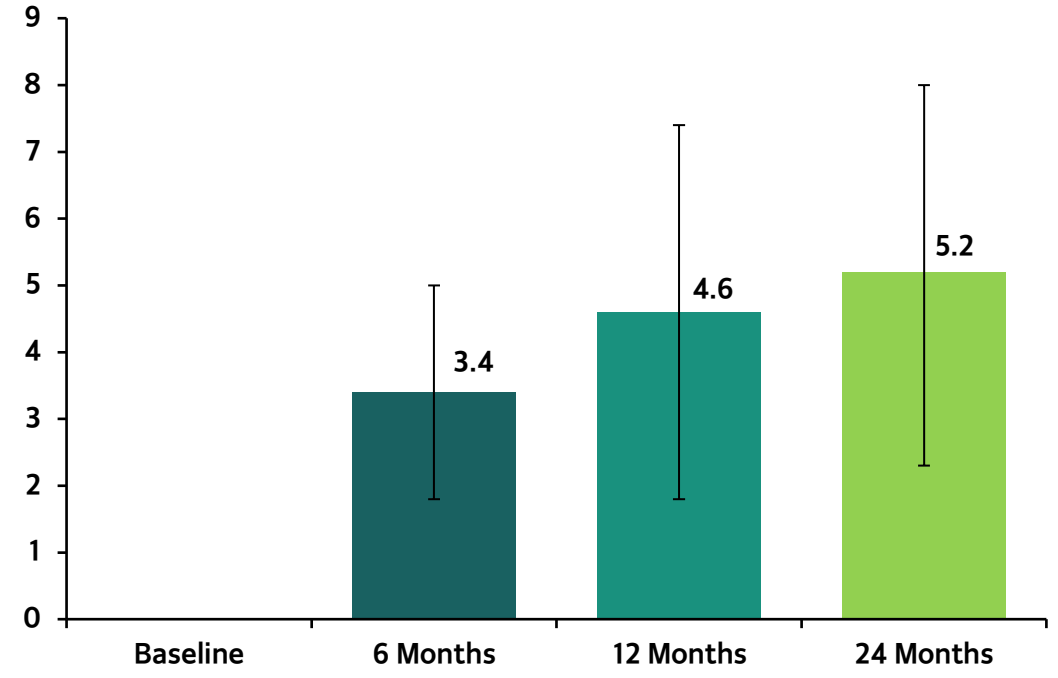
## Pooled Non-Ambulatory Patients Excluding Data Post Scoliosis Surgery (all dose groups)

### 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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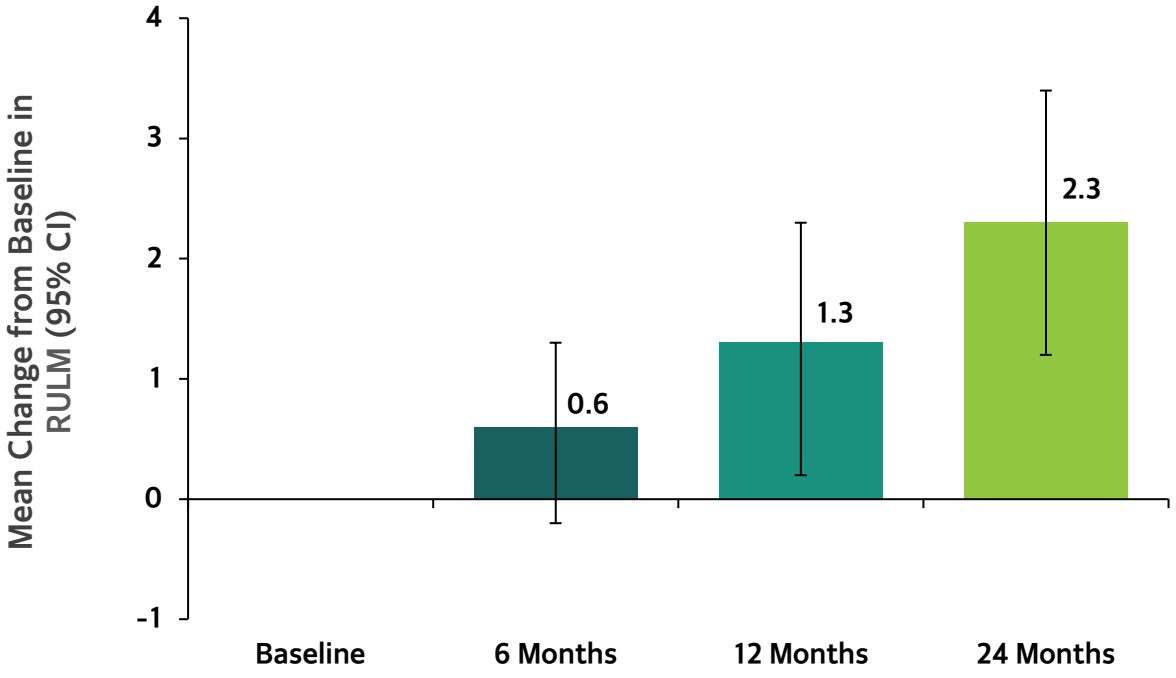
# Continued Increase in RULM Observed at 24 Months of Apitegromab

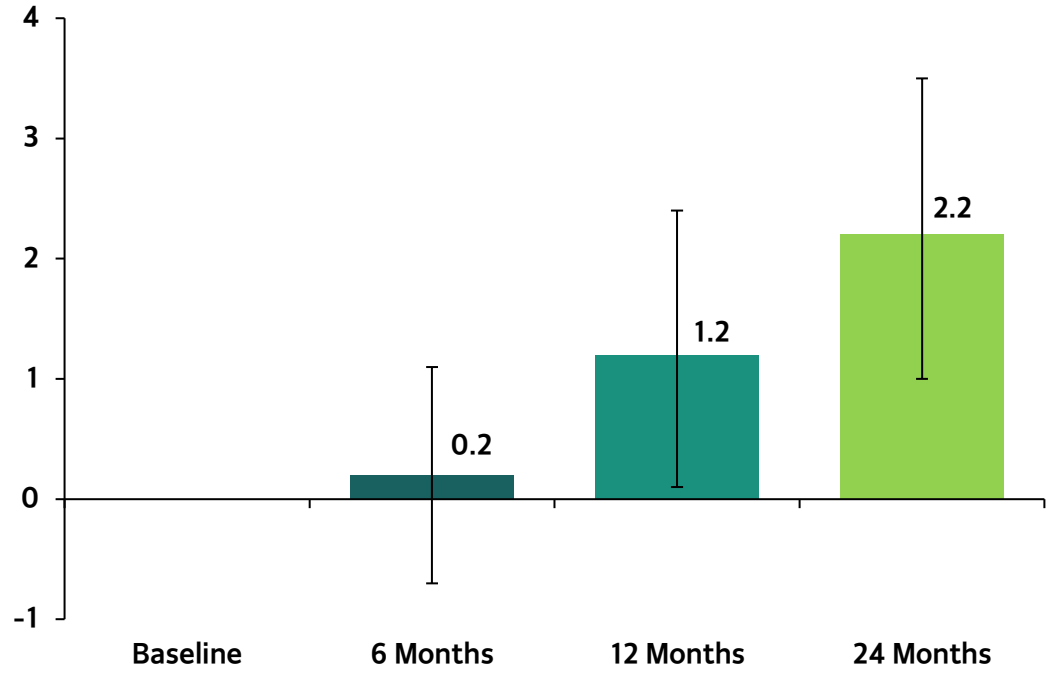
## Pooled Non-Ambulatory Patients Excluding Data Post Scoliosis Surgery (all dose groups)

### 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.

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# 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)

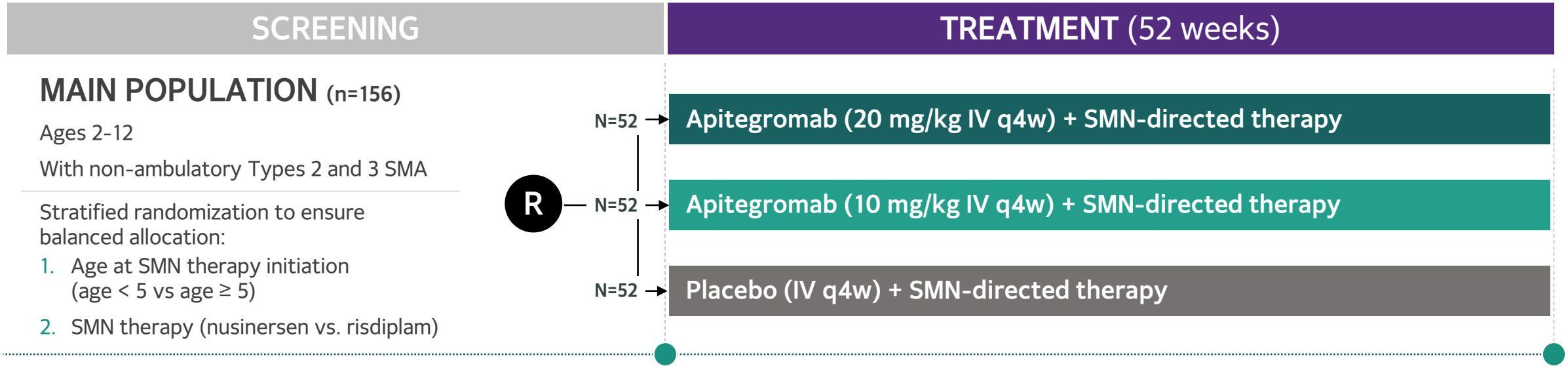
**51/57 patients

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.

# Ongoing SAPPHIRE Phase 3 Trial Overview

SAPPHIRE

Randomized, double-blind, placebo-controlled, parallel arm design (n=204)
Enrolling patients on SMN-directed 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**

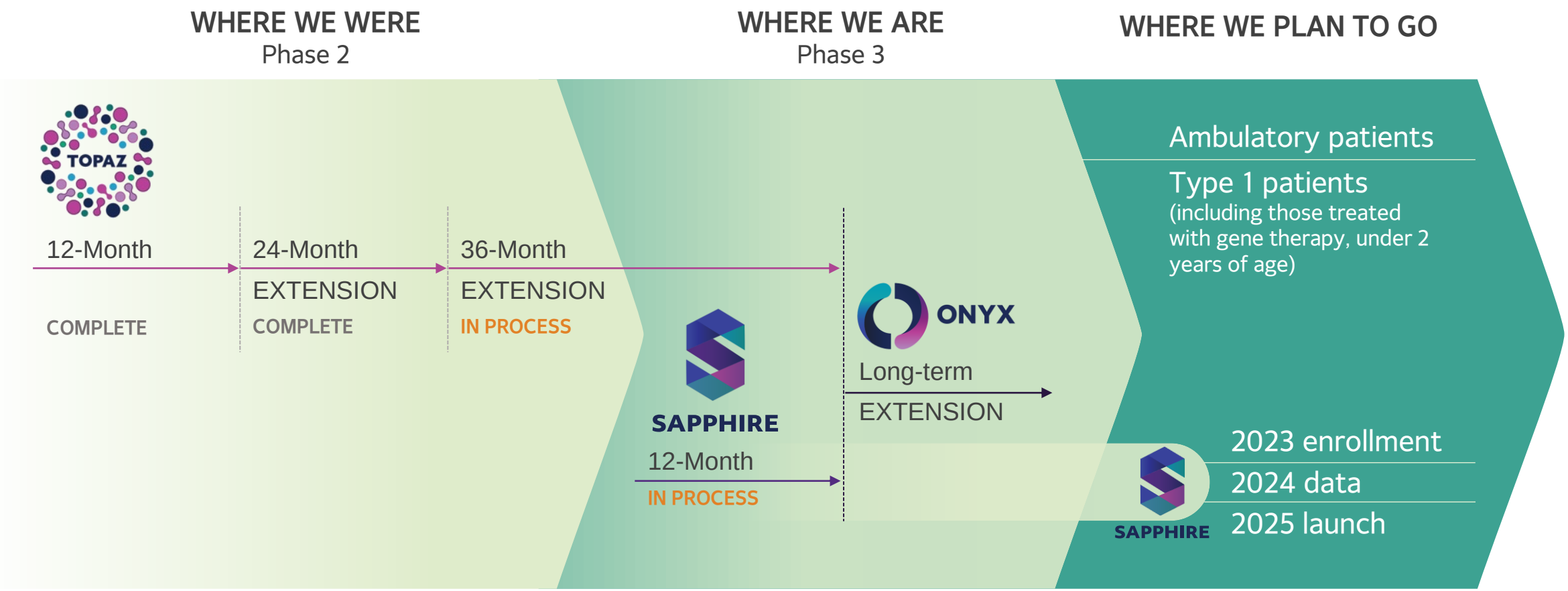
## Additional Data Opportunities

**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



DRAGON

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

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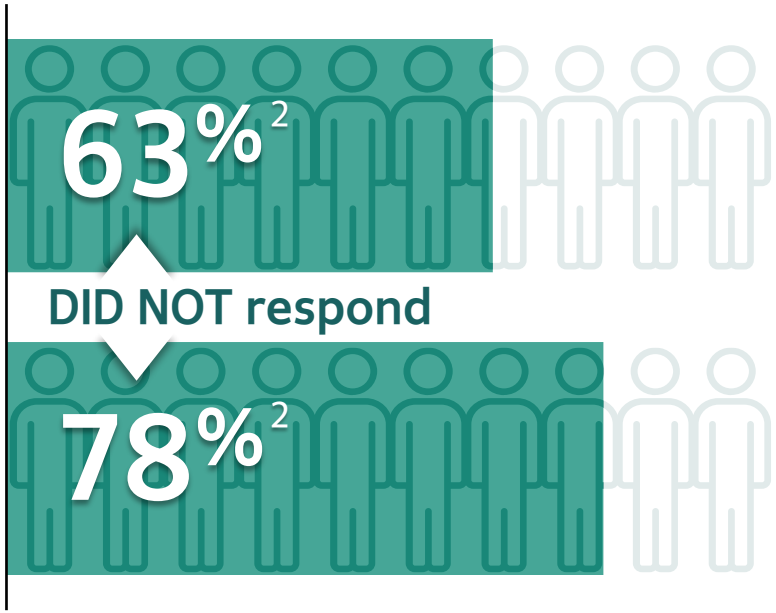
# Resistance to Checkpoint Inhibitor (CPI) Therapies Remains a Significant Clinical Challenge

**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

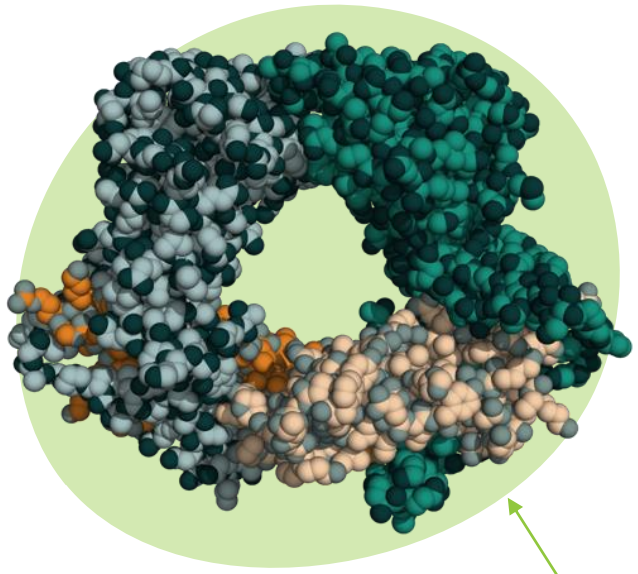
Rik Derynck[1,2,3], Shannon J. Turley[4] and Rosemary J. Akhurst[2,3]

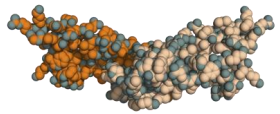
July 24, 2020: https://doi.org/10.1038/ s41571-020-0403-1

August 2022.

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

# 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.

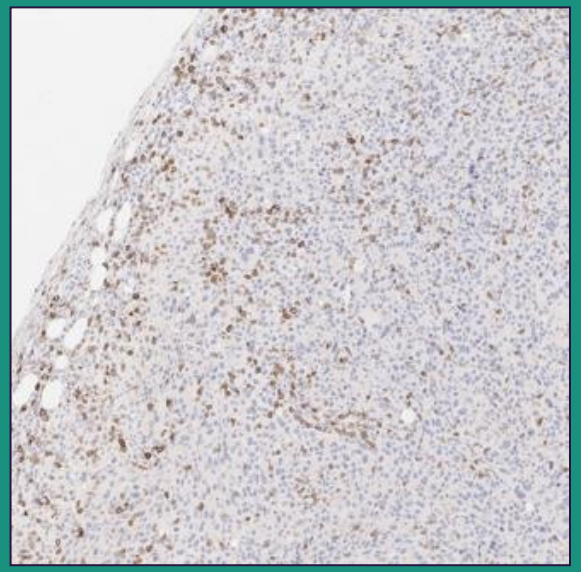
# SRK-181-mIgG1 + Anti-PD1 Overcomes Immune Exclusion

## Overcoming immune exclusion

### Tumor micro-environment

**Anti-PD1**

**Immune Exclusion**



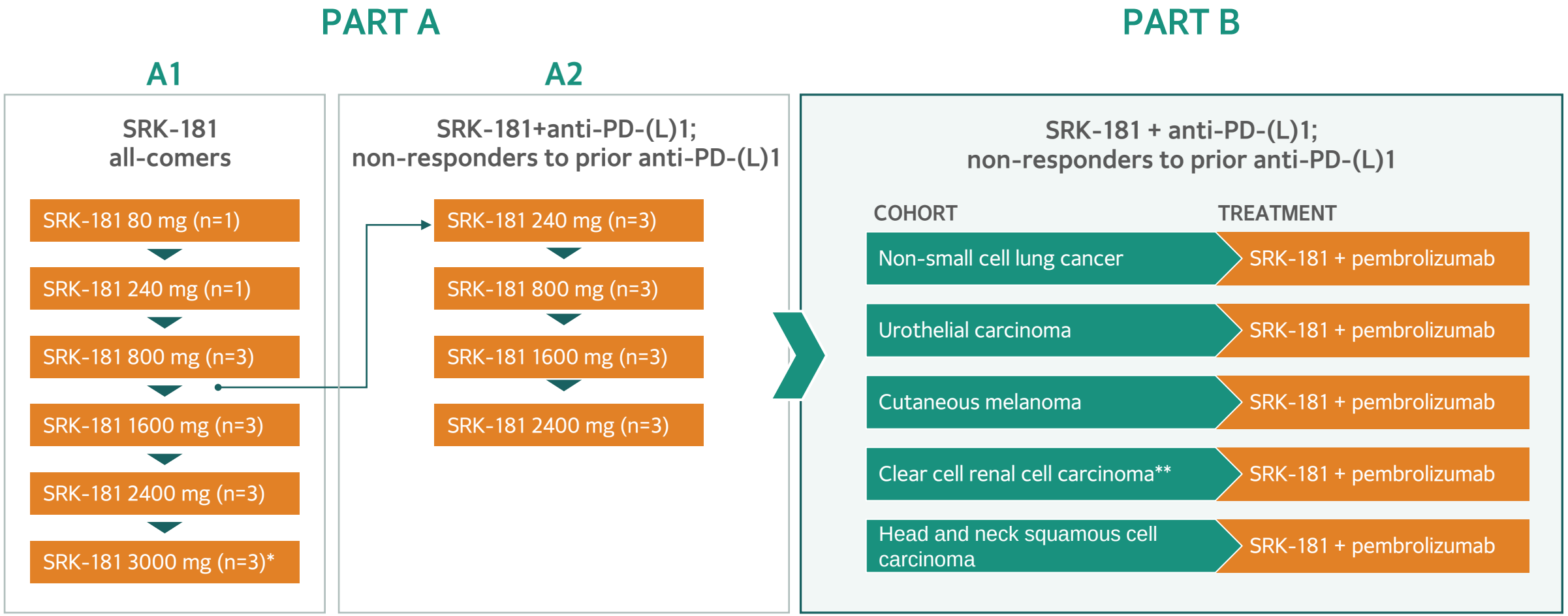
**Anti-PD1/ SRK-181-mIgG1**

**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-(L)1 treatment.
1. NCT04291079 on www.clinicaltrials.gov.

# DRAGON Part A: Safety

## PART A1

### 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 SAE were elevated troponin I (1 patient, at 2000 mg q2w)

## PART A2

### 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=19 |
|---|---|---|---|---|---|
| Pruritis | 1 | 0 | 1 | 1 | 3 (20.0%) |
| Rash | 0 | 1 | 0 | 2 | 3 (20.0%) |
| Rash maculo-papular | 1 | 0 | 1 | 1 | 3 (20.0%) |
| Diarrhea | 0 | 0 | 2 | 0 | 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:**

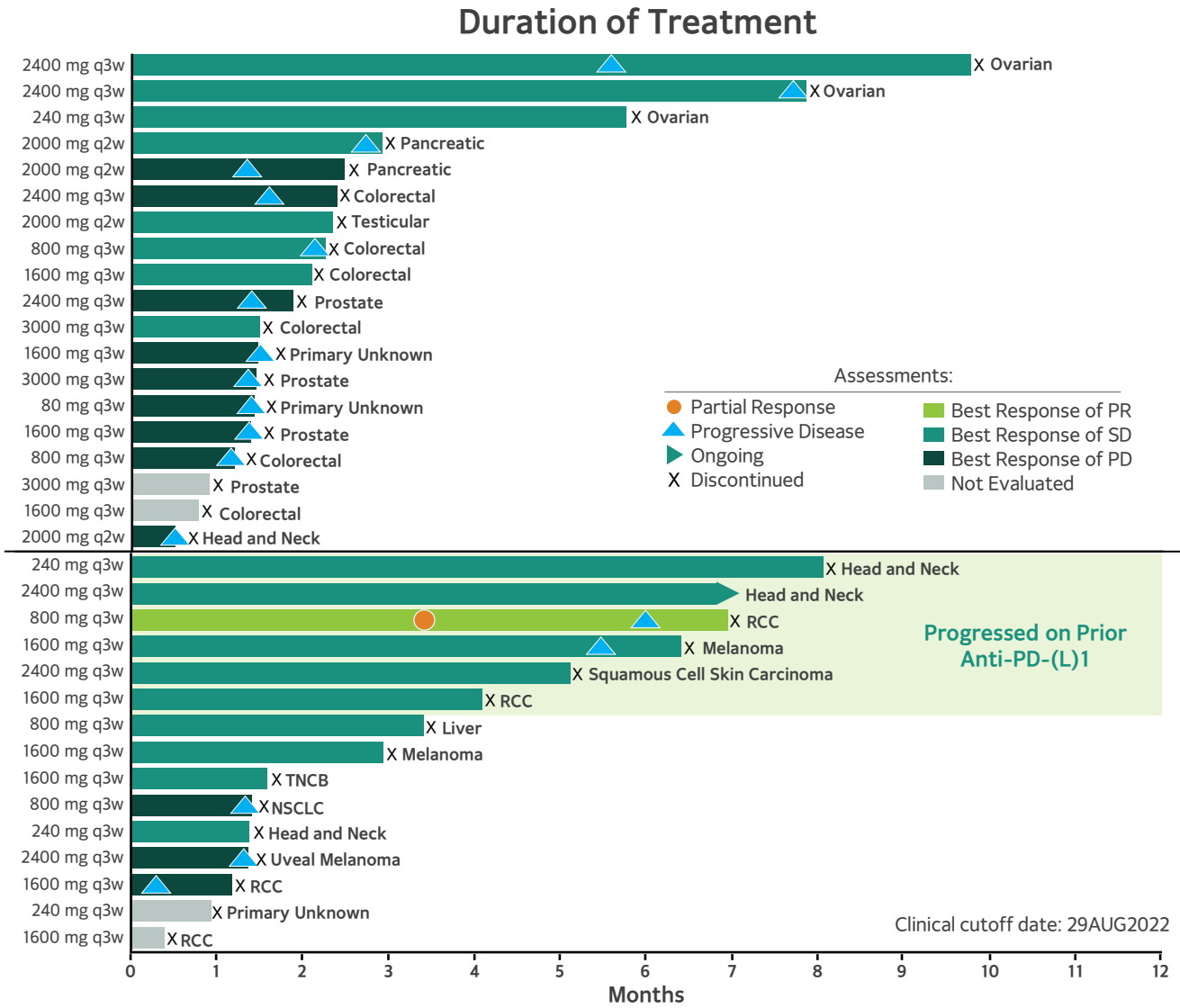
- Puritus (2 patients), blister, immune-mediated lung disease, rash and rash maculo-popular (1 patient each)

**Treatment-related SAEs:**

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

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. Clinical cutoff date: August 29, 2022. All dose levels were administered q3w except 2000 mg, which was administered q2w.
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* Presented at SITC November 2022




## **Part A1** (n=19)

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

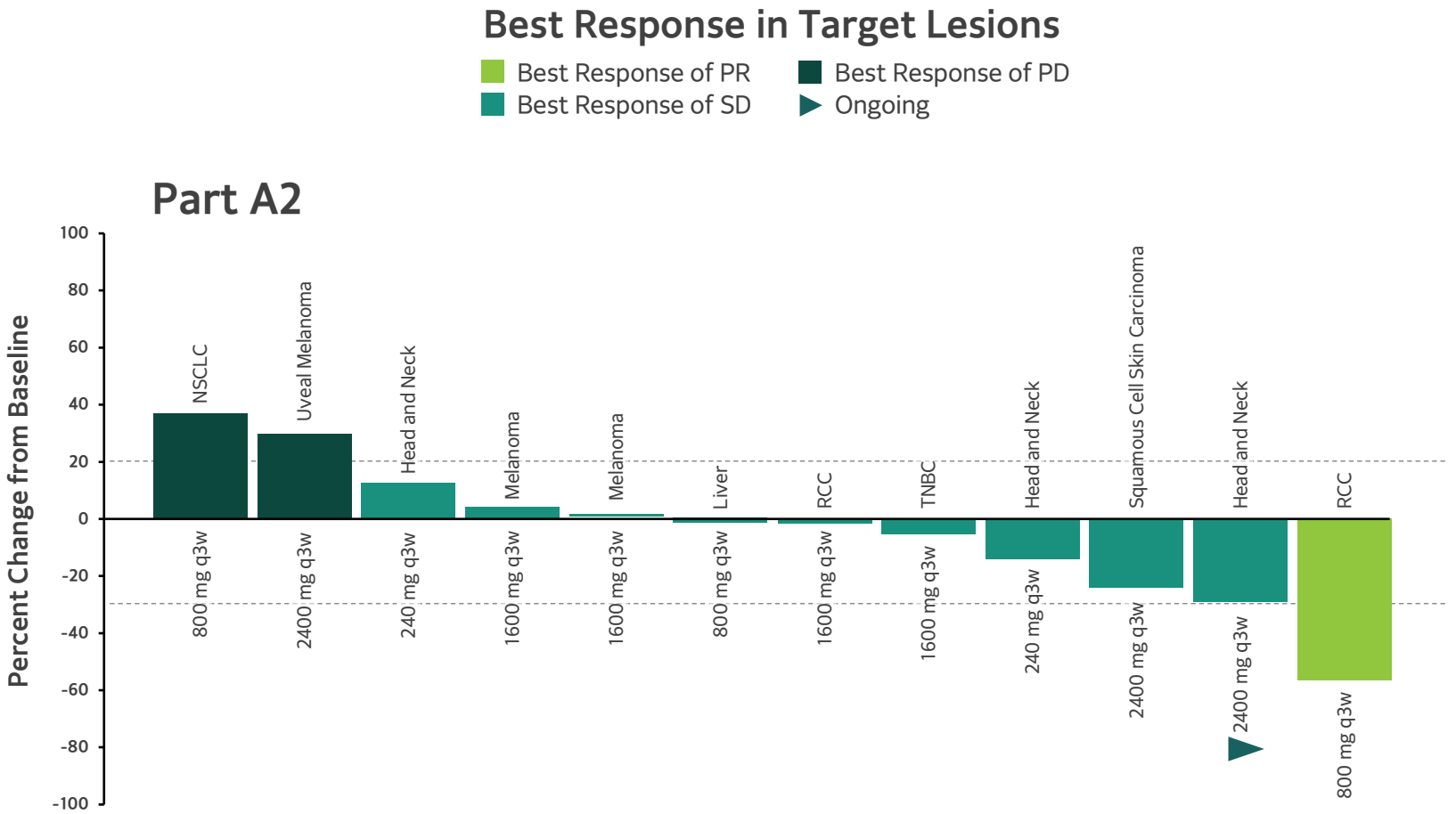
  All 3 patients with ovarian cancer were stable beyond the 16-week cutoff

## **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. 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. *Preliminary anti-tumor effects were assessed using RECIST1.1 and reported based upon local investigator reads: as of August 29, 2022. 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 8/29/22)

- **14 patients enrolled**
- **One additional confirmed PR**
  ongoing patient with anti-PD-1 resistant clear cell renal cell carcinoma
- **All dose levels were generally well tolerated**
  including recommended 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. 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. *Clinical cutoff date: August 29, 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.

# 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)

ScholarRock

# Next Horizon: Fibrosis

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# TGFβ is Established as Key Driver of Fibrosis Across Multiple Diseases

*Nature Reviews* , April 25, 2016 NATURE REVIEWS | NEPHROLOGY

## TGF-β: the master regulator of fibrosis

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

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

## Targeting TGF-β Signaling in Kidney Fibrosis

Yoshitaka Isaka

*Nature Reviews.* August 19, 2014 NATURE REVIEWS | RHEUMATOLOGY

## Transforming growth factor β—at the centre of systemic sclerosis

Robert Lafyatis

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

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

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

*J Pathol*, July 25, 2021

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

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

*J Receptors Sign Trans, Feb 13, 2020*

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

Bhagyalakshmi Nair and Lekshmi R. Nath

*Proc Am Thorac Soc*, July 3, 2006

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

Dean Sheppard

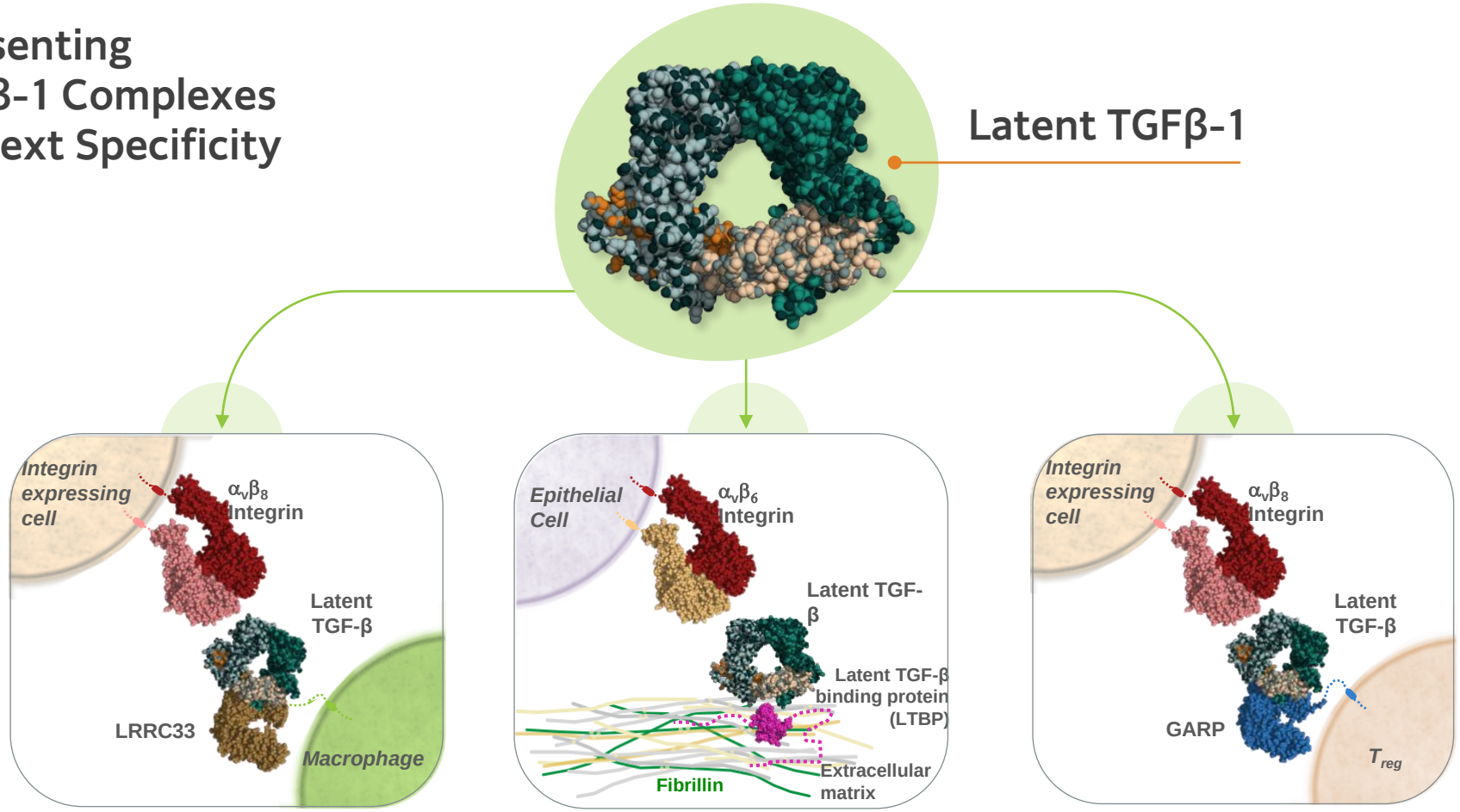
*PNAS*, February 24, 1986 PNAS

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

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

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

## Targeting Presenting Molecule/TGFβ-1 Complexes Provides Context Specificity



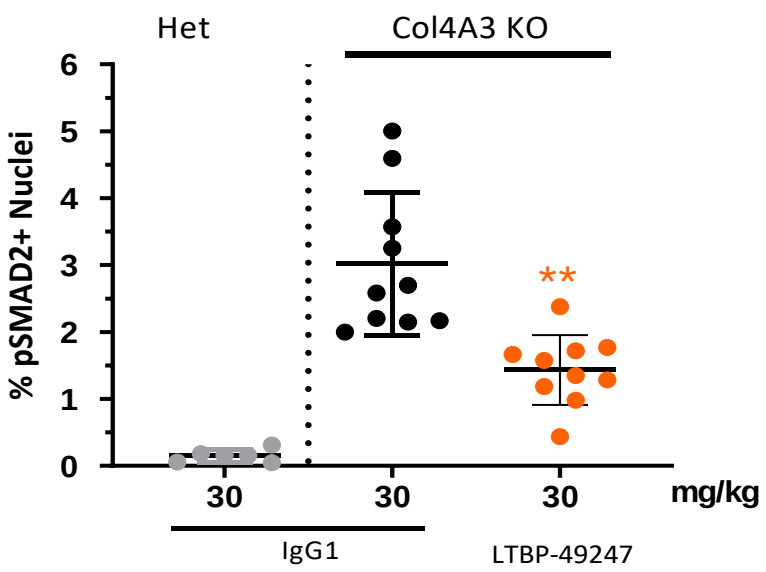

LRRC33 Presents TGFβ on Macrophages

LTBP1 & 3 Present TGFβ in Connective Tissue

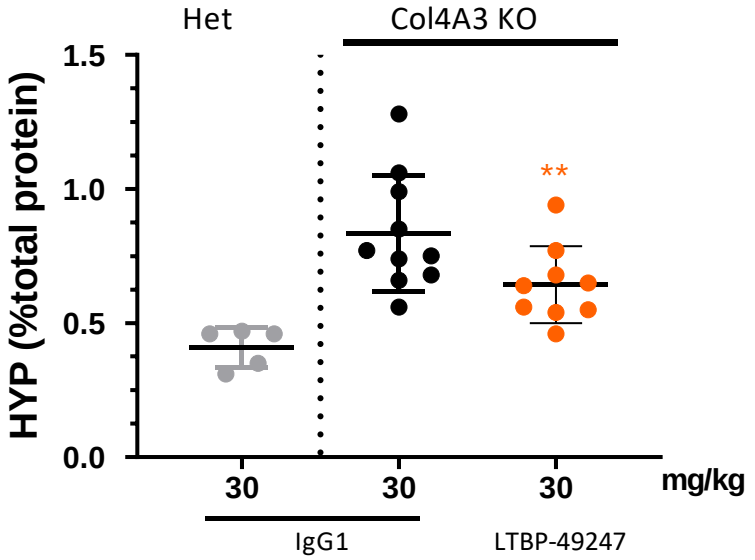
GARP Presents TGFβ on Tregs

# LTBP-49247 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)**



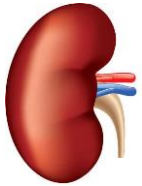

**LTBP-49247 reduces fibrosis in kidneys of Alport model**



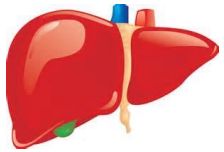

** p < 0.01
One way ANOVA vs. IgG
HYP=hydroxyproline

- 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

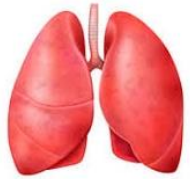
# Significant Opportunities to Address High Unmet Need Across Multiple Fibrotic Indications



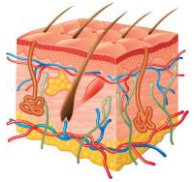
**Alport Syndrome (AS)**
**Focal Segmental Glomerulosclerosis (FSGS)**
**IgA Nephropathy (IgAN)**



**Primary Sclerosing Cholangitis (PSC)**



**Idiopathic Pulmonary Fibrosis (IPF)**



**Diffuse Cutaneous Systemic Sclerosis (dcSSc)**

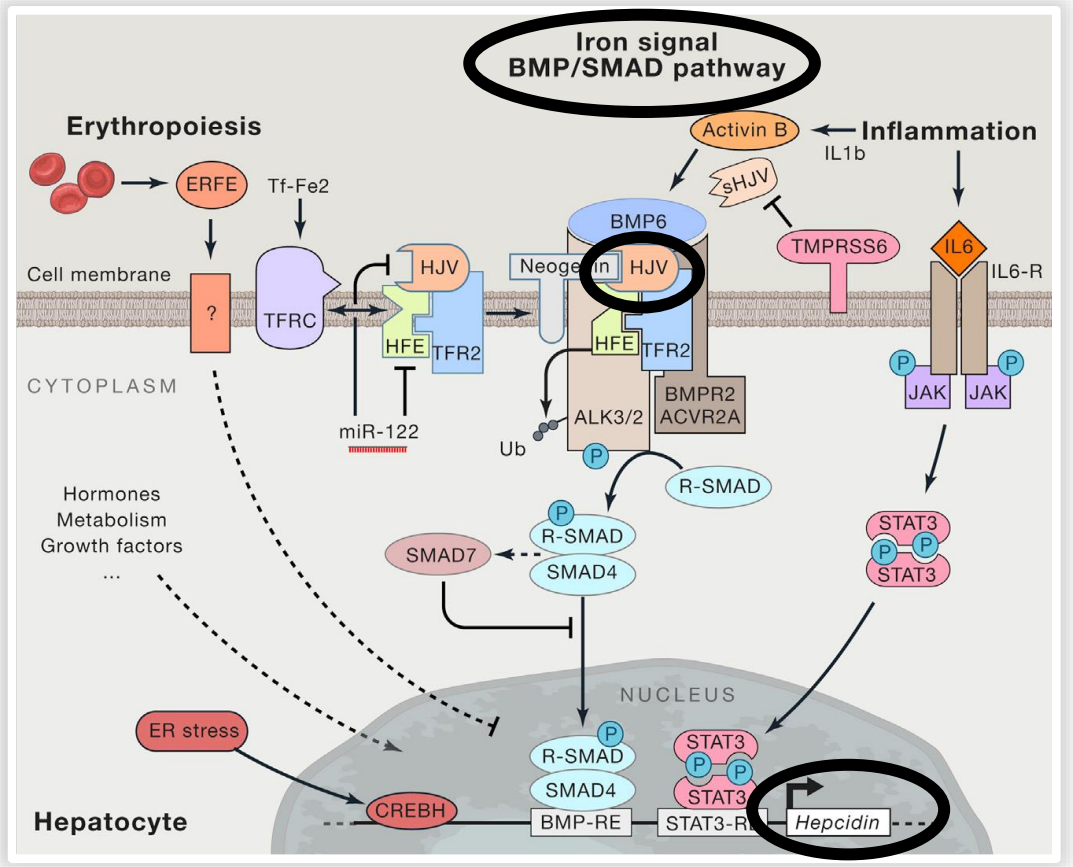
**Collectively, significant commercial potential given large patient population with clear high unmet need given poor outcomes and lack of effective therapeutics**

- 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

ScholarRock

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




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

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

## Anemia of Inflammation/ Chronic Disease

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

| Untreated | Ab treated |
|---|---|
| ↑ Hepcidin | ↓ Hepcidin |
| ↓ Serum iron | ↑ Serum iron |

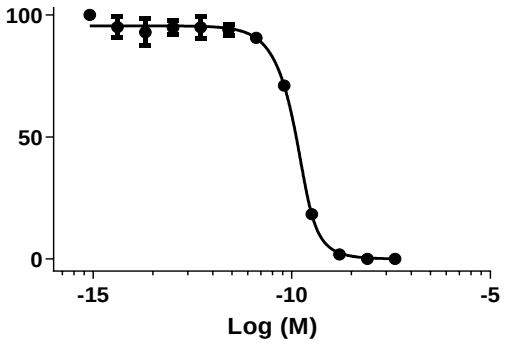

Fig: Muckenthaler, M.U., Rivella, S., Hentze, M.W. and Galy, B. (2017) A Red Carpet for Iron Metaboism. *Cell*, 168(3): 344-361
1: *Kuns-Hashimoto R, et al.* (2008) Selective binding of RGMc/hemojuvelin, a key protein in systemic iron metabolism, to BMP-2 and neogenin. *Am J Physiol Cell Physiol* 294(4):C994-C1003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

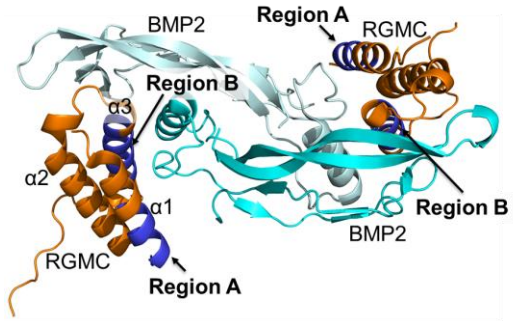
## Key Attributes of HJV-35202:[1,2]

- 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)

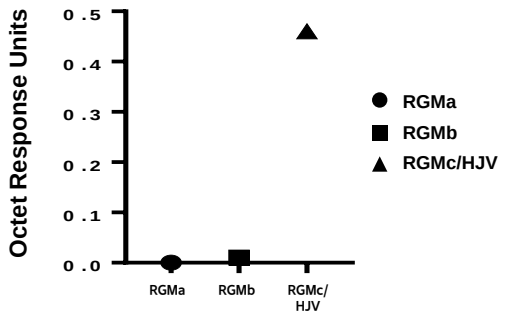
Potent in vitro binding affinity (KD=3.9E-11)



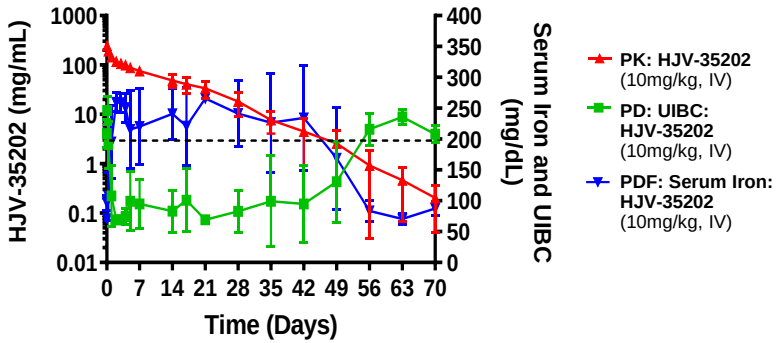

Highly specific to RGMc/HJV with well understood mechanism




Specific to RGMc over other RGM family members



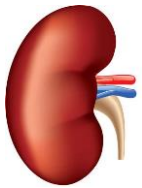

Sustained PD effect in single dose Cyno study





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

ScholarRock™

# 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**
- Year end cash balance of $315M, anticipated runway into 2025