



# Deep Insights Advancing Impactful Medicines

January 2023

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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 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.

# Scholar Rock:

## Transforming Patient Lives, Targeting High Unmet Medical Need



### Revolutionary Platform

- Global leader in TGF $\beta$  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

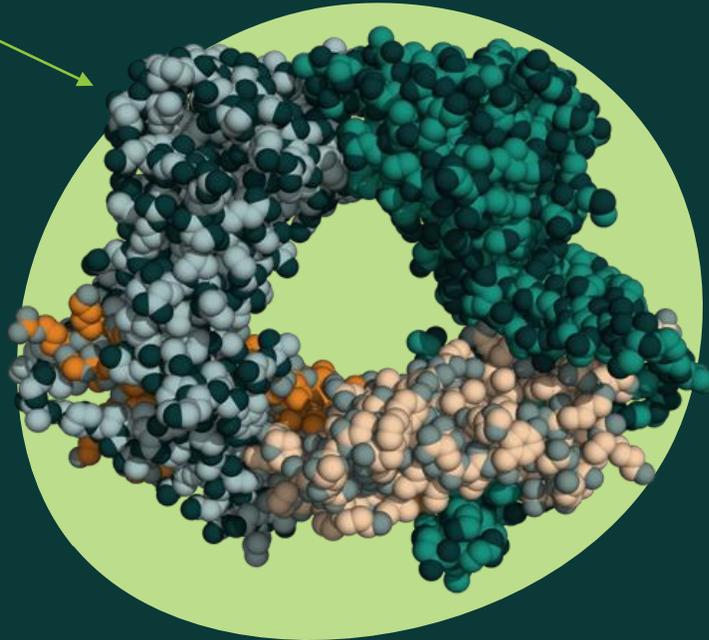


### Strategic Optionality

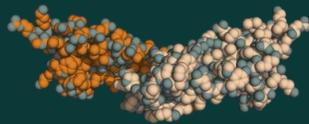
- Commercial planning underway for apitegromab (SMA) in US and Europe
- Broad platform, including promising early-stage assets, provides opportunities to advance alone or in partnership

# Revolutionary Approach to Regulating TGF $\beta$ Superfamily Implicated in Devastating Diseases

Scholar Rock's Target  
Latent Growth Factor



Traditional Target  
"mature" growth factor



## TGF $\beta$ Superfamily: Highly Sought-After Targets

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

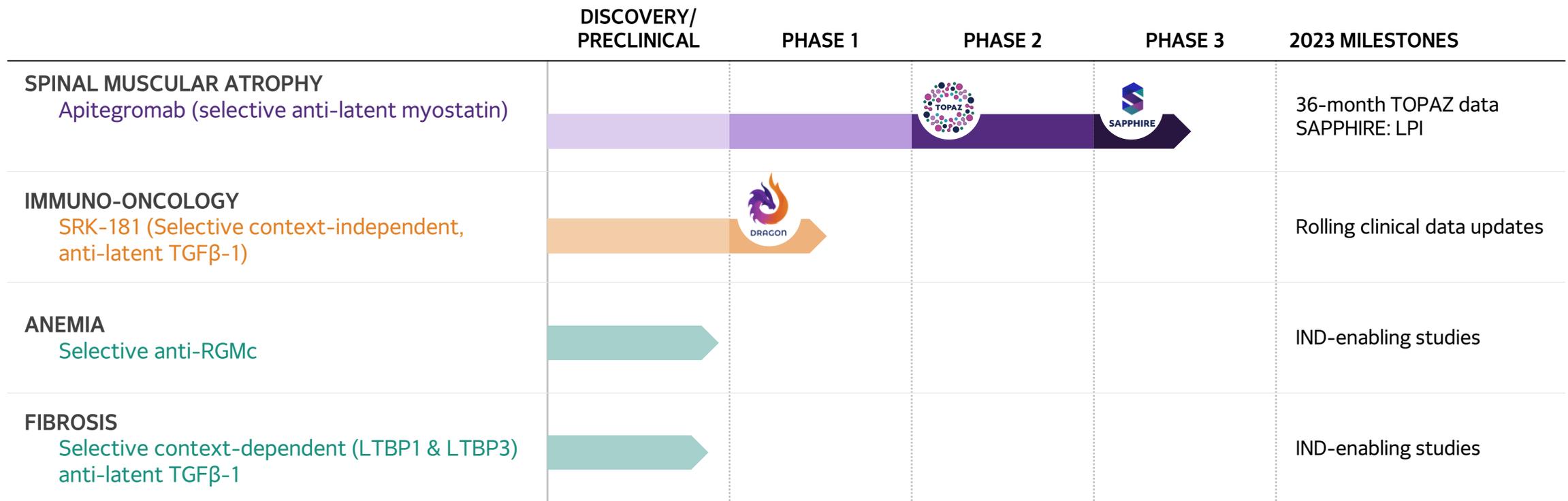
Dysregulation plays a role in devastating diseases that have a high unmet need, including:

- 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



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

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



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

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



**Caryn Parlavecchio**  
Chief Human Resources Officer

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



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

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



**Mo Qatanani, PhD**  
SVP, Research

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



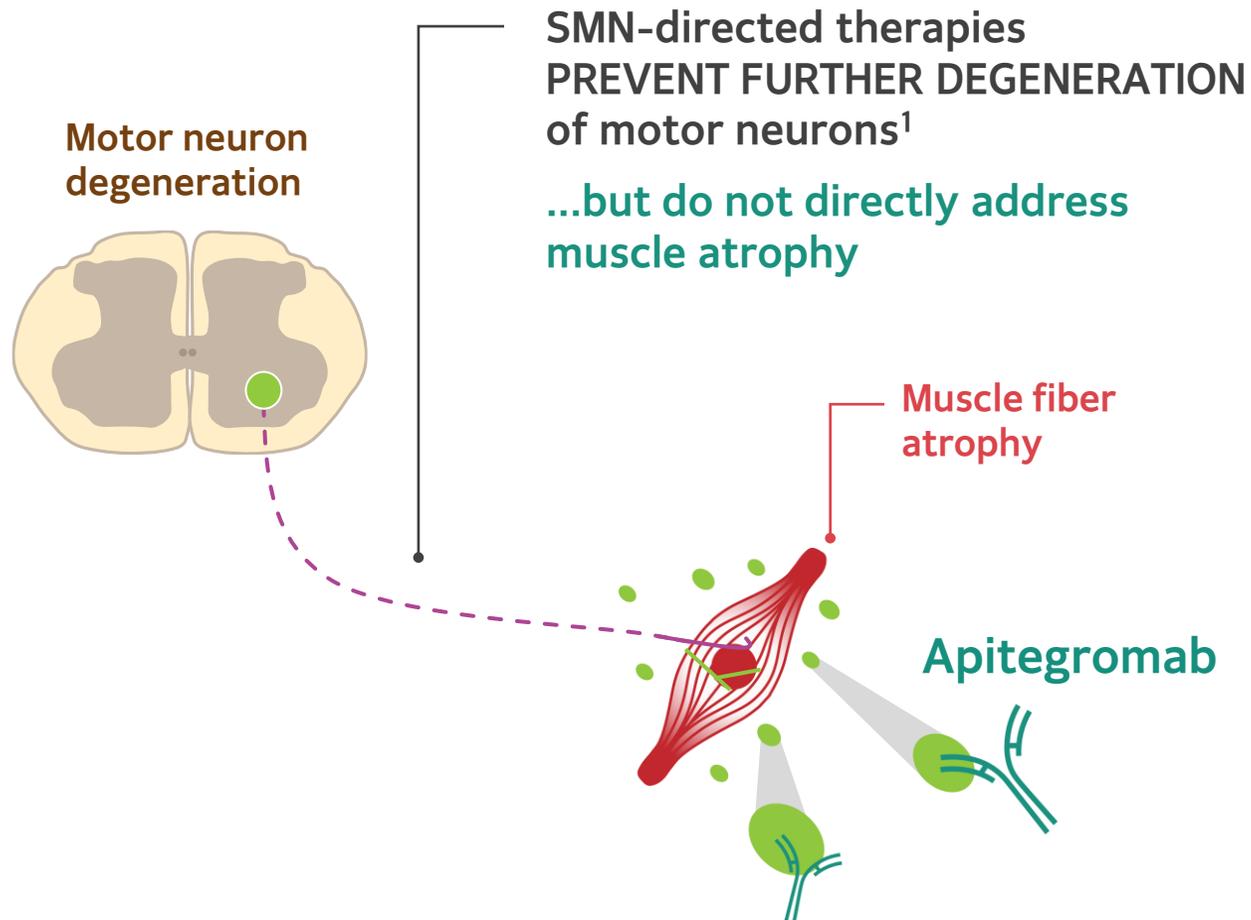


# Apitegromab: The Next Potential Transformative Therapy for Patients with Spinal Muscular Atrophy (SMA)



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# Apitegromab: Potential Muscle-Directed Therapy for SMA



**Apitegromab is a MUSCLE-DIRECTED APPROACH** aimed at improving motor function\*<sup>2,3</sup>

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<sup>1, 2, 3,4</sup>

\*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](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.



## 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

Significant, progressive motor function impairment; many lose ambulation

Type 3  
35%

Severe, progressive disabilities and unable to walk independently

Type 2  
51%

Infantile onset; unable to sit up independently

Type 1  
14%

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

>2/3 of overall patient population

# Potential to Pioneer a New Treatment Era: Opportunity for Muscle-Directed Therapy to Complement SMN-Directed Therapies



	SPINRAZA <sup>®</sup> (nusinersen) injection 12 mg/5 mL	Evrysdi <sup>™</sup> (risdiplam) 60 mg powder for oral solution	Zolgensma <sup>®</sup> (onasemnogene abeparvovec-xioi) suspension for intravenous infusion
<b>PHASE 3 TRIAL DESIGN</b>	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)
<b>PRIMARY ENDPOINT</b>	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
<b>INITIAL INDICATION<sup>†</sup></b>	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
<b>CURRENT MARKET PENETRATION</b>	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-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.

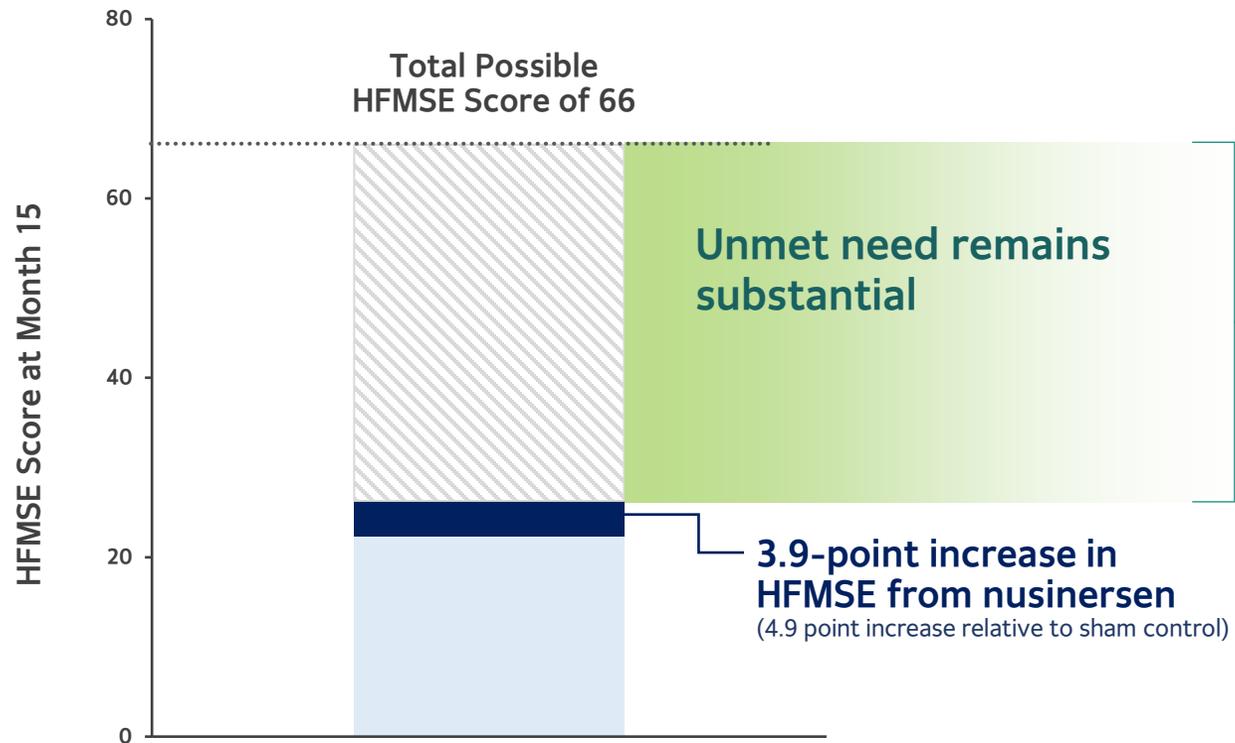
\*\*As of Roche [YTD Sep'2022 financial update](#) on 10/18/22; includes patients treated worldwide between clinical trials, commercial, and compassionate use program.

\*\*\*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

<sup>†</sup>Refer to most current USPI

# 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.



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

# TOPAZ Age 2-12 Analysis\* in Pooled Non-Ambulatory Cohorts (20mg/kg) Transformative Potential as Add-On for Apitegromab<sup>1,2</sup>



## Mean HFMSE Increase OF 4.4 POINTS

with majority experiencing  $\geq$  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 $\geq$ 5:

- 75% (6/8) with  $\geq$  1-point increase
- 50% (4/8) with  $\geq$  3-point increase

TOPAZ results showed HFMSE improvement from baseline or RHS stabilization across all three pre-specified cohorts.<sup>1</sup>

### Non-Ambulatory Types 2/3 SMA (Apitegromab 20 mg/kg; Intent-to-Treat Population)

Age 2-12 years  
(n=16<sup>†</sup>)

Mean HFMSE change from baseline, (95% CI)

**+4.4 (1.3, 7.4)**

Patients with  $\geq$  1-pt increase in HFMSE, n (%)

**13 (81%)**

Patients with  $\geq$  3-pt increase in HFMSE, n (%)

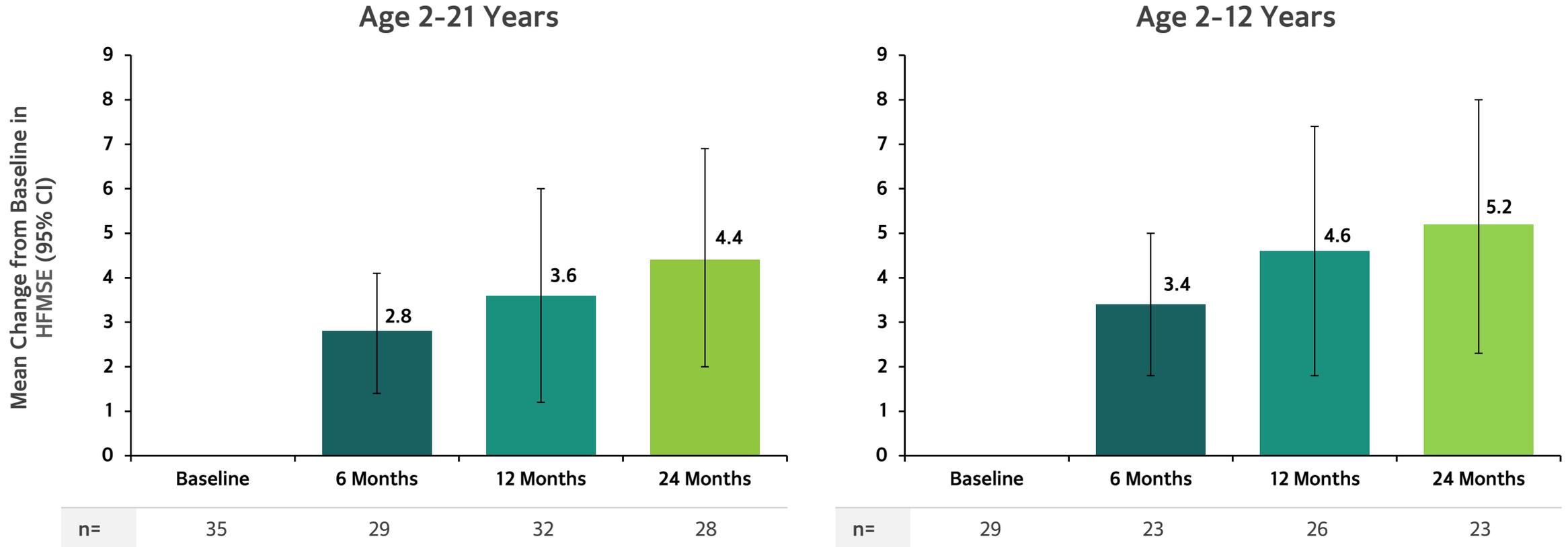
**9 (56%)**

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; <sup>†</sup>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 \(scholarrock.com\)](https://www.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

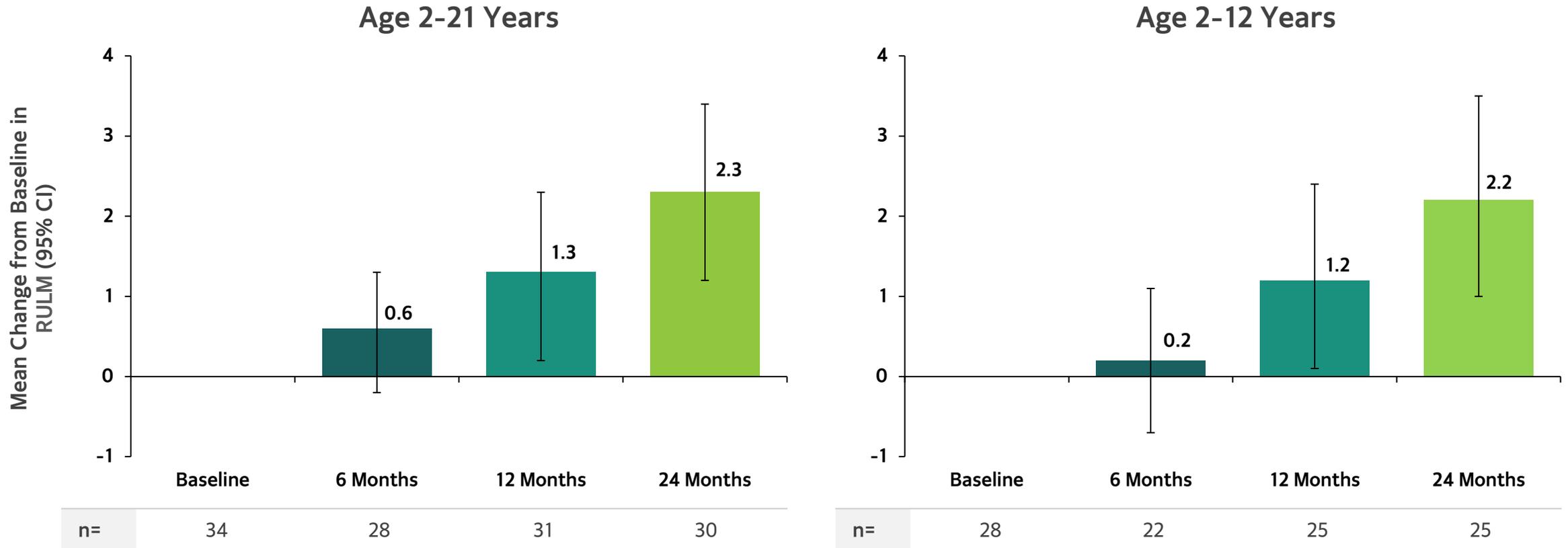
Pooled Non-Ambulatory Patients Excluding Data Post Scoliosis Surgery (all dose groups)



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 parentheses 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.

# Continued Increase in RULM Observed at 24 Months of Apitegromab

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



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 parentheses 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.

# 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.



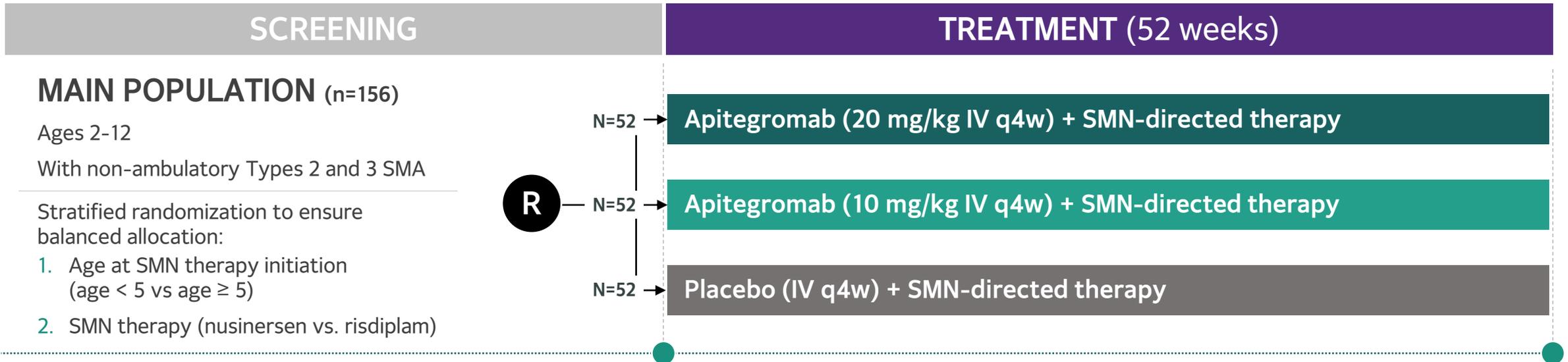
**SAPPHIRE**

## Sapphire Phase 3 Pivotal Trial

# Ongoing SAPHIRE Phase 3 Trial Overview



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

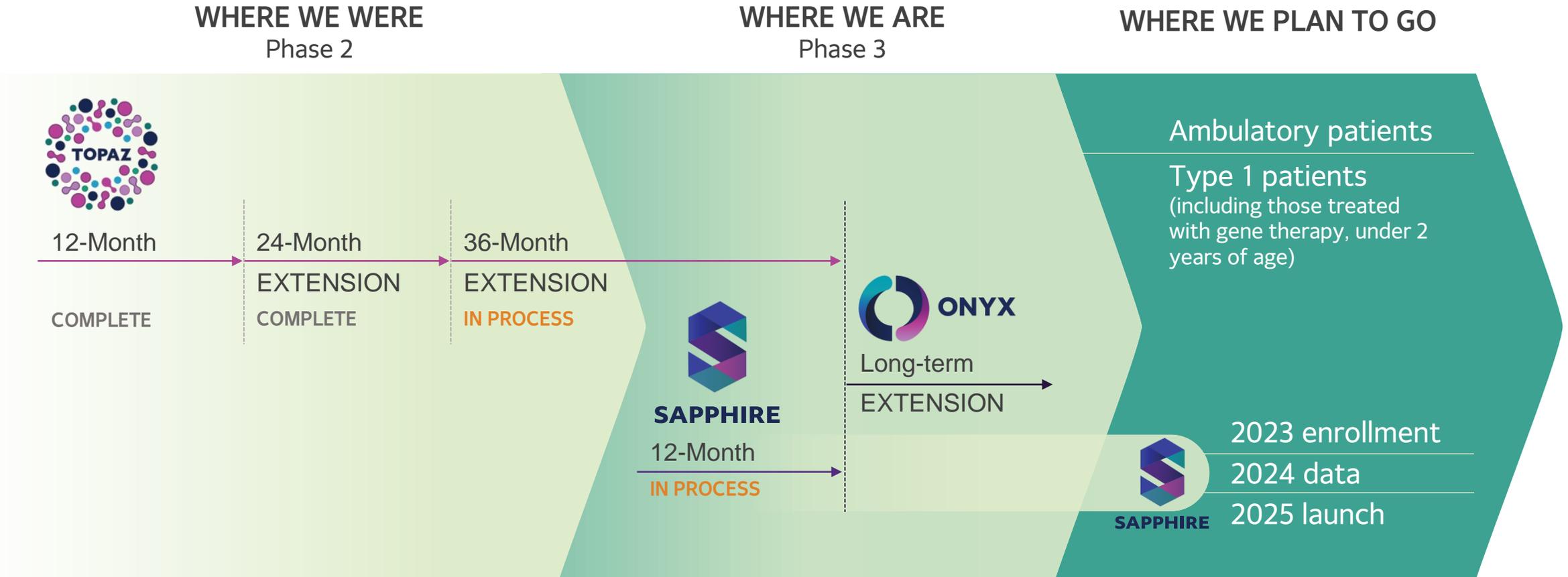
### Exploratory population (age 13-21), in patients using SMN therapy

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

# Executing on the Promise: Apitegromab SMA Trials





DRAGON

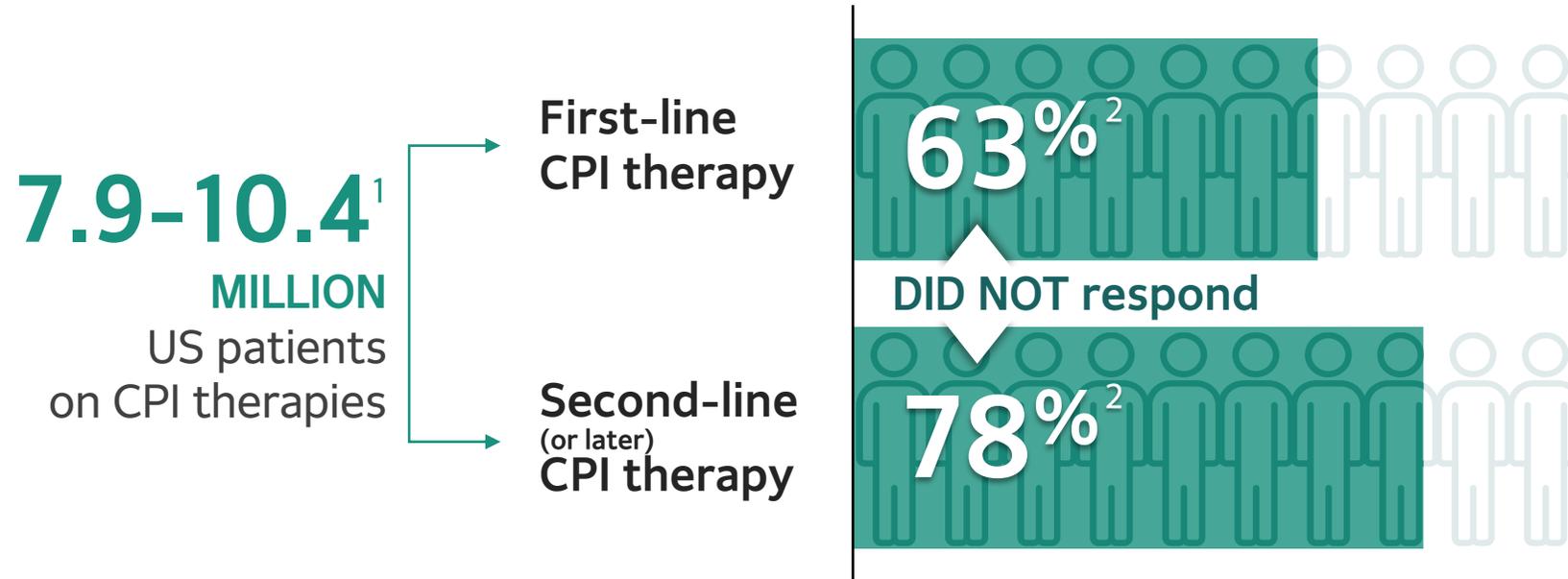
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## SRK-181: Potential Transformative Backbone for a New Era of Cancer Immunotherapy



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



Clinically derived rationale points to significant opportunity to increase checkpoint therapy responses by targeting TGF $\beta$ -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 TGF $\beta$ Inhibition in Immuno-Oncology

*Nature* (online), February 14, 2018.

## TGF $\beta$ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells

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

*Science Translational Medicine*, March 25, 2020.

## Selective inhibition of TGF $\beta$ -1 activation overcomes primary resistance to checkpoint blockade therapy by altering tumor immune landscape

Constance J. Martin, et al.

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

June 2019.

## “Merck to Acquire Tilos Therapeutics: Merck Gains Portfolio of Investigational Antibodies Modulating TGF $\beta$ ”

- \$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

## TGF $\beta$ : biology in cancer progression and immunotherapy

Rik Derynck<sup>1,2,3</sup>, Shannon J. Turley<sup>4</sup> and Rosemary J. Akhurst<sup>2,3</sup>

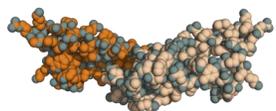
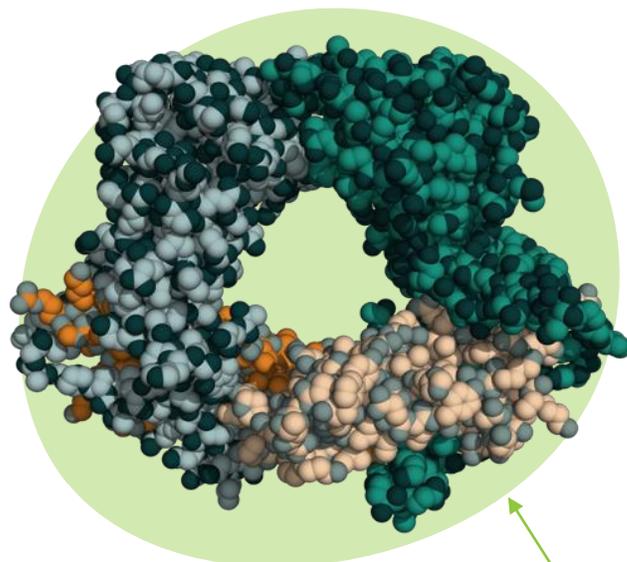
July 24, 2020: <https://doi.org/10.1038/s41571-020-0403-1>

August 2022.

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

# SRK-181: Unique Latent TGFβ-1 Selective Approach to Overcoming Checkpoint Inhibitor Resistance

## SRK-181: Latent TGFβ-1 Inhibitor



Traditional Target  
“Mature” growth factor

### 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)

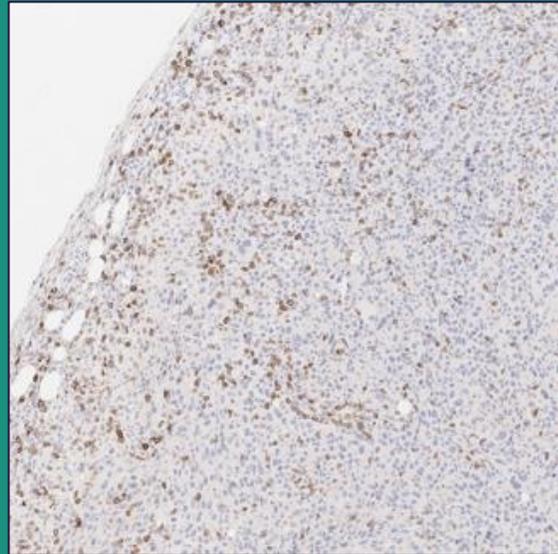
Some programs only target one source

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

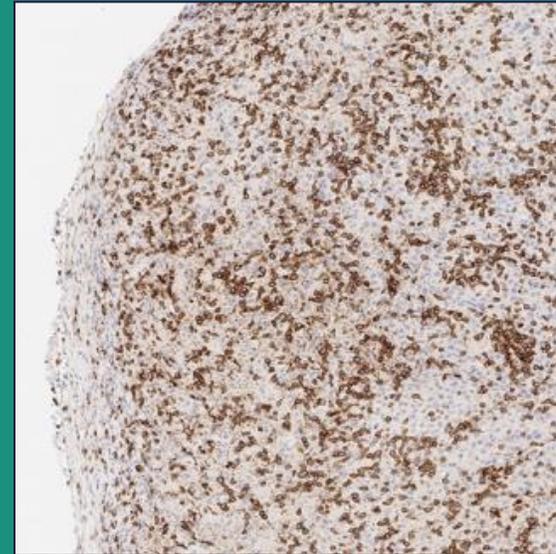
## Overcoming immune exclusion Tumor micro-environment

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



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

## PART A

### A1

SRK-181  
all-comers

SRK-181 80 mg (n=1)

SRK-181 240 mg (n=1)

SRK-181 800 mg (n=3)

SRK-181 1600 mg (n=3)

SRK-181 2400 mg (n=3)

SRK-181 3000 mg (n=3)\*

### A2

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

SRK-181 240 mg (n=3)

SRK-181 800 mg (n=3)

SRK-181 1600 mg (n=3)

SRK-181 2400 mg (n=3)

## PART B

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

COHORT

TREATMENT

Non-small cell lung cancer

SRK-181 + pembrolizumab

Urothelial carcinoma

SRK-181 + pembrolizumab

Cutaneous melanoma

SRK-181 + pembrolizumab

Clear cell renal cell carcinoma\*\*

SRK-181 + pembrolizumab

Head and neck squamous cell  
carcinoma

SRK-181 + pembrolizumab

\* A cohort of 2000 mg Q2W (n=3) was also evaluated.

\*\*The clear cell RCC and HNSCC cohorts will also explore the effects of SRK-181 in patients with relapsed response after anti-PD-(L)1 treatment.

1. NCT04291079 on [www.clinicaltrials.gov](http://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=15
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:

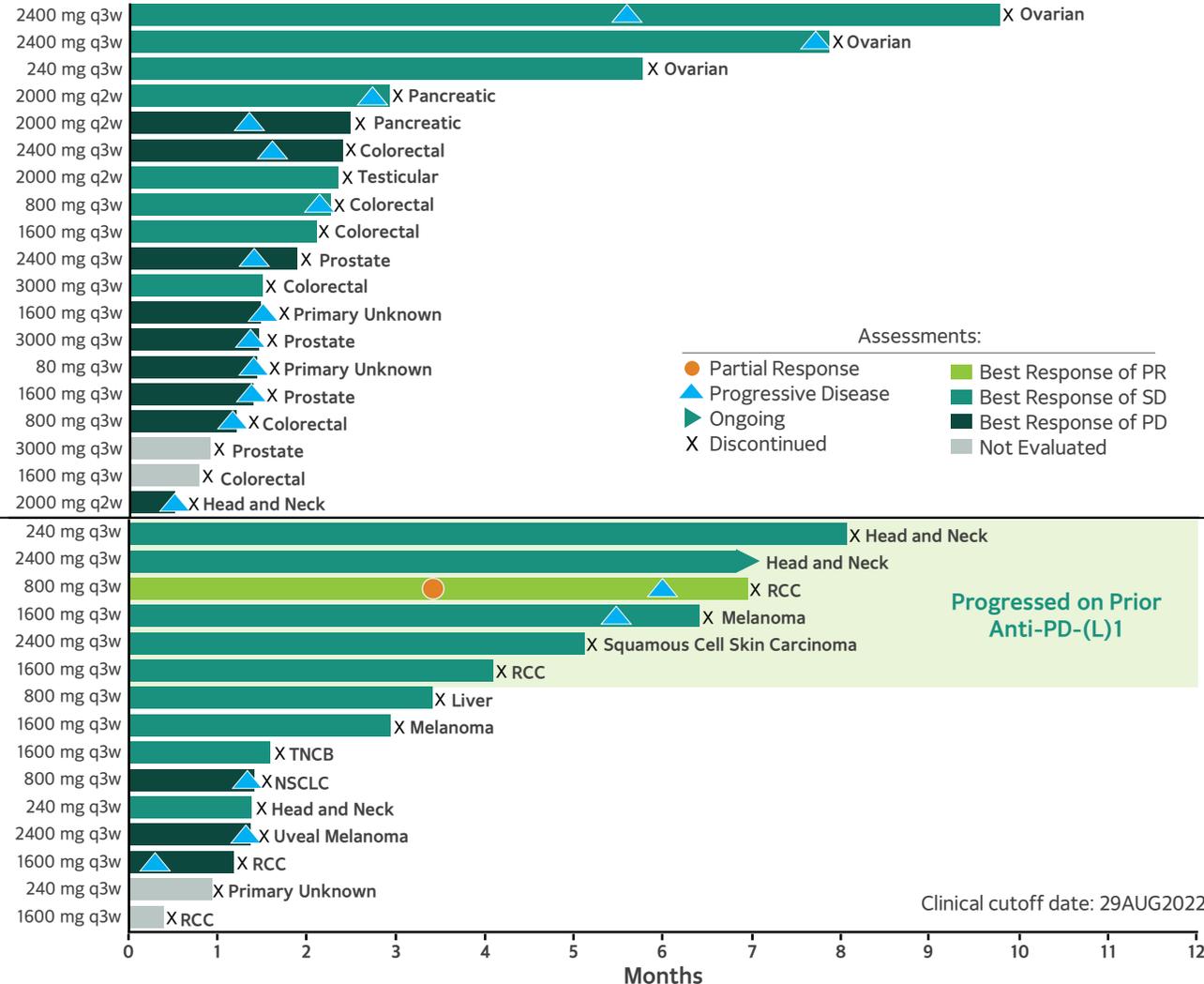
- Pruritis (2 patients), blister, immune-mediated lung disease, rash and rash maculo-papular (1 patient each)

#### Treatment-related SAEs:

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

# DRAGON Part A: Preliminary Efficacy Data\* Presented at SITC November 2022

## Duration of Treatment



## 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

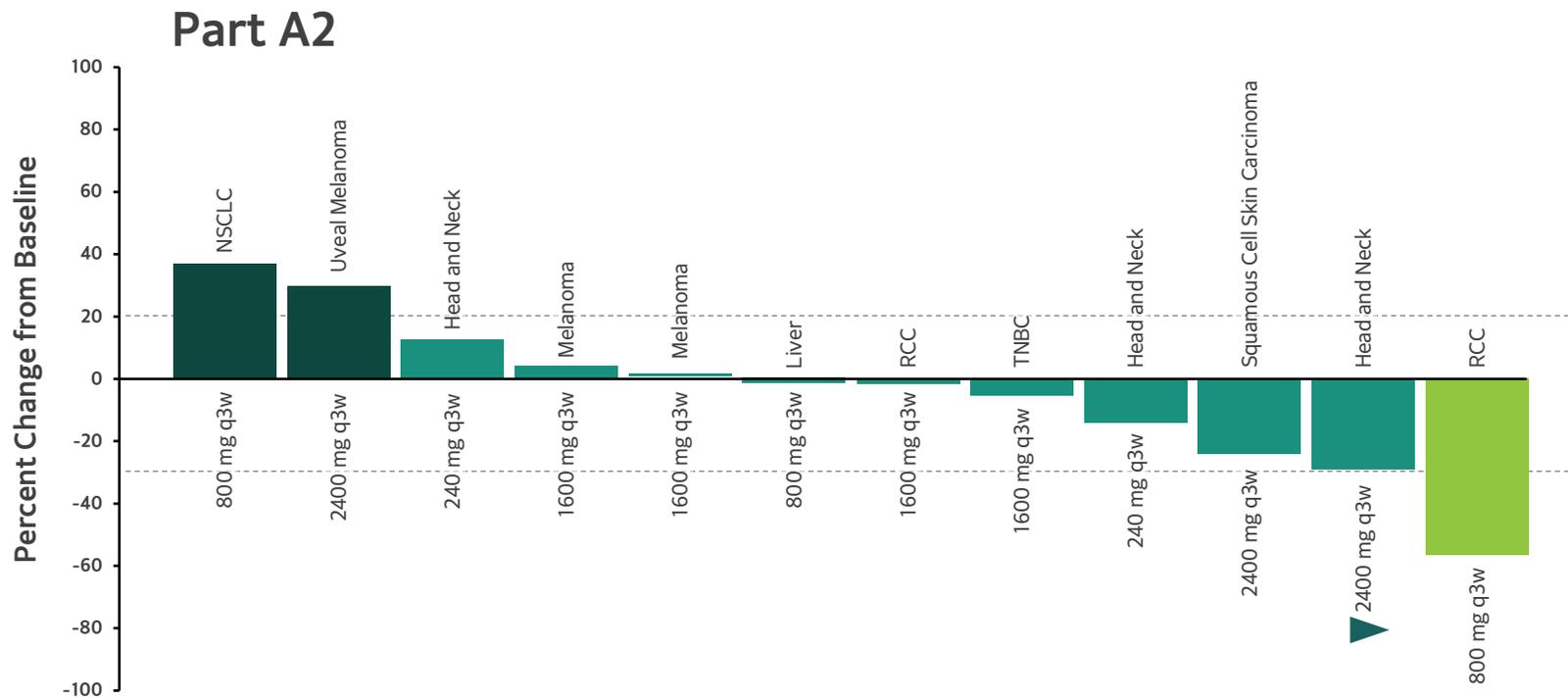
- 1 ongoing patient with head and neck cancer had a 29.4% tumor reduction

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

## Best Response in Target Lesions

■ Best Response of PR    ■ Best Response of PD  
■ Best Response of SD    ▶ Ongoing



## 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

### TGF $\beta$ pathway evaluation (PD)

- ✓ Target engagement (blood)
- ✓ TGF $\beta$ -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

### TGF $\beta$ pathway evaluation (PD)

- ✓ Target engagement (blood)
- ⌚ TGF $\beta$ -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)



## Next Horizon: Fibrosis

# TGF $\beta$ is Established as Key Driver of Fibrosis Across Multiple Diseases

*Nature Reviews*, April 25, 2016

NATURE REVIEWS | NEPHROLOGY

## TGF- $\beta$ : the master regulator of fibrosis

Xiao-ming Meng<sup>1</sup>, David J. Nikolic-Paterson<sup>2</sup> and Hui Yao Lan<sup>3</sup>

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

## Targeting TGF- $\beta$ Signaling in Kidney Fibrosis

Yoshitaka Isaka

*Nature Reviews*. August 19, 2014

NATURE REVIEWS | RHEUMATOLOGY

## Transforming growth factor $\beta$ —at the centre of systemic sclerosis

Robert Lafyatis

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

## Targeting Anti-TGF- $\beta$ Therapy to Fibrotic Kidneys with a Dual Specificity Antibody Approach

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

*J Pathol*, July 25, 2021

## TGF- $\beta$ as a driver of fibrosis: physiological roles and therapeutic opportunities

Erine H Budi<sup>1</sup>, Johanna R Schaub<sup>1</sup>, Martin Decaris<sup>1</sup>, Scott Turner<sup>1</sup>, Rik Derynck<sup>2</sup>

*J Receptors Sign Trans*, Feb 13, 2020

## Inevitable role of TGF- $\beta$ in progression of nonalcoholic fatty liver disease

Bhagyalakshmi Nair and Lekshmi R. Nath

*Proc Am Thorac Soc*, July 3, 2006

## Transforming Growth Factor $\beta$ A Central Modulator of Pulmonary and Airway Inflammation and Fibrosis

Dean Sheppard

*PNAS*, February 24, 1986

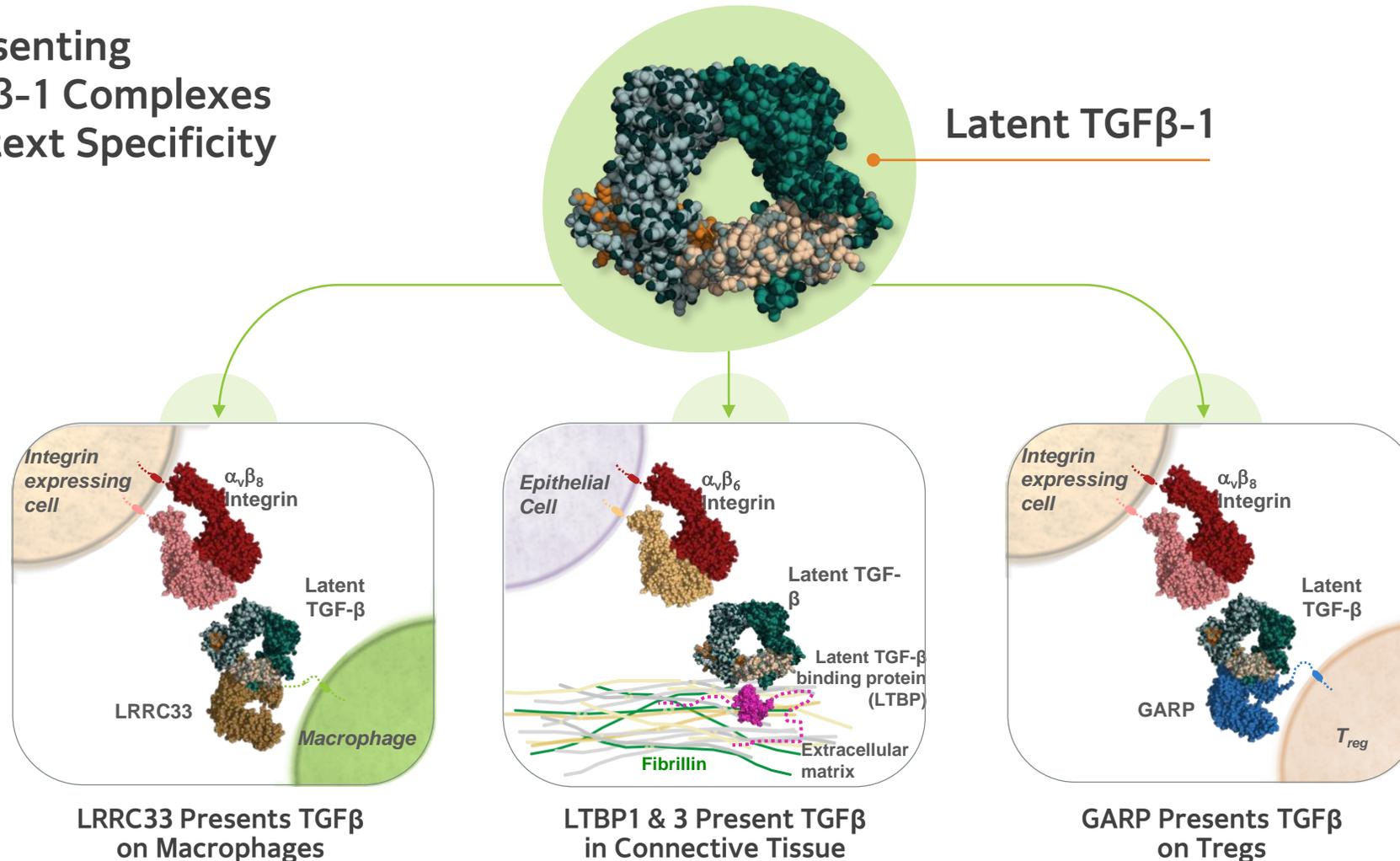
**PNAS**

## Transforming growth factor type $\beta$ : 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<sup>†</sup>, JOHN H. KEHRL<sup>‡</sup>, AND ANTHONY S. FAUCI<sup>‡</sup>

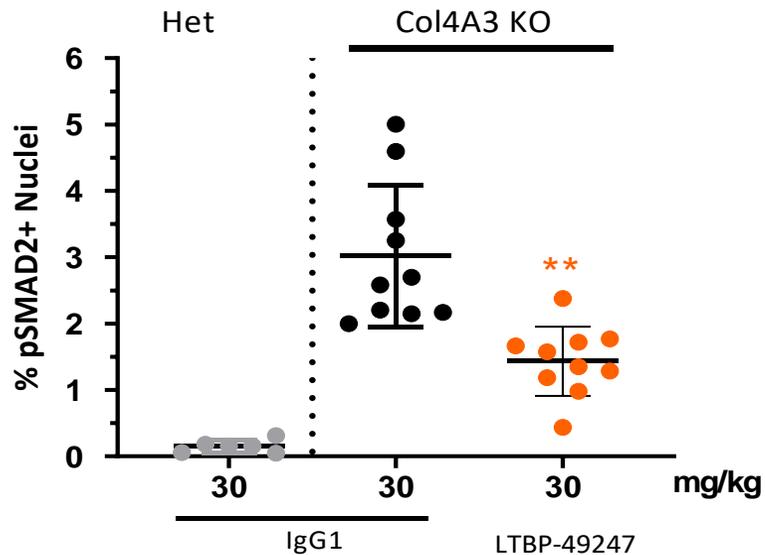
# Targeting Latent TGF $\beta$ -1 Complexes Creates Multiple “Handles” For Selectivity

Targeting Presenting Molecule/TGF $\beta$ -1 Complexes Provides Context Specificity

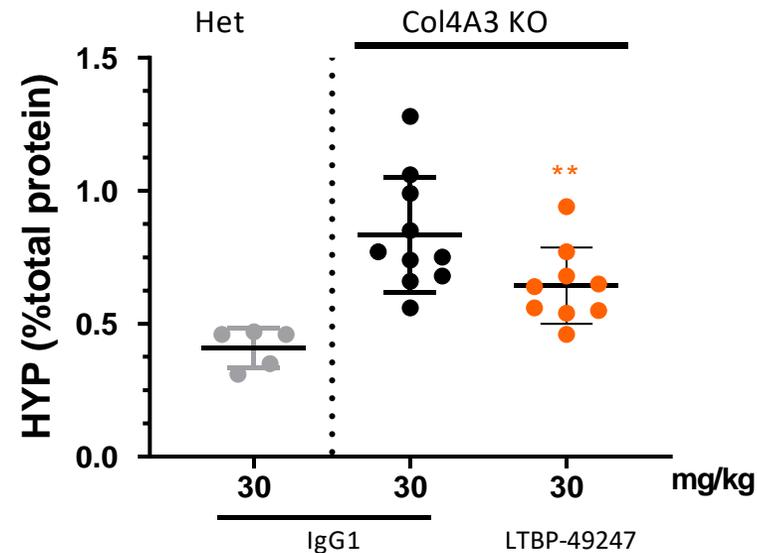


# LTBP-49247 Reduces TGF $\beta$ Signaling and Fibrosis in Preclinical Models of Kidney Fibrosis

LTBP-49247 reduces a TGF $\beta$  PD biomarker in kidneys of *Col4a3*KO mice (Alport Syndrome model)



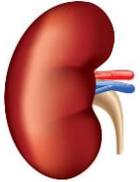
LTBP-49247 reduces fibrosis in kidneys of Alport model



\*\* 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 (t<sub>1/2</sub> ~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



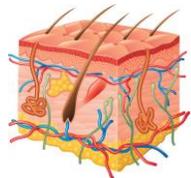
**Alport Syndrome (AS)**  
**Focal Segmental Glomerulosclerosis (FSGS)**  
**IgA Nephropathy (IgAN)**



**Primary Sclerosing Cholangitis (PSC)**



**Idiopathic Pulmonary Fibrosis (IPF)**



**Diffuse Cutaneous Systemic Sclerosis (dcSSc)**

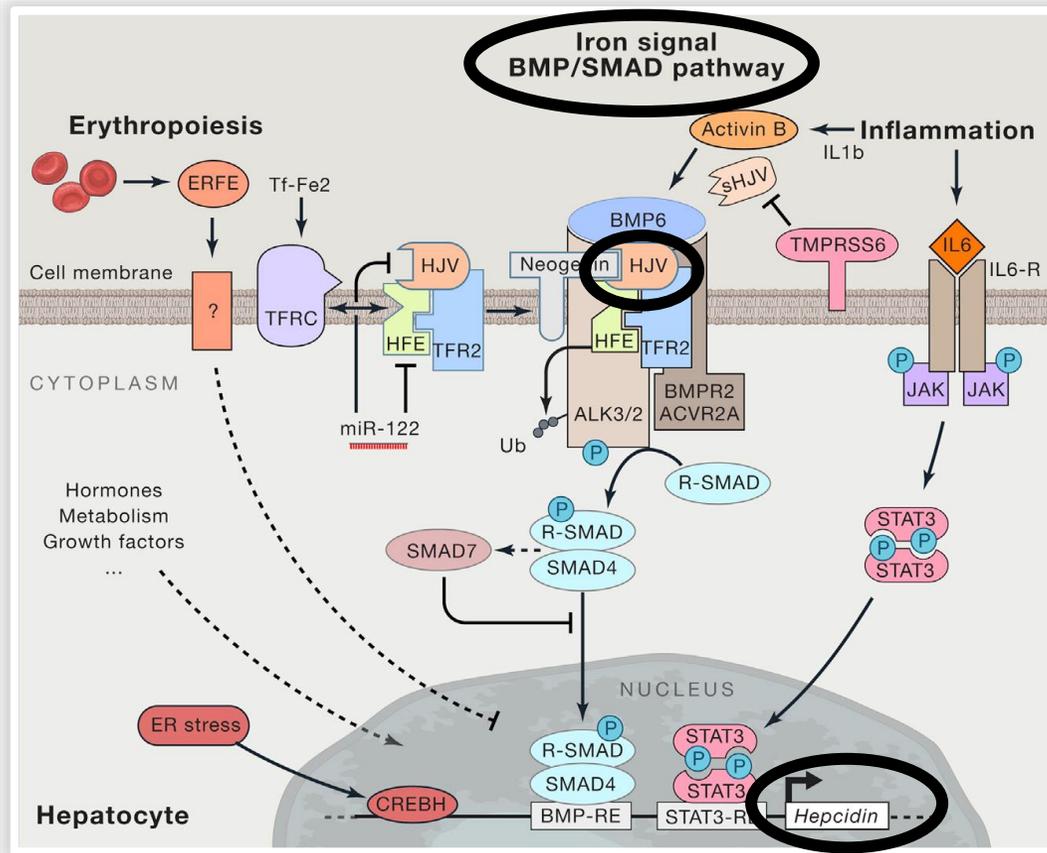
Collectively, significant commercial potential given large patient population with clear high unmet need given poor outcomes and lack of effective therapeutics

- 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

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

## Anemia of Inflammation/ Chronic Disease

- Elevation of proinflammatory cytokines drives increased hepcidin expression and results in anemia due to functional iron deficiency<sup>4</sup>

Untreated

↑ Hepcidin

↓ Serum iron

Ab treated

↓ Hepcidin

↑ Serum iron

Fig: Muckenthaler, M.U., Rivella, S., Hentze, M.W. and Galy, B. (2017) A Red Carpet for Iron 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: Constanze 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.

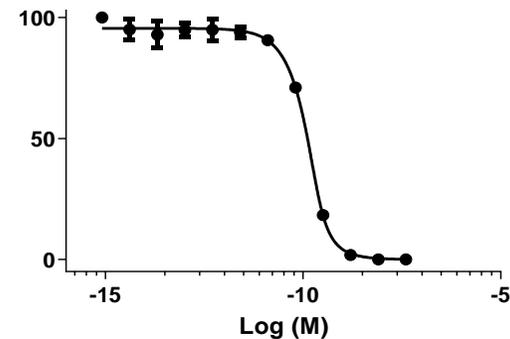
4. Wang CY and Babitt JL. (2016) Hepcidin Regulation in the Anemia of Inflammation. *Curr Opin Hematol* 23(3): 189-197.

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

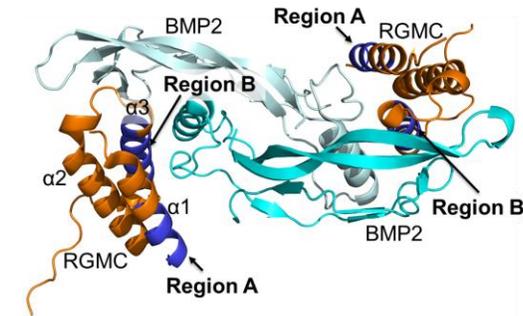
## Key Attributes of HJV-35202:<sup>1,2</sup>

- 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)

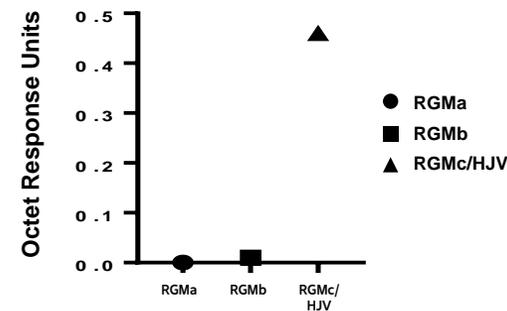
Potent in vitro binding affinity (KD=3.9E-11)



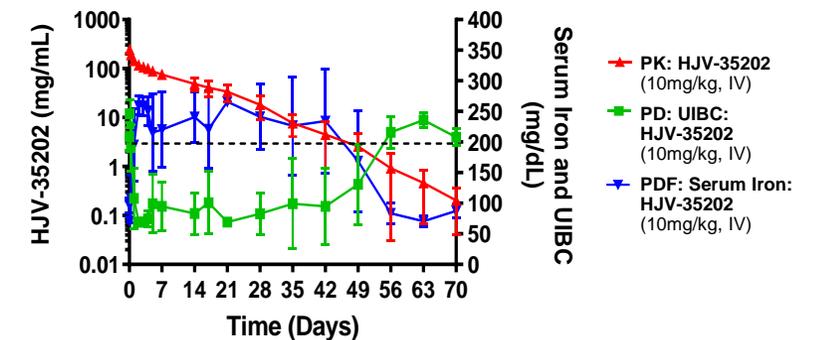
Highly specific to RGMC/HJV with well understood mechanism



Specific to RGMC over other RGM family members

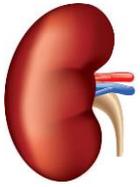


Sustained PD effect in single dose Cyno study



1. Nicholls S.B., et al. Poster: RGMC-selective antibodies modulate iron homeostasis in vivo, *12<sup>th</sup> 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



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# 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

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

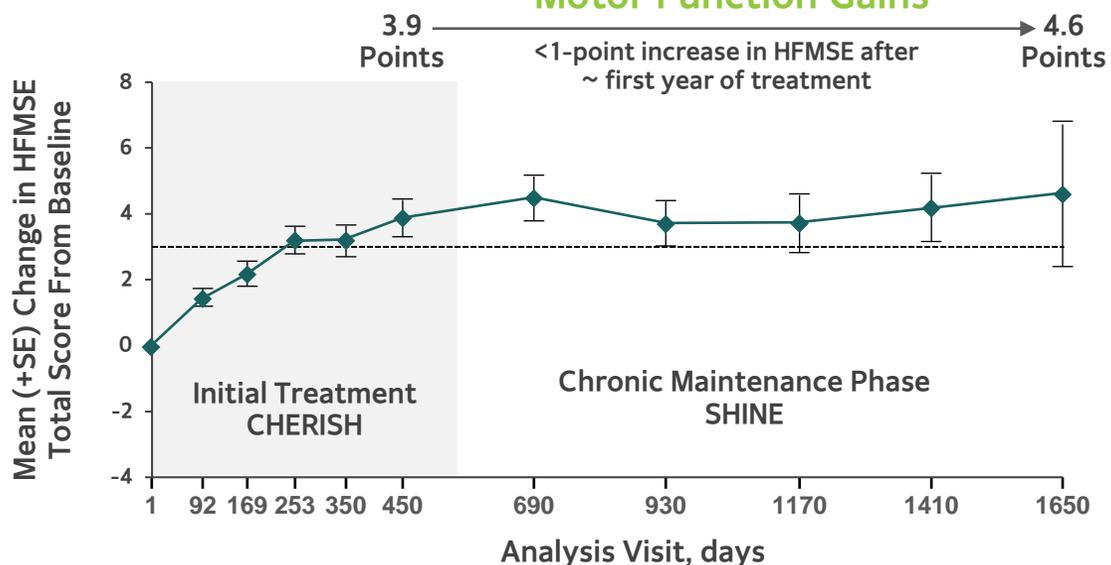
# Appendix

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

## NUSINERSEN<sup>1</sup>

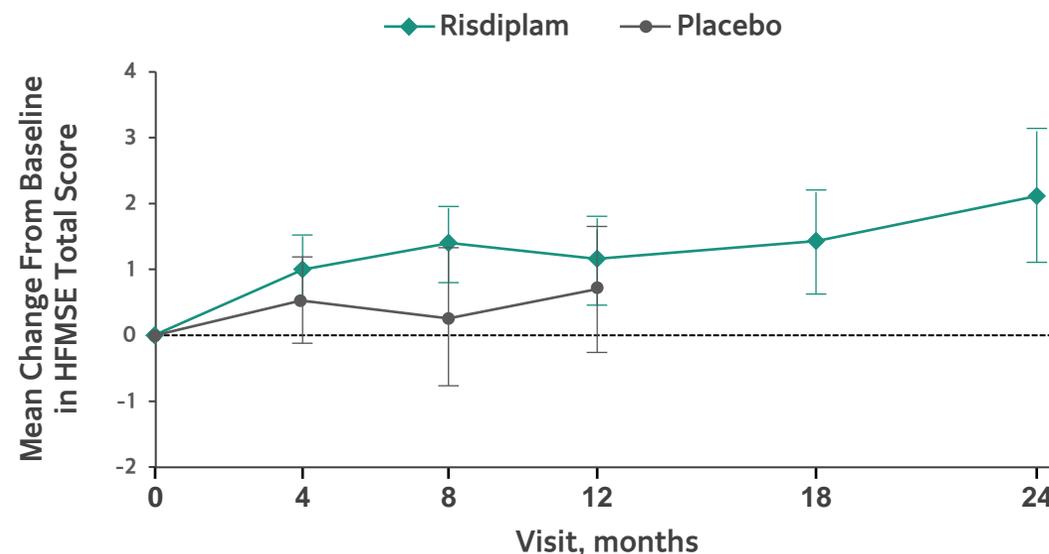
Plateauing of HFMSE increases observed following initial treatment effects for nusinersen

Unmet Need for Motor Function Gains



## RISDIPLAM<sup>2\*</sup>

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.

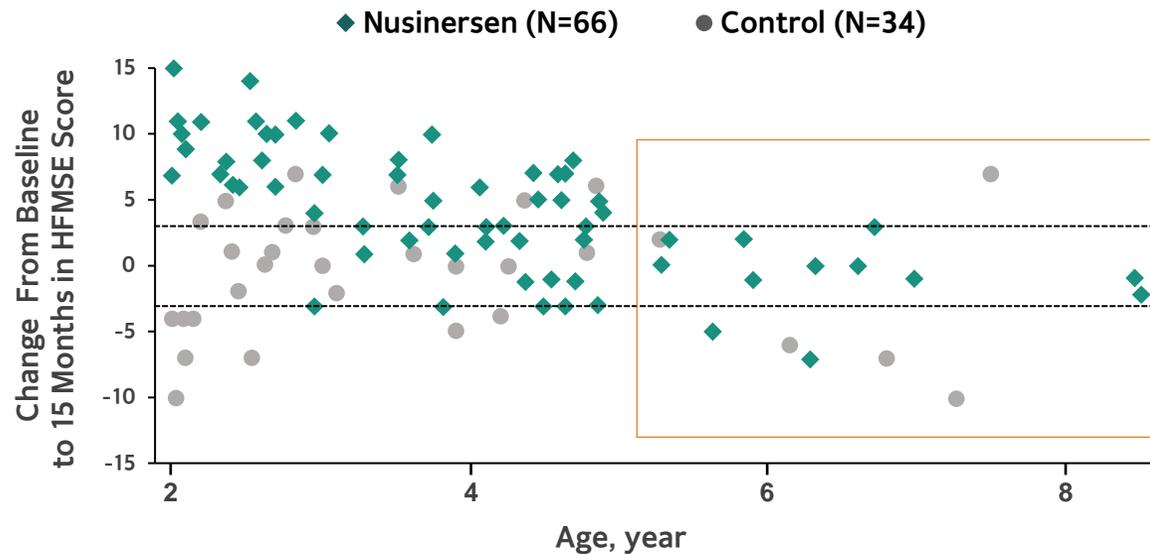
\* Overall population 2-25 years old.

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.

# Non-Ambulatory Type 2/3 SMA:

## Majority of Patients Started on SMN Therapy After Age 5 Do Not Experience Motor Function Increases

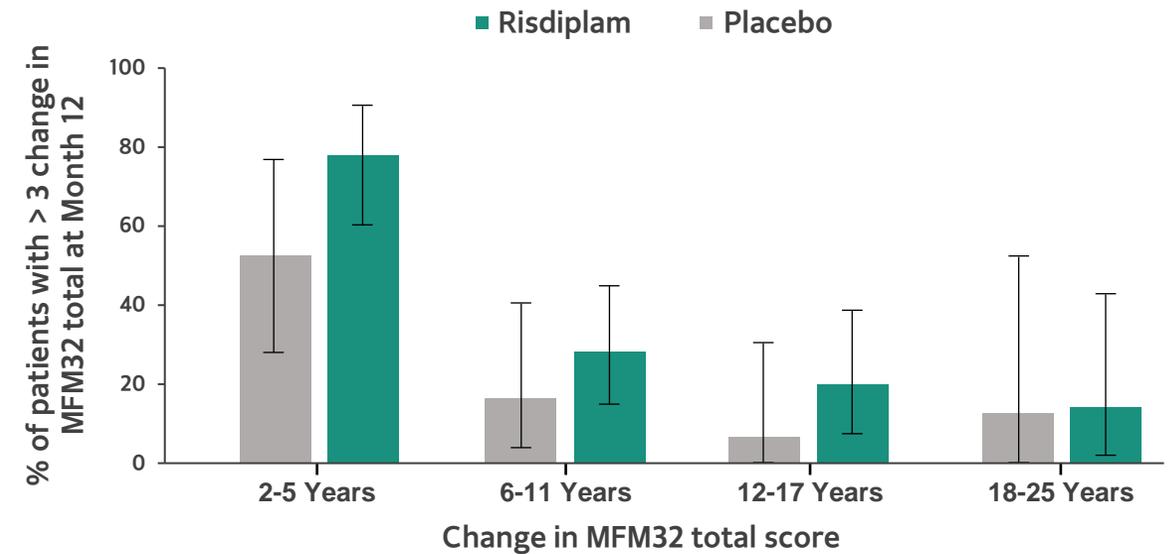
### Nusinersen CHERISH Trial in Later-Onset SMA<sup>1</sup>



In patients with later-onset SMA who were age  $\geq 5$  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<sup>2</sup>



- Low percentage of patients over the age of 5 achieved  $\geq 3$ -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

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Largest HFMSE gains observed in the non-ambulatory Type 2/3 SMA cohorts

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

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HFMSE gains evident by 12 months of treatment

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

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SAPPHIRE

## SAPPHIRE Design Elements

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- Study population: Non-ambulatory Type 2/3 SMA
  - Primary efficacy endpoint: HFMSE
- 



Age 2-12 main efficacy population

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12-month treatment duration

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- 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<sup>1,2</sup>

	AMBULATORY PATIENTS COHORT 1		NON-AMBULATORY PATIENTS COHORT 2	NON-AMBULATORY PATIENTS 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 <sup>†</sup>	1 <sup>†</sup>	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.

<sup>†</sup>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<sup>1,2</sup>



Sizable increases in HFMSE observed in patients already treated with chronic maintenance nusinersen

- Improved: **88% (7/8)**
- $\geq 5$ -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:

$\geq 1$ -pt increase in HFMSE

**7/8 (88%)**

$\geq 3$ -pt increase in HFMSE

**5/8 (63%)**

$\geq 5$ -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 $\geq 5$ <sup>1,2</sup>



Majority of patients improved in HFMSE (despite initiating background nusinersen age  $\geq 5$ )

- $\geq 1$ -point increase: ~67%
- $\geq 3$ -point increase: ~30%

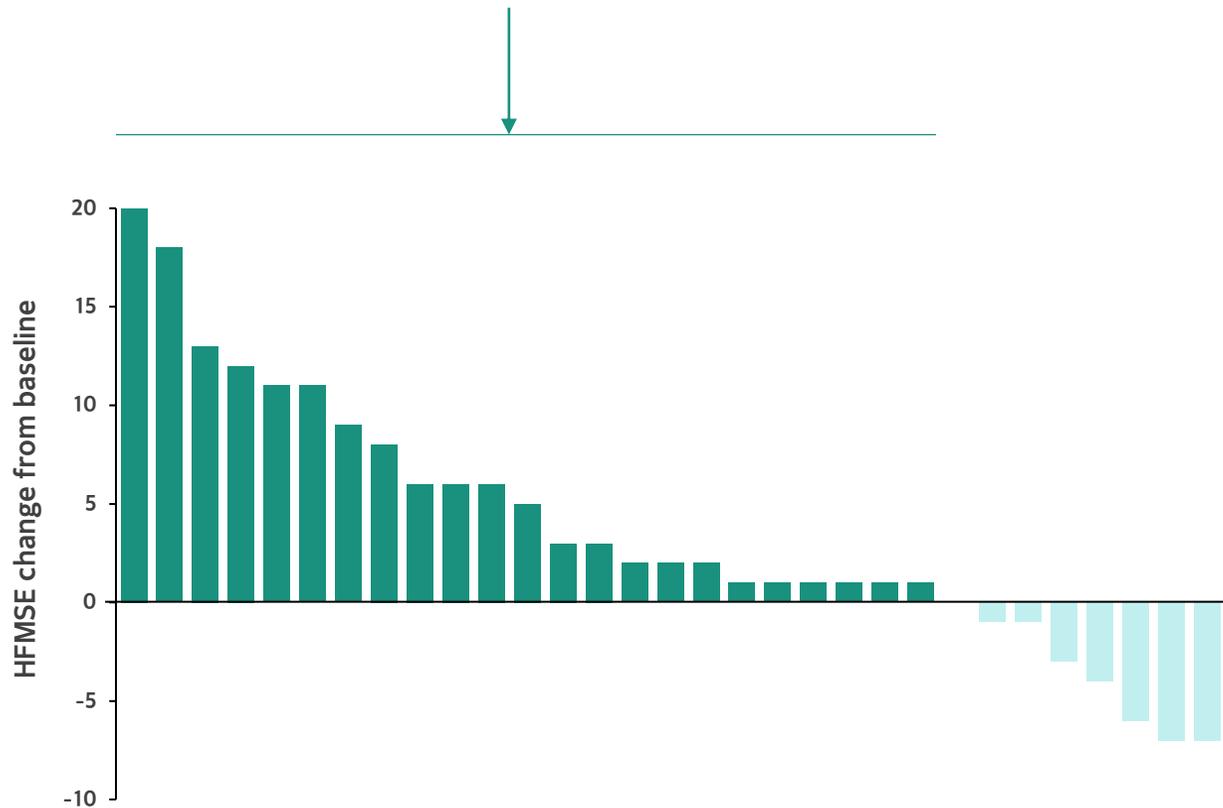
Durability of effect observed through 12-months of treatment

	Per Protocol Population* (n=13)	Intent-to-Treat Population (n=14)
<b>Apitegromab (20 mg/kg) + nusinersen</b>		
<b>Mean change from baseline in HFMSE (95% CI)</b>	<b>+1.2 (-0.5, 2.9)</b>	<b>+0.6 (-1.4, 2.7)</b>
# (%) patients achieving:		
<b><math>\geq 1</math>-pt increase in HFMSE</b>	<b>9/13 (69%)</b>	9/14 (64%)
<b><math>\geq 3</math>-pt increase in HFMSE</b>	<b>4/13 (31%)</b>	4/14 (29%)
<b><math>\geq 5</math>-pt increase in HFMSE</b>	<b>2/13 (15%)</b>	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  $\geq 5$

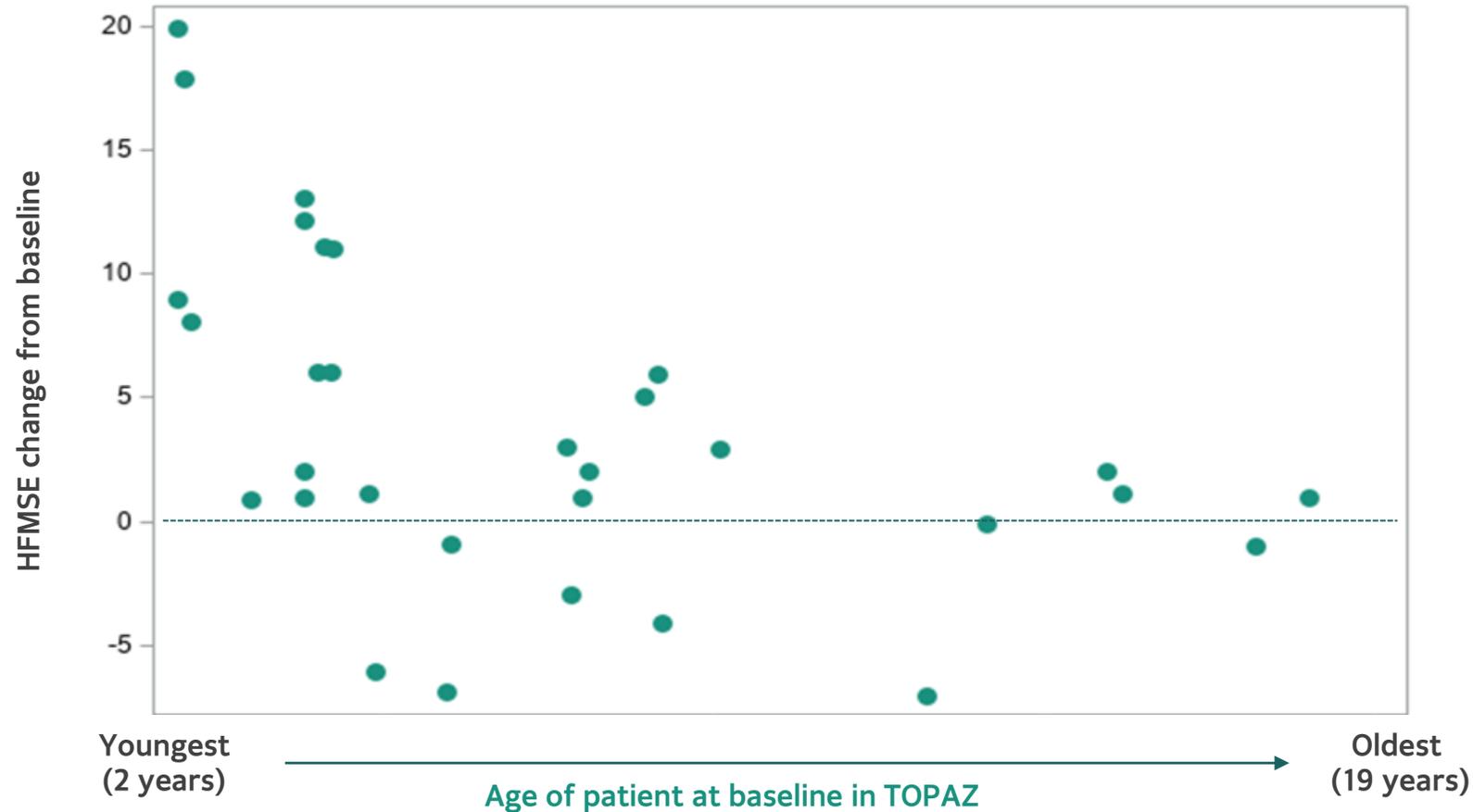
	Initiated background nusinersen	
	Age < 5**	Age $\geq 5$
Mean HFMSE Increase	+7.1 points	+0.6 points
$\geq 1$ -point Increase % (n/N)	88% (7/8)	64% (9/14)
$\geq 3$ -point Increase % (n/N)	63% (5/8)	29% (4/14)

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



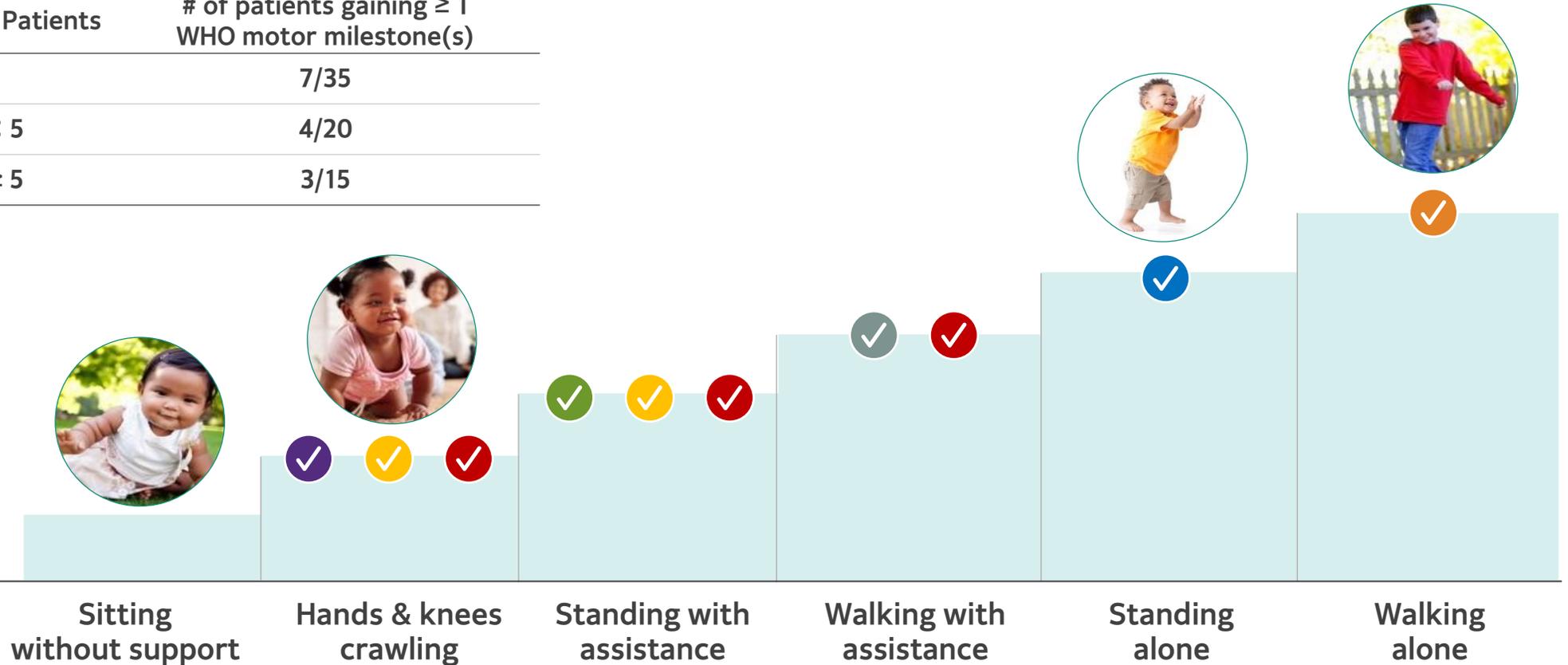
\*Pooled cohorts of non-ambulatory patients treated with apitegromab 20 mg/kg and 2 mg/kg; excludes 4 patients who each missed 3 doses of apitegromab due to COVID-19-related site access restrictions and were not included in the primary (intent-to-treat) analysis.

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<sup>1</sup>

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

# TOPAZ Extension Period: 24-Month Patient Disposition

	Cohort 1 Ambulatory	Non-Ambulatory		Total
		Cohort 2	Cohort 3	
# 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.

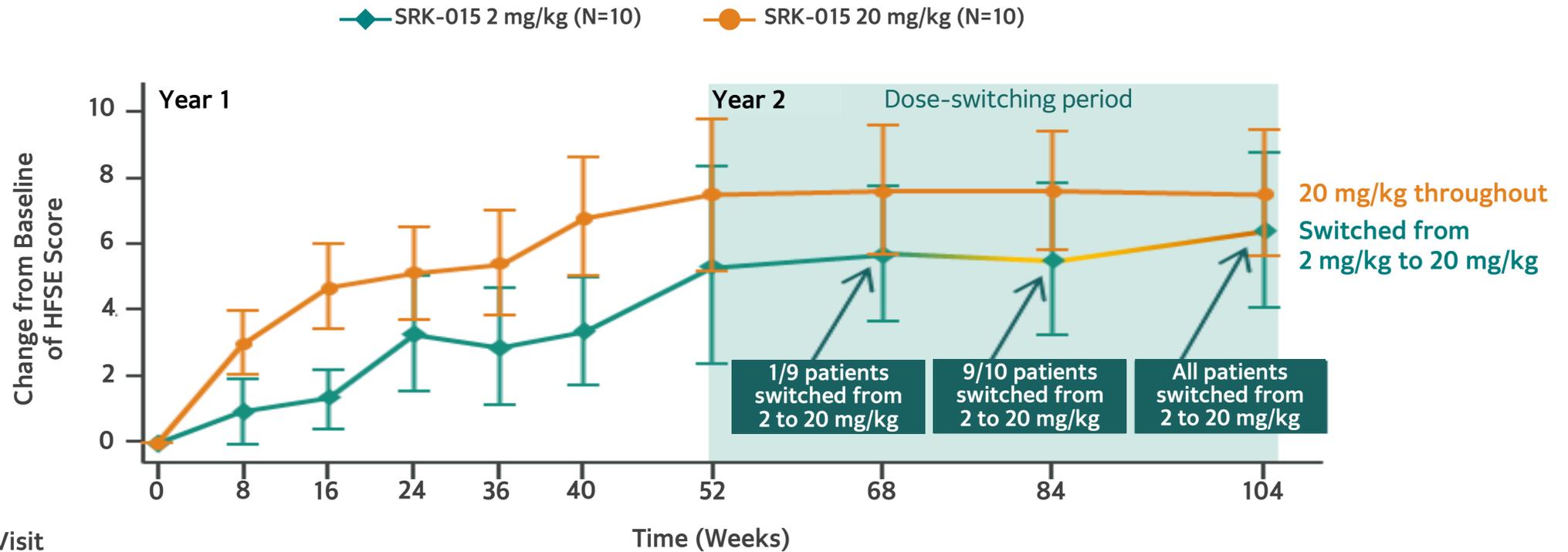
\*\*\*\*\* Patients did not have valid HFMSE test at 24 months.

# 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

	0	8	16	24	36	40	52	68	84	104
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

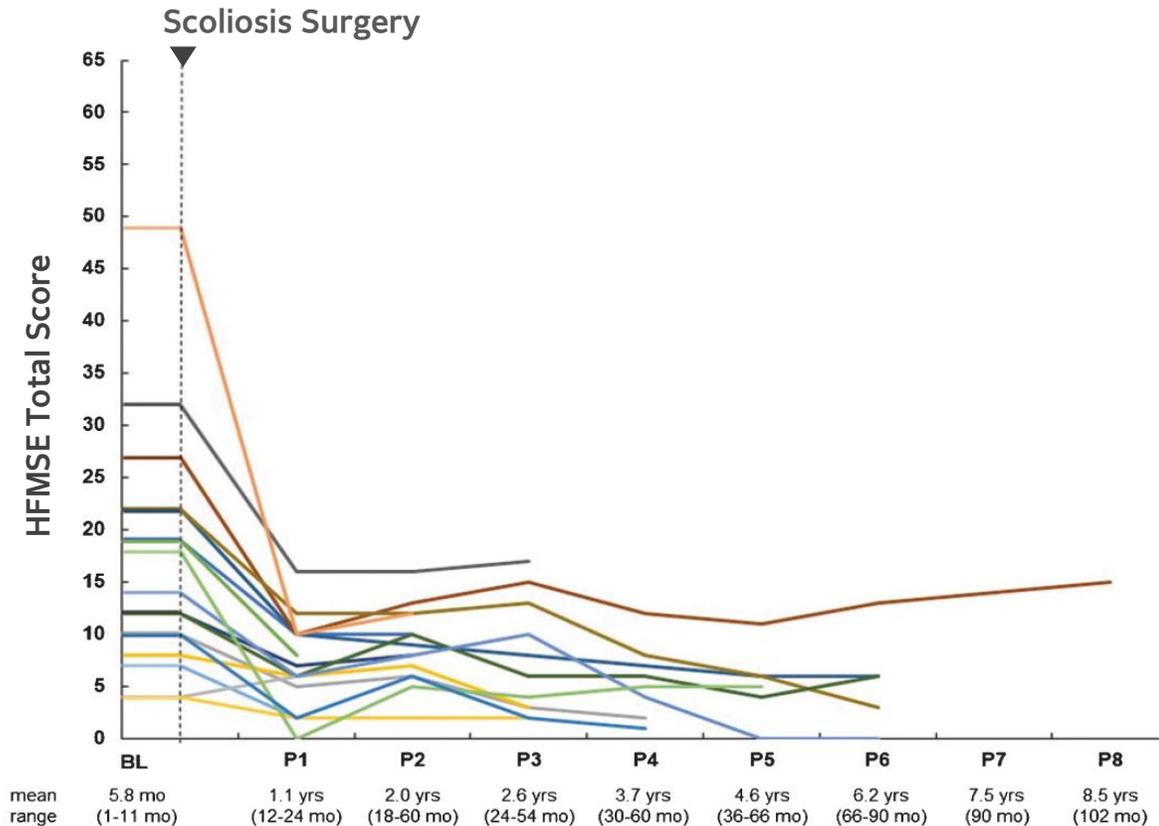
Crawford T et al. TOPAZ EXTENSION: 24-MONTH EFFICACY AND SAFETY OF APITEGROMAB IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TYPE 2 AND TYPE 3 SMA) Podium Presentation Presented at CureSMA; June 2022

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

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.

# Reported Impact of Scoliosis Surgery on Motor Abilities in SMA

## Post-Surgery HFMSE scores Type 2/3 SMA peer-reviewed study

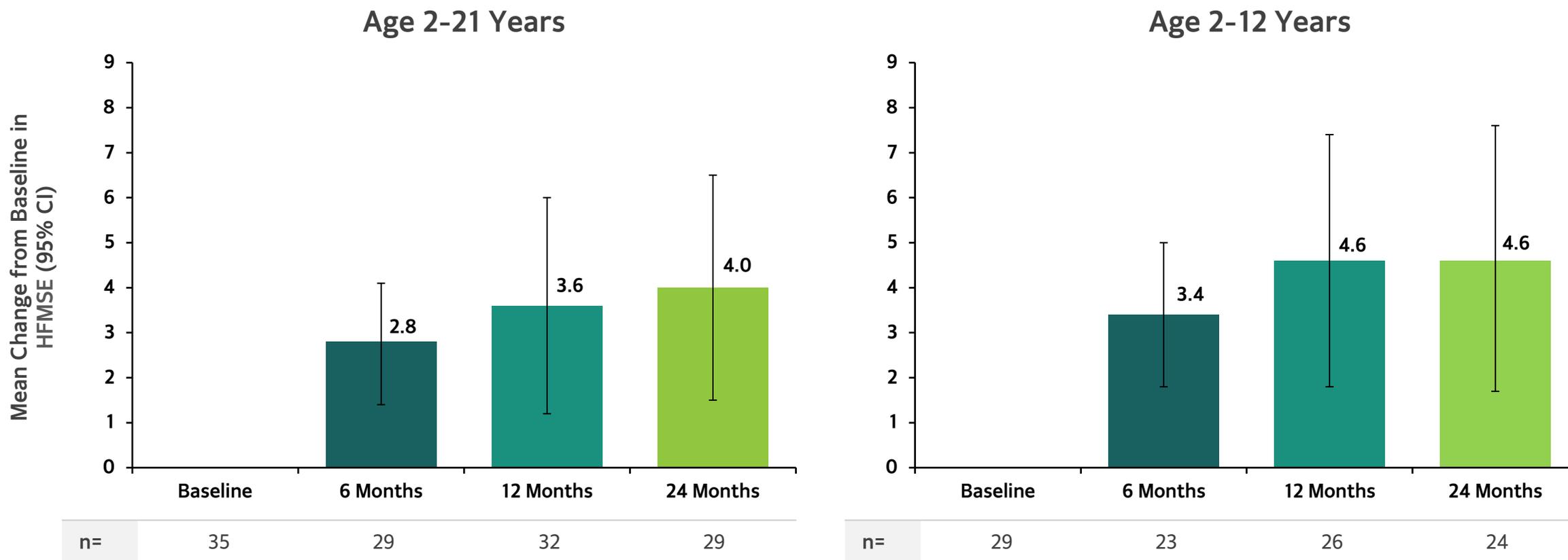


### 3-month post-surgery assessment

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

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

## Pooled Non-Ambulatory Patients

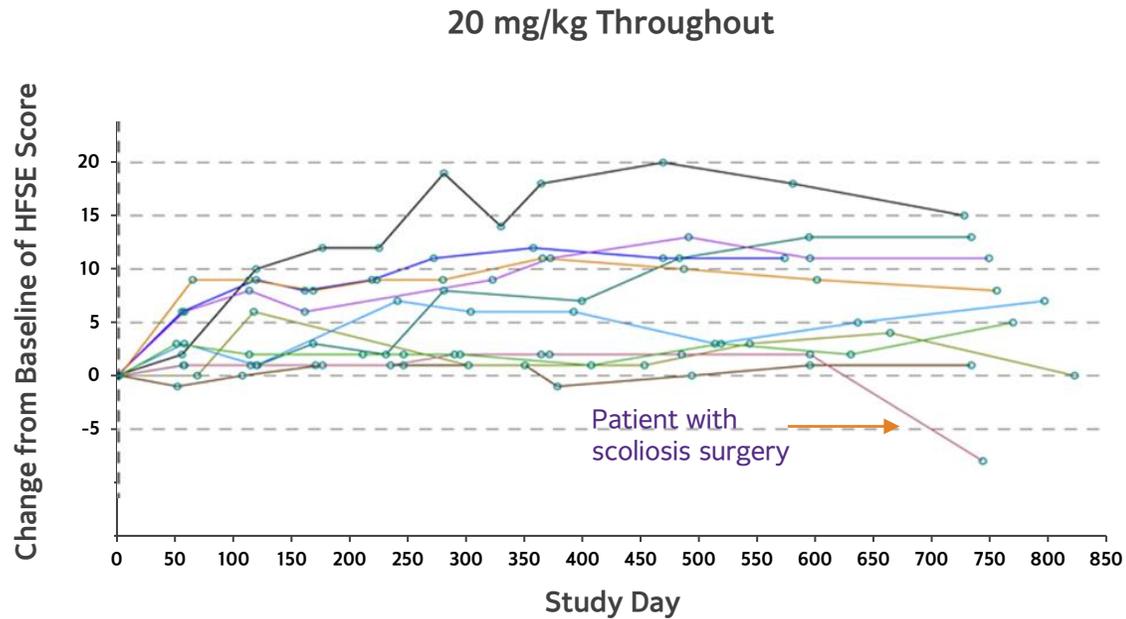


Observed Case Analysis is based upon data available for a given timepoint, and this analysis population includes patients treated with the lower dose 2 mg/kg and does not exclude any patients who missed apitegromab doses due to COVID-19 site access restrictions. Error bars represent standard error of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

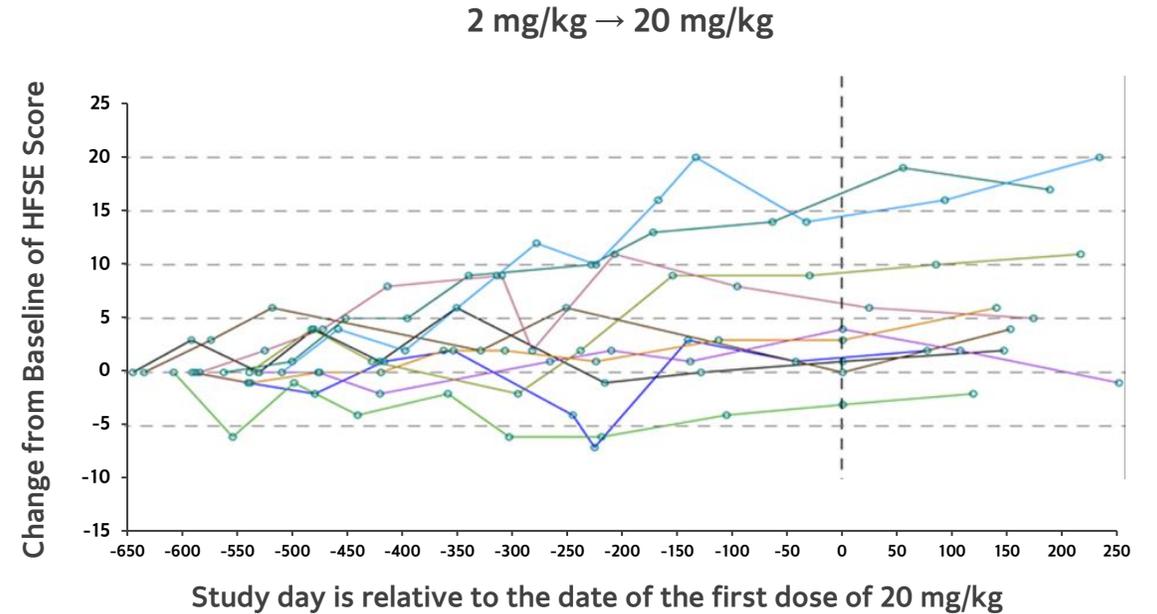
## Further Supported by Data from Low Dose to High Dose Switch in Non-Ambulatory Patients

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

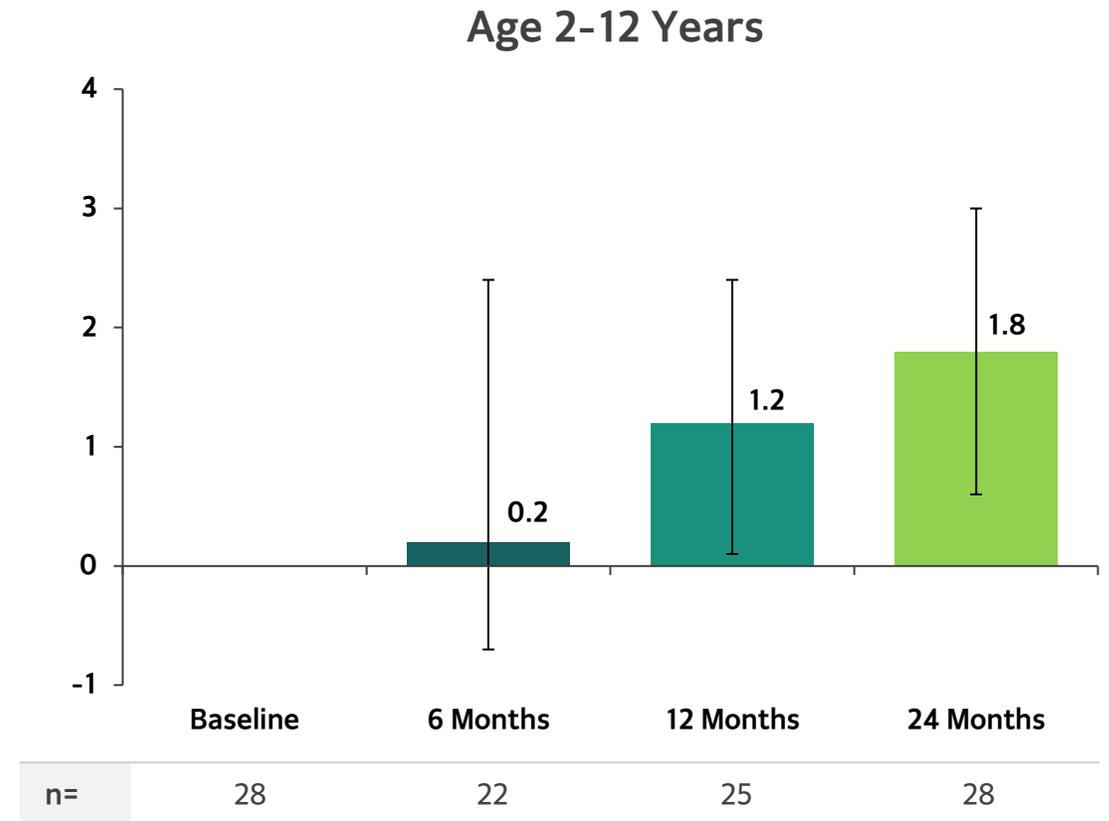
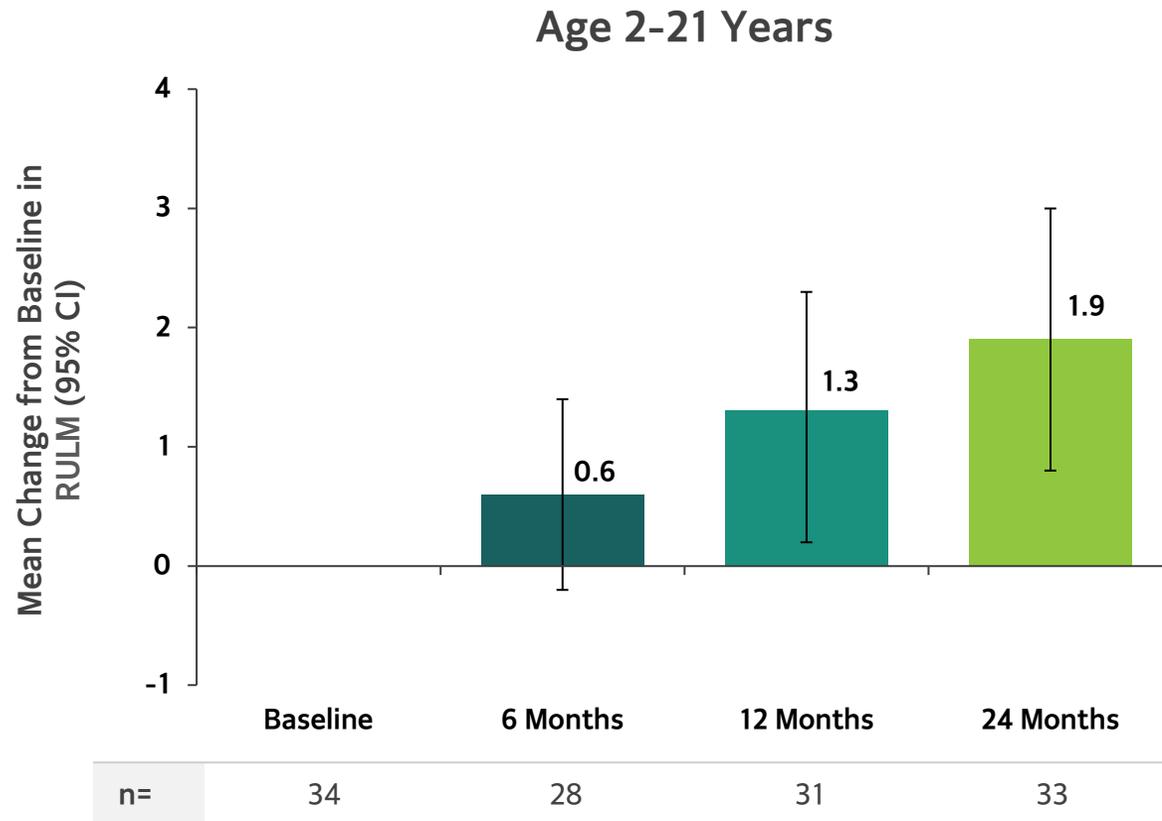
Continued improvement after switch

Switch to 20 mg/kg

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.

# Continued Increase in RULM Observed at 24 Months of Apitegromab

## Pooled Non-Ambulatory Patients

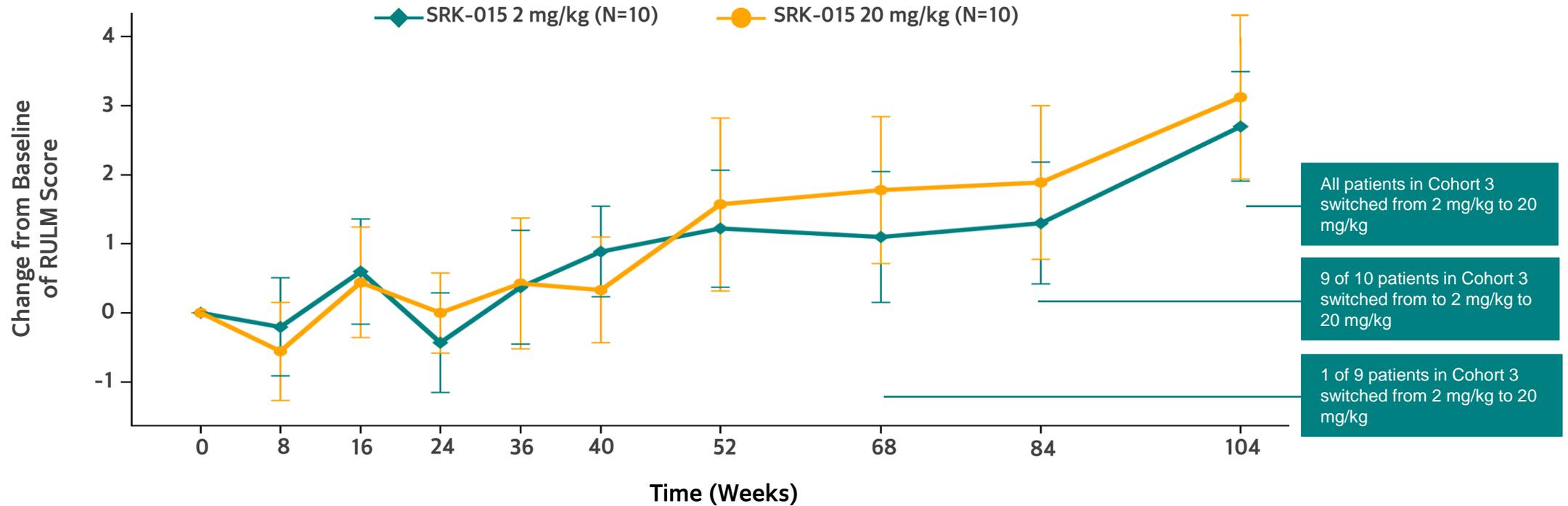


Observed Case Analysis is based upon data available for a given timepoint, and this analysis population includes patients treated with the lower dose 2 mg/kg and does not exclude any patients who missed apitegromab doses due to COVID-19 site access restrictions. Data on File. Scholar Rock, Inc. Cambridge,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



### 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.

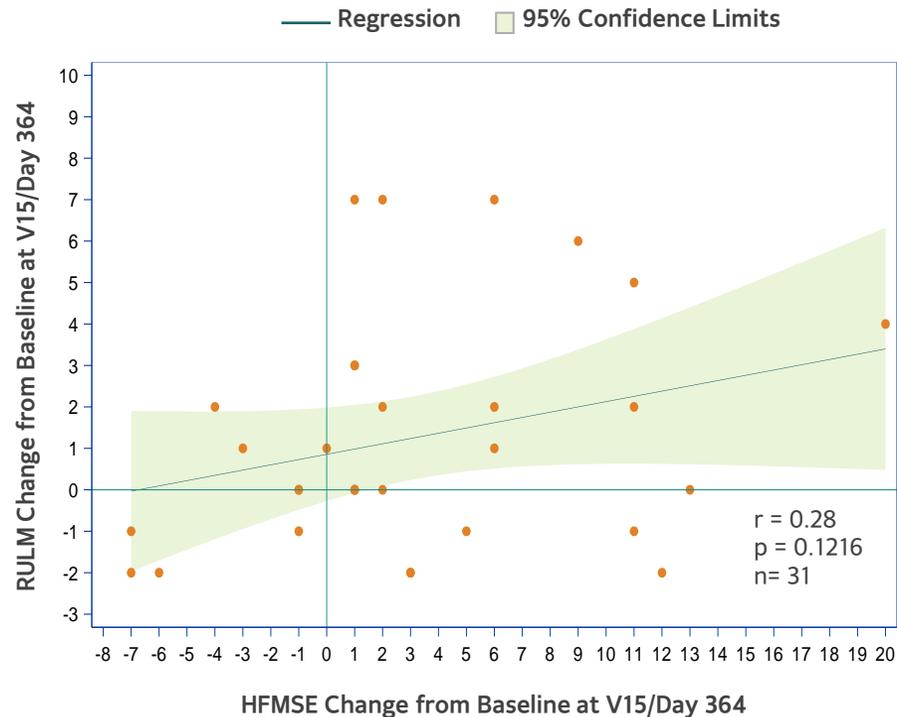
# Correlation of HFMSE to RULM Increased Over 24 Months

## Pooled Non-Ambulatory Patients

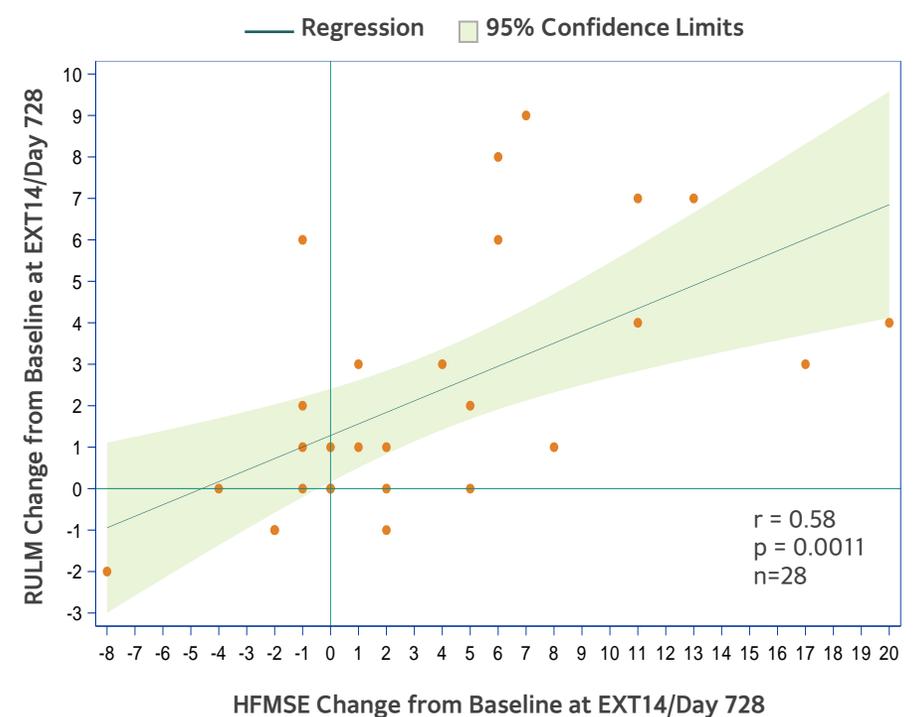
“The observation that the majority of patients in this analysis experienced gains in both the HFMSE and RULM over 24 months further supports the therapeutic potential of apitegromab.”

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

RULM and HFMSE  
Change from Baseline at 12 Months  
Observed Cases



RULM and HFMSE  
Change from Baseline at 24 Months  
Observed Cases



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<sup>1</sup>

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

**2 PROMIS (Fatigue):**  
Measure of Patient Fatigue  
PRO measurement tool<sup>4</sup>

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

**3 ESBBT (Fatigability):**  
Measure of how fast a patient fatigues  
Muscle endurance measurement tool<sup>6</sup>

- 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)<sup>6</sup>
- Patients are asked to move blocks individually from one box to another in one minute, with **higher numbers of blocks suggesting higher muscle endurance**<sup>6</sup>
- The endurance shuttle tests have been validated for use in patients with SMA<sup>7</sup>

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.

# Non-Ambulatory Patients Showed Continuous Improvements in ADL and Fatigue Measures Over 24 Months of Apitegromab Treatment<sup>1,2</sup>

## Tertiary Endpoints: Improvements in ADL and Fatigue

✓ Improvement



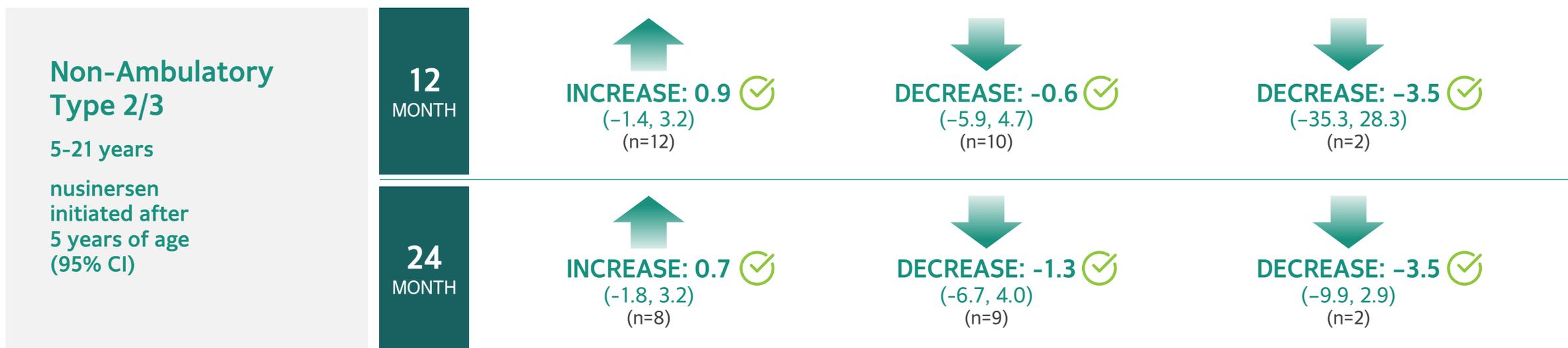
**Apitegromab treatment in non-ambulatory type 2 resulted in patients improving in patient-reported outcomes related to self-sufficiency and fatigue**

ADL, activities of daily living; PEDI-CAT, the Pediatric Evaluation of Disability Inventory computer adaptive test; PROMIS, Patient-Reported Outcome Measurement Information System. 1. 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; 2. 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. 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 Patients Showed Stabilization or Improvements in ADL and Fatigue Measures over 24 Months of Apitegromab Treatment<sup>1,2</sup>

## Tertiary Endpoints: Improvements in ADL and Fatigue

✓ Improvement



**Apitegromab treatment in non-ambulatory types 2 and 3 resulted in patients improving in patient-reported outcomes related to self-sufficiency and fatigue**

ADL, activities of daily living; PEDI-CAT, the Pediatric Evaluation of Disability Inventory computer adaptive test; PROMIS, Patient-Reported Outcome Measurement Information System. 1. 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; 2. 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. 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 Patients Continued to Improve in Fatigability and Endurance Measures, Which May be Complementary to Upper Limb Function Improvements over 24 Months<sup>1</sup>

## Tertiary Endpoints: Improvements in Fatigability

✓ Improvement

### ENDURANCE

Mean change in  
ESBBT activities



- The ESBBT is the first validated and sensitive fatigability test for proximal arm function in SMA and may be complementary to outcome measures that focus on arm motor function such as the RULM, by adding the dimension of endurance<sup>2</sup>
- Trends of improvements with ESBBT correlate with RULM over 24 months

**Apitegromab treatment in non-ambulatory types 2 and 3 (cohort 2) resulted in patients improving in QoL assessments related to self-sufficiency and endurance**

ESBBT, endurance shuttle box and block test; SMA, spinal muscular atrophy; SMN, survival motor neuron; QoL, quality of life. 1. Darras BT, et al. Apitegromab in SMA (TOPAZ trial): Efficacy, Safety, and PK/PD Assessments From 24- Month Data; Podium Presentation presented at SMAEU; October 2022. 2. Mazzone ES, et al. RULM for SMA: development of a new module. Muscle Nerve. 2017;55(6):869-74. Baseline is defined as the last measurement prior to the first dose of study drug. Subject visits after an intercurrent event of 3 consecutive missed doses during the Extension A period, or after taking nusinersen for SMN up-regulator therapy if in Cohort1, are excluded from the Efficacy Eligible Set. 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.

# Therapeutic Potential of Apitegromab Observed in the Ambulatory Type 3 SMA Cohort at 24 Months<sup>1-4</sup>

## Ambulatory Patients (Revised Hammersmith Scale; RHS)

24-Month Analysis	COHORT 1		
	20 mg/kg pooled <sup>1</sup> (n=21)	20 mg/kg Monotherapy <sup>4</sup> (n=11)	20 mg/kg + nusinersen <sup>2,3</sup> (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 $\geq$ 1-pt increase, n (%)	9/21 (42.9%)	5/11 (45.5%)	4/10 (40%)
Patients achieving $\geq$ 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.

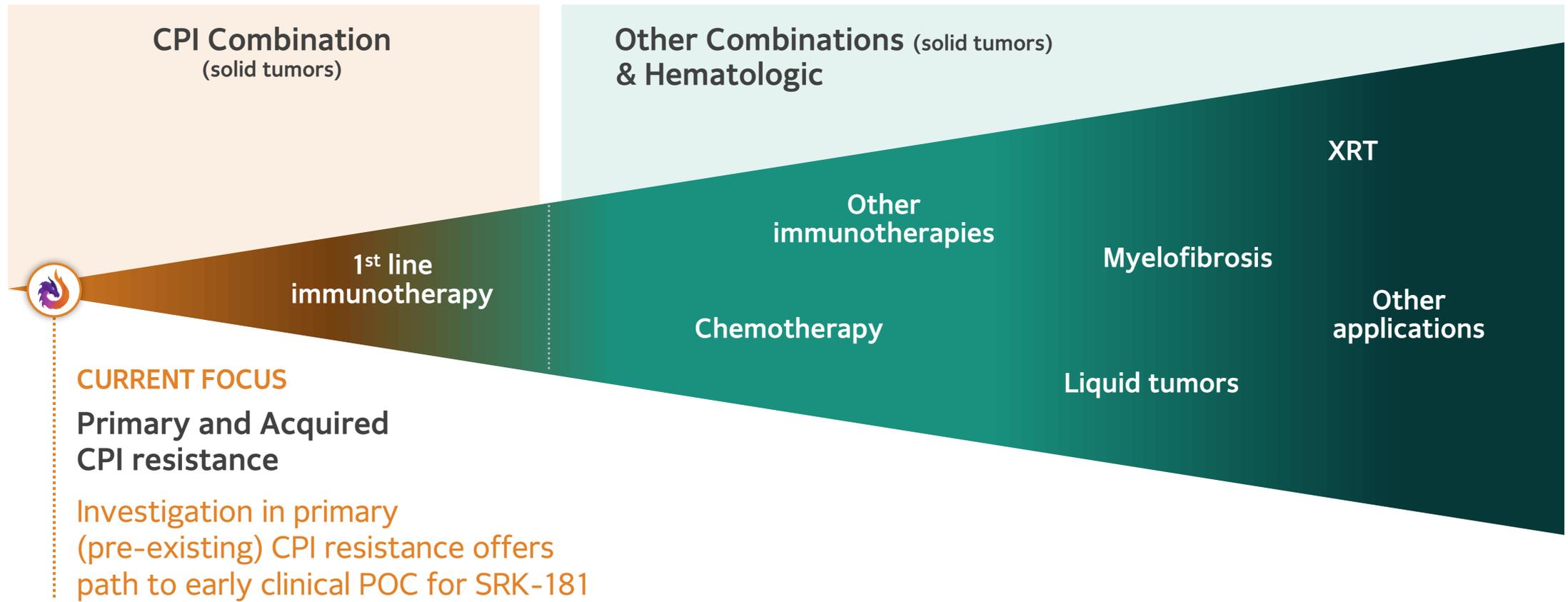
# Overall Safety and Tolerability Profile Over 24 Months of Treatment: Serious TEAEs

- 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.

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

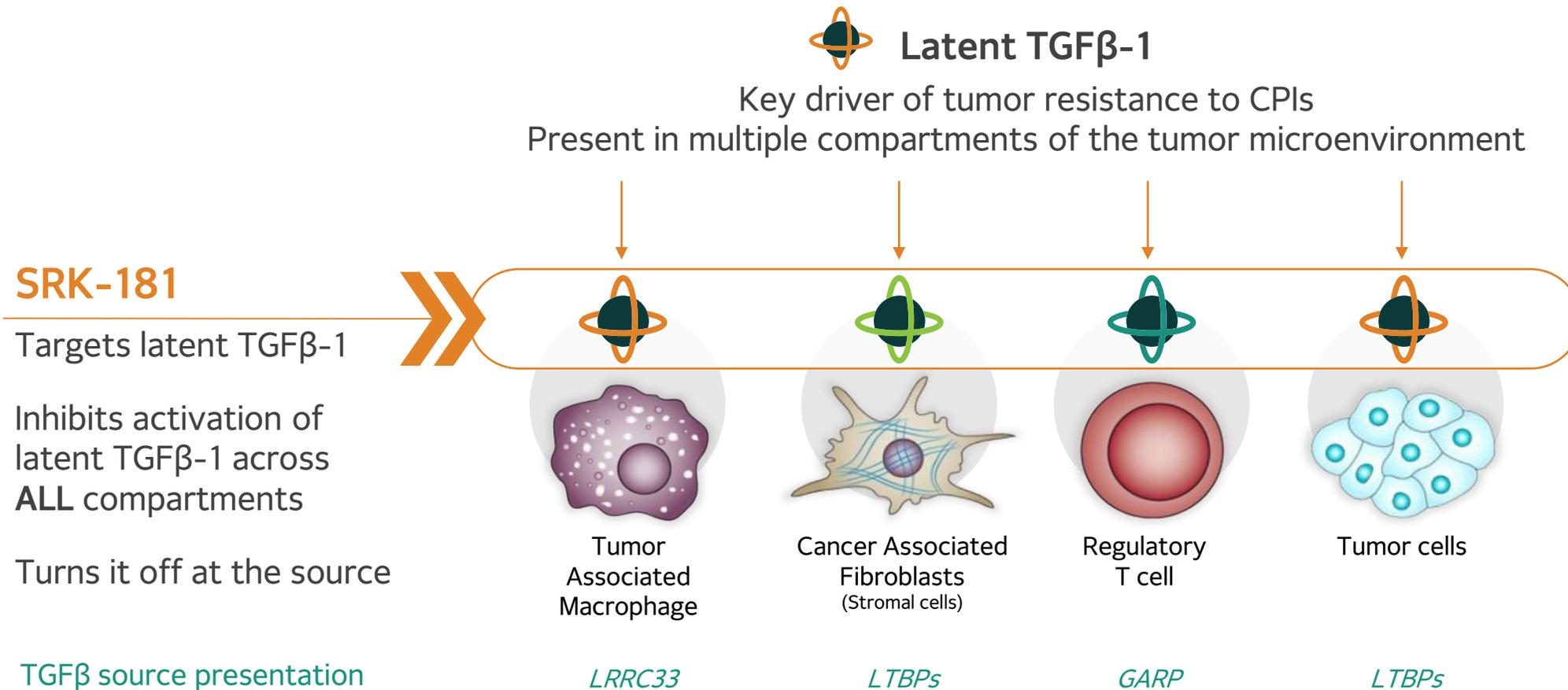
- Four patients presented with non-serious Grade 3 events, all assessed by the respective trial investigator as unrelated to apitegromab:
  - One patient treated with 20 mg/kg dose (Cohort 1) presented with post lumbar puncture syndrome. Event resolved without sequelae.
  - One patient treated with 20 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.

# 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



 TGFβ Latent growth factor

LRRC33: leucine-rich-repeat-containing protein family member 33 | LTBP5: latent transforming growth factor β binding proteins | GARP: glycoprotein A repetitions predominant

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

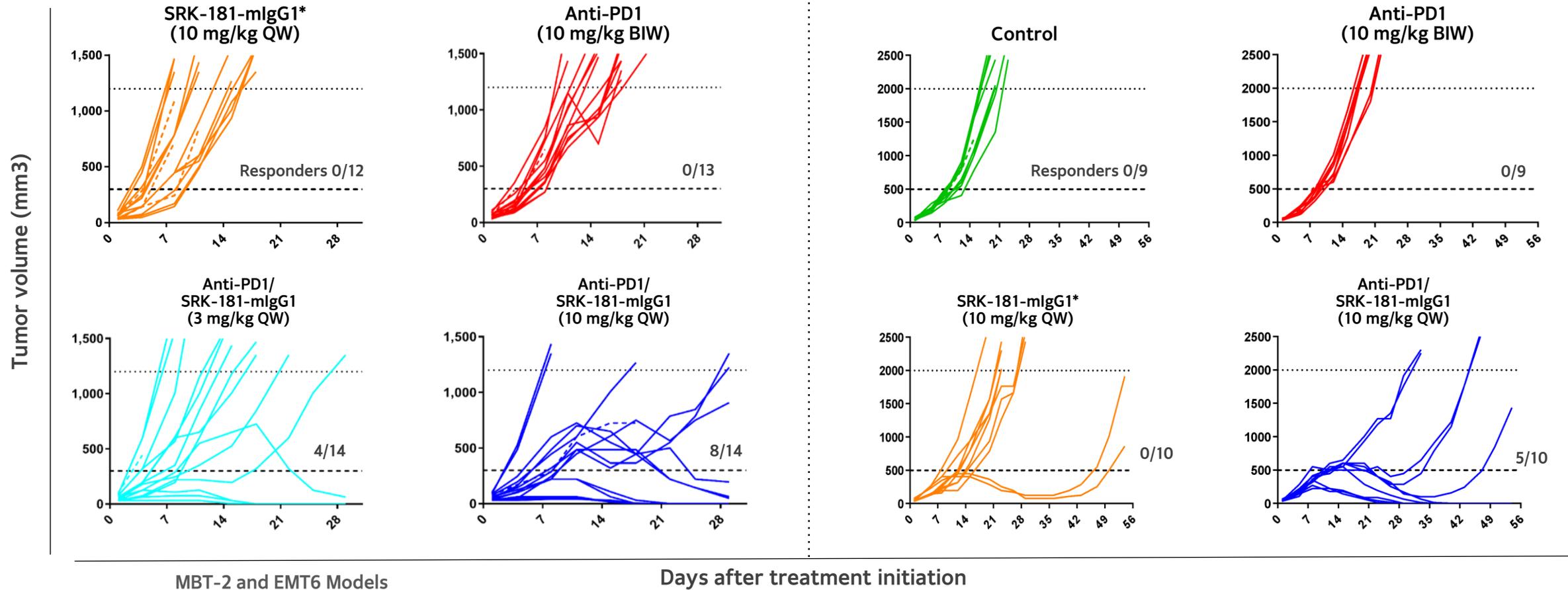
	SRK-181*	Bifunctional TGFβ/CPI	ALK5 Inhibitor	Nonselective TGFβ antibody
Selectivity for TGFβ-1: potential for wider therapeutic window and improved safety	✓	✗	✗	✗
Ability to combine with any anti-PD-(L)1	✓	✗	✓	✓
Ability to optimize dosing of each component of combination therapy	✓	✗	✓	✓
Activity spatially 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

## Bladder Cancer

## Breast Cancer (TGFβ-1/3 co-expressing)

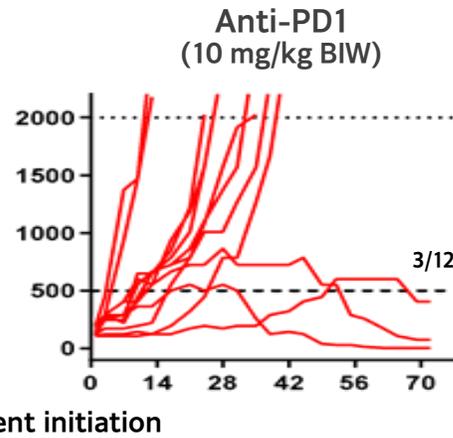
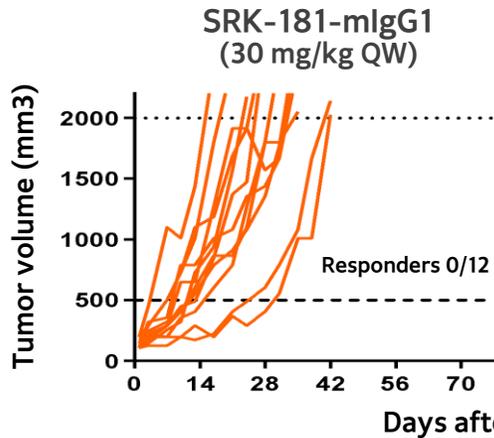


Preclinical data published in Science Translational Medicine. Martin CJ, et al. Sci Transl Med. 2020 Mar 25;12(536):eaay8456.  
<https://scholarrock.com/platform/publications/>.  
 \*SRK-181-mIgG1 is the murine version of SRK-181; responder defined as tumor size <25% endpoint volume at study end.

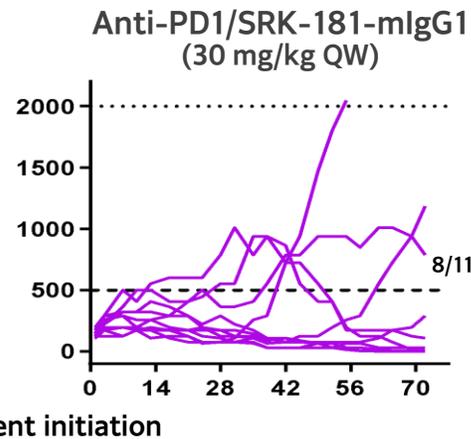
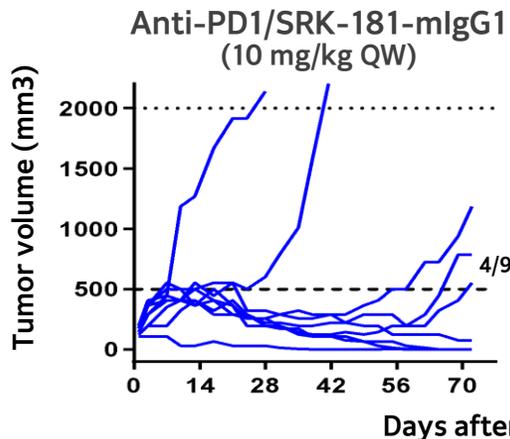
# SRK-181-mIgG1 Combination Treatment Led to Melanoma Tumor Regression and Survival Benefit

Monotherapy

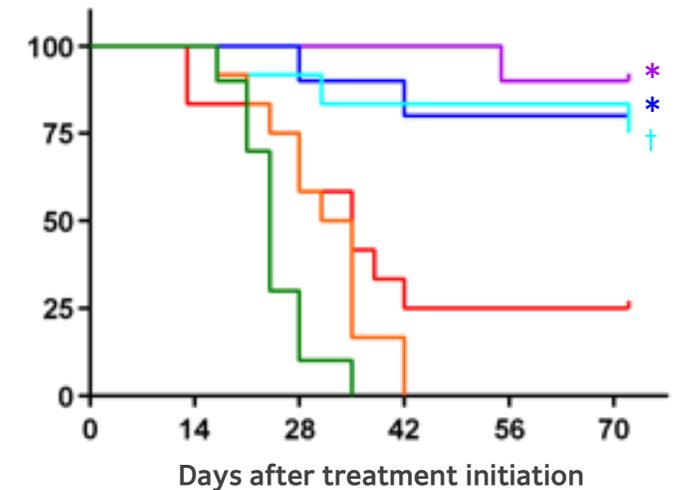
## Tumor Regression



Combination Therapy  
Led to tumor regression and survival benefit



## Survival Benefit



- Anti-PD1 + SRK-181-mIgG1 (30 mg/Kg/wk)
- Anti-PD1 + SRK-181-mIgG1 (3 mg/Kg/wk)
- Anti-PD1 + SRK-181-mIgG1 (10 mg/Kg/wk)
- Anti-PD1 (10 mg/Kg/2xwk)
- SRK-181-mIgG1 (30 mg/Kg/wk)
- Control

\* $P < 0.01$ .

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

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

## Toxicology:



## Microscopic Observations in Heart

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

	CONTROL Vehicle iv, qwk x 4	LY2109761 300 mg/kg po, qd x 8	PanTGFβAb 30 mg/kg iv, 1 dose
Valvulopathy		Minimal	Slight
Atrium—Mixed cell infiltrate		Minimal	Slight
Myocardium—Degeneration/necrosis		Slight	Slight
Myocardium—Hemorrhage			Minimal
Myocardium—Mixed cell infiltrate, base			Slight
Coronary artery—Necrosis with inflammation		Moderate	
Cardiomyocyte—Necrosis/inflammatory cell infiltrate			



## Selective TGFβ-1

Toxicity: Minimal

	SRK-181		
	10 mg/kg iv, qwk x 4	30 mg/kg iv, qwk x 4	100 mg/kg iv, qwk x 4
Valvulopathy			
Atrium—Mixed cell infiltrate			
Myocardium—Degeneration/necrosis			
Myocardium—Hemorrhage	Not test article related		
Myocardium—Mixed cell infiltrate, base			
Coronary artery—Necrosis with inflammation			
Cardiomyocyte—Necrosis/inflammatory cell infiltrate	Not test article related		

\* 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

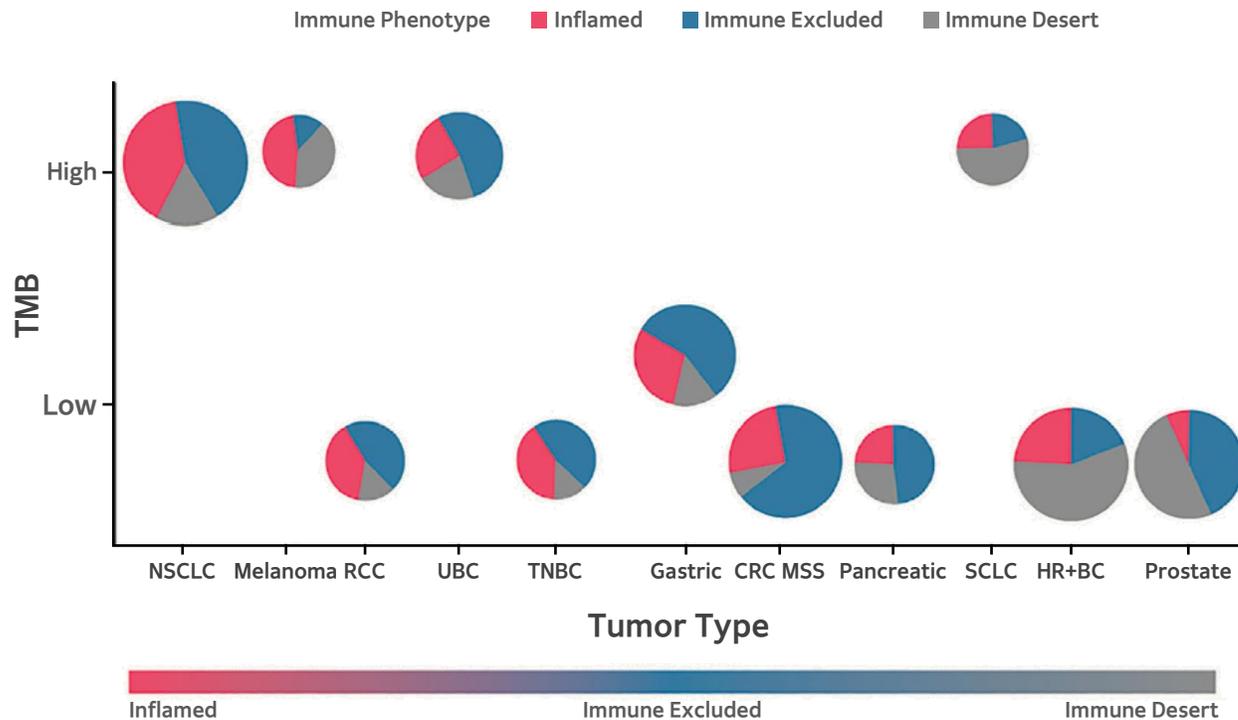
NOAEL for SRK-181: 300 mg/kg (highest dose evaluated)

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

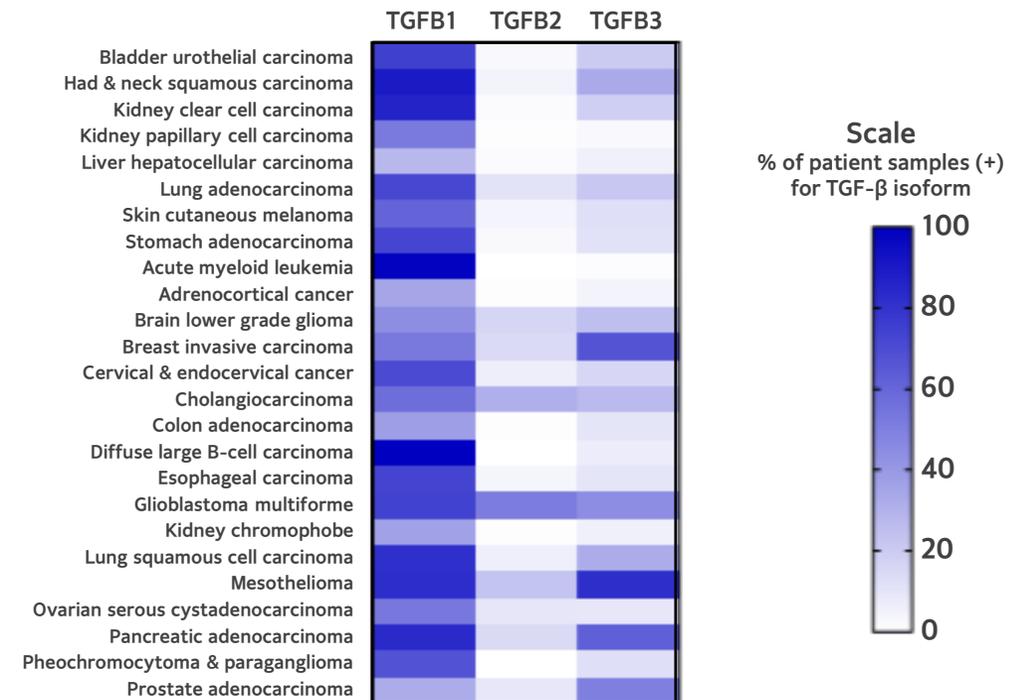
\*Source: Anderton MJ, et al. Induction of heart valve lesions by small-molecule ALK5 inhibitors. *Toxicol Pathol*. 2011;39: 916-924.; and Stauber AJ, et al. Nonclinical safety evaluation of a transforming growth factor β Receptor I kinase inhibitor in Fischer 344 rats and beagle dogs. *J Clin Pract*.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

<sup>†</sup>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

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- 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)
- 



### TGF $\beta$ -1 pathway evaluation Assessment of signaling pathway

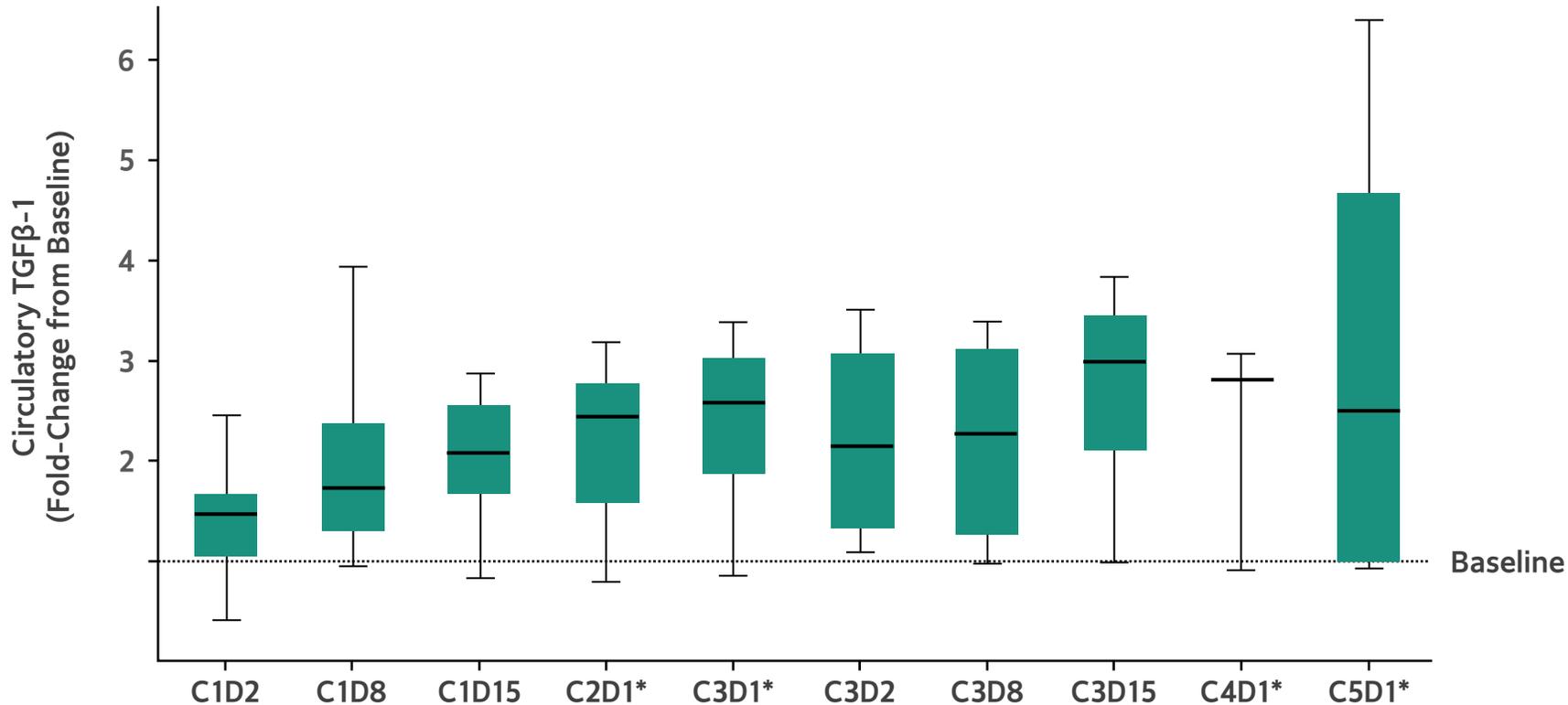
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- Show evidence of the SRK-181 target engagement
    - e.g. circulating TGF $\beta$ -1 levels
  - TGF $\beta$  pathway modulation:
    - e.g. Histochemical analysis of pSMAD
    - e.g. RNA-based TGF $\beta$  gene signatures and pathway analyses
  - 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

Median Circulatory TGFβ-1 Increased Post-treatment with SRK-181 (Q3W, All Patients)



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.

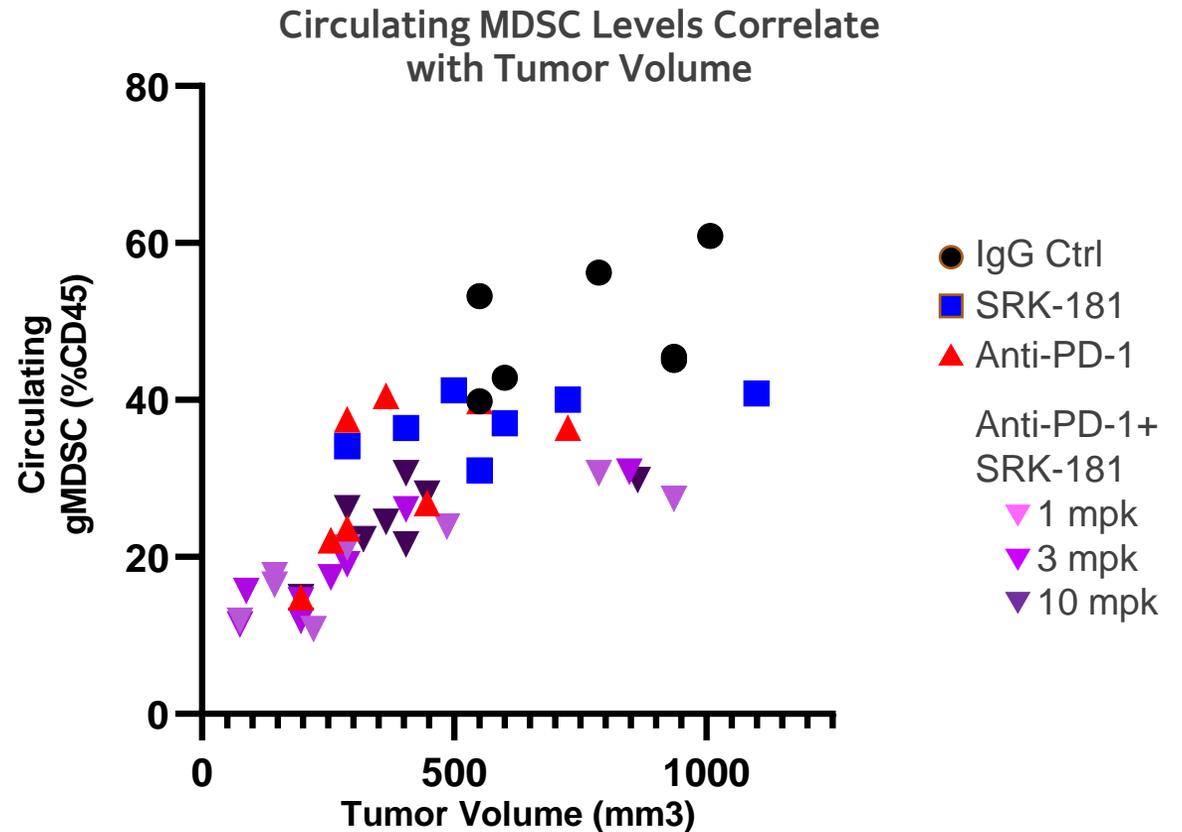
# Preclinical Data Provide Scientific Rationale to Evaluate Peripheral Samples for Evidence of SRK-181 Activity

## 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