UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event Reported): June 30, 2023

Scholar Rock Holding Corporation

(Exact Name of Registrant as Specified in Charter)

Delaware	**001-38501**	**82-3750435**
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

301 Binney Street, 3rd Floor, Cambridge, MA 02142
(Address of Principal Executive Offices) (Zip Code)

(857) 259-3860
(Registrant's telephone number, including area code)

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.001 per share	SRRK	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR §230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR §240.12b-2). Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 7.01. Regulation FD Disclosure.

On June 30, 2023, Scholar Rock Holding Corporation (the "Company") issued a press release announcing 36-month topline results from its TOPAZ Phase 2 clinical trial for apitegromab for patients with nonambulatory spinal muscular atrophy ("SMA"). A copy of the press release is attached hereto as Exhibit 99.1.

On June 30, 2023, Thomas O. Crawford, M.D., Professor of Neurology and Pediatrics at Johns Hopkins University and the lead principal investigator of the Company's TOPAZ trial, presented at two podium presentations at the Cure SMA Research & Clinical Care Meeting ("Cure SMA") and presented new data from the Company's Phase 2 TOPAZ trial extension period evaluating patient outcomes after 36 months of treatment with apitegromab. A copy of the podium presentations at Cure SMA may be accessed by visiting the Publications & Posters section of the Company's website at https://scholarrock.com/our-science/publications-posters/.

On July 12, 2023, the Company will host a conference call and webcast at 9:00 am ET to discuss the 36-month data from the TOPAZ Phase 2 clinical trial and apitegromab's potential to advance the standard of care in SMA. A copy of the presentation slides to be used by the Company during the conference call and webcast is attached hereto as Exhibit 99.2. A live webcast of the conference call may be accessed by visiting the Investors & Media section of the Company's website at http://investors.scholarrock.com.

The information in this report furnished pursuant to Item 7.01 and Exhibit 99.1 shall not be deemed "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section nor shall such information be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, regardless of the general incorporation language of such filing, except as shall be expressly set forth by specific reference in such filing. It may only be incorporated by reference in another filing under the Exchange Act or the Securities Act of 1933, as amended, if such subsequent filing specifically references the information furnished pursuant to Item 7.01 and Exhibit 99.1 of this report.

Item 8.01. Other Events.

TOPAZ Phase 2 Clinical Trial Update

On June 30, 2023, the Company announced new data from the Phase 2 TOPAZ trial extension period evaluating patient outcomes at 36-months of treatment with apitegromab. These data showed that continued treatment with apitegromab over the extended treatment period was associated with substantial and sustained improvement in motor function, as well as improvements in patient-reported outcome measures in patients with nonambulatory Types 2 and 3 SMA receiving survival motor neuron (SMN)-targeted therapy.

Nonambulatory patients (ages 2-21) experienced substantial and sustained gains in Hammersmith Functional Motor Scale-Expanded (HFMSE) and Revised Upper Limb Module (RULM) scores over the 36-month extended treatment period from baseline:

	12-Month Data	**24-Month Data**	**36-Month Data**
Mean Change from Baseline in HFMSE (95% Confidence Interval)	**3.6 points** (1.2, 6.0) N=32	**4.2 points** (1.9, 6.6) N=29	**4.0 points** (1.0, 6.9) N=28
Mean Change from Baseline in RULM (95% Confidence Interval)	**1.3 points** (0.2, 2.3) N=31	**2.3 points** (1.2, 3.3) N=31	**2.4 points** (1.1, 3.7) N=27

For the 36-month data, an observed case analysis was conducted, which pooled data for all nonambulatory patients (including those patients on 20 mg/kg of apitegromab for the full duration of the trial, and those who switched from 2 mg/kg to 20 mg/kg at various time intervals in year 2) and was based upon the available data. These analyses exclude data for patients post scoliosis surgery.

Nonambulatory patients (ages 2-21) had improvements in PEDI-CAT (measure of activities of daily living) and PROMIS-Fatigue (a patient-reported outcome tool measuring fatigue) that were consistent and sustained at 36 months. The mean change in PEDI-CAT daily activity domain from baseline at 36 months was 2.2 (95% CI: –0.1, 4.5; N=17), indicating an improvement in the ability to perform daily activities. The mean change in PROMIS-Fatigue from baseline at 36 months was –4.6 (95% CI: –8.7, –0.5; N=14), indicating a decline in fatigue. These improvements in PEDI-CAT and PROMIS-Fatigue were generally consistent with improvements in motor function across the 36 months of the study period.

Treatment-emergent adverse events (TEAEs) at 36 months were consistent with previous reports at 12 and 24 months, with no new findings after an aggregate of 198 patient-years of exposure. TEAEs were mostly mild to moderate in severity, and generally consistent with the underlying patient population and background therapy. The five most common TEAEs were headache, pyrexia, COVID-19, nasopharyngitis, and upper respiratory tract infection. No deaths or suspected unexpected serious adverse reactions or hypersensitivity reactions were observed with apitegromab at 36 months. A total of 21 serious TEAEs were reported over the 36-month treatment period. No patients displayed positive titers for apitegromab antibodies (ADA).

More than 90 percent of nonambulatory patients remained on treatment in the extension study.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	**Description**
99.1	Press Release issued by the Company on June 30, 2023.
99.2	Presentation Slide Deck
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Scholar Rock Holding Corporation

Date: June 30, 2023

By: /s/ Junlin Ho
Junlin Ho
General Counsel and Corporate Secretary

Exhibit 99.1

New 36-Month Apitegromab Extension Data Reinforce Long-Term Substantial and Sustained Improvement of Motor Function in Phase 2 TOPAZ Trial Patients with Nonambulatory Spinal Muscular Atrophy

- Improvements in patient-reported outcomes consistent with gains in motor function scores

- Safety profile at 36 months consistent with previous reports with no new safety findings; more than 90 percent of nonambulatory patients remained on study

- Enrollment progressing in pivotal Phase 3 SAPPHIRE registrational trial, anticipated completion in Q3 2023

- Scholar Rock to host virtual investor event on July 12 at 9:00 AM EST to discuss the current SMA treatment landscape and apitegromab's potential to advance the standard of care

CAMBRIDGE, Mass.--(BUSINESS WIRE)--June 29, 2023--Scholar Rock (NASDAQ: SRRK), a Phase 3, clinical-stage biopharmaceutical company focused on the treatment of serious diseases in which protein growth factors play a fundamental role, today announced new data from the Phase 2 TOPAZ trial extension period evaluating patient outcomes at 36 months of treatment with apitegromab. These data showed that continued treatment with apitegromab over the extended treatment period was associated with substantial and sustained improvement in motor function, as well as improvements in patient-reported outcome measures in patients with nonambulatory Types 2 and 3 spinal muscular atrophy (SMA) receiving survival motor neuron (SMN)-targeted therapy. Detailed results were presented today by Thomas Crawford, M.D., of Johns Hopkins Medicine, and the lead principal investigator of the TOPAZ trial, during two podium presentations at the Cure SMA Research & Clinical Care Meeting in Orlando, Florida.

"These promising long-term data highlight the therapeutic potential of muscle-targeted therapies, such as apitegromab, to help those with SMA address persistent weakness," said Dr. Crawford. "While SMN-targeted therapies play an important role in preventing further loss of motor neurons, many people still experience persistent or progressive symptoms due to preexisting motor neuron degeneration. Incorporating a muscle-targeted therapy with apitegromab's clinical profile into the treatment paradigm could allow patients to sustain or potentially achieve new gains in motor functioning."

"We are excited to share these new Phase 2 data that support apitegromab's long-term durability of effect and consistent tolerability and safety profile. The results further strengthen our confidence in apitegromab's therapeutic potential for patients with SMA, as well as validate Scholar Rock's unique approach to selectively inhibiting the pro and latent forms of myostatin," said Jay Backstrom, M.D., MPH, President and Chief Executive Officer of Scholar Rock. "In addition to the sustained benefit observed with consistent HFMSE scores, we saw continued improvement in RULM scores, and reductions in fatigue as reported by patients—all of which can be important factors in performing activities of daily living. We remain committed to advancing the standard of care for people with SMA, and we look forward to sharing updates on our pivotal Phase 3 SAPPHIRE trial, which we anticipate will complete enrollment in the third quarter of 2023."

Substantial and Sustained Gains in Motor Function Observed Over the Extended Treatment Period: Nonambulatory patients (ages 2-21) experienced substantial and sustained gains in Hammersmith Functional Motor Scale-Expanded (HFMSE) and Revised Upper Limb Module (RULM) scores over the 36-month extended treatment period from baseline:

	12-Month Data	24-Month Data	36-Month Data
Mean Change from Baseline in HFMSE (95% Confidence Interval)	**3.6 points** (1.2, 6.0) N=32	**4.2 points** (1.9, 6.6) N=29	**4.0 points** (1.0, 6.9) N=28
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For the 36-month data, an observed case analysis was conducted, which pooled data for all nonambulatory patients (including those patients on 20 mg/kg of apitegromab for the full duration of the trial, and those who switched from 2 mg/kg to 20 mg/kg at various time intervals in year 2) and was based upon the available data. These analyses exclude data for patients post scoliosis surgery.

Improvement in Patient-Reported Outcomes Consistent with Improvements in Motor Function: Nonambulatory patients (ages 2-21) had improvements in PEDI-CAT (measure of activities of daily living) and PROMIS-Fatigue (a patient-reported outcome tool measuring fatigue) that were consistent and sustained at 36 months. The mean change in PEDI-CAT daily activity domain from baseline at 36 months was 2.2 (95% CI: –0.1, 4.5; N=17), indicating an improvement in the ability to perform daily activities. The mean change in PROMIS-Fatigue from baseline at 36 months was –4.6 (95% CI: –8.7, –0.5; N=14), indicating a decline in fatigue. These improvements in PEDI-CAT and PROMIS-Fatigue were generally consistent with improvements in motor function across the 36 months of the study period.

Consistent Safety Data: Treatment-emergent adverse events (TEAEs) at 36 months were consistent with previous reports at 12 and 24 months, with no new findings after an aggregate of 198 patient-years of exposure. TEAEs were mostly mild-to-moderate in severity, and generally consistent with the underlying patient population and background therapy. The five most common TEAEs were headache, pyrexia, COVID-19, nasopharyngitis, and upper respiratory tract infection. No deaths or suspected unexpected serious adverse reactions or hypersensitivity reactions were observed with apitegromab at 36 months. A total of 21 serious TEAEs were reported over the 36-month treatment period. No patients displayed positive titers for apitegromab antibodies (ADA).

More than 90 percent of nonambulatory patients remained on treatment in the extension study.

Details of the podium presentations at SMA Research & Clinical Care Meeting are as follows:

Title: Effect of apitegromab on PEDI-CAT and PROMIS-Fatigue questionnaire at 36 months in patients with Type 2 and nonambulatory Type 3 spinal muscular atrophy
Presentation type: Oral presentation
Presenter: Thomas O. Crawford, M.D., Professor of Neurology and Pediatrics, Johns Hopkins University
Date and time: Friday, June 30, 2023, 10:40 AM EST
Location: Disney Swan and Dolphin Hotels, Orlando, FL

Title: Effect of apitegromab on motor function at 36 months in patients with Type 2 and nonambulatory Type 3 spinal muscular atrophy
Presentation type: Oral presentation
Presenter: Thomas O. Crawford, M.D., Professor of Neurology and Pediatrics, Johns Hopkins University
Date and time: Friday, June 30, 2023, 11:00 AM EST
Location: Disney Swan and Dolphin Hotels, Orlando, Florida
For conference information, visit https://www.researchandclinicalcaremeeting.com/

The presentations will be made available in the Publications & Posters section of Scholar Rock's website following the presentation.

Conference Call/Webcast:

Scholar Rock will host a virtual investor event on July 12 at 9:00 AM EST to discuss the current SMA treatment landscape and apitegromab's potential to advance the standard of care for patients with nonambulatory Types 2 and 3 SMA. Click here to register and listen to the webcast. A link to the webcast of this event is also available on the Investors & Media section of the Scholar Rock website at http://investors.scholarrock.com.

An archived replay of the webcast will be available on Scholar Rock's website at: https://scholarrock.com/ for approximately 90 days following the presentation.

About the Phase 2 TOPAZ Trial

The TOPAZ trial is an ongoing proof-of-concept, open-label Phase 2 trial evaluating the safety and efficacy of apitegromab in patients with Types 2 and 3 SMA. In the main treatment period, patients were dosed intravenously every four weeks as monotherapy or with nusinersen, an approved SMN-targeted therapy. The trial enrolled 58 patients in the U.S. and Europe. The primary efficacy endpoints were mean change from baseline in Revised Hammersmith Scale (RHS) score at 12 months for the ambulatory population (Cohort 1), and mean change from baseline in HFMSE score at 12 months for the nonambulatory population (Cohorts 2 and 3). The trial also includes multiple 12-month extension periods designed to evaluate longer-term patient outcomes.

About the Phase 3 SAPPHIRE Trial

SAPPHIRE is an ongoing randomized, double-blind, placebo-controlled, phase 3 clinical trial evaluating the safety and efficacy of apitegromab in nonambulatory patients with Types 2 and 3 SMA who are receiving SMN therapy (either nusinersen or risdiplam). Approximately 156 patients aged 2-12 years old are anticipated to be enrolled in the main efficacy population. These patients will be randomized 1:1:1 to receive for 12 months either apitegromab 10 mg/kg, apitegromab 20 mg/kg, or placebo by intravenous (IV) infusion every 4 weeks. An exploratory population of approximately 48 patients aged 13-21 years old will also separately be evaluated. These patients will be randomized 2:1 to receive either apitegromab 20 mg/kg or placebo. For more information about SAPPHIRE, visit www.clinicaltrials.gov.

About Apitegromab

Apitegromab is an investigational fully human monoclonal antibody inhibiting myostatin activation by selectively binding the pro- and latent forms of myostatin in the skeletal muscle. It is the first muscle-targeted treatment candidate to demonstrate clinical proof of concept in spinal muscular atrophy (SMA). Myostatin, a member of the TGFβ superfamily of growth factors, is expressed primarily by skeletal muscle cells, and the absence of its gene is associated with an increase in muscle mass and strength in multiple animal species, including humans. Scholar Rock believes that our highly selective targeting of pro- and latent forms of myostatin with apitegromab may lead to a clinically meaningful improvement in motor function in patients with SMA. The U.S. Food and Drug Administration (FDA) has granted Fast Track, Orphan Drug and Rare Pediatric Disease designations, and the European Medicines Agency (EMA) has granted Priority Medicines (PRIME) and Orphan Medicinal Product designations, to apitegromab for the treatment of SMA. The efficacy and safety of apitegromab have not been established and apitegromab has not been approved for any use by the FDA or any other regulatory agency.

About SMA

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease that afflicts an estimated 30,000 to 35,000 people in the United States and Europe. The disease is characterized by the loss of motor neurons, atrophy of the voluntary muscles of the limbs and trunk, and progressive muscle weakness. While there has been progress in the development of therapeutics that address the loss of motor neurons, there continues to be a high unmet need for therapies that directly address the progressive muscle weakness that leads to loss of motor function in SMA.

About Scholar Rock

Scholar Rock is a clinical-stage biopharmaceutical company focused on the discovery and development of innovative medicines for the treatment of serious diseases in which signaling by protein growth factors plays a fundamental role. Scholar Rock is creating a pipeline of novel product candidates with the potential to transform the lives of patients suffering from a wide range of serious diseases, including neuromuscular disorders, cancer, and fibrosis. Scholar Rock's approach to targeting the molecular mechanisms of growth factor activation enabled it to develop a proprietary platform for the discovery and development of monoclonal antibodies that locally and selectively target these signaling proteins at the cellular level. By developing product candidates that act in the disease microenvironment, the Company intends to avoid the historical challenges associated with inhibiting growth factors for therapeutic effect. Scholar Rock believes its focus on biologically validated growth factors may facilitate a more efficient development path. For more information, please visit www.ScholarRock.com or follow Scholar Rock on Twitter (@ScholarRock) and LinkedIn (https://www.linkedin.com/company/scholar-rock/).

Availability of Other Information About Scholar Rock

Investors and others should note that we communicate with our investors and the public using our company website www.scholarrock.com, including, but not limited to, company disclosures, investor presentations and FAQs, Securities and Exchange Commission filings, press releases, public conference call transcripts and webcast transcripts, as well as on Twitter and LinkedIn. The information that we post on our website or on Twitter or LinkedIn could be deemed to be material information. As a result, we encourage investors, the media and others interested to review the information that we post there on a regular basis. The contents of our website or social media shall not be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended.

Scholar Rock® is a registered trademark of Scholar Rock, Inc.

Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding Scholar Rock's future expectations, plans and prospects, including without limitation, Scholar Rock's expectations regarding its growth, strategy, progress and timing of its clinical trials for apitegromab, and other product candidates and indication selection and development timing, 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," "might," "could," "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. 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 clinical trial of apitegromab, and are not predictive of, may be inconsistent with, or more favorable than, data generated from future clinical trials of the same product candidates, including, without limitation, the Phase 3 clinical trial of apitegromab in SMA , 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, 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 public health pandemics 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 March 31, 2023, 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.

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Deep Insights Advancing Impactful Medicines

Company Overview | June 2023

ScholarRock™

Forward-Looking Statements

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, 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 March 31, 2023, as well as discussions of potential risks, uncertainties, and other important factors in Scholar Rock's subsequent filings with the Securities and Exchange Commission. Any forward-looking statements represent Scholar Rock's views only as of today and should not be relied upon as representing its views as of any subsequent date. All information in this press release is as of the date of the release, and Scholar Rock undertakes no duty to update this information unless required by law.

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

ScholarRock

Scholar Rock:

Transforming Patient Lives, Addressing High Unmet Medical Need

Revolutionary Platform

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

Neuromuscular and Beyond

- Rich preclinical pipeline focused on high unmet patient needs
- Phase 3 SAPPHIRE study underway, enrollment completion expected in Q3 2023; data readout expected in 2024
- Phase 1 proof-of-concept DRAGON study underway in immuno-oncology

Positioned for Success

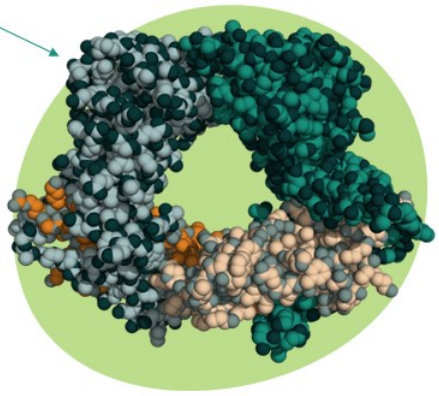
- Compelling proof-of-concept TOPAZ data informed Phase 3 SAPPHIRE study design
- Seasoned leadership team with track record of clinical and commercial success
- Anticipated cash runway into 2025

Strategic Optionality

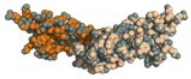
- Commercial planning underway for apitegromab (SMA) in US and Europe
- Broad platform, including promising early-stage assets, provides opportunities to advance alone or in partnership

Revolutionary Approach to Regulating TGFβ Superfamily Implicated in Devastating Diseases

Scholar Rock's Target
Latent Growth Factor



Traditional Target
"mature" growth factor



TGFβ Superfamily: Highly Sought-After Targets

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

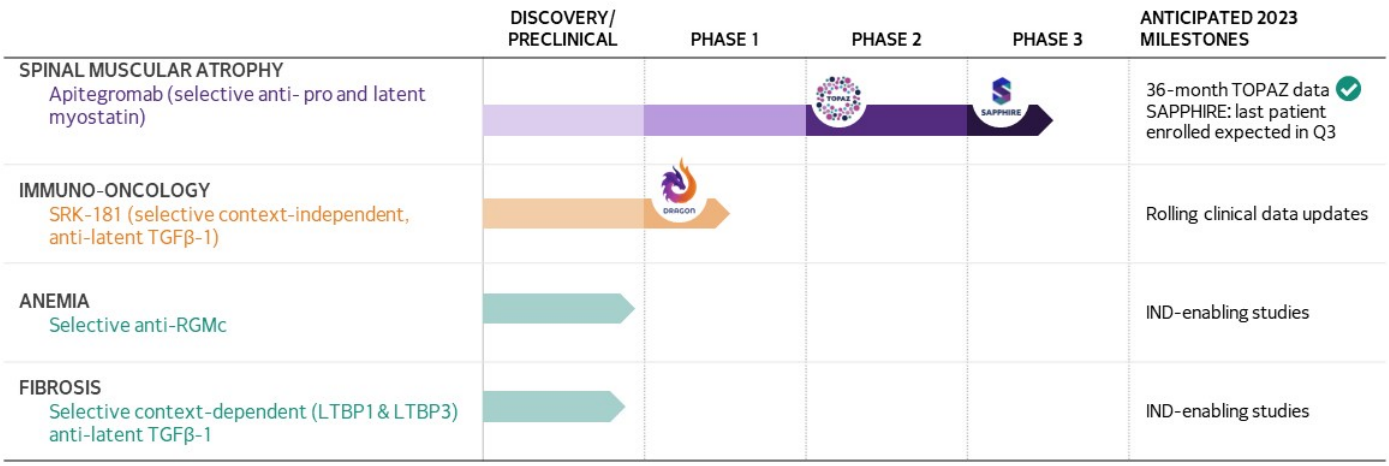
Dysregulation plays a role in devastating diseases that have a high unmet need, including:

- 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 or its receptors, which are difficult to differentiate and lead to unintended negative effects

Robust Pipeline of Novel Product Candidates



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

LTBP3=latent transforming growth factor beta binding protein 3; LTBP1=Latent Transforming Growth Factor Beta Binding Protein 1; RGM=Repulsive guidance molecule; TGFβ-1 =Transforming Growth Factor Beta-1

Leadership Team: Experienced in Drug Development and Commercialization

Jay Backstrom, MD, MPH
President & CEO

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

ACCELERON PHARMA · Celgene

Ted Myles, MBA
Chief Operating Officer & CFO

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

amag · OCATA THERAPEUTICS

Jing Marantz, MD, PhD
Chief Medical Officer

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

ACCELERON PHARMA · Alnylam · ALEXION

Tracey Sacco
Chief Commercial Officer

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

ACCELERON PHARMA · SANOFI

Mo Qatanani, PhD
SVP, Research

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

Dyne · ALEXION

Caryn Parlavecchio
Chief Human Resources Officer

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

HolyName · NOVARTIS

Junlin Ho, JD
General Counsel & Corporate Secretary

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

FOUNDATION MEDICINE · Ziopharm ONCOLOGY

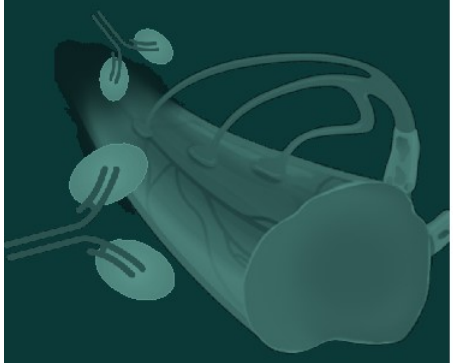
TOPAZ

SAPPHIRE

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

ScholarRock

Apitegromab: Transformative Potential to Change the Standard of Care



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

Apitegromab at a Glance

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

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

Phase 3 SAPPHIRE Trial
Registrational trial with topline 12-month data readout expected in 2024

ONYX Open-Label Extension Study
Evaluating the **long-term safety and efficacy** of apitegromab in **patients who have completed TOPAZ or SAPPHIRE**

Progressive Motor Neuron Loss and Muscle Atrophy Leading to Progressive Muscle Weakness

SMN therapies

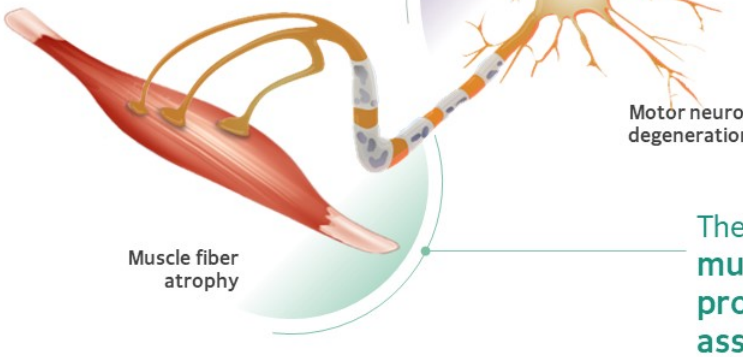
slow further degeneration of motor neurons[1]

...but do not directly address muscle atrophy

Evrysdi risdiplam

SPINRAZA (nusinersen)

zolgensma (onasemnogene abeparvovec-xioi)



There is further potential to **regain vital muscle function** by also addressing the **progressive muscle atrophy and associated weakness** of SMA

SMA, spinal muscular atrophy; SMN, survival motor neuron.
1. Hua Y, et al. Nature. 2011;478(7367):123-6.
2. Figure adapted from: SMA Foundation Overview. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf.; Accessed April 18, 2021.

GLOBAL DISEASE:

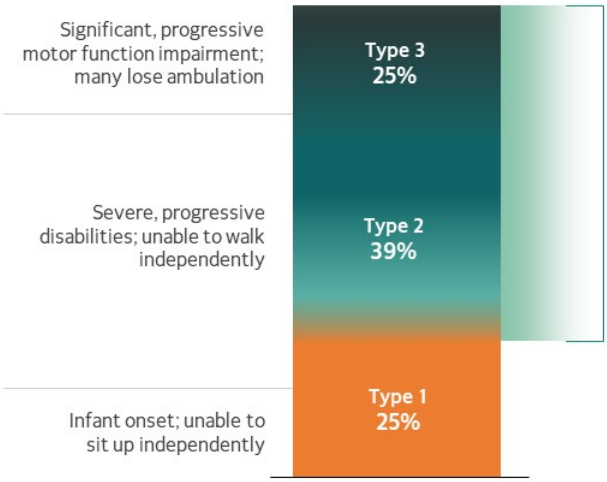
30,000-35,000 affected

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

*TOPAZ Phase 2 trial evaluated patients with Type 2 and 3 SMA (did not include Type 1)
** 2/3 of overall patient population has type 2 or 3 SMA, including ambulatory and nonambulatory patients.
Percentages reflected here do not add up to 100% because the prevalences of Types 0, 4, and unknown are excluded.
Percentages represent percent of prevalent patients.
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. 5. Cure SMA. State of SMA 2022. May 31, 2022. https://www.curesma.org/wp-content/uploads/2022/06/9042022_State-of-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.

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

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



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

~2/3 of overall patient population[5]**

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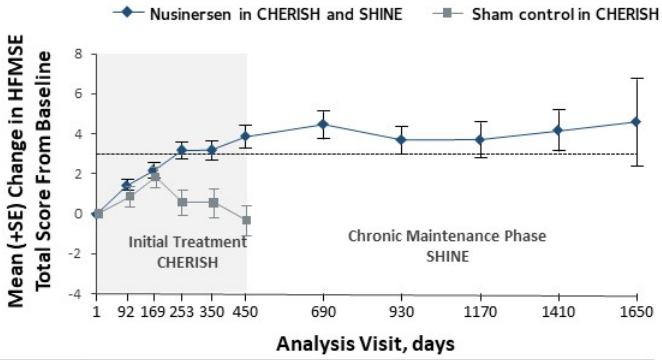
Motor Function With SMN Therapies as Assessed by HFMSE

HFMSE appears to Plateau After Initial Gains

Change in HFMSE Over Four Years with Nusinersen[1]

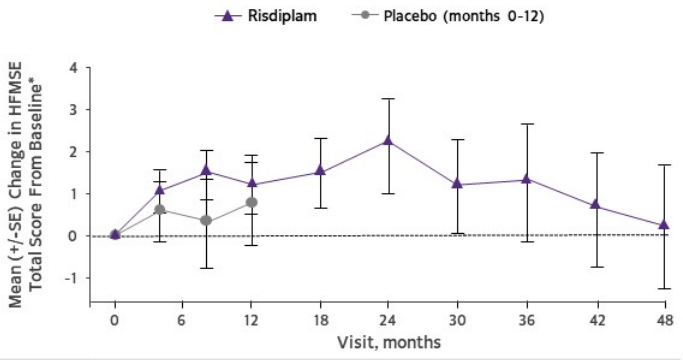
Overall population age 2-12



Nusinersen	n=	84	82	84	84	83	76	83	83	79	61	20
Placebo	n=	42	41	41	42	42	39					

Change in HFMSE* Over Four Years with Risdiplam[2]

Overall population age 2-25



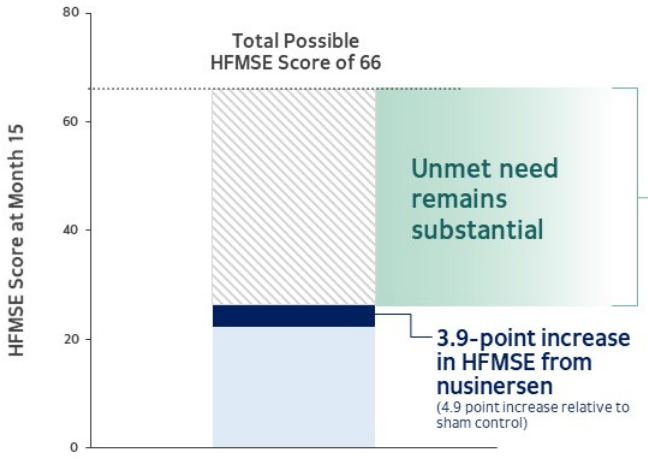
Risdiplam	n=	120	120	119	117	109	106	89	99	101	97
Placebo	n=	60	60	58	58						

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

HFMSE, Hammersmith Functional Motor Scale–Expanded; SE, standard error.

*MFM was primary efficacy endpoint of SUNFISH. HFMSE was a secondary endpoint. This third-party information is provided for background only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results.

Improving and Sustaining Muscle Function Remains an Unmet Need



Mean improvement in HFMSE experienced by patients with nonambulatory Types 2/3 SMA in nusinersen Phase 3 CHERISH trial[1]

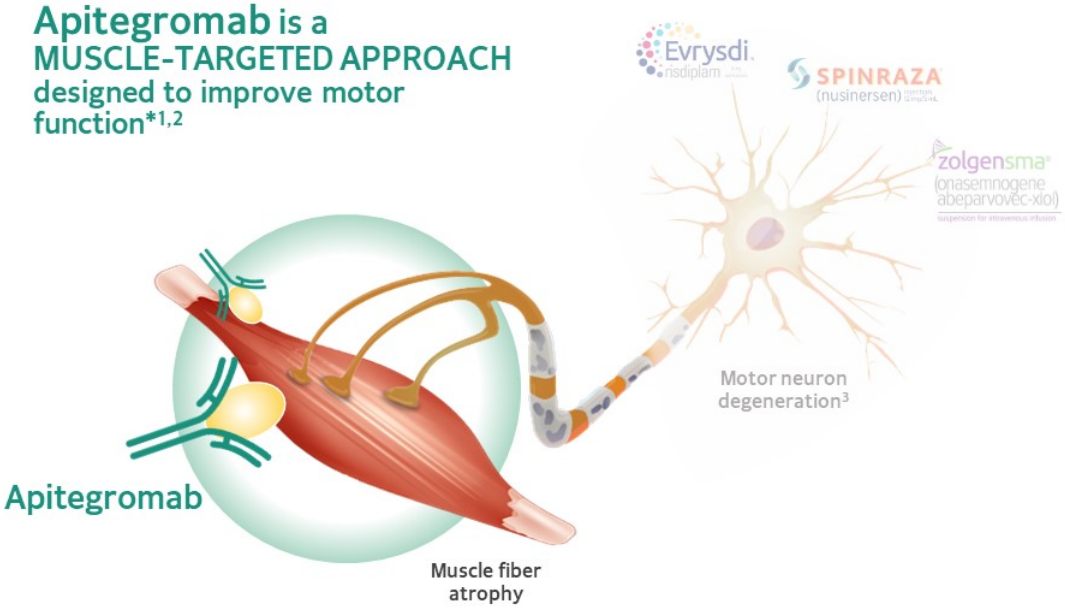
Patients and caregivers want new therapies to address the following unmet needs[2*]:

Increase muscle strength	Improve daily activities	Stabilize or gain new motor function	Reduce fatigue
97%	92%	89%	83%

HFMSE=Hammersmith Functional Motor Scale-Expanded
*Percentages represent percent of patients who named these unmet needs when asked "What are your most significant current unmet needs that you hope new therapies would address"?
1. Mercuri E et al.: N Engl J Med 2018; 378:625-635; DOI: 10.1056/NEJMoa1710504; cherish trial results. 2. 2022 Community Update Survey, Cure SMA.
This third-party information is provided for background only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results.

Apitegromab Offers Significant Potential to Address Unmet Needs

Apitegromab is a MUSCLE-TARGETED APPROACH designed to improve motor function*[1,2]



Myostatin is a negative modulator of muscle growth

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

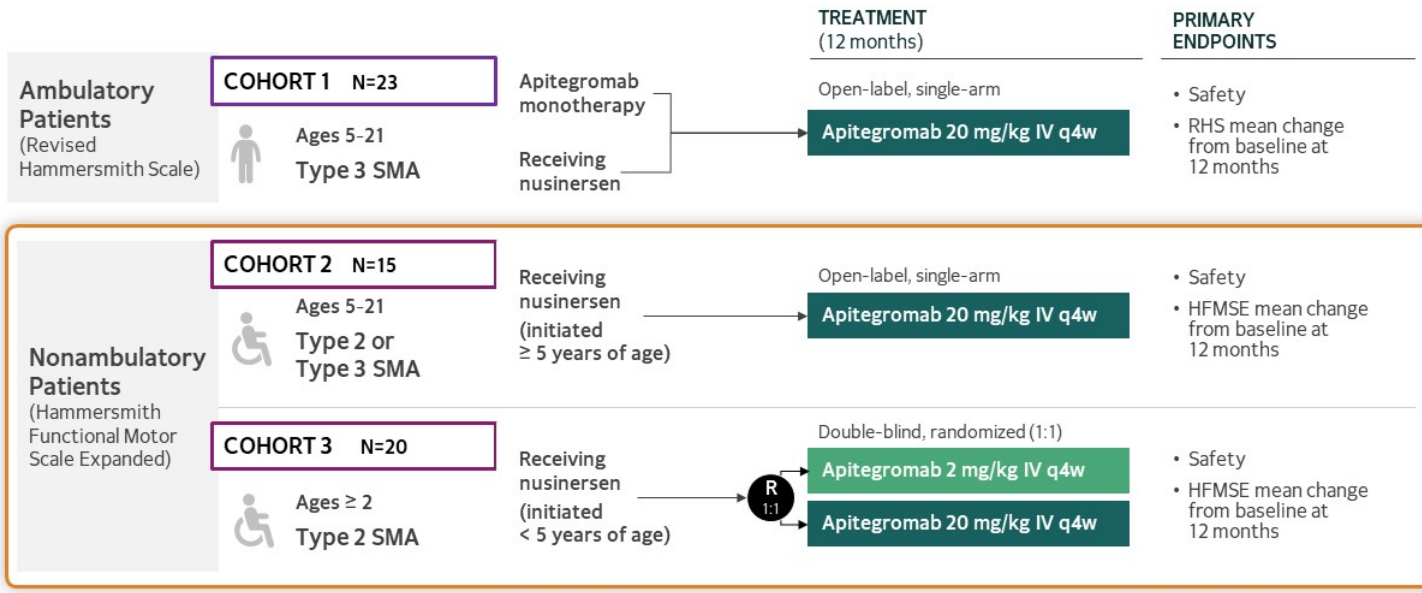
Apitegromab selectively inhibits myostatin and has the potential to build muscle and strength to improve certain patient outcomes

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

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

ScholarRock

TOPAZ Phase 2 Trial Design[1,2]



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

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

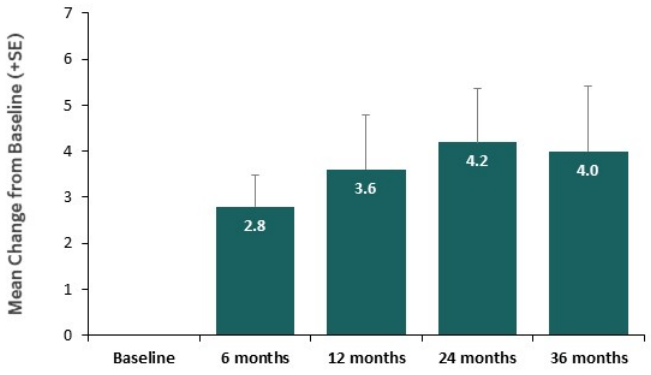
Motor Function Outcomes by HFMSE Over 36 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients

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

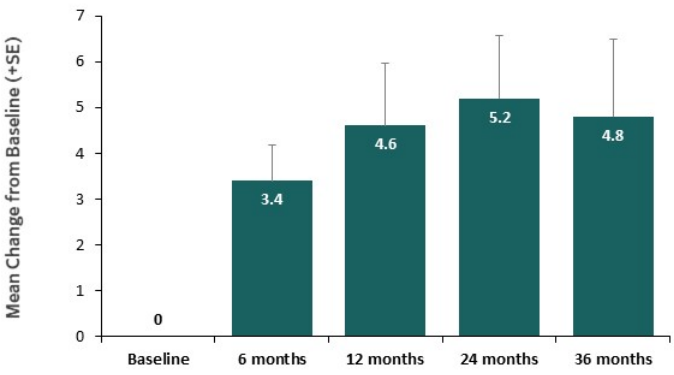
Baseline mean age=7.3 | Time on SMN Rx=24.1m



	Baseline	6 months	12 months	24 months	36 months
n=	35	29	32	29	28
95% CI=		(1.4, 4.1)	(1.2, 6.0)	(1.9, 6.6)	(1.0, 6.9)

Age 2-12 Years
All Doses (N=29)

Baseline mean age=5.5 | Time on SMN Rx=24.6m



	Baseline	6 months	12 months	24 months	36 months
n=	29	23	26	23	23
95% CI=		(1.8, 5.0)	(1.8, 7.4)	(2.3, 8.0)	(1.3, 8.3)

For the 36-month evaluation, an observed case analysis was conducted, which pooled all the nonambulatory 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 post scoliosis surgery from seven patients. One patient did not conduct HFMSE at time of database lock for 24 months, however, this patient had an unscheduled HFMSE score one month prior to their scheduled visit. In the most recent analysis, this result was included in the 24-month analysis. Error bars represent SE. CI represents confidence interval. SMN Rx=SMN therapy. In the age 2-21 group, 18/28 patients achieved ≥ 1-pt gains, and 11/28 patients ≥ 3-pt gains at 36 months. Data cutoff date as of March 13, 2023. 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.

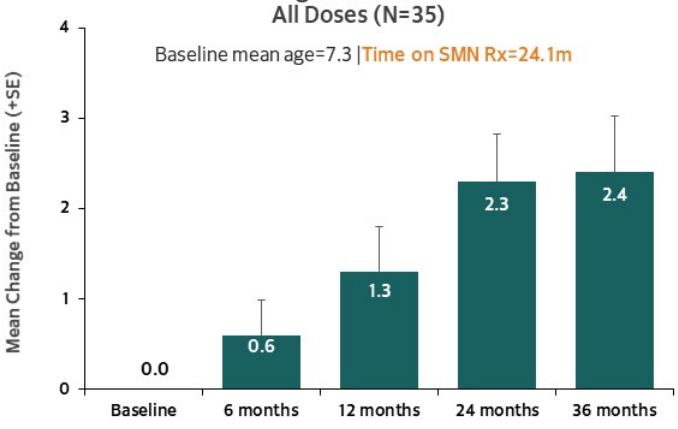
Motor Function Outcomes by RULM Over 36 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients

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

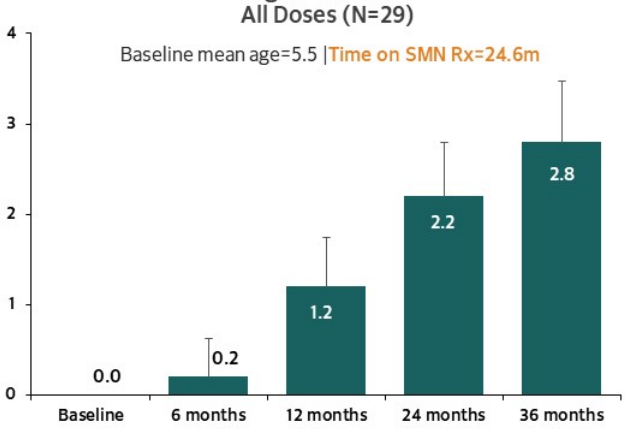
Baseline mean age=7.3 | Time on SMN Rx=24.1m



n=	35	28	31	31	27
95% CI=		(-0.2, 1.4)	(0.2, 2.3)	(1.2, 3.3)	(1.1, 3.7)

Age 2-12 Years
All Doses (N=29)

Baseline mean age=5.5 | Time on SMN Rx=24.6m

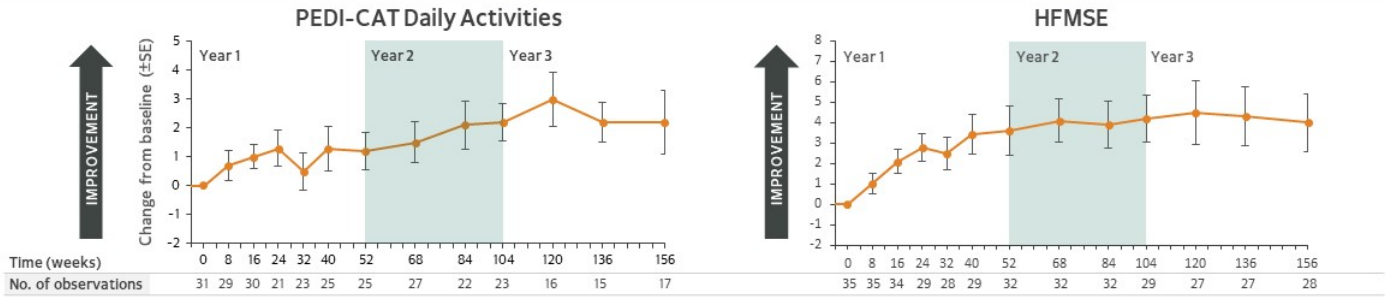


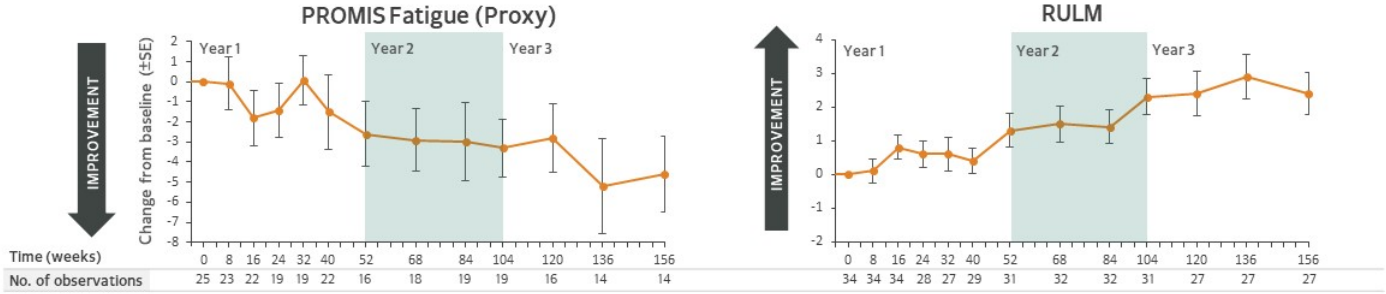
n=	29	22	25	25	22
95% CI=		(-0.7, 1.1)	(0.1, 2.4)	(1.0, 3.5)	(1.4, 4.2)

For the 36-month evaluation, an observed case analysis was conducted, which pooled all the nonambulatory 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 post scoliosis surgery from seven patients. One patient did not conduct RULM at month 24, however, had an unscheduled RULM score one month prior to their scheduled visit. In the most recent analysis, this result was included in the 24-month analysis. Error bars represent standard error (SE). CI represents confidence interval. SMN Rx=SMN therapy. In the age 2-21 group, 15/27 patients achieved ≥ 1-pt gains, and 18/27 patients ≥ 3-pt gains at 36 months. Data cutoff date as of March 13, 2023. 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.

Pooled Nonambulatory Patients | Age 2 – 21 | All Doses | Over 36 Months

Improvements in PRO Measures Were Consistent with Motor Function





N = 35; Baseline mean age=7.3 | Time on SMN Rx=24.1m

HFMSE=Hammersmith Functional Motor Scale Expanded; OC=observed case; PEDI-CAT=Pediatric Evaluation of Disability Inventory Computer Adaptive Test; PROMIS=Patient Reported Outcome Measurement Information System; RULM=Revised upper limb module; SE=standard error of the mean. SMN Rx=SMN therapy. Data on File. Scholar Rock, Inc. Cambridge, MA. Data cutoff date as of March 13, 2023. The updated PEDI-CAT analysis included additional records (2 at 12 months and 1 at 24 months) that were not available at the time of previous analysis. Apitegromab is an investigational drug candidate being evaluated for the treatment of spinal muscular atrophy. Apitegromab has not been approved for any use by the US FDA or any other health authority, and its safety and efficacy have not been established.

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Pooled Nonambulatory Patients

New WHO Development Milestones Achieved Over 36 Months

Proportion of patients gaining new milestones in TOPAZ
Cohort 2: BL (0%), 12m (20%), 24m (7%), 36m (0%)
Cohort 3 (all doses): BL (0%,) 12m (24%), 24m (26%), 36m (30%)
Cohort 3: Randomized to 20mg/kg dose: 12m (25%), 24m (33%), 36m (40%)
*Includes patients who crossed over from 2 mg/kg to 20mg/kg starting week 68 through week 104.
SMN Rx=SMN therapy. Data cutoff date as of March 13, 2023. 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.

Key Takeaways

- Patients receiving nusinersen ≥ age 5 mostly maintained WHO milestones
- Patients receiving nusinersen < age 5 improved overall: 6 out of 20 gained new milestones over 36 months

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TOPAZ Safety Summary Over 36 Months

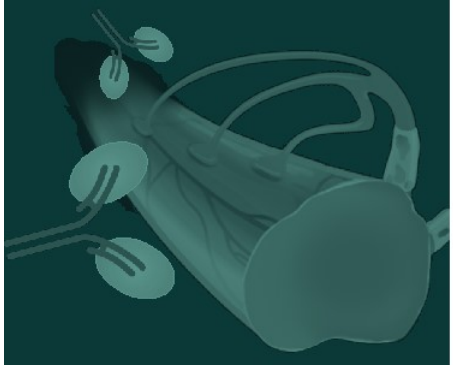
Treatment-Emergent Adverse Events (TEAEs)*	2 mg/kg dose (N=10) n (%)	20 mg/kg dose (N=48) n (%)	Total (N=58) n (%)
Any TEAE	10 (100)	46 (95.8)	56 (96.6)
Any serious TEAE	5 (50)	16 (33.3)	21 (36.2)
Any TEAE leading to study drug discontinuation	0	1 (2.1)	1 (1.7)
Any Grade 3 (severe) or higher TEAE	4 (40)	16 (33.3)	20 (34.5)

- TEAEs were consistent with previous reports with no new findings after 198 patient-years of exposure
  - Most frequently reported TEAEs*: headache (38%), pyrexia (38%), COVID-19 (36%), nasopharyngitis (36%), & upper respiratory tract infection (33%)
  - TEAEs were mostly mild to moderate in severity and generally consistent with the underlying patient population and nusinersen therapy
- No deaths or suspected unexpected serious adverse reactions or hypersensitivity reactions to apitegromab were reported
- No patients displayed positive titers for apitegromab antibodies (ADA)

*Defined as 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. % = 100 x n/N; % at 12 month. AE, adverse event; TEAE, treatment emergent adverse events. Data cutoff date as of March 13, 2023. 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.

Summary of TOPAZ Data

Substantial and Sustained Improvement Over 36 MONTHS



TOPAZ

Data to date has shown substantial clinical benefit that is dose-dependent

Benefit continued to improve or was sustained over 36 months

Consistency across functional scales and patient-reported outcomes

Well tolerated profile and low discontinuation rate supports durability of treatment

TOPAZ data suggest that apitegromab has the potential to transform care in SMA by directly addressing progressive muscle weakness

PRO=Patient Reported Outcome

SAPPHIRE

Sapphire Phase 3 Pivotal Trial

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SAPPHIRE Phase 3 Design is Optimized by Insights from TOPAZ

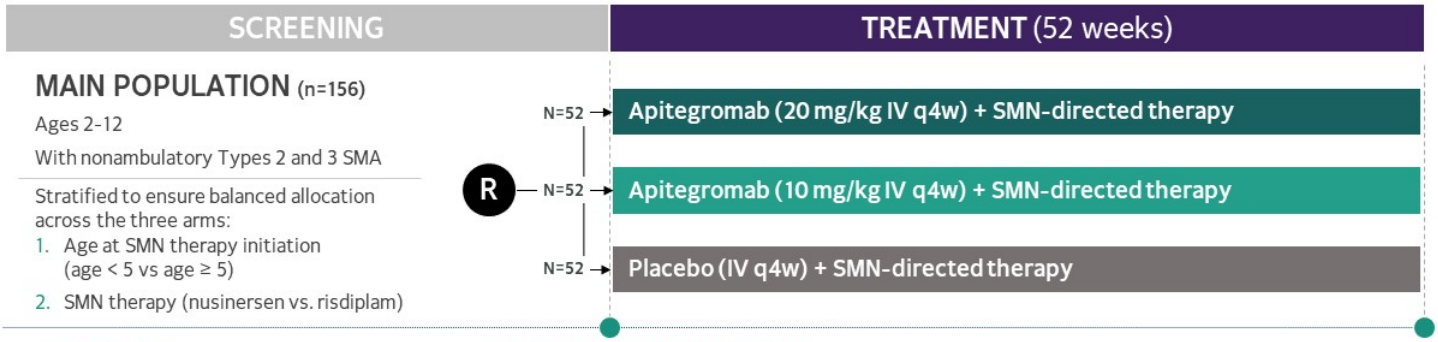
TOPAZ Learnings	SAPPHIRE Design Elements
Substantial HFMSE gains observed in the nonambulatory Type 2/3 SMA cohorts	• Study population: nonambulatory Type 2/3 SMA • Primary efficacy endpoint: HFMSE
Exploratory age 2-12 analysis in nonambulatory Type 2/3 showed transformative potential	Age 2-12 main efficacy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

HFMSE=Hammersmith Functional Motor Scale Expanded

Ongoing SAPPHIRE Phase 3 Trial Overview

SAPPHIRE

Randomized, double-blind, placebo-controlled, parallel arm design (n=204)
Enrolling patients who are on SMN-directed therapy (nusinersen or risdiplam)
Anticipate completing enrollment in 3Q 2023



ENDPOINTS

Primary Efficacy:
Mean HFMSE change from baseline at 12 months

Additional Efficacy Measures:
RULM, WHO, other outcome measures

Safety, PK/PD, ADA

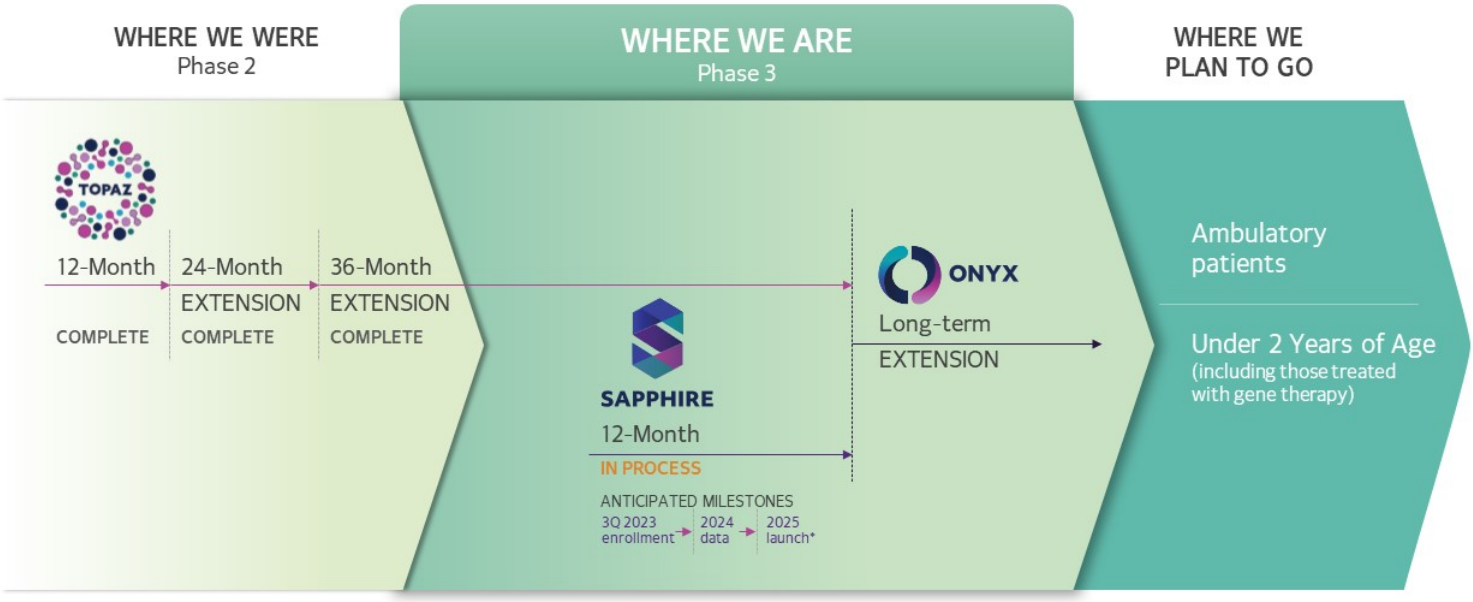
Additional Data Opportunities

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

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

ClinicalTrials.gov Identifier: NCT05156320
HFMSE=Hammersmith Functional Motor Scale Expanded; RULM=Revised Upper Limb Module; R=randomization; SMA=spinal muscular atrophy; SMN=survival motor neuron.

Executing on the Promise: Apitegromab SMA Trials



SMA=Spinal Muscular Atrophy
*Subject to regulatory approval

Apitegromab Summary

Differentiation

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

Strong Scientific Rationale

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

Clear Clinical Pathway

- TOPAZ has demonstrated sustained motor function gains to date in patients with nonambulatory Types 2 and 3 SMA
- Pivotal Phase 3 SAPPHIRE trial: enrollment completion expected in Q3 2023
- FDA has granted Fast Track, Orphan Drug, and Rare Pediatric Disease designations
- European Medicines Agency (EMA) has granted Priority Medicines (PRIME) and Orphan designations

High Unmet Medical Need & Significant Commercial Opportunity

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

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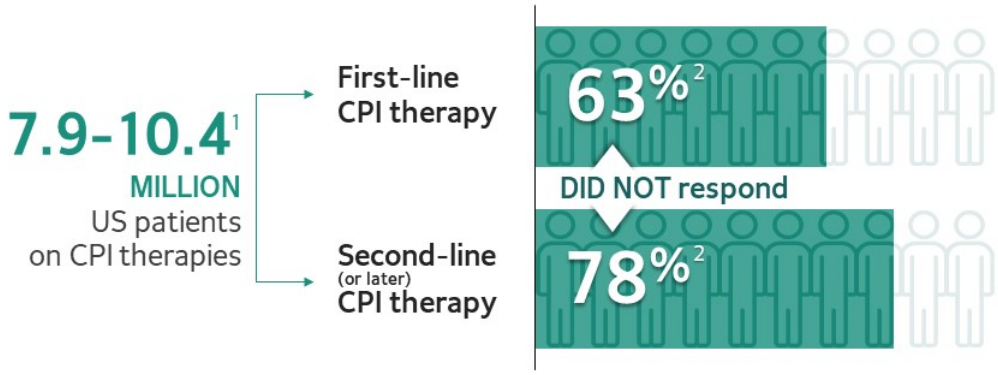
DRAGON

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

ScholarRock

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



Clinically derived rationale points to significant opportunity to

increase checkpoint therapy responses by targeting TGFβ-1

1. Source: Gores, M. (2022). *In the eye of the storm: PD-(L)1 inhibitors weathering turbulence* [White paper]. IQVIA. https://www.iqvia.com/library/white-papers/in-the-eye-of-the-storm-pd-l-1-inhibitors-weathering-turbulence
2. Source: Carretero-Gonzalez et al. (2018) Oncotarget 9:8706-8715
Meta-analysis of twelve randomized trials with control arm or adequate safety profile (includes nivolumab, pembrolizumab, and atezolizumab)

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

Nature (online), February 14, 2018.

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

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

Science Translational Medicine, March 25, 2020.

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

Constance J. Martin, et al.

Vol 12, Issue 536. DOI: 10.1126/scitranslmed.aay8456

June 2019.

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

- $773 million total potential deal value

Cell

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

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

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

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

TGFβ: biology in cancer progression and immunotherapy

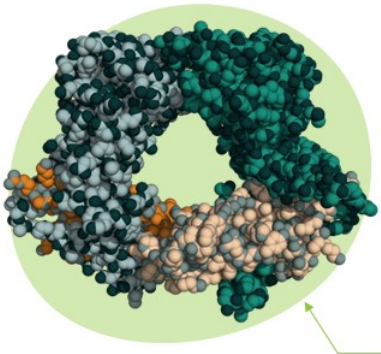
Rik Derynck[1,2,3], Shannon J. Turley[4] and Rosemary J. Akhurst[2,3]

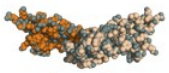
July 24, 2020: https://doi.org/10.1038/ s41571-020-0403-1

August 2022.

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

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





Traditional Target
"Mature" growth factor

SRK-181: Latent TGFβ-1 Inhibitor

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

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

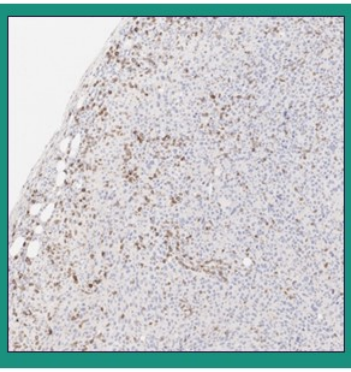
SRK-181-mIgG1 + Anti-PD1 Overcomes Immune Exclusion

Overcoming immune exclusion

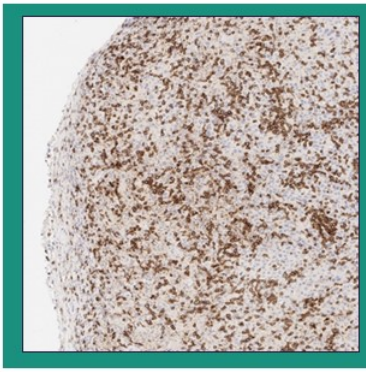
Tumor micro-environment

Anti-PD1

Immune Exclusion



Anti-PD1/ SRK-181-mIgG1

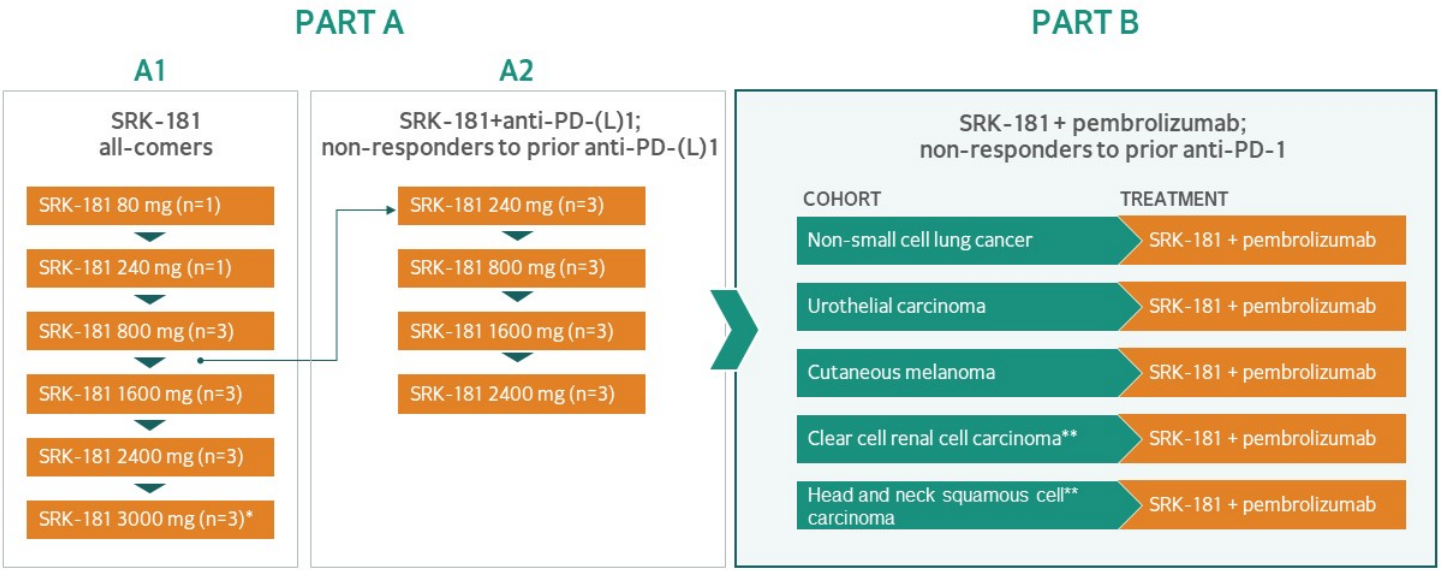


Overcome Exclusion

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

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

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



* A cohort of 2000 mg Q2W (n=3) was also evaluated.
**The clear cell RCC and HNSCC cohorts will also explore the effects of SRK-181 in patients with relapsed response after anti-PD-1 treatment.
1. NCT04291079 on www.clinicaltrials.gov.

DRAGON Part A: Safety

PART A1 Monotherapy

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

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

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

No Grade 4 or 5 treatment-related AEs occurred

Treatment-related Grade 3 AEs:

- Alanine aminotransferase increased (1 patient)

Treatment-related SAEs:

- None

PART A2 Combination Treatment

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

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

No DLTs were observed up to 2400 mg q3w

No Grade 4 or 5 treatment-related AEs occurred

Treatment-related Grade 3 AEs:

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

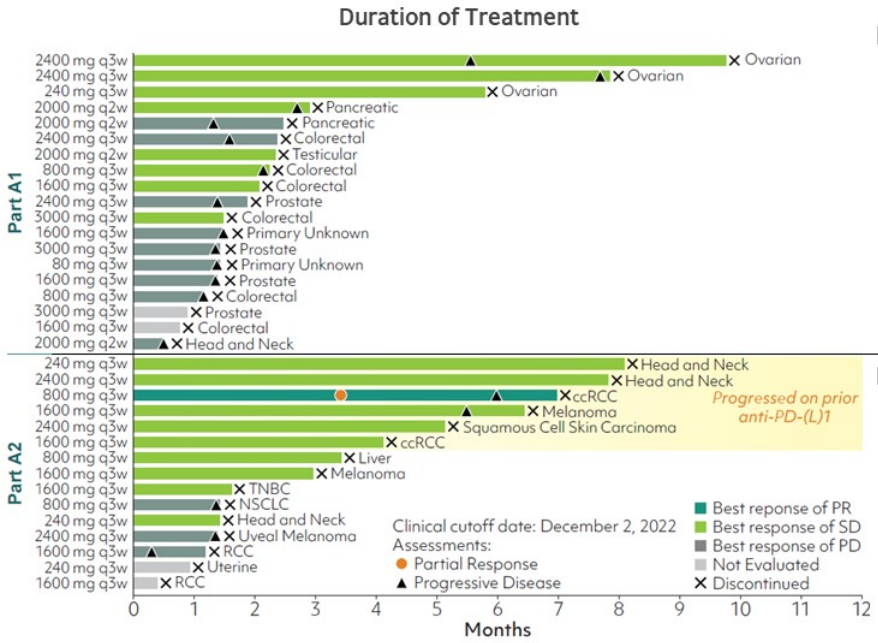
Treatment-related SAEs:

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

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

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

DRAGON Part A: Preliminary Efficacy Data*



Part A1 (n=19)

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

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

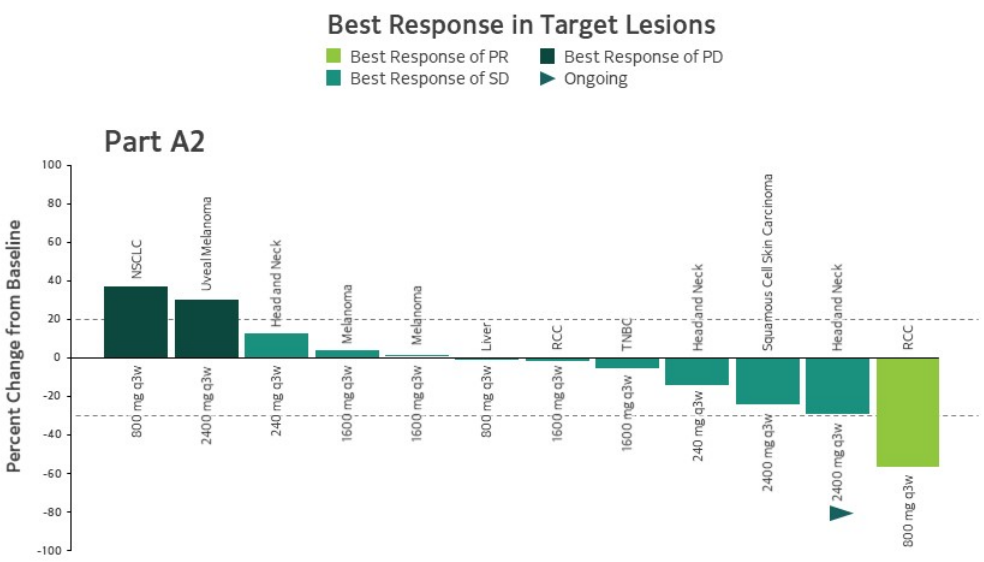
Part A2 (n=15)

- At 800 mg q3w, 1 partial response (PR) was observed in patient with anti-PD-1-resistant clear cell renal cell carcinoma (ccRCC)
- 9 patients had best response of SD

  6 patients (green highlight) were stable beyond the 16-week cutoff
  - 1 ongoing patient with head and neck cancer had a 29.4% tumor reduction

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

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



Part B (as of 12/2/22)

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

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

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

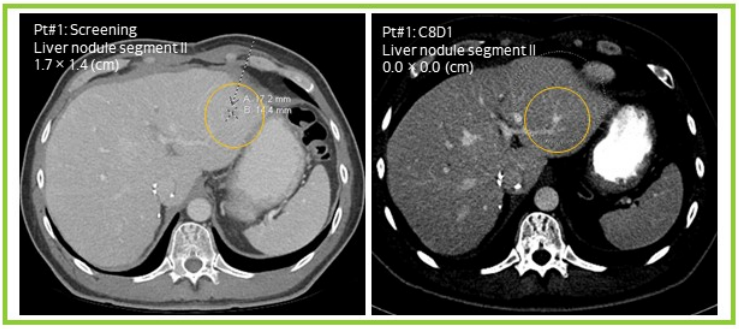
- **11 ccRCC patients enrolled**
  - n=2 in Part A2 (all discontinued from study) and n=9 in Part B (5 pts remain on study)
  - enrollment in Part B continues
- **3 confirmed PRs observed in ccRCC patients**
  - Patients are anti-PD-1 resistant patient (no response on prior anti-PD-1 therapy and disease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

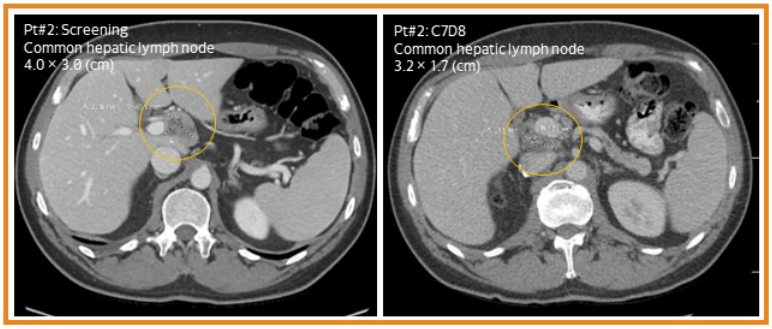
As of clinical cutoff date of Dec 2, 2022

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

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

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





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

SRK-181: Encouraging Early Clinical Data Consistent with Hypothesis

Preclinical Data		Phase 1 DRAGON proof-of-concept trial
TGFβ pathway evaluation (PD) ✓ Target engagement (blood) ✓ TGFβ-1 signaling (tumor p-SMAD2 & RNAseq)	»	TGFβ pathway evaluation (PD) ✓ Target engagement (blood) ⧖ TGFβ-1 signaling (tumor p-SMAD2 & RNAseq)
Immunophenotyping, including immune exclusion status ✓ Tumor immune contexture (e.g., tumor CD8+ T cells) ✓ Immune cell contexture (tumor & blood MDSCs) ✓ Immune response markers (e.g., IO gene signature)	»	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 ✓ Drug exposure needed for efficacy	»	Therapeutically relevant dose ✓ Dosing regimens achieved target steady state levels
Objective response ✓ Anti-tumor response and survival benefits	»	Objective response ✓ Anti-tumor response observed (partial responses)

SRK-181 Summary

Differentiation

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

Strong Scientific Rationale

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

Clear Clinical Pathway

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

High Unmet Medical Need & Large Commercial Opportunity

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

*(PD-1/PD-L1)

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Next Horizon: Fibrosis

ScholarRock™

TGFβ is Established as Key Driver of Fibrosis Across Multiple Diseases

Nature Reviews , April 25, 2016 NATURE REVIEWS | NEPHROLOGY

TGF-β: the master regulator of fibrosis

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

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

Targeting TGF-β Signaling in Kidney Fibrosis

Yoshitaka Isaka

Nature Reviews. August 19, 2014 NATURE REVIEWS | RHEUMATOLOGY

Transforming growth factor β—at the centre of systemic sclerosis

Robert Lafyatis

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

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

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

J Pathol, July 25, 2021

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

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

J Receptors Sign Trans, Feb 13, 2020

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

Bhagyalakshmi Nair and Lekshmi R. Nath

Proc Am Thorac Soc, July 3, 2006

Transforming Growth Factor β

A Central Modulator of Pulmonary and Airway Inflammation and Fibrosis

Dean Sheppard

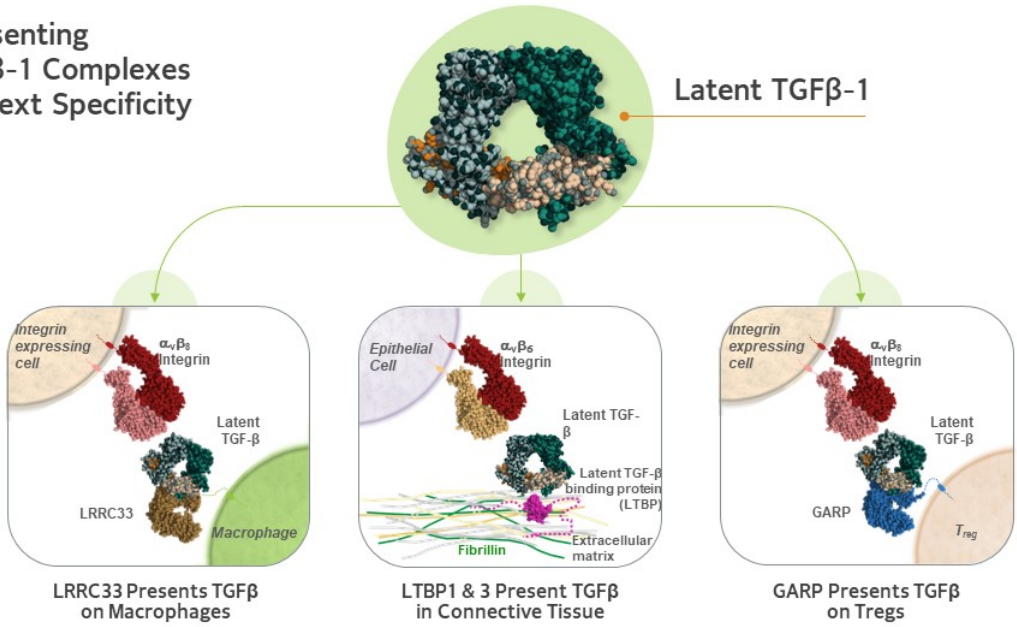
PNAS, February 24, 1986 PNAS

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

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

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

Targeting Presenting Molecule/TGFβ-1 Complexes Provides Context Specificity



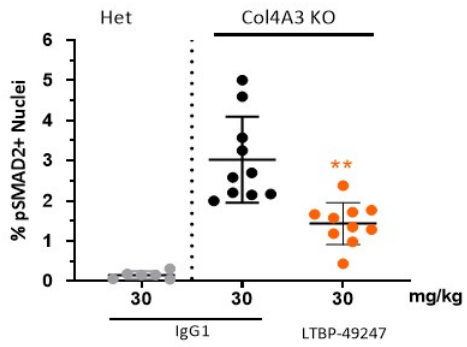
LRRC33 Presents TGFβ on Macrophages

LTBP1 & 3 Present TGFβ in Connective Tissue

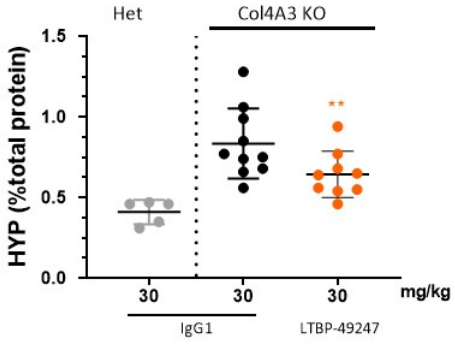
GARP Presents TGFβ on Tregs

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

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



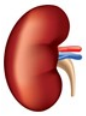
LTBP-49247 reduced fibrosis in kidneys of Alport model



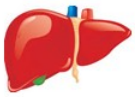
** p < 0.01
One way ANOVA vs. IgG
HYP=hydroxyproline

- Efficacy also seen in rat model of kidney fibrosis
- No observed toxicity in mouse 13-week non-GLP repeat dose study
- Favorable PK in cynomolgus monkeys (t1/2 ~28 days) suggests LTBP-49247 is amenable to clinical subcutaneous dosing with promising developability profile

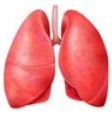
Significant Opportunities to Address High Unmet Need Across Multiple Fibrotic Indications



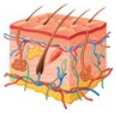
Alport Syndrome (AS)
Focal Segmental Glomerulosclerosis (FSGS)
IgA Nephropathy (IgAN)



Primary Sclerosing Cholangitis (PSC)



Idiopathic Pulmonary Fibrosis (IPF)



Diffuse Cutaneous Systemic Sclerosis (dcSSc)

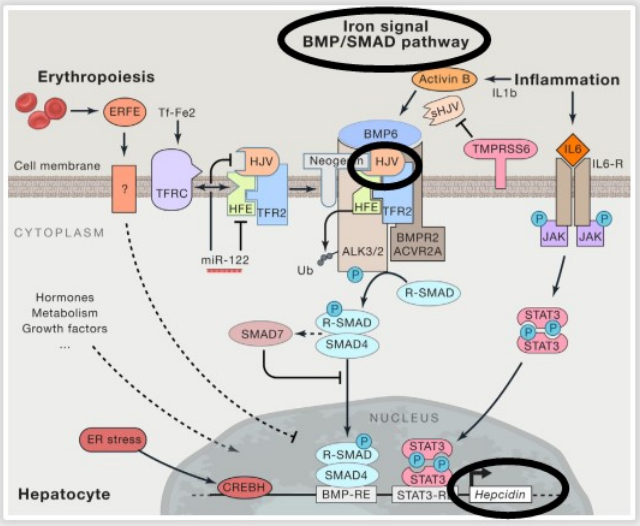
Collectively, significant commercial potential given large patient population with clear high unmet need given poor outcomes and lack of effective therapeutics

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

Next Horizon: Iron-Restricted Anemia

ScholarRock.

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



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

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

Anemia of Inflammation/ Chronic Disease

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

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

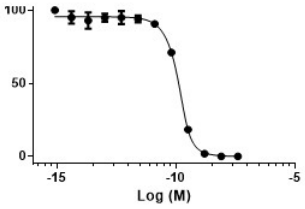
Fig: Muckenthaler, M.U., Rivella, S., Hentze, M.W. and Galy, B. (2017) A Red Carpet for Iron Metabolism. *Cell*, 168(3): 344-361
1: *Kuns-Hashimoto R. et al.* (2008) Selective binding of RGMc/hemojuvelin, a key protein in systemic iron metabolism, to BMP-2 and neogenin. *Am J Physiol Cell Physiol* 294(4):C994-C1003
2: *Constante M. et al. (2007)* Repression of repulsive guidance molecule C during inflammation is independent of Hfe and involves tumor necrosis factor-alpha. *Am J Pathol* 170(2):497-504
3: *Core A.B., et al.* (2014) Hemojuvelin and bone morphogenetic protein (BMP) signaling in iron homeostasis. *Front Pharmacol.* 5:104.
4. Wang CY and Babitt JL. (2016) Hepcidin Regulation in the Anemia of Inflammation. *Curr Opin Hematol* 23(3): 189-197.

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

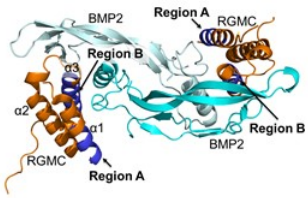
Key Attributes of HJV-35202:[1,2]

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

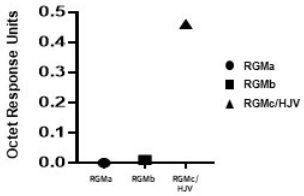
Potent in vitro binding affinity (KD=3.9E-11)



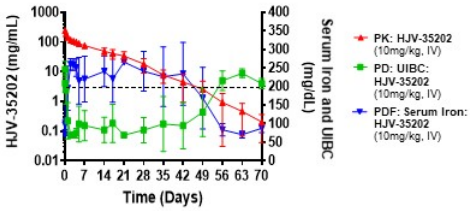
Highly specific to RGMc/HJV with well understood mechanism



Specific to RGMc over other RGM family members

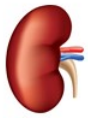


Sustained PD effect in single dose Cyno study



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

Significant Opportunities to Target Iron-Restricted Anemias Across Multiple Indications



Chronic Kidney Disease (CKD)

Anemia of Chronic Inflammation (AI)

Myelofibrosis (MF)

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

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

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

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

Collectively, sizeable commercial opportunity given relatively large population

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

Scholar Rock Summary

ScholarRock

Key Investment Highlights

Revolutionary Platform

Discover and Develop
monoclonal antibodies with extraordinary selectivity

Overcome the Challenges
targeting the latent forms of growth factors

Robust Clinical Pipeline

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

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

Upcoming Data Readouts
for both clinical programs

Positioned For Success

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

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

Appendix

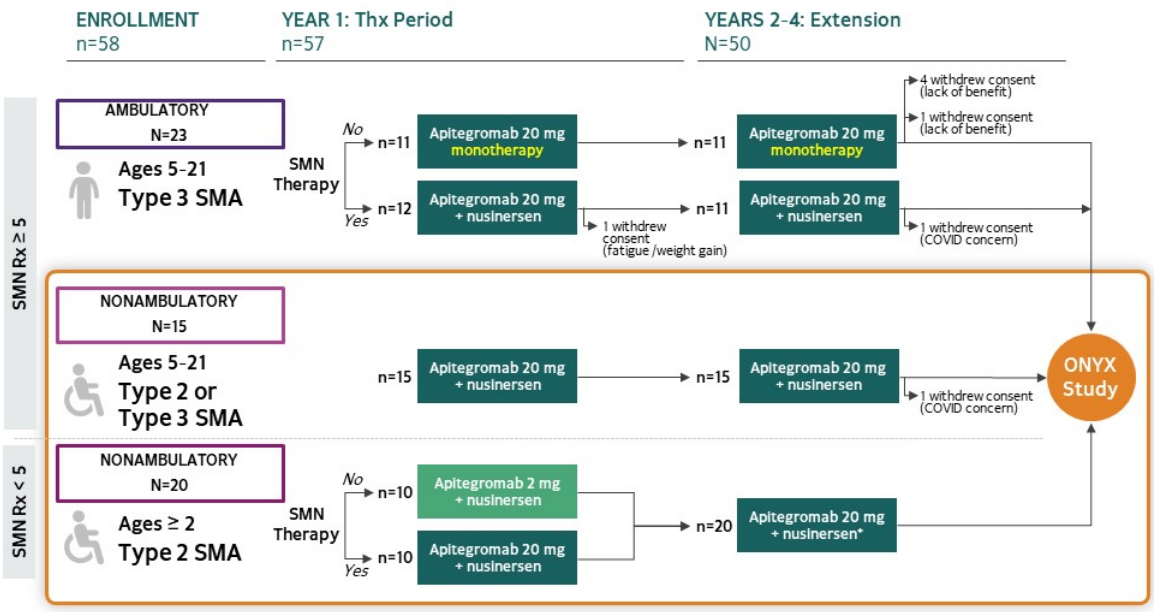
ScholarRock

TOPAZ Baseline Characteristics[1,2]

			N (dosed)	Mean age (min, max)	Mean RHS (min, max)	Mean HFMSE (min, max)	Prior Nusinersen, Months Mean (min, max)*	No. of patients with 2,3, or 4 SMN2 copies	Discontinuation(s)
Ambulatory	COHORT 1: Age 5-21	20 mg/kg monotherapy	11	12 (7, 19)	48 (26, 63)		**N/A**	1, 4, 4	0
		20 mg/kg + nusinersen	12	13 (7, 21)	51 (43, 62)		**20 (12, 28)**	0, 9, 1	1†
		Pooled	23	13 (7, 21)	50 (26, 63)		**N/A**	1, 13, 5	1†
Nonambulatory	COHORT 2: Age 5-21	20 mg/kg + nusinersen	15	12 (8, 19)		23 (13, 39)	**25 (12, 39)**	0, 11, 2	0
	COHORT 3: Age 2+	20 mg/kg + nusinersen	10	4 (2, 6)		24 (14, 42)	**24 (10, 34)**	1, 8, 0	0
		2 mg/kg + nusinersen	10	4 (2, 6)		26 (12, 44)		1, 8, 1	0
		Pooled	20	4 (2, 6)		25 (12, 44)		2, 16, 1	0

*Patients on average received ~2 years of nusinersen treatment at baseline and ~3 years of nusinersen treatment by the end of the TOPAZ study (12-months). SMN2 copy numbers were not available for all patients. †12-month baseline characteristics recorded in the table, 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; max, maximum; min, minimum; RHS, Revised Hammersmith Scale; SMN, survival motor neuron.
1. Crawford T, et al. Neuromuscul Disord. 2022;32(Suppl1):S86-S87. P102. 2. 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). Presented at CureSMA Annual Conference; June 16-19, 2022.

TOPAZ Patient Disposition Over 36 Months



a. Patients stratified based on previous treatment with approved SMN therapy.
b. Patients randomized to receive 2 or 20 mg/kg apitegromab.
*Includes patients who crossed over from 2 mg/kg to 20mg/kg starting week 68 through week 104
** Excludes patients on monotherapy
SMN Rx=SMN therapy.

TOPAZ patient retention

PRIMARY TREATMENT:

58 ENROLLED

57 completed primary treatment period and enrolled in the extension study

- 1 withdrew consent due to fatigue & weight gain

EXTENSION:

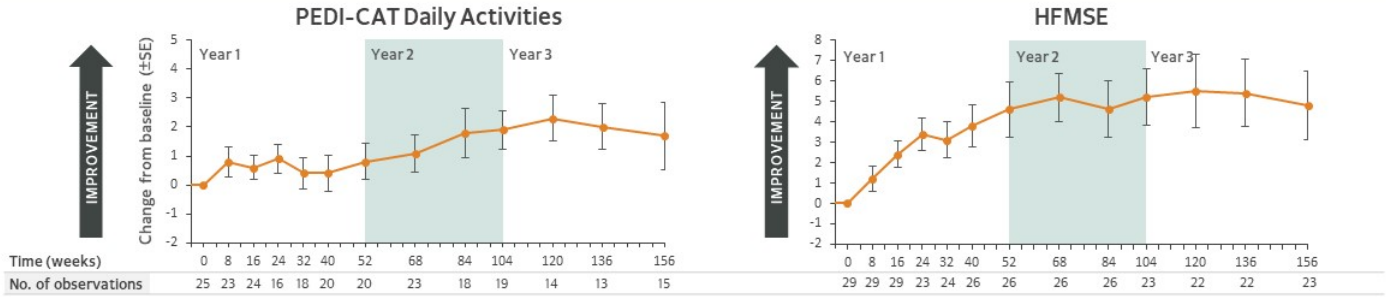
57 ENROLLED

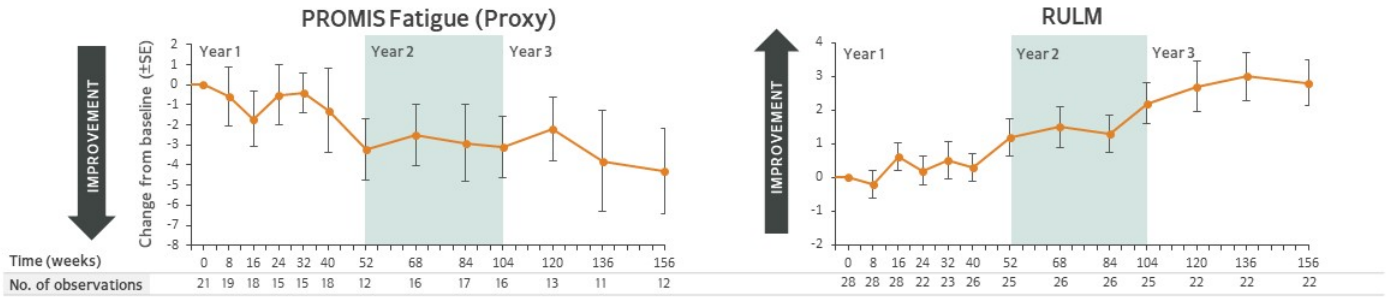
7 discontinued

- 2 due to concerns with COVID-19
- 5 on monotherapy due to lack of benefit
- >90% of patients on combination therapy remained in study**

Pooled Nonambulatory Patients | Age 2 – 12 | All Doses | Over 36 Months

Improvements in PRO Measures Consistent With Motor Function





N = 29.; Baseline mean age=5.5 |Time on SMN Rx=24.6m

HFMSE=Hammersmith Functional Motor Scale Expanded; OC=observed case; PEDI-CAT=Pediatric Evaluation of Disability Inventory Computer Adaptive Test; PROMIS=Patient Reported Outcome Measurement Information System; RULM=Revised upper limb module; SE=standard error of the mean. SMN Rx=SMN therapy. Data on File. Scholar Rock, Inc. Cambridge, MA. Data cutoff date as of March 13, 2023. Error bars represent standard error (SE). Data cutoff date as of March 13, 2023. The updated PEDI-CAT analysis included additional records (2 at 12 months and 1 at 24 months) that were not available at the time of previous analysis. 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.

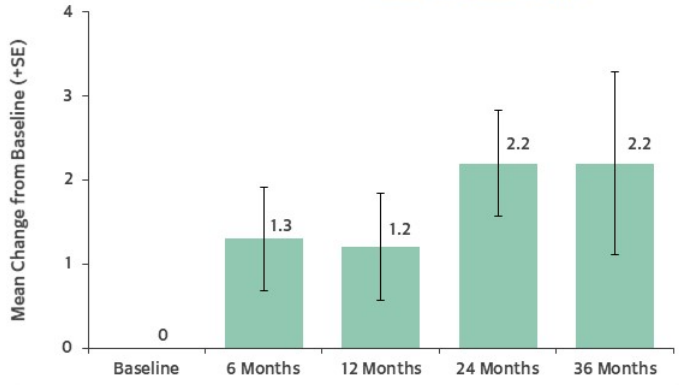
PEDI-CAT Daily Activities Over 36 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients

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

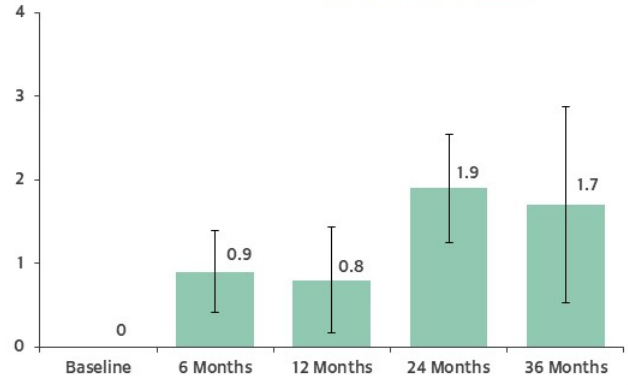
Baseline mean age=7.3 | Time on SMN Rx=24.1m



	Baseline	6 Months	12 Months	24 Months	36 Months
n=	35	21	25	23	17
95% CI=		(-0.0, 2.6)	(-0.1, 2.6)	(0.9, 3.5)	(-0.1, 4.5)

Age 2-12 Years
All Doses (N=29)

Baseline mean age=5.5 | Time on SMN Rx=24.6m



	Baseline	6 Months	12 Months	24 Months	36 Months
n=	29	16	20	19	15
95% CI=		(-0.1, 2.0)	(-0.5, 2.1)	(0.5, 3.2)	(-0.8, 4.2)

For the 36-month evaluation, an observed case analysis was conducted, which pooled all the nonambulatory 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). Error bars represent SE. CI represents confidence interval. SMN Rx=SMN therapy. Data cutoff date as of March 13, 2023. The updated analysis included additional records (2 at 12 months and 1 at 24 months) that were not available at the time of previous analysis. 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.

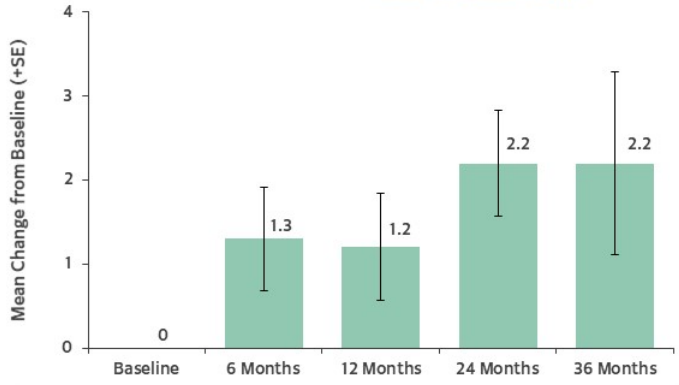
PEDI-CAT Daily Activities Over 36 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients

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

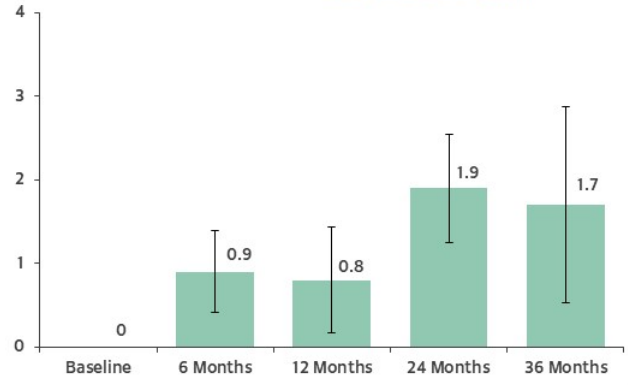
Baseline mean age=7.3 | Time on SMN Rx=24.1m



	Baseline	6 Months	12 Months	24 Months	36 Months
n=	35	21	25	23	17
95% CI=		(-0.0, 2.6)	(-0.1, 2.6)	(0.9, 3.5)	(-0.1, 4.5)

Age 2-12 Years
All Doses (N=29)

Baseline mean age=5.5 | Time on SMN Rx=24.6m



	Baseline	6 Months	12 Months	24 Months	36 Months
n=	29	16	20	19	15
95% CI=		(-0.1, 2.0)	(-0.5, 2.1)	(0.5, 3.2)	(-0.8, 4.2)

For the 36-month evaluation, an observed case analysis was conducted, which pooled all the nonambulatory 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). Error bars represent SE. CI represents confidence interval. SMN Rx=SMN therapy. Data cutoff date as of March 13, 2023. 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.

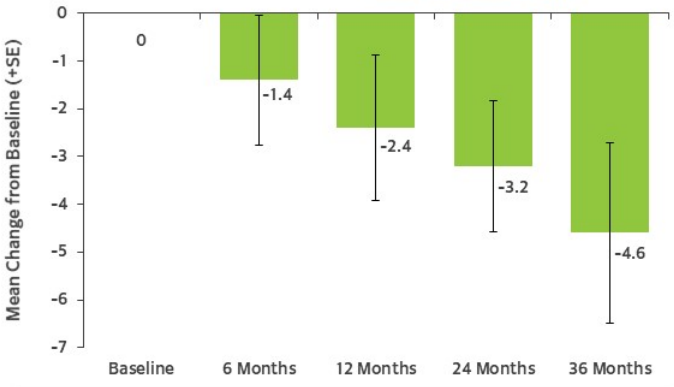
PROMIS Fatigue (Proxy) Over 36 Months

Improvements Were Substantial and Sustained

Pooled Nonambulatory Patients

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

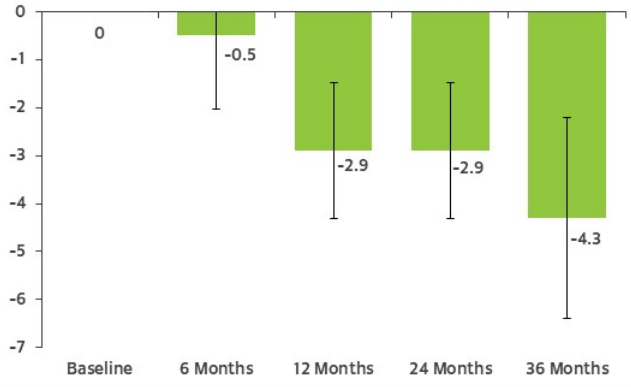
Baseline mean age=7.3 | Time on SMN Rx=24.1m



	Baseline	6 Months	12 Months	24 Months	36 Months
n=	35	19	17	20	14
95% CI=		(-4.3, 1.4)	(-5.7, 0.8)	(-6.0, -0.3)	(-8.7, -0.5)

Age 2-12 Years
All Doses (N=29)

Baseline mean age=5.5 | Time on SMN Rx=24.6m



	Baseline	6 Months	12 Months	24 Months	36 Months
n=	29	15	13	17	12
95% CI=		(-3.7. 2.8)	(-6.0, 0.2)	(-6.0. 0.1)	(-8.9, 0.4)

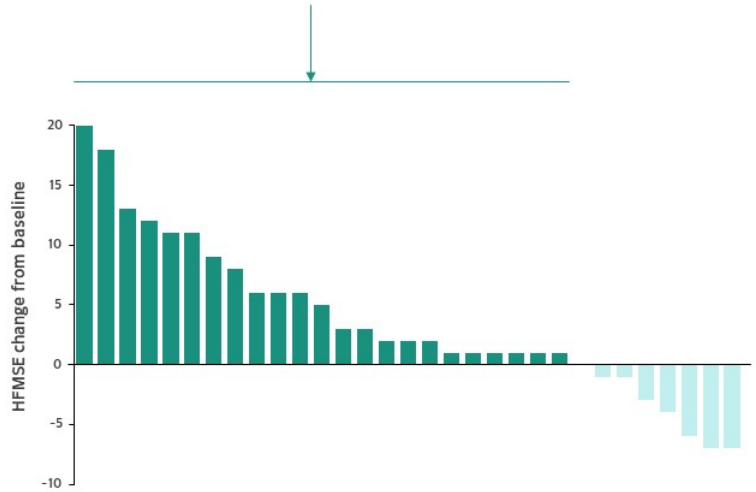
For the 36-month evaluation, an observed case analysis was conducted, which pooled all the nonambulatory patients (Cohorts 2 and 3) and was based upon the available data for given timepoints. This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who switched from 2 mg/kg to 20 mg/kg in Year 2). Error bars represent SE. CI represents confidence interval. SMN Rx=SMN therapy. Data cutoff date as of March 13, 2023. 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 nonambulatory patients* experienced HFMSE increases from apitegromab

during chronic maintenance phase of SMN therapy



Apitegromab led to HFMSE improvements in both nonambulatory cohorts

including patients started on nusinersen at age ≥ 5

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

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

* Pooled cohorts of nonambulatory patients treated with apitegromab 20 mg/kg and 2 mg/kg

**Nonambulatory 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.

TOPAZ Age 2-12 Analysis* in Pooled Nonambulatory Cohorts (20mg/kg) at 12 Months

Mean Increase of Motor Function Outcomes by HFMSE was Significant

Mean HFMSE Increase OF 4.4 POINTS

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

HFMSE Gains Also Notable

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

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

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

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

No safety signals for apitegromab were identified through month 12 of TOPAZ; the five most frequently reported treatment-emergent adverse events were headache, pyrexia, upper respiratory tract infection, cough, and nasopharyngitis

*Exploratory, post hoc analysis. †For 12-month endpoint, if participants skipped three consecutive doses due to site restrictions caused by COVID-19, records after dose skipping were excluded from analysis. The last observation carried forward was used for other missing data.

1. Crawford T et al. TOPAZ topline results. Presented at Muscular Dystrophy Association, 2023 Clinical & Scientific Conference, March 22, 2023. CI, confidence interval; HFMSE, Hammersmith functional motor scale expanded; SMA, spinal muscular atrophy. 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.

Initiated nusinersen age <5[1,2]

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

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

Continuous and durable improvements observed through 12-months of treatment

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

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

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

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

TOPAZ 12-Month Data | Nonambulatory Type 2/3 Cohort

Initiated nusinersen age ≥5[1,2]

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

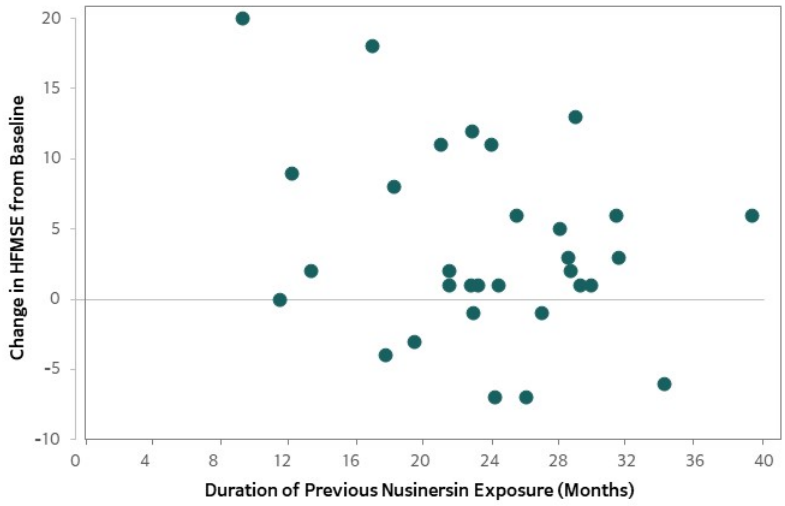
- ≥ 1-point increase: ~67%
- ≥ 3-point increase: ~30%

Durability of effect observed through 12-months of treatment

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

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

TOPAZ 12-Month HFMSE Changes and Duration of Prior Nusinersen



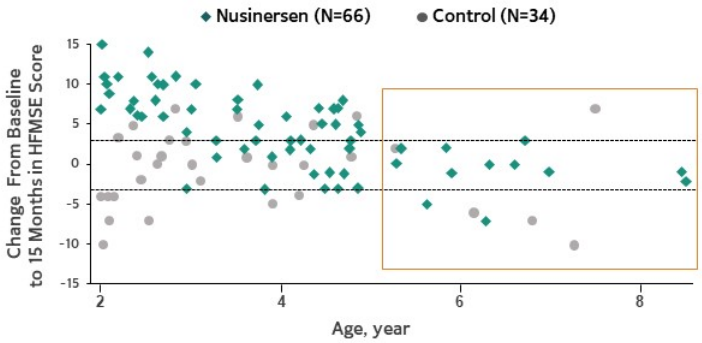
- Patients enrolled were already in the chronic maintenance phase of nusinersen
- Lack of clear correlation between 12-month HFMSE & duration of prior nusinersen exposure in patients aged 2 – 21 suggests motor function improvement mainly attributable to apitegromab

Post hoc analysis: Scatter plot of prior nusinersen treatment duration vs change in HFMSE from baseline; in nonambulatory Types 2 and 3 participants in TOPAZ, there was no clear relationship between duration of nusinersen treatment and change in motor function. Patients skipped 3 or more doses due to COVID-site restrictions excluded; apitegromab is an investigational product candidate under development. HFMSE, Hammersmith Functional Motor Scale–Expanded

Nonambulatory Type 2/3 SMA

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

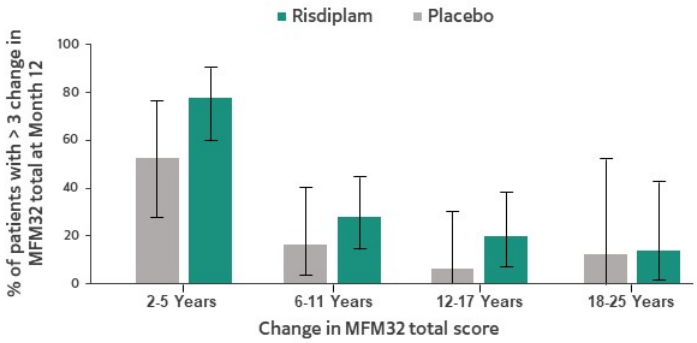
Nusinersen CHERISH Trial in Later-Onset SMA[1]



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

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

Risdiplam SUNFISH Trial in Later-Onset SMA[2]



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

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

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

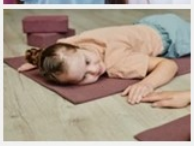
Significance of Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM)

HFMSE

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

ABLE TO:

- **Touch Head Above Ear Level** whilst maintaining stable trunk and head
- **Roll From Supine to Prone** over the right side without pulling/ pushing on hands



33 Items
Graded on scale 0 to 2

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

Item scores are summed to give a total score

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

Maximum score: 66

Examples of items:

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

RULM

Evaluates Motor Performance in Upper Limbs

ABLE TO:

- **Bring Token to Cup** placed vertically at shoulder height
- **Bring Weight at Eye Level** using two hands

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

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

Evaluated upper limb tasks correspond to ability to perform everyday activities

Maximum score: 37

Examples of items:

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

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

Activities of Daily Living and Fatigue: Assessed by Three Measures

PEDI-CAT, PROMIS, and ESBBT

Used to assess:

- ADL
- Fatigue
- Muscle Endurance

1 PEDI-CAT:

Measure of activities of daily living

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

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

2 PROMIS (Fatigue):

Measure of Patient Fatigue

PRO measurement tool[4]

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

3 ESBBT (Fatigability):

Measure of how fast a patient fatigues

Muscle endurance measurement tool[6]

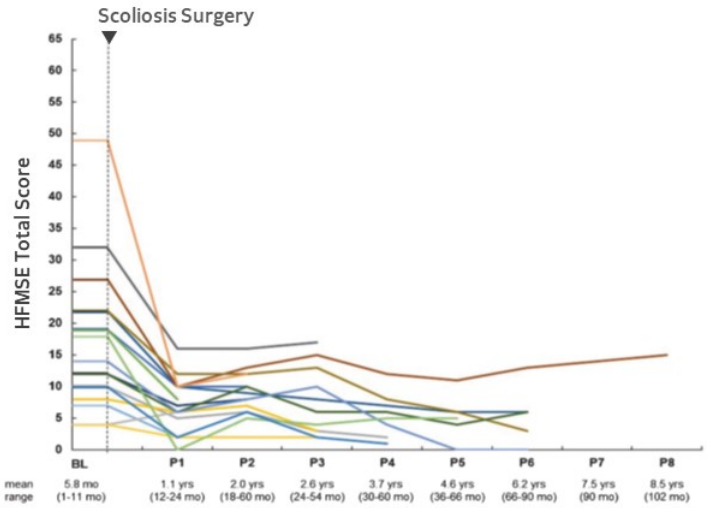
- Part of a series of endurance shuttle tests that include: nine-hole peg test, box and block test, and walk test (ESNHPT, ESBBT, and ESWT)[6]
- Patients are asked to move blocks individually from one box to another in one minute, with **higher numbers of blocks suggesting higher muscle endurance**[6]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

ADL, activities of daily living; ESBBT, endurance shuttle box and block test; ESNHPT, endurance shuttle nine-hole peg test; ESWT, endurance shuttle walk test; PEDI-CAT, pediatric evaluation of disability inventory computer adaptive test; PROMIS, patient-reported outcomes measurement information system; PRO(s), patient-reported outcome(s); SMA, spinal muscular atrophy. 1. Cre Care. PEDI-CAT. Accessed April 26, 2022. https://www.pedicat.com/. 2. Data on file: Scholar Rock. 2022. 3. Pasternak A, et al. *Muscle Nerve*. 2016;54(6):1097-1107. 4. NIH. PROMIS. Accessed April 26, 2022. https://commonfund.nih.gov/promis/index. 5. Belter L, et al. *Orphanet Journal of Rare Diseases*. 2020;15:217. 6. Cure SMA. Best Practices for Physical Therapists and Clinical Evaluators in Spinal Muscular Atrophy (SMA). 2021. Available at: https://www.curesma.org/wp-content/uploads/2021/09/Clinical-Evaluators-Best-Practices-13-August-2021.pdf. 7. Bartels B, et al. *Orphanet Journal of Rare Diseases*. 2020;15:75.

Reported Impact of Scoliosis Surgery on Motor Abilities in SMA

Post-Surgery HFMSE scores Type 2/3 SMA

peer-reviewed study

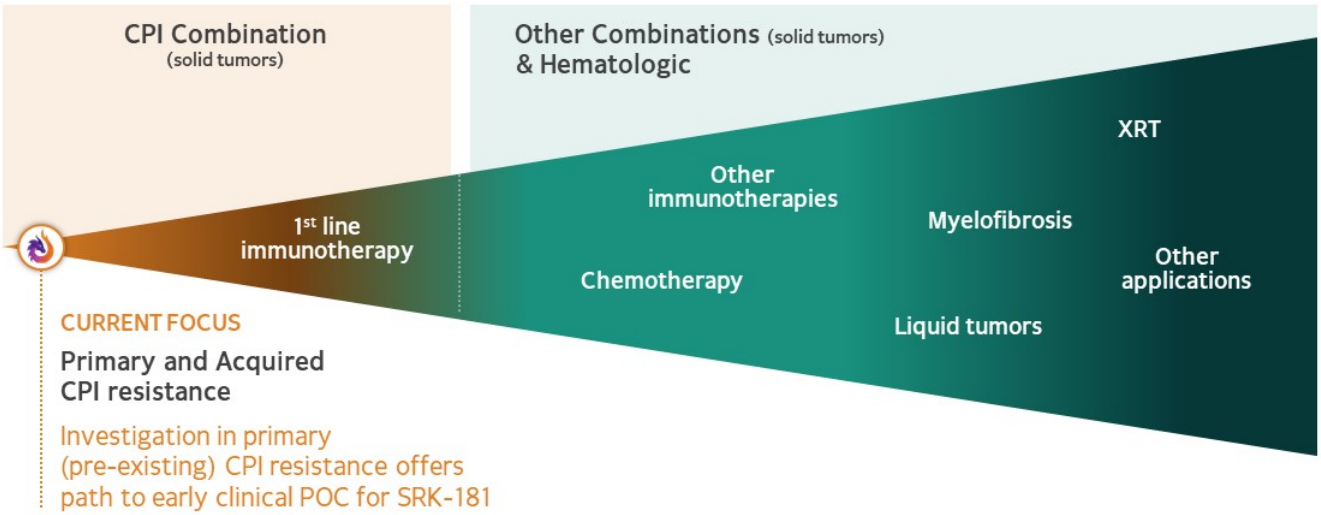


3-month post-surgery assessment

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

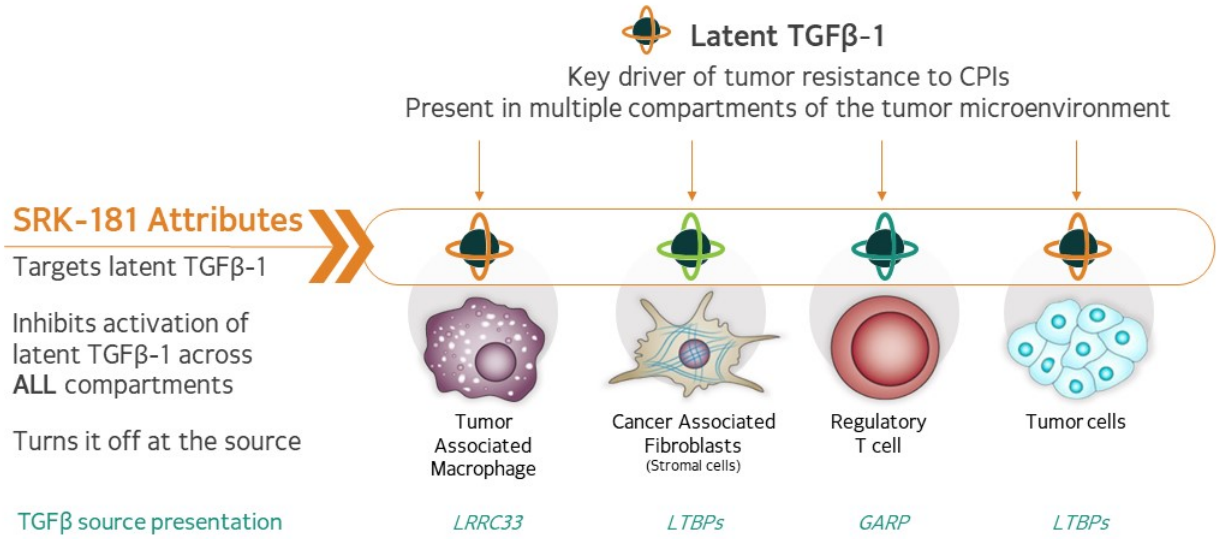
Dunaway Young et al. 2020

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 Designed to Inhibit Latent TGFβ-1 Across All Compartments of the Tumor Microenvironment



TGFβ Latent growth factor

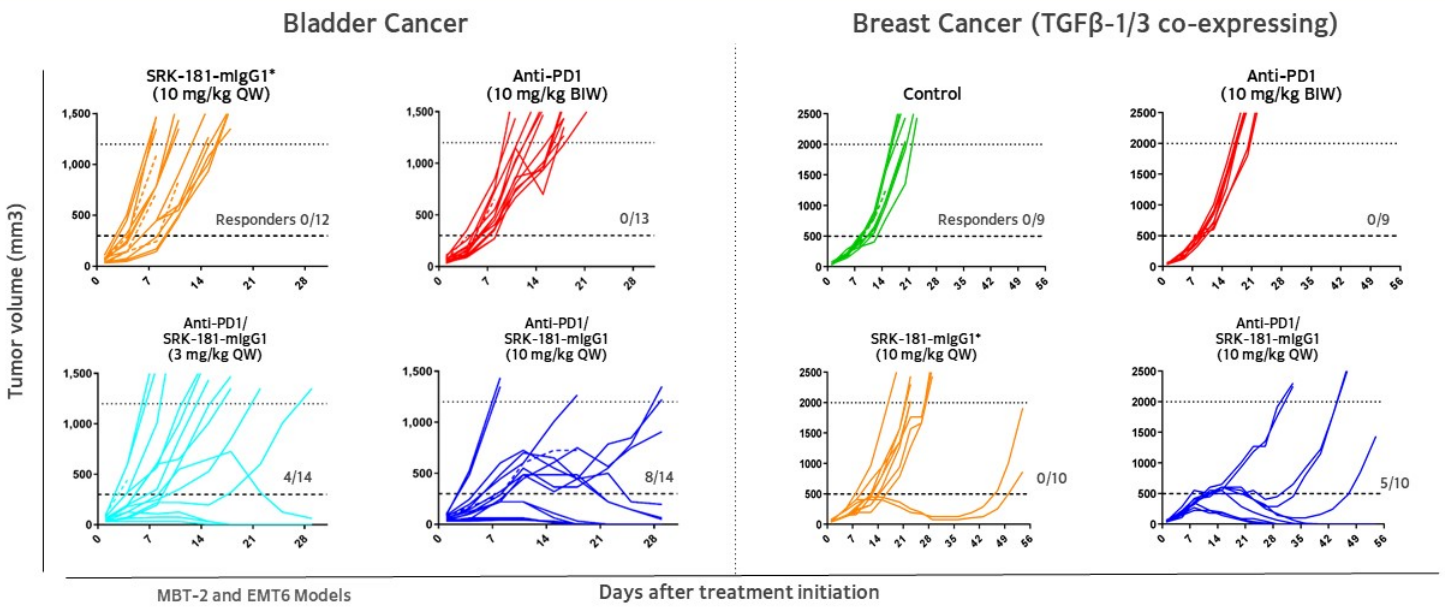
LRRC33: leucine-rich-repeat-containing protein family member 33 | LTBPs: latent transforming growth factor β binding proteins | GARP: glycoprotein A repetitions predominant

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

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

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

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

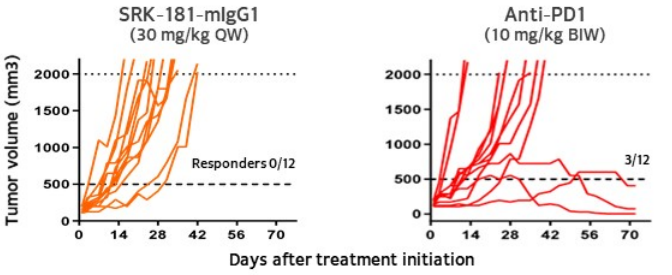


Preclinical data published in Science Translational Medicine. Martin CJ, et al. Sci Transl Med. 2020 Mar 25;12(536):eaay8456. https://scholarrock.com/platform/publications/.
*SRK-181-mIgG1 is the murine version of SRK-181; responder defined as tumor size <25% endpoint volume at study end.

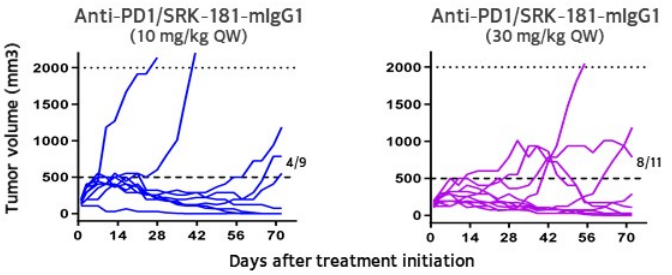
SRK-181-mIgG1 Combination Treatment Led to Melanoma Tumor Regression and Survival Benefit

Tumor Regression

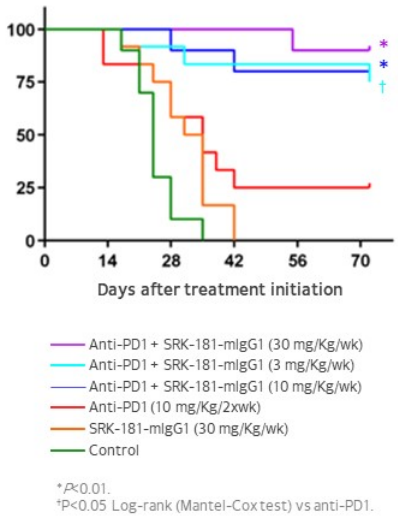
Monotherapy



Combination Therapy
Led to tumor regression and survival benefit



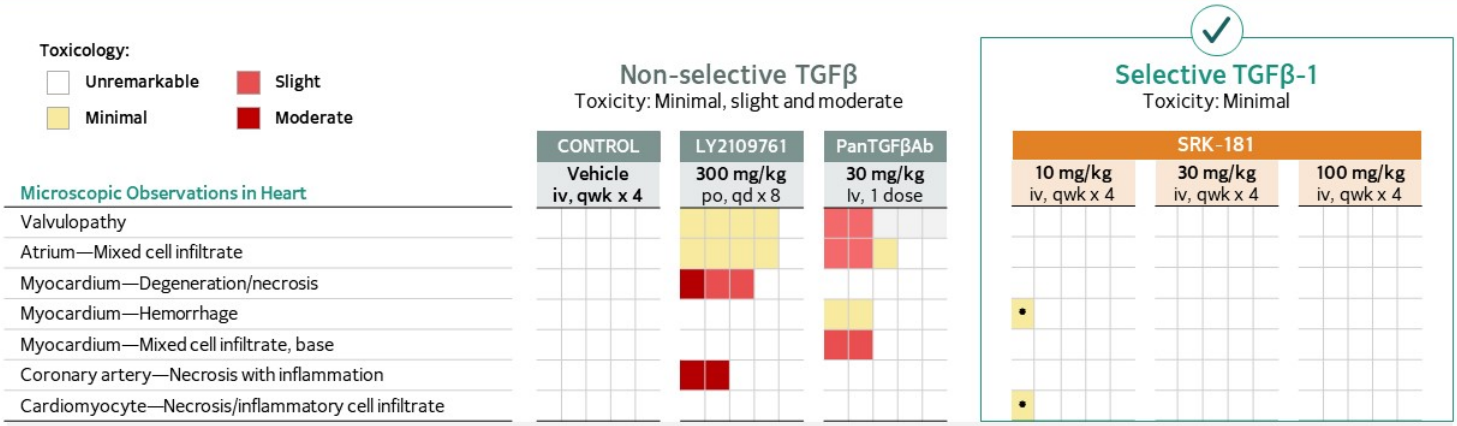
Survival Benefit



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

Melanoma (Cloudman S91) model
Preclinical data published in Science Translational Medicine. Martin CJ, et al. Sci Transl Med. 2020 Mar 25;12(536):eaay8456. https://scholarrock.com/platform/publications.

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



• Not test article related

Repeat Dose Pilot Toxicology Study

Adult female Sprague Dawley rats

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

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

4-week GLP toxicology studies

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

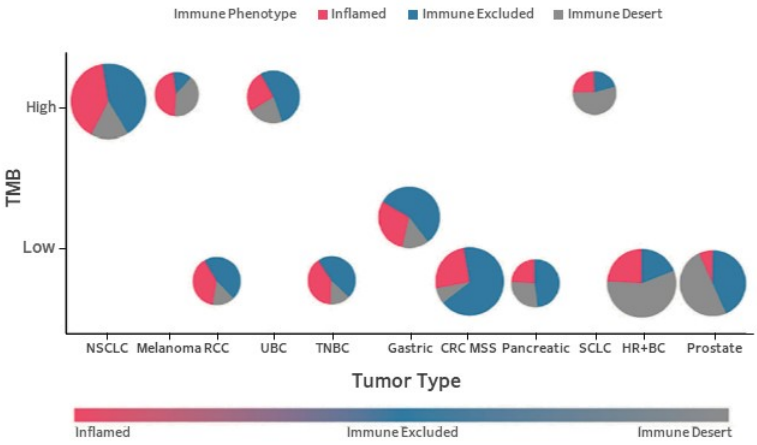
NON-HUMAN PRIMATES
NOAEL for SRK-181: 300 mg/kg
(highest dose evaluated)

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

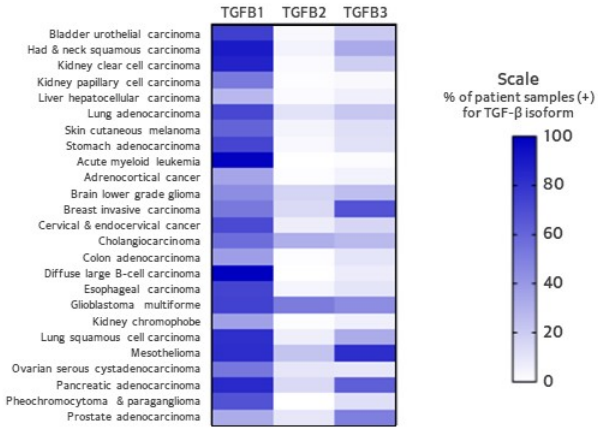
*Source: Anderton MJ, et al. Induction of heart valve lesions by small-molecule ALK5 inhibitors. *Toxicol Pathol*. 2011;39: 916-924.; and Stauber AJ, et al. Nonclinical safety evaluation of a transforming growth factor β Receptor I kinase inhibitor in Fischer 344 rats and beagle dogs. *J Clin Pract*.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

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

Substantial % of Solid Tumors Exhibit Immune Exclusion



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



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

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

Biomarker Strategies Employed in DRAGON Trial

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

Immunophenotyping
Assessment of immune landscape

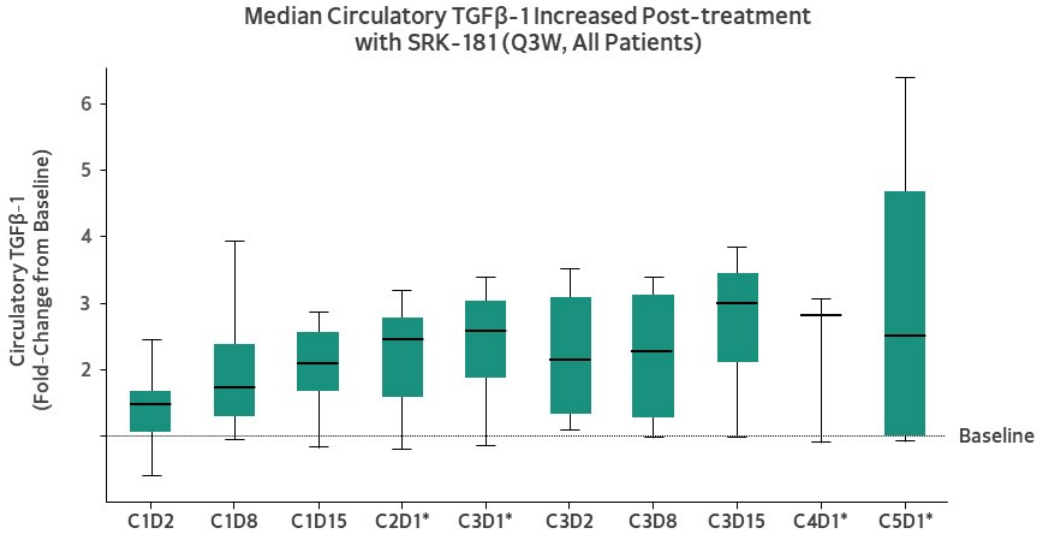
- Higher resolution histochemical characterization of tumor immune contexture (e.g. CD8+)
  - Classification of inflamed, excluded or immune desert tumors and tumor nests
  - Ability of SRK-181 to overcome tumor immune exclusion
- Analysis of immune response markers (e.g. PD-L1)
- Changes to intra-tumoral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

TGFβ-1 pathway evaluation
Assessment of signaling pathway

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

Clear Evidence of Target Engagement

Pharmacodynamic Biomarker Results for Part A: Circulatory TGFβ-1



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

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

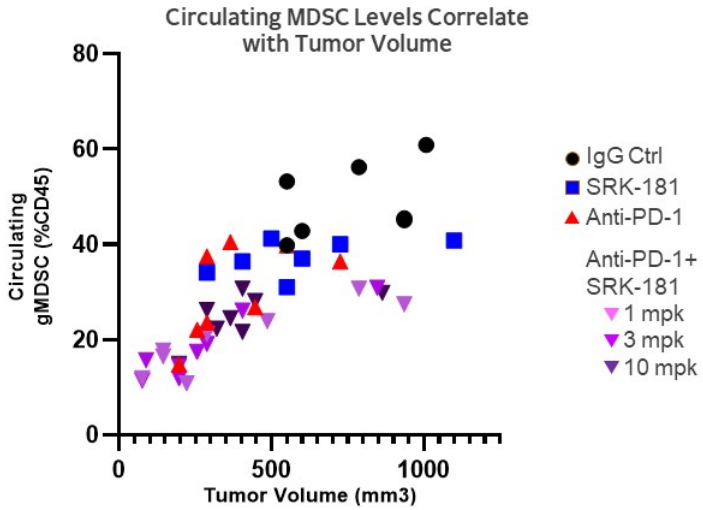
Yap T et al. SRK-181, a latent TGFβ1 inhibitor: safety, efficacy, and biomarker results from the dose escalation portion of a phase I trial (DRAGON trial) in patients with advanced solid tumors (Poster 780); Presented at SITC; Nov. 10-11, 2022. Circulatory TGFβ-1 and PF4 levels were quantitated by using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

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

Immunophenotyping
Assessment of immune landscape

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

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



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

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