



# Deep Insights, Impactful Medicines

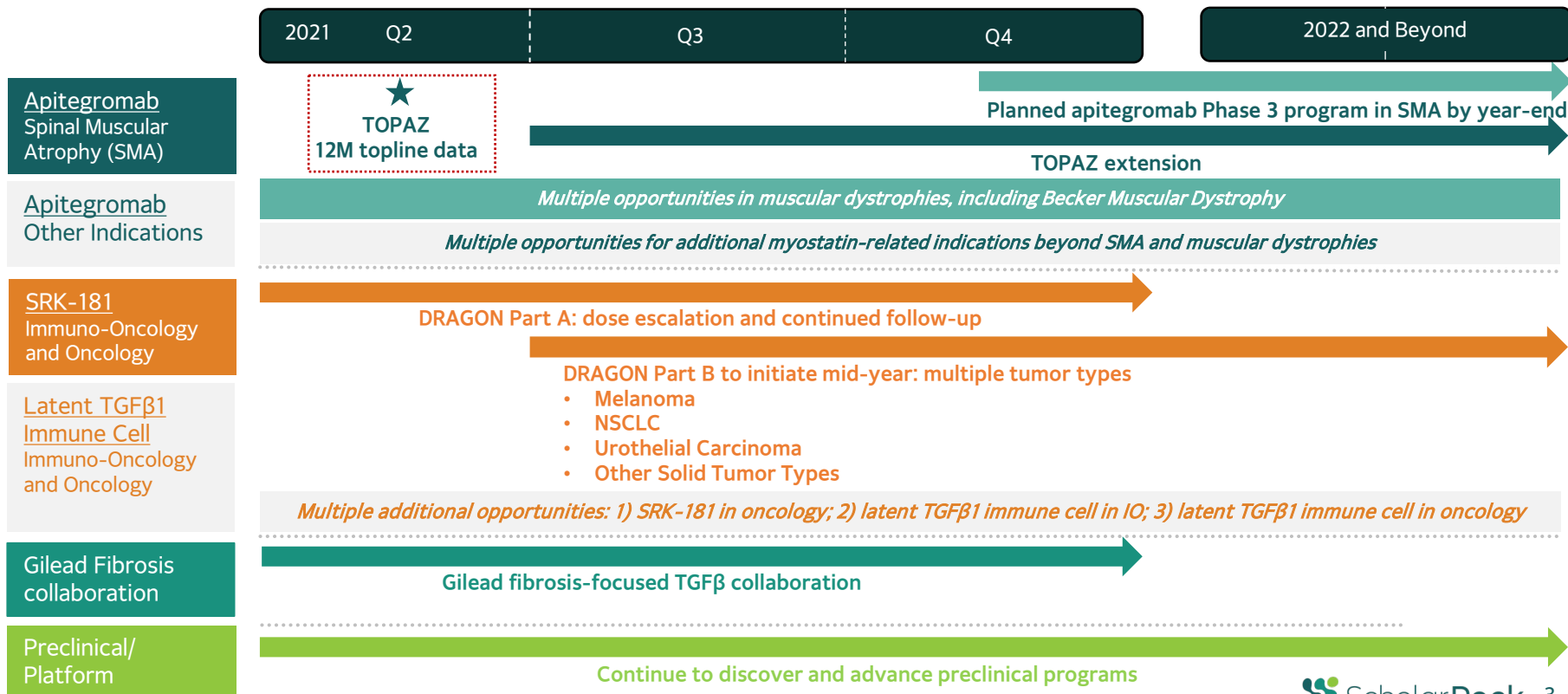
May 2021



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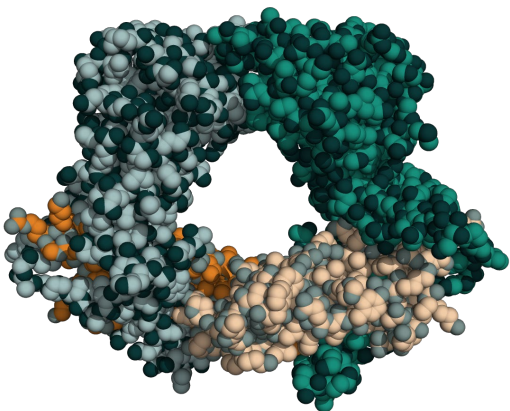
# 2021: Potential for Another Transformative Year



# Bringing a Revolutionary Approach to Highly Sought-After Growth Factors Implicated in Devastating Diseases

## Scholar Rock's Target

*Growth Factor Precursor (Latent Form)*



## Scholar Rock's R&D Platform

*Transform Medical Practice*

- Pursue important targets with well-validated biology but are difficult to drug
- Apply revolutionary approach to tough targets
  - Leverage deep insights into structure and function
  - Engineer antibodies to deliver differentiated therapeutic profiles (i.e. exquisite selectivity)

TOPAZ demonstrated the therapeutic potential of inhibiting the latent forms of growth factors



# Apitegromab: Transformative Potential Demonstrated in TOPAZ Phase 2 Trial for Patients with Type 2 and 3 SMA

# Apitegromab Positioned to be Next Potential Transformative Therapy for Patients Suffering with SMA

- ✓ Spinal Muscular Atrophy (SMA) remains a devastating and debilitating illness despite the availability of SMN upregulators
  - To improve motor function, a muscle-directed approach like apitegromab is needed to complement the disease stabilizing effects of SMN upregulators
- ✓ Apitegromab demonstrated transformative potential in SMA through the TOPAZ Phase 2 trial, especially in non-ambulatory Type 2 and 3 patients
  - **Patients 2-6 years of age:** +7.1-point increase in HFMSE and 63% attained a  $\geq 3$ -point increase with 20 mg/kg dose
  - **Patients 8-19 years of age:** +1.2-point\* increase in HFMSE and 31% attained a  $\geq 3$ -point increase
  - Non-ambulatory Type 2 and 3 patients represent  $\sim 2/3$  of overall population
- ✓ TOPAZ results offer exciting path forward for investigating apitegromab in a rational, targeted, and efficient Phase 3 trial in non-ambulatory Type 2 and 3 patients

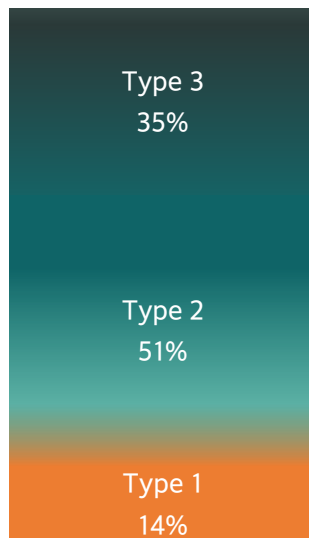
# Spinal Muscular Atrophy Overview

Global disease with 30,000-35,000 affected in U.S. and Europe alone

- Significant, progressive motor function impairment, many lose ambulation

- Severe, progressive disabilities and Unable to walk independently

- Infantile onset; unable to sit up independently



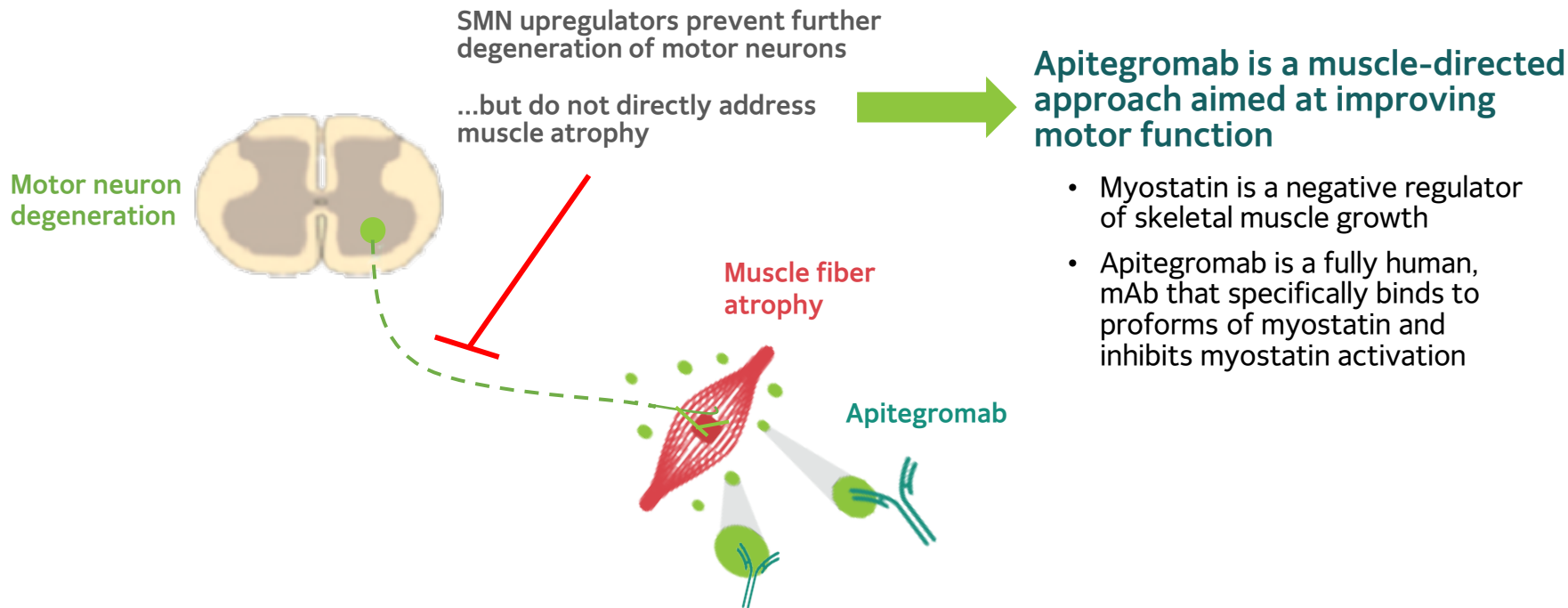
TOPAZ\* 12-month results demonstrated transformative efficacy in non-ambulatory Type 2 and 3 patients

Represents ~2/3 of overall patient population

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

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

# Apitegromab: Muscle-Directed Therapy Aimed at Complementing SMN Upregulators





# Stage is Set for New Treatment Era: *Muscle-Directed Therapy + SMN Upregulators*



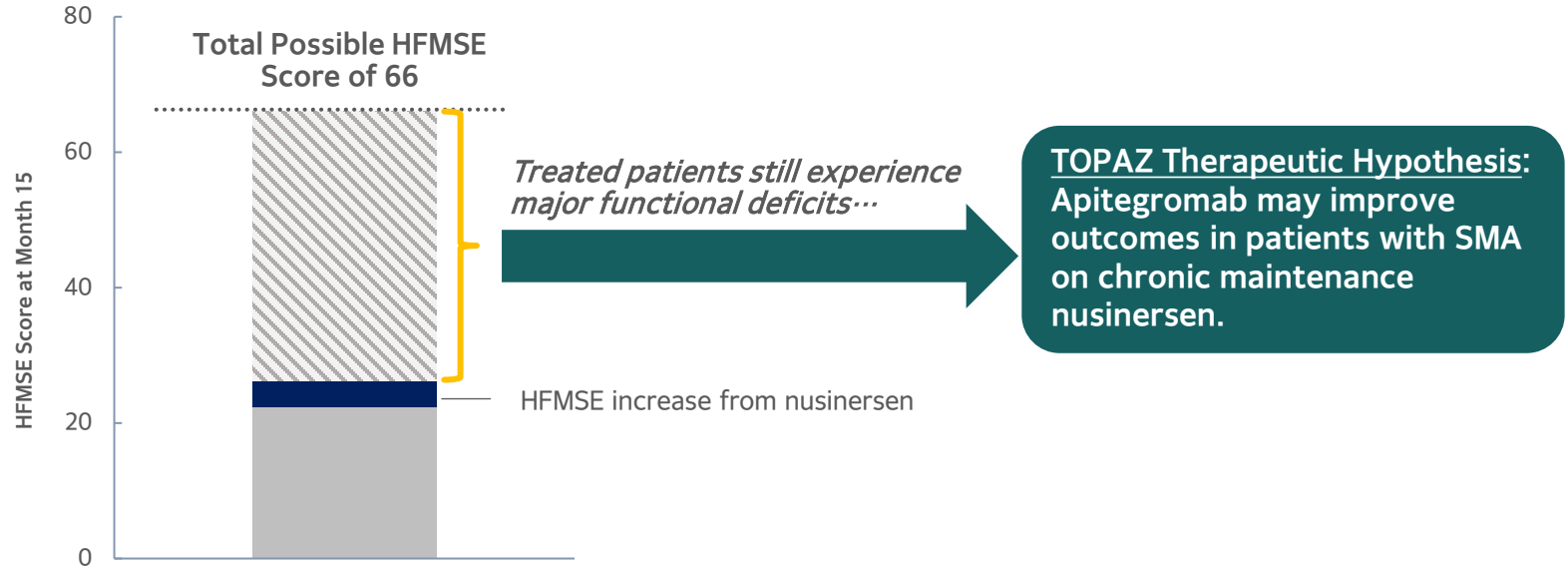
Phase 3 Trial Design	<ul style="list-style-type: none"> <li>Non-ambulatory Type 2/3</li> <li>2-12 years of age</li> <li><b>Primary endpoint:</b> Mean change from baseline in HFMSE at 15 months</li> </ul>	<ul style="list-style-type: none"> <li>Non-ambulatory Type 2/3</li> <li>2-25 years of age</li> <li><b>Primary endpoint:</b> Mean change from baseline in MFM-32 at 12 months</li> </ul>	<ul style="list-style-type: none"> <li>Infantile-onset Type 1</li> <li>&lt;6 months of age</li> <li><b>Primary endpoints:</b> Ability to sit independently and event-free survival</li> </ul>
Indication	<ul style="list-style-type: none"> <li>Type 1, 2, and 3 SMA in pediatric and adult patients</li> </ul>	<ul style="list-style-type: none"> <li>Type 1, 2, 3 SMA in patients 2 months of age and older</li> </ul>	<ul style="list-style-type: none"> <li>Approved for SMA less than 2 years of age</li> </ul>
Market Penetration	<ul style="list-style-type: none"> <li>&gt;11,000* patients treated WW</li> <li>\$2+ billion in revenues (LTM)</li> </ul>	<ul style="list-style-type: none"> <li>~3,000** patients treated WW</li> <li>~CHF135 million in revenues (LTM)</li> </ul>	<ul style="list-style-type: none"> <li>~1,200*** patients treated WW</li> <li>~\$1.1 billion in revenues (LTM)</li> </ul>
Persistent Need	<ul style="list-style-type: none"> <li>Major functional deficits remain</li> <li>HFMSE improvements only in younger patients and rapidly plateaus</li> </ul>	<ul style="list-style-type: none"> <li>Major functional deficits remain</li> <li>Increases in MFM-32 primarily limited to youngest patients</li> <li>HFMSE effects not as pronounced</li> </ul>	<ul style="list-style-type: none"> <li>Limited data and eligibility for use beyond very young patients</li> </ul>

\*As of 1Q21 financial update on 4/22/21; includes patients treated worldwide in post-marketing setting, expanded access program, and clinical trials.

\*\*As of 1Q21 financial update on 4/21/21; includes patients treated worldwide between clinical trials, commercial, and compassionate use program.

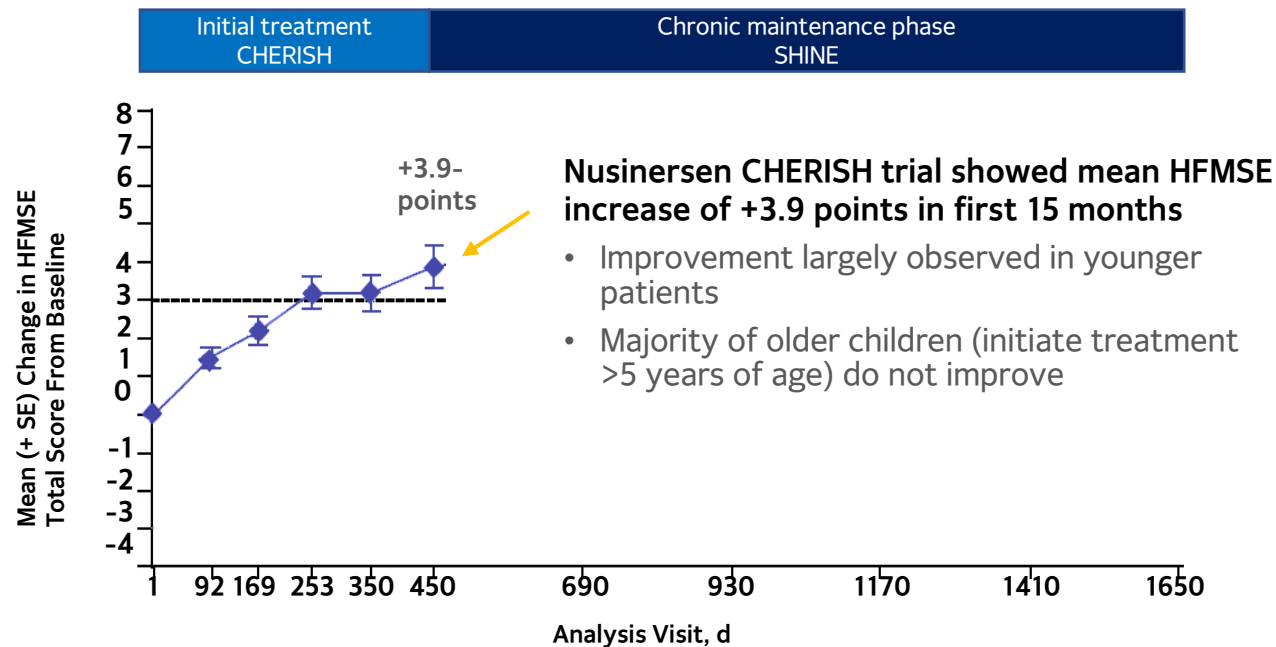
\*\*\*As of 1Q21 financial update on 4/27/21; commercially, via managed access programs and in clinical trials

# Patients Continue to Experience Major Functional Deficits Despite Availability of Multiple SMN Upregulator Therapies



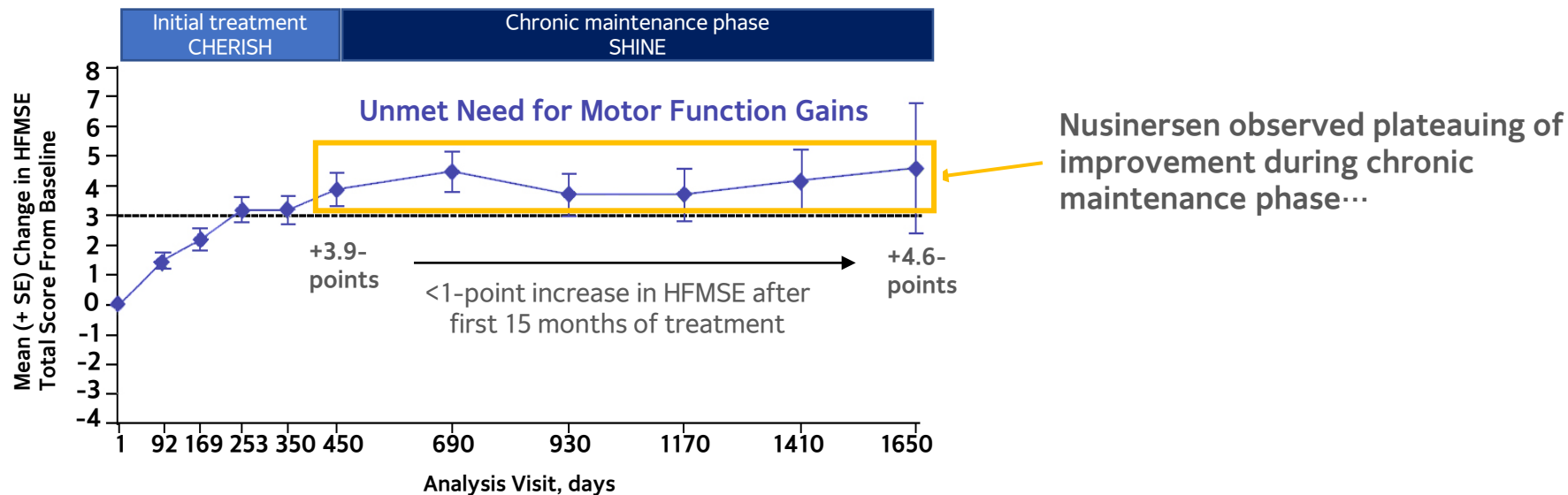
*Mean improvement in HFMSE score experienced by patients with non-ambulatory Type 2/3 SMA in the Phase 3 CHERISH clinical trial of nusinersen*

# Non-Ambulatory Type 2/3 SMA: Nusinersen Offers HFMSE Increases Primarily in First Year of Treatment



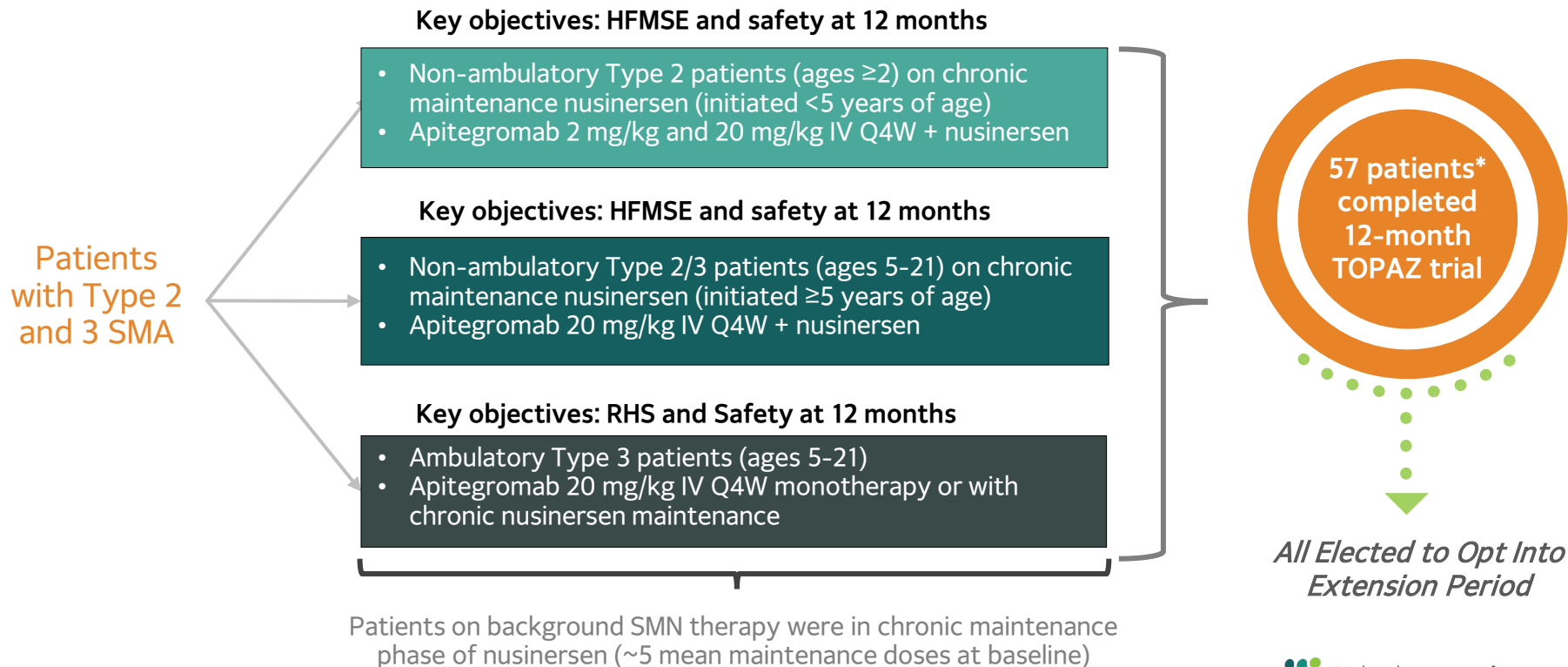
Most nusinersen-treated patients in CHERISH were <5 years at therapy initiation

# Plateauing of Nusinersen Effect Observed Post Initial 15 Months of Treatment in Non-Ambulatory Type 2/3 SMA



Most nusinersen-treated patients in CHERISH were <5 years at therapy initiation

# Apitegromab Phase 2 Trial Design



\*Excludes one patient from Cohort 1 that discontinued from the trial

# Baseline Characteristics

*Nusinersen-treated patients well into chronic maintenance phase*



	Non-Ambulatory, Ages 2-6			Non-Ambulatory, Ages 8-19	Ambulatory		
	20 mg/kg +nusinersen	2 mg/kg +nusinersen	Pooled	20 mg/kg +nusinersen	20 mg/kg monotherapy	20 mg/kg +nusinersen	Pooled
N	10	10	20	15	11	12	23
Mean age (min, max)	3.8 (2, 6)	4.1 (2, 6)	4.0 (2, 6)	11.7 (8, 19)	12.1 (7, 19)	13.1 (7, 21)	12.6 (7, 21)
Mean RHS score (min, max)					47.6 (26, 63)	51.3 (43, 62)	49.6 (26, 63)
Mean HFMSE score (min, max)	23.5 (14, 42)	26.1 (12, 44)	24.8 (12, 44)	22.7 (13, 39)			
Mean # of nusinersen maintenance doses (min, max)	5.4 (3, 8)	5.5 (2, 9)	5.5 (2, 9)	5.1 (2, 9)	N/A	5.6 (2, 8)	N/A
SMN2 Gene Copy* (#, %)							
2	1 (10%)	1 (10%)	2 (10%)		1 (9%)	0 (0%)	1 (4%)
3	8 (80%)	8 (80%)	16 (80%)	11 (73%)	4 (36%)	9 (75%)	13 (57%)
4	0 (0%)	1 (10%)	1 (5%)	2 (13%)	4 (36%)	1 (8%)	5 (22%)
Discontinuation(s)	0	0	0	0	0	1**	1**

\*Data not available for all patients

\*\*Patient who discontinued study for reasons unrelated to study drug

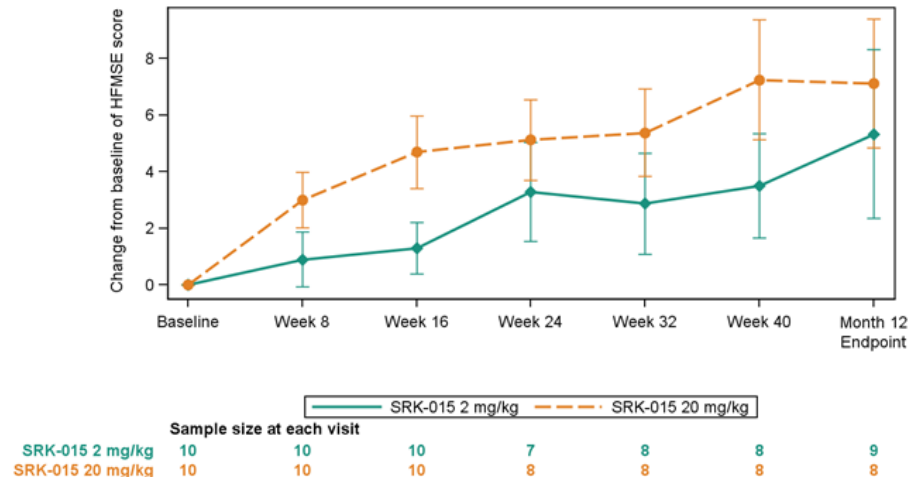
HFMSE=Hammersmith Functional Motor Scale Expanded; RHS=Revised Hammersmith Scale

Data on file. Scholar Rock, Inc. Cambridge, MA

# Non-Ambulatory Cohort (Ages 2-6): Sizable HFMSE Increases of Up to 20-points



Non-Ambulatory Type 2 SMA (Intent-to-Treat Population)	Apitegromab 20 mg/kg + nusinersen (n=8)	Apitegromab 2 mg/kg + nusinersen (n=9)	Pooled (n=17)
Mean change from baseline in HFMSE (95% CI)	+7.1 (1.8, 12.5)	+5.3 (-1.5, 12.2)	+6.2 (2.2, 10.1)
# (%) patients achieving ≥1-pt increase in HFMSE	7/8 (88%)	7/9 (78%)	14/17 (82%)
# (%) patients achieving ≥3-pt increase in HFMSE	5/8 (63%)	5/9 (56%)	10/17 (59%)
# (%) patients achieving ≥5-pt increase in HFMSE	5/8 (63%)	5/9 (56%)	10/17 (59%)

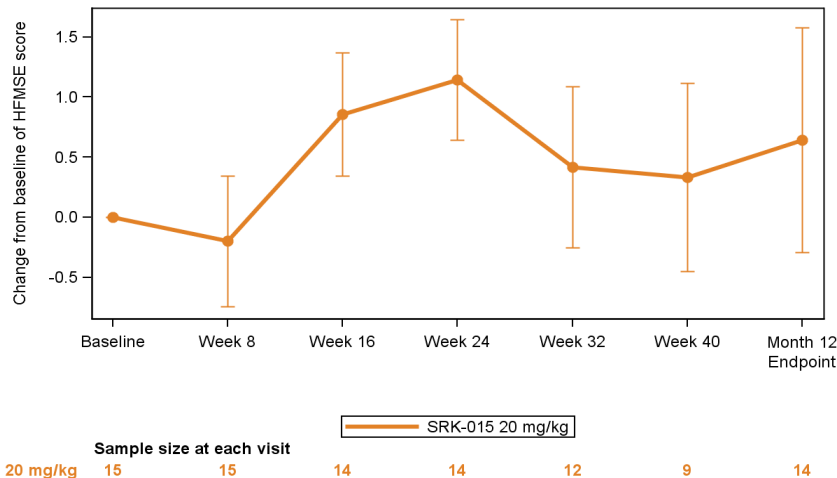


- 35% (6/17) with >10-point increase in HFMSE
  - Up to 20-point increases in HFMSE observed
- Sizable, dose-dependent increases in HFMSE observed in patients already on chronic maintenance nusinersen
  - Durable and continuous improvements observed through 12-months
- CHERISH and SHINE nusinersen studies suggest substantial HFMSE increases do not occur in younger patients following first year of treatment

# Non-Ambulatory Cohort (Ages 8-19): Majority of Patients Attained Increases in HFMSE



Non-Ambulatory Type 2 and Type 3 SMA	Apitegromab (20 mg/kg) + nusinersen Per Protocol Population* (n=13)	Apitegromab (20 mg/kg) + nusinersen 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 $\geq 1$ -pt increase in HFMSE	9/13 (69%)	9/14 (64%)
# (%) patients achieving $\geq 3$ -pt increase in HFMSE	4/13 (31%)	4/14 (29%)
# (%) patients achieving $\geq 5$ -pt increase in HFMSE	2/13 (15%)	2/14 (14%)



- Majority of patients attained increases in HFMSE
  - ~30% achieved  $\geq 3$ -point increase in HFMSE
  - Durability of effect observed through 12-months
- Improvements not seen with other therapies in this older patient population
  - Patients already on chronic maintenance nusinersen
- CHERISH data suggest older patients on average observe declines and rarely observe a 3-point increase in HFMSE

\*Patient had concomitant exposure to an acetylcholinesterase inhibitor, which is not permitted per the TOPAZ trial protocol  
Data on file. Scholar Rock, Inc. Cambridge, MA



# Safety Results from TOPAZ 12-Month Top-Line Analysis

## Support Evaluation of Apategromab in Phase 3 Trial

Treatment-emergent adverse events (TEAEs)	Apategromab 2 mg/kg (n=10)	Apategromab 20 mg/kg (n=48)	Total (n=58)
Any TEAE	9 (90.0%)	44 (91.7%)	53 (91.4%)
Any Serious TEAE	1 (10.0%)	4 (8.3%)	5 (8.6%)
Any TEAE leading to study drug discontinuation	0 (0.0%)	1 (2.1%)	1 (1.7%)
Any Grade 3 (severe) or higher TEAE	0 (0.0%)	3 (6.2%)	3 (5.2%)

- **Five most frequently reported TEAEs\***: Headache (24%), pyrexia (22%), upper respiratory tract infection (22%), cough (22%), and nasopharyngitis (21%).
- SAEs, Grade 3 AEs and AE leading to early study discontinuation were all assessed by investigators as unrelated to study drug
- **Anti-drug antibodies (ADA)** were present at low titers following apitegromab treatment in 3 out of 58 enrolled patients. No apparent impact on drug exposure was observed and was not associated with any hypersensitivity reactions.
- No safety signals identified as of the TOPAZ 12-month top-line analysis.

Incidence and severity of AEs were consistent with the underlying patient population and background therapy

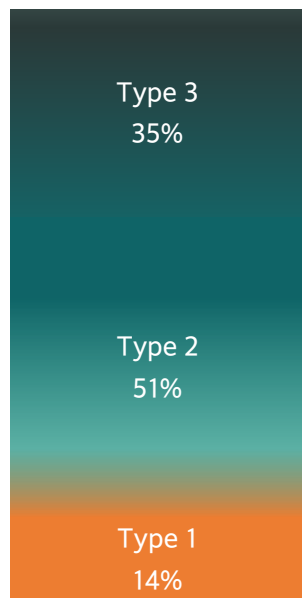
*Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug or start prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug.*

*\*TEAE rates are across all patients in TOPAZ trial*

*Data on file. Scholar Rock, Inc. Cambridge, MA*

# Initial Regulatory Strategy Focuses on Non-Ambulatory Patients on Background SMN Therapy

Global disease with  
30,000-35,000 affected in  
U.S. and Europe alone



1

## Apitegromab in non-ambulatory Type 2 and 3 with background SMN upregulators

- Represents 2/3 of overall patients
- Many patients already treated with or are eligible for SMN upregulator therapy
- Improvements in motor function on top of SMN upregulators observed in TOPAZ

2

## Type 1 patients, including those treated with gene therapy

- Highest incidence population and growing prevalence due to SMN upregulator treatment
- TOPAZ showed benefits of early treatment suggesting potential in Type 1 patients

3

## Ambulatory patients

- Smaller population but high unmet need as benefits of SMN regulators not well-established
- TOPAZ suggests potential clinical benefit in a subset of patients

Anticipated  
Focus of  
Phase 3 Trial

# Preliminary Thoughts on Apitegromab Phase 3 Trial Design

Registrational  
trial design  
subject to  
regulator  
interactions and  
feedback

## Design

- 12-month treatment period
- Apitegromab IV Q4W as add-on to nusinersen or risdiplam
- TOPAZ data support investigation of 20 mg/kg dose

## Subjects

- Non-ambulatory Type 2 and Type 3 SMA
- Pediatric population in chronic maintenance phase of SMN therapy

## Key Objectives

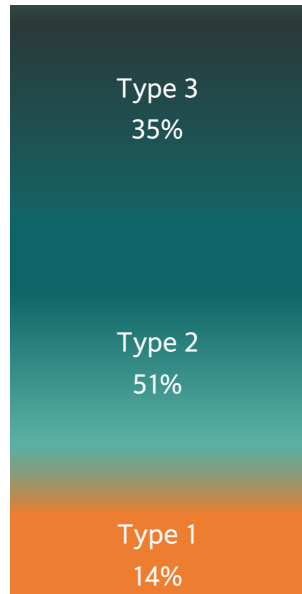
- HFMSE
- Safety

## Timeline

- Aim to initiate by end of 2021

# Additional Opportunities May Be Pursued With Separate Regulatory Strategies

Global disease with  
30,000-35,000 affected in  
U.S. and Europe alone



1

Apitegromab in non-ambulatory Type 2 and 3 with background SMN upregulators

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Type 1 patients, including those treated with gene therapy

- Highest incidence population and growing prevalence due to SMN upregulator treatment
- TOPAZ showed benefits of early treatment suggesting potential in Type 1 patients

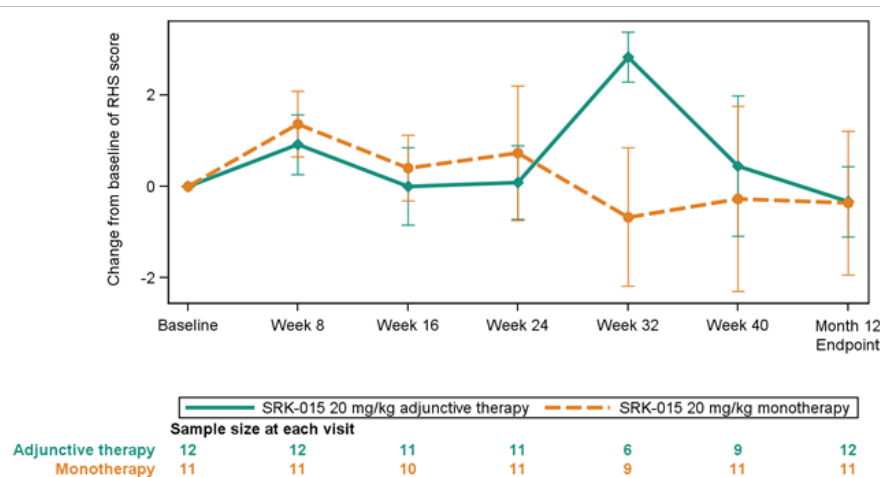
3

Ambulatory patients

- Smaller population but high unmet need as benefits of SMN regulators not well-established
- TOPAZ suggests potential clinical benefit in a subset of patients

# Majority of Ambulatory Patients Maintained or Improved in RHS Score from Baseline

Ambulatory Type 3 SMA (Intent-to-Treat Population)	Apitegromab (20 mg/kg) monotherapy (n=11)	Apitegromab (20 mg/kg) + nusinersen (n=12)	Pooled (n=23)
Mean change from baseline in RHS (95% CI)	-0.4 (-3.9, 3.1)	-0.3 (-2.0, 1.4)	-0.3 (-2.1, 1.4)
# (%) patients achieving $\geq 0$ -pt increase in RHS	6/11 (55%)	7/12 (58%)	13/23 (57%)
# (%) patients achieving $\geq 1$ -pt increase in RHS	4/11 (36%)	5/12 (42%)	9/23 (39%)
# (%) patients achieving $\geq 3$ -pt increase in RHS	3/11 (27%)	2/12 (17%)	5/23 (22%)



- Majority of patients maintained or improved
  - 57% (13/23) with  $\geq 0$ -point increase in RHS
  - 39% (9/23) with  $\geq 1$ -point increase in RHS
  - Increases of up to 8-points observed
- Potential signal for therapeutic benefit observed in this population

# Additional TOPAZ Data and Analyses Will Further Our Understanding of Apitegromab's Potential in SMA

*TOPAZ trial enrolled  
in ~8 months*



*All Elected to Opt Into  
Extension Period*



- Exploratory analyses, including patient-level data
- Additional outcome measures
- Additional safety data



Plan to present 12-month top-line data and additional analyses at medical congresses in coming months

*\*Excludes one patient from Cohort 1 that discontinued from the trial*

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



# Significant Interest in Potential Role of TGF $\beta$ Inhibition in Immuno-Oncology

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

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

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

**February 2019:** *“GSK and Merck KGaA, Darmstadt, Germany announce global alliance to jointly develop and commercialise M7824, a novel immunotherapy with potential in multiple difficult-to-treat cancers”*

- €300 million upfront and up to €3.7 billion total

**June 2019:** *“Merck to Acquire Tilos Therapeutics: Merck Gains Portfolio of Investigational Antibodies Modulating TGF $\beta$ ”*

- \$773 million total potential deal value

**Cell**

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

Authors

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

Article

NATURE REVIEWS | CLINICAL ONCOLOGY

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

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

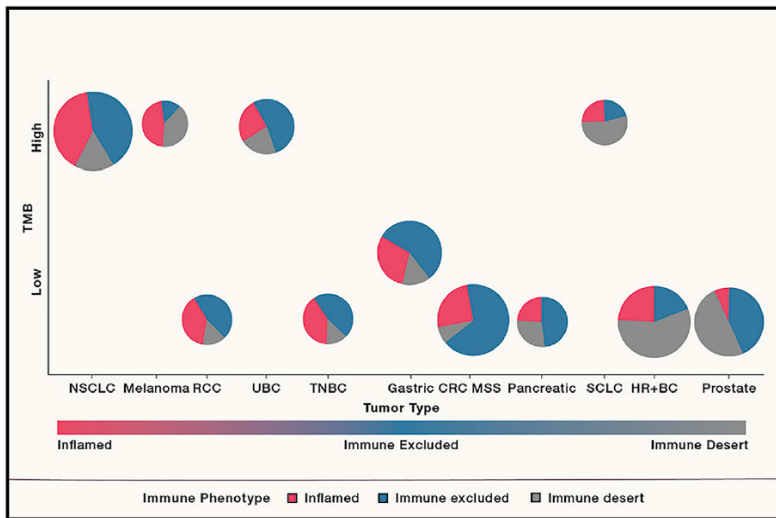
July 24, 2020: <https://doi.org/10.1038/s41571-020-0403-1>

**August 2020:** *“Bristol Myers Squibb Enters Agreement to Acquire Forbius TGF-beta Program”*

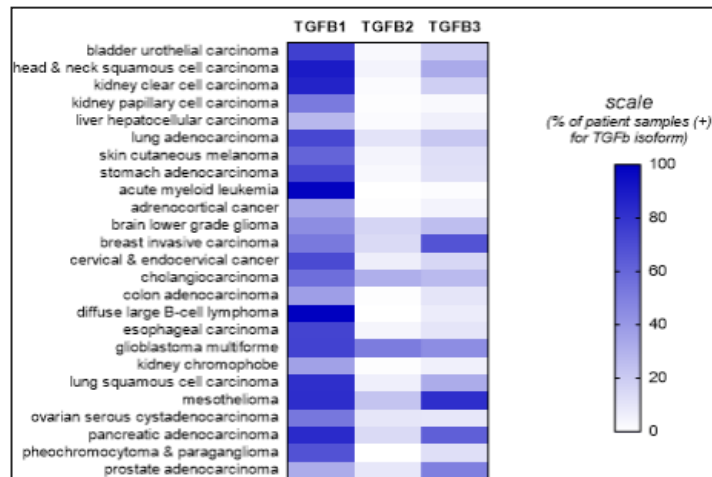


# Emerging Evidence Implicates TGF $\beta$ 1 as Driving Primary Resistance to Checkpoint Inhibitors

## Substantial % of solid tumors exhibit immune exclusion



## Cancer Genome Atlas RNAseq analysis of >10,000 samples spanning 33 tumor types\*



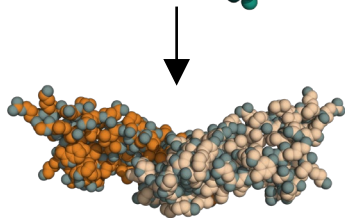
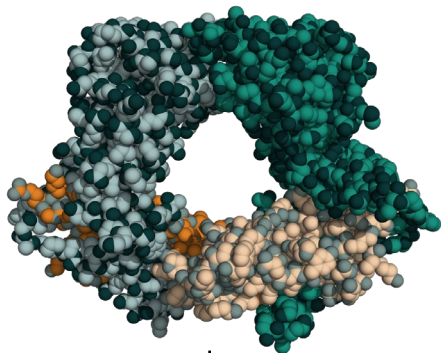
## Human Tumor Analyses Reveal TGF $\beta$ 1 as Most Likely Driver of TGF $\beta$ Signaling Pathway in Cancers

\*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.

# SRK-181: Unique TGF $\beta$ 1-Selective Approach to Overcoming Checkpoint Inhibitor Resistance

## Scholar Rock's Target SRK-181: Latent TGF $\beta$ 1 Inhibitor



Traditional target:  
"Mature" growth factor

- ✓ Inhibits TGF $\beta$ 1 pathway - implicated in CPI resistance
- ✓ Highly selective targeting - avoids inhibiting latent TGF $\beta$ 2 and TGF $\beta$ 3 isoforms
- ✓ Aimed at increasing therapeutic window - potentially avoids toxicities associated with non-selective TGF $\beta$  inhibition
- ✓ Therapeutic flexibility - pair with any CPI and optimize dosing of each component of combination therapy

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



## Part A

A1: SRK-181  
all-comers

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

A2: SRK-181+anti-PD-(L)1; non-  
responders to prior anti-PD-(L)1

SRK-181 240 mg (n=3)  
↓  
SRK-181 800 mg (n=3)  
↓  
SRK-181 1600 mg (n=3)  
↓  
SRK-181 2400 mg (n=3)  
↓  
Different dose regimen if  
needed (n=3)

## Part B

SRK-181 + anti-PD-(L)1; non-responders to prior anti-PD-(L)1  
n=up to 40/cohort

**Cohort A:** non-small cell  
lung cancer (NSCLC)

SRK-181 +  
pembrolizumab

**Cohort B:** urothelial  
carcinoma (UC)

SRK-181 +  
pembrolizumab

**Cohort C:** cutaneous  
melanoma

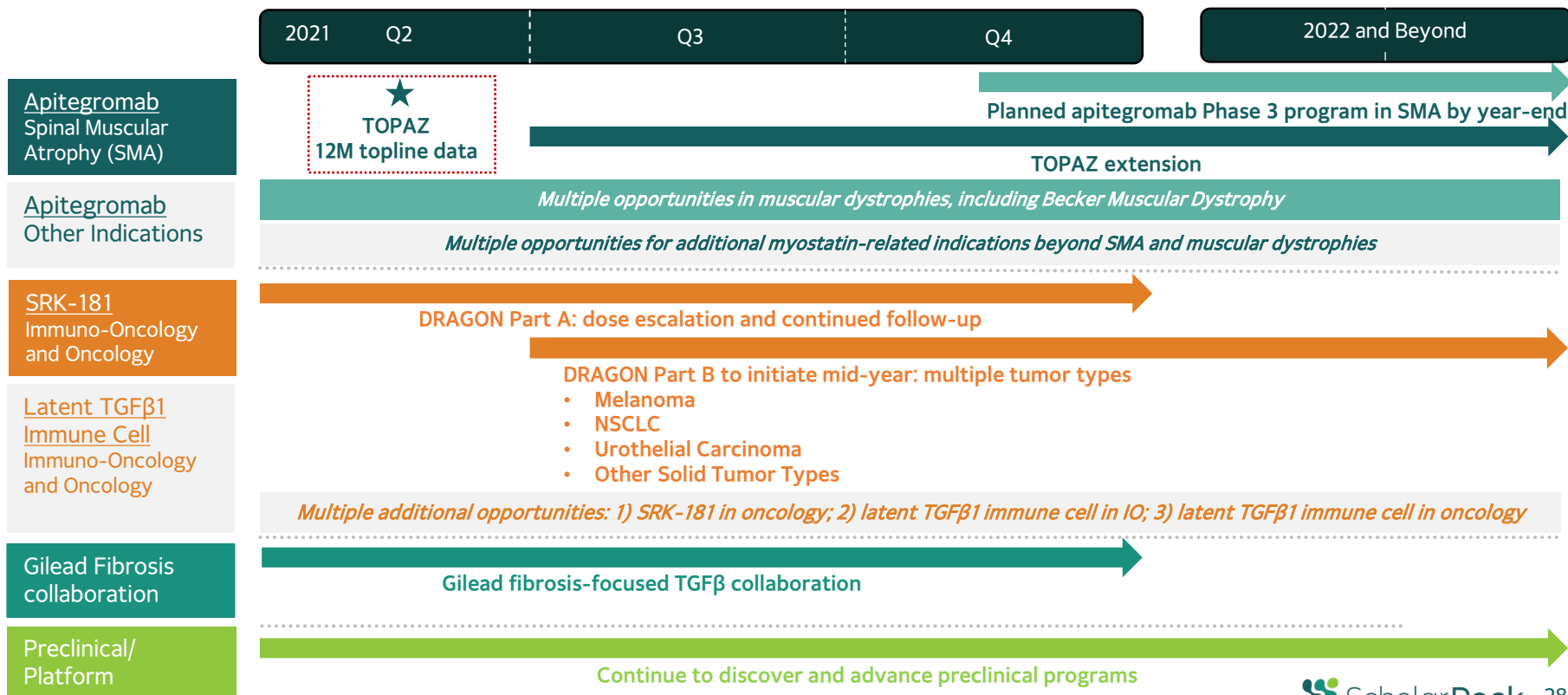
SRK-181 +  
pembrolizumab

**Cohort D:** Other  
solid tumor types

SRK-181 + any  
anti-PD-(L)1

- As of March 9, 2021:
  - Part A1: 3000 mg Q3W dose being evaluated
  - Part A2: 1600 mg Q3W dose being evaluated
- Part B initiation planned mid-year
- Initial clinical response and safety data anticipated by year-end 2021

# 2021: Potential for Another Transformative Year



# Appendix

# Apitegromab: Pairing the latent form with important translational insights

## Scholar Rock's Guiding Principles for Neuromuscular Indication Selection

Younger population



Genetic disorder with onset in childhood

At least partially intact innervation and no structural muscle abnormalities



Partial neural connectivity and atrophied muscles that largely retain structural integrity

Need for increase in fast-twitch muscle fibers



Substantial deficit in fast-twitch fibers

Clinical trial endpoint driven by fast-twitch fiber function

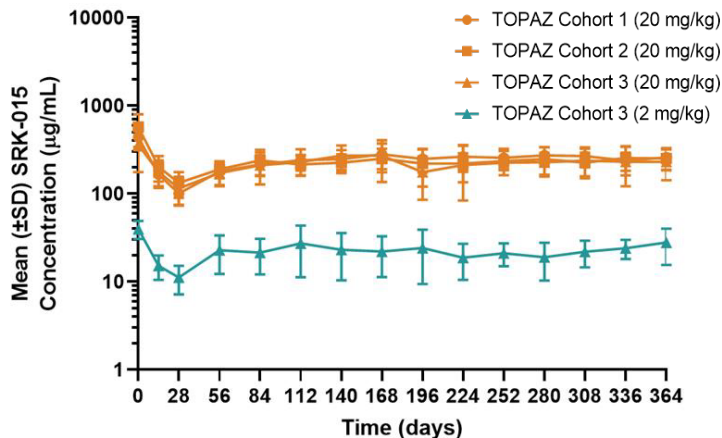


Fast-twitch fiber function has a prominent role in SMA outcome measures

## Key Characteristics of Spinal Muscular Atrophy (SMA)

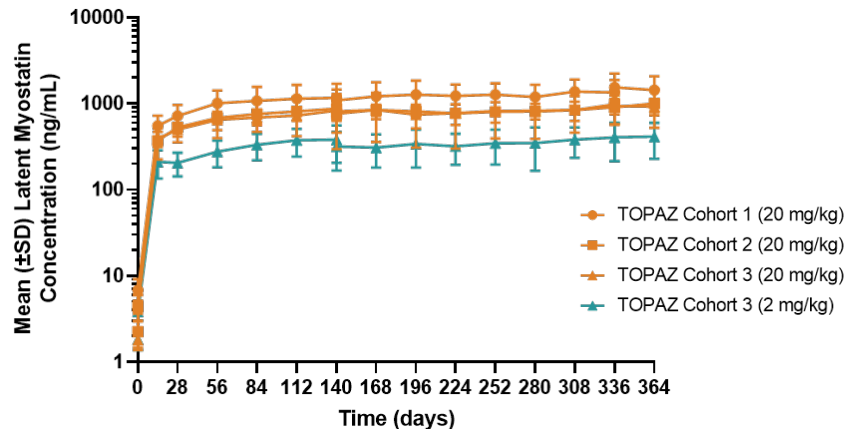
# Pharmacokinetic and Pharmacodynamic Data are Supportive of Clinically Observed Effects

## Pharmacokinetics\* (PK)



- Dose-proportional and sustained drug exposure following chronic administration of apitegromab

## Pharmacodynamics (PD)



- Both 2 mg/kg and 20 mg/kg doses yielded high levels of target engagement (>100-fold increase from baseline)
- 20 mg/kg dose offers relatively higher magnitude of target engagement than 2 mg/kg dose

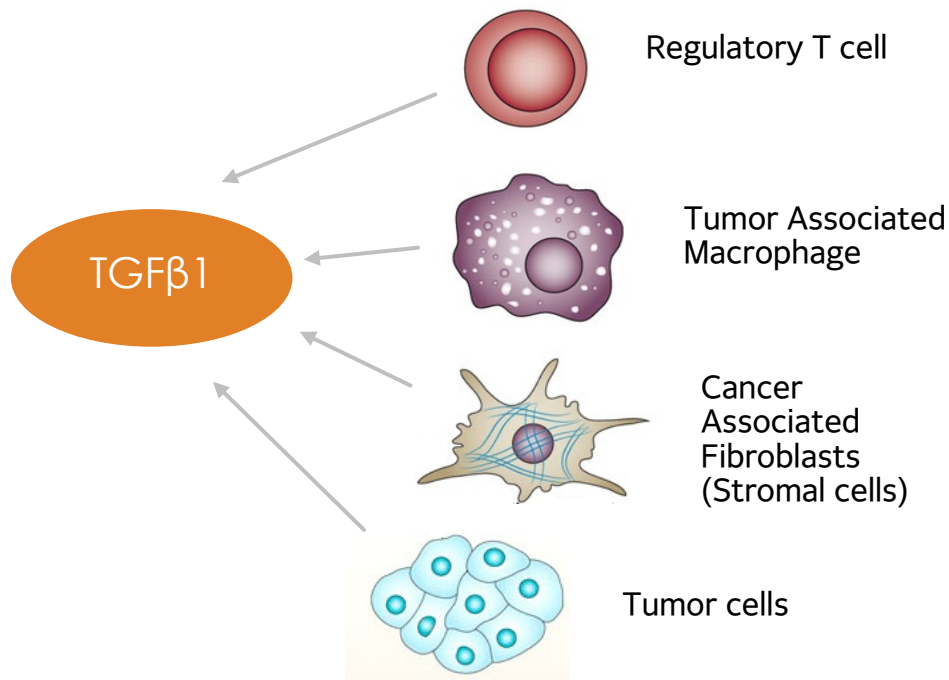
High levels of target engagement achieved by both doses, with relatively higher absolute levels with high dose

\*Starting at day 28, measures are pre-dose trough levels

Data on file. Scholar Rock, Inc. Cambridge, MA

# Inhibition of TGF $\beta$ 1: Multipronged Approach for Immuno-Oncology

*TGF $\beta$ 1 is a key driver of immune system evasion by cancer cells*



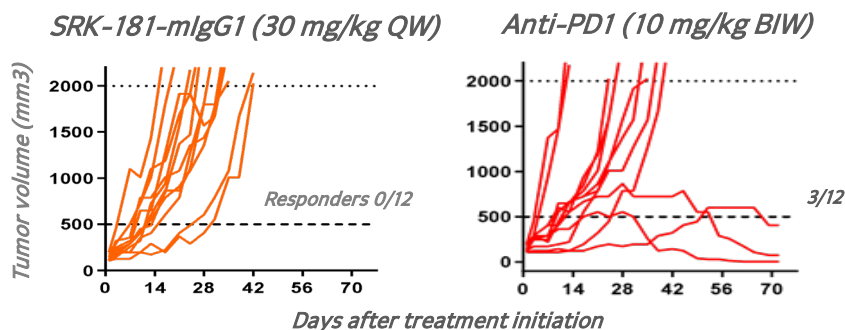
- Pathway analysis in patient tumors points to TGF $\beta$ 1 as major determinant of primary resistance to anti-PD-(L)1 therapy
- TGF $\beta$ 1 creates 'immune excluded' tumor microenvironment



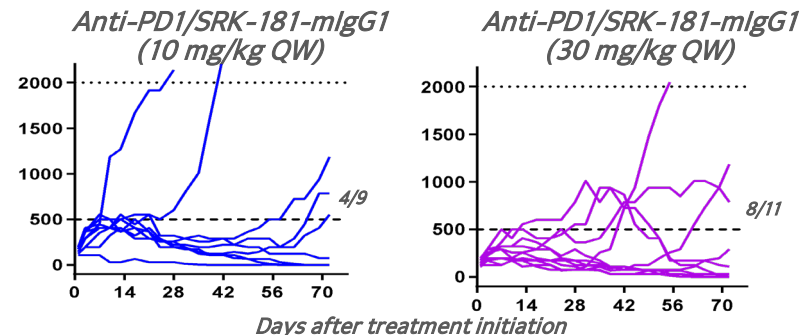
# TGF $\beta$ 1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

## Melanoma (Cloudman S91) model: Combination treatment led to tumor regression and survival benefit

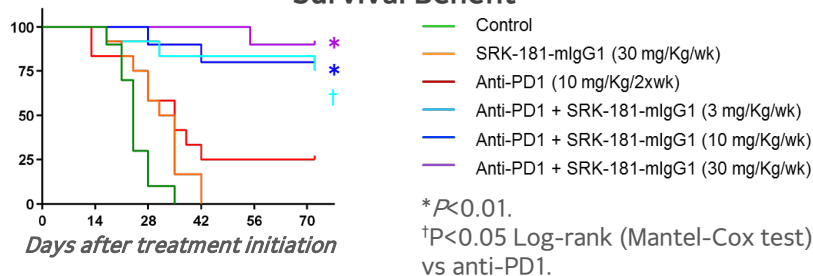
### Tumor Regression: Monotherapy



### Tumor Regression: Combination Therapy

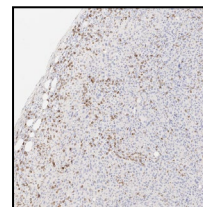


### Survival Benefit

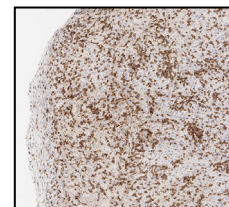


### Overcoming immune exclusion

Anti-PD1

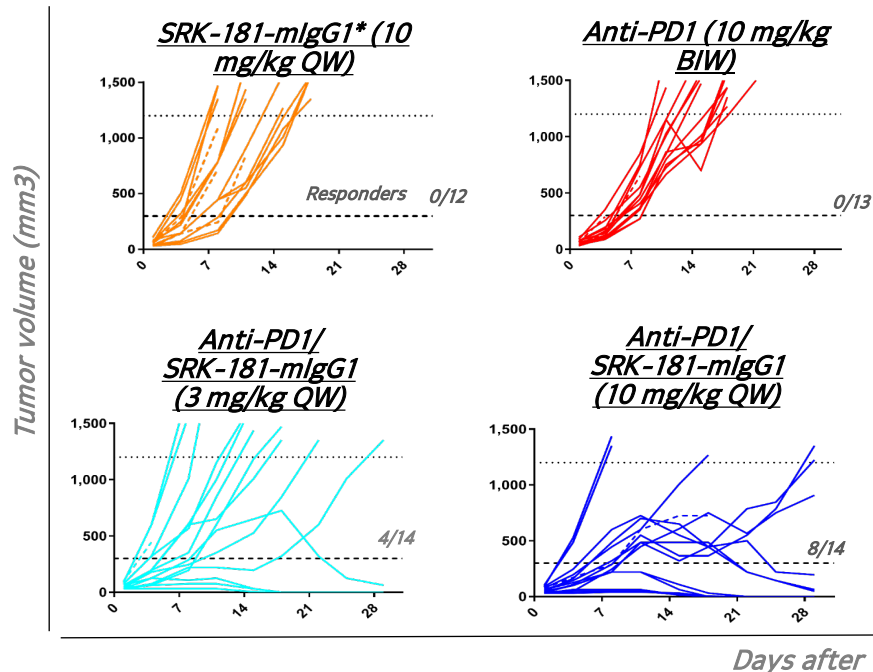


Anti-PD1/ SRK-181-mIgG1 led to influx of CD8+ cells in preclinical bladder tumor model

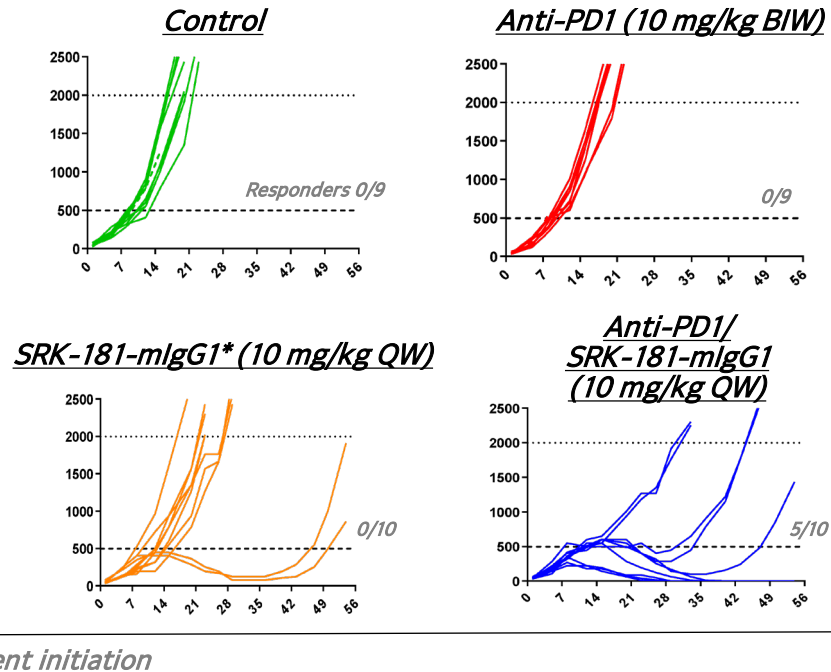


# TGF $\beta$ 1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

## Bladder Cancer



## Breast Cancer (TGF $\beta$ 1/3 co-expressing)



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

<https://scholarrock.com/platform/publications/>.

\*SRK-181-mIgG1 is the murine version of SRK-181; responder defined as tumor size <25% endpoint volume at study end.

# TGFβ1 Isoform Specificity of SRK-181 Improved Preclinical Toxicity Profile

Microscopic observations in heart	Control	LY2109761	PanTGFβAb	SRK-181			LEGEND
Valvulopathy	Vehicle	300 mg/kg	30 mg/kg	10 mg/kg	30 mg/kg	100 mg/kg	<div>□ Unremarkable</div> <div>■ Minimal</div> <div>■ Slight</div> <div>■ Moderate</div>
Atrium—Mixed cell infiltrate	iv, qwk x 4	po, qd x 8	iv, 1 dose	iv, qwk x 4	iv, qwk x 4	iv, qwk x 4	
Myocardium—Degeneration/necrosis							
Myocardium—Hemorrhage							
Myocardium—Mixed cell infiltrate, base							
Coronary artery—Necrosis with inflammation							
Cardiomyocyte—Necrosis/inflammatory cell infiltrate							

## Repeat dose pilot toxicology study in adult female Sprague Dawley rats:

- Cardiac findings were exhibited in animals dosed with a 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 was the highest dose evaluated of 100 mg/kg QW

## 4-week GLP toxicology studies:

- Rats: NOAEL for SRK-181 was up to highest evaluated dose of 200 mg/kg QW
- Non-human primates: NOAEL for SRK-181 was up to highest evaluated dose of 300 mg/kg QW

Selectivity of SRK-181 offers potential to overcome toxicity and dose-limiting challenges of non-selective TGFβ pathway approaches

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.