Scholar Rock Announces Positive 12-Month Top-Line Results From the TOPAZ Phase 2 Clinical Trial Evaluating Apitegromab in Patients With Type 2 and Type 3 Spinal Muscular Atrophy (SMA)

April 6, 2021

- Data further demonstrate proof-of-concept for the therapeutic potential of apitegromab in patients with Type 2 and Type 3 SMA

- Phase 3 registrational trial initiation expected by the end of 2021

- European Medicines Agency (EMA) granted Priority Medicines (PRIME) designation to apitegromab, recognizing unmet medical needs of patients with SMA

- Scholar Rock to host webcast today at 8:00am ET

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Apr. 6, 2021-- Scholar Rock (NASDAQ:SRRK), a clinical-stage biopharmaceutical company focused on the treatment of serious diseases in which protein growth factors play a fundamental role, today announced positive top-line data from the TOPAZ Phase 2 clinical trial evaluating apitegromab (SRK-015) in patients with Type 2 and Type 3 spinal muscular atrophy (SMA).

“These top-line 12-month data provide further support towards establishing apitegromab as a potential first muscle-directed therapy for patients with SMA,” said Yung Chyung, M.D., Chief Medical Officer of Scholar Rock. “The findings also offer important insights into myostatin biology and our scientific approach of targeting the latent forms of growth factors. We look forward to advancing the development and investigation of apitegromab as we plan to initiate a pivotal trial in SMA by the end of 2021 and explore its potential in additional disease areas.”

Key findings from the 12-month top-line analysis include:

- **Cohort 1:** 5-21 years of age, ambulatory Type 3, 20 mg/kg dose monotherapy and in conjunction with nusinersen:
  - Observed a mean change from baseline in Revised Hammersmith Scale (RHS) of a 0.3-point decline.
  - Majority of patients across the cohort (57%, 13/23 of patients) maintained or improved their motor function, as reflected by a ≥0-point change from baseline in RHS score, and 22% of patients (5/23) attained a ≥3-point increase from baseline.
  - Results suggest potential clinical effect in certain patients in this population.
- **Cohort 2:** 5-21 years of age, Type 2 and non-ambulatory Type 3 who initiated nusinersen ≥5 years old, 20 mg/kg dose:
  - Observed a mean change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) of a 0.6-point improvement.
  - Majority of patients (64%, 9/14 of patients) attained a ≥1-point increase from baseline and 29% of patients (4/14) attained a ≥3-point increase from baseline.
  - Results support the potential durability of the improvements in motor function observed at the six-month interim analysis.
- **Cohort 3:** ≥2 years of age, Type 2 who initiated nusinersen <5 years of age:
  - Observed a mean change from baseline in HFMSE of 7.1-point and 5.3-point improvements in the 20 mg/kg dose and the 2 mg/kg dose arms, respectively.
  - Across the full cohort, 59% of patients (10/17) attained a ≥5-point increase and 35% of patients (6/17) attained a >10-point increase from baseline.
  - Results demonstrate further improvements in motor function beyond what had been observed at the six-month interim analysis.
  - Dose response continued to be observed based upon clinical efficacy (HFMSE improvements) and pharmacodynamics (target engagement).
- No safety signals for apitegromab were identified as of the 12-month top-line analysis. The five most frequently reported treatment-emergent adverse events (TEAEs) were headache, pyrexia, upper respiratory tract infection, cough, and nasopharyngitis.
- All 57 patients who completed the 12-month TOPAZ trial have opted into the extension period.

“These 12-month results from the Phase 2 apitegromab TOPAZ trial have built upon the previously announced exciting 6-month interim results,” said Thomas Crawford, M.D., Professor of Neurology at the Johns Hopkins School of Medicine and Lead Investigator of the TOPAZ trial. “There looks to be promising potential for a muscle-directed therapy that will complement the unmet need still evident, and likely emerging, in many individuals with SMA who receive SMN-enhancing therapies. Though much work remains to be done, I believe the results are wonderful news for the SMA community, and I am enthusiastic about the potential that apitegromab may offer for further meaningful functional improvements.”

Detailed summary of the TOPAZ 12-month top-line results by cohort

Apitegromab is a selective inhibitor of the activation of latent myostatin. The TOPAZ Phase 2 proof-of-concept trial enrolled 58 patients with Type 2 and

Type 3 SMA across 16 study sites in the United States and Europe. The trial evaluated the safety and efficacy of intravenous apitegromab dosed every four weeks (Q4W) over a 12-month treatment period. Four patients (one in Cohort 2 and three in Cohort 3) each missed three consecutive doses of apitegromab over the course of the 12-month treatment period due to COVID-19-related site access restrictions and are excluded from the prespecified intent-to-treat primary analysis.

Cohort 1: This open-label, single-arm cohort enrolled 23 patients with ambulatory Type 3 SMA. Patients were treated with 20 mg/kg of apitegromab either as a monotherapy or in conjunction with an approved SMN upregulator therapy (nusinersen). The primary objectives of Cohort 1 were to assess safety and the mean change from baseline in RHS following 12 months of treatment.

In Cohort 1 (pooled population), the mean change from baseline in RHS score was a 0.3-point decline. The Cohort 1 efficacy data suggest a potential clinical effect of apitegromab in certain patients in this population, as 57% of patients observed a maintenance or improvement in RHS score (>0-point change from baseline) and 22% of patients achieved at least a 3-point increase in RHS score from baseline.

Cohort 1 (Intent-to-treat population)	**Apitegromab 20 mg/kg monotherapy (n=11)**	**Apitegromab 20 mg/kg + nusinersen (n=12)**	**Apitegromab pooled (n=23)**
Mean change from baseline in RHS score (95% CI)	-0.4 (-3.9, +3.1)	-0.3 (-2.0, +1.4)	-0.3 (-2.1, +1.4)
% of patients attaining ≥0-point increase in RHS score	6/11 (55%)	7/12 (58%)	13/23 (57%)
% of patients attaining ≥1-point increase in RHS score	4/11 (36%)	5/12 (42%)	9/23 (39%)
% of patients attaining ≥3-point increase in RHS score	3/11 (27%)	2/12 (17%)	5/23 (22%)
% of patients attaining ≥5-point increase in RHS score	1/11 (9%)	0/12 (0%)	1/23 (4%)

Cohort 2: This open-label, single-arm cohort enrolled 15 patients with Type 2 or non-ambulatory Type 3 SMA and who were already receiving treatment with an approved SMN upregulator (nusinersen) initiated at age five years or older. One patient missed three consecutive doses of apitegromab due to COVID-19-related site access restrictions and was excluded from the prespecified intent-to-treat primary analysis. The primary objectives of the cohort were to assess safety and the mean change from baseline in HFMSE following 12 months of treatment.

Cohort 2 efficacy data demonstrate improvement of motor function from baseline. The mean change from baseline in HFMSE score was a 0.6-point increase. The majority (64%) of patients achieved at least a 1-point increase in HFMSE and 29% of patients achieved at least a 3-point increase in HFMSE from baseline. Potential durability of effect was observed up to 12 months of treatment.

One patient in Cohort 2 was identified as having received concomitant treatment with an acetylcholinesterase inhibitor before and during the study, which was not permitted by the trial protocol. This patient experienced a 7-point decline in HFMSE score at the 12-month timepoint. In the per protocol analysis conducted in accordance with the prespecified approach, which excludes this patient as well as the patient who missed three consecutive doses due to COVID-19-related site access restrictions, the mean change from baseline in HFMSE score for Cohort 2 was a 1.2-point improvement.

Cohort 2	**Apitegromab 20 mg/kg + nusinersen**	
	Intent-to-treat (n=14)	**Per Protocol (n=13)**
Mean change from baseline in HFMSE score (95% CI)	+0.6 (-1.4, +2.7)	+1.2 (-0.5, 2.9)
% of patients attaining ≥1 point increase in HFMSE score	9/14 (64%)	9/13 (69%)
% of patients attaining ≥3 point increase in HFMSE score	4/14 (29%)	4/13 (31%)
% of patients attaining ≥5 point increase in HFMSE score	2/14 (14%)	2/13 (15%)

Cohort 3: This randomized, double-blind, parallel arm portion of the trial enrolled patients with Type 2 SMA who had initiated treatment with an approved SMN upregulator (nusinersen) before five years of age. Twenty patients were randomized in a 1:1 ratio to receive the low dose (apitegromab 2 mg /kg Q4W) or high dose (apitegromab 20 mg/kg Q4W); both treatment arms were in conjunction with an approved SMN upregulator therapy (nusinersen). Three patients (two in high-dose arm and one in low-dose arm) each missed three consecutive doses of apitegromab due to COVID-19-related site access restrictions and were excluded from the prespecified intent-to-treat primary analysis. The primary objectives of the cohort were to assess safety and the mean change from baseline in HFMSE following 12 months of treatment.

Cohort 3 efficacy data demonstrate further improvements in motor function relative to what was observed at the six-month interim analysis. The mean change from baseline in HFMSE score was a 7.1-point and a 5.3-point improvement for the 20 mg/kg and 2 mg/kg dose arms, respectively. The majority (59%) of patients in Cohort 3 achieved at least a 5-point increase in HFMSE and 35% of patients achieved greater than a 10-point increase in HFMSE over baseline.

Dose response was observed; the 20 mg/kg dose achieved numerically greater mean improvements from baseline in HFMSE scores than the 2 mg/kg dose across all assessed timepoints in the 12-month treatment period. The clinically observed dose response was consistent with the pharmacodynamic (target engagement) results. Both the 20 mg/kg and 2 mg/kg doses yielded high levels of target engagement (>100-fold increase from baseline), but the 20 mg/kg dose led to a relatively higher absolute level of target engagement.

Cohort 3 (Intent-to-treat population)	**Apitegromab 20 mg/kg + nusinersen (n=8)**	**Apitegromab 2 mg/kg + nusinersen (n=9)**	**Apitegromab pooled (n=17)**
Mean change from baseline in HFMSE score (95% CI)	+7.1 (+1.8, +12.5)	+5.3 (-1.5, +12.2)	+6.2 (+2.2, +10.1)
% of patients attaining ≥1-point increase in HFMSE score	7/8 (88%)	7/9 (78%)	14/17 (82%)
% of patients attaining ≥3-point increase in HFMSE score	5/8 (63%)	5/9 (56%)	10/17 (59%)
% of patients attaining ≥5-point increase in HFMSE score	5/8 (63%)	5/9 (56%)	10/17 (59%)
% of patients attaining >10-point increase in HFMSE score	3/8 (38%)	3/9 (33%)	6/17 (35%)

Overall safety and tolerability profile:

- Incidence and severity of adverse events were consistent with the underlying patient population and background therapy.

- Five most frequently reported TEAEs: Headache (24%), pyrexia (22%), upper respiratory tract infection (22%), cough (22%), and nasopharyngitis (21%).
- Five patients experienced a serious treatment-emergent adverse event, all assessed by the respective trial investigator as unrelated to apitegromab:
    - One patient treated with 2 mg/kg dose (Cohort 3) hospitalized due to adenoidal hypertrophy and tonsillar hypertrophy to perform scheduled adenotonsillectomy (Grade 2). Event resolved without sequelae.
    - Two patients treated with 20 mg/kg dose (both Cohort 1) with gait inability considered a significant disability (both Grade 3). Events remain ongoing.
    - One patient treated with 20 mg/kg dose (Cohort 1) hospitalized with post lumbar puncture syndrome (Grade 2). Event resolved without sequelae.
    - One patient treated with 20 mg/kg dose (Cohort 1) hospitalized due to viral upper respiratory tract infection (Grade 2). Event resolved without sequelae.
- One patient (Cohort 1) presented with a non-serious Grade 3 post lumbar puncture syndrome; assessed by trial investigator as unrelated to apitegromab. Event resolved without sequelae.
- One patient (Cohort 1) discontinued from the trial due to Grade 2 muscle fatigue that started prior to initiation of dosing with study drug; assessed by the trial investigator as unrelated to apitegromab.
- Anti-drug antibodies (ADA) were present at low titers following apitegromab treatment in three out of the 58 enrolled patients. No apparent impact on drug exposure was observed and was not associated with any hypersensitivity reactions.

Additional potential disease areas for apitegromab: Scholar Rock believes apitegromab has potential for applicability across multiple SMA types, as well as in other neuromuscular indications. Based upon ongoing indication assessments, the Company has identified Becker Muscular Dystrophy (BMD), which affects approximately 20,000 individuals in the US and EU[(a)], as the next potential indication for apitegromab. The Company is in the process of planning a proof-of-concept trial with an aim to initiate the trial in 2022. Scholar Rock is continuing to explore other myostatin-related indications for which fast-twitch fibers may play an important role in motor function.

Conference call/webcast:
Scholar Rock will host a conference call and audio webcast to discuss the apitegromab TOPAZ Phase 2 clinical trial top-line results today at 8:00 a.m. Eastern Time. To participate in the call, please dial 833-519-1308 (domestic) or 914-800-3874 (international) and refer to conference ID: 4196782. A webcast of the call will also be 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 180 days following the presentation.

(a) "Muscular Dystrophy: Disease Landscape and Forecast." DRG Reports, June 2020

About SMA
Spinal muscular atrophy (SMA) is a rare, and often fatal, genetic disorder that typically manifests in young children. An estimated 30,000 to 35,000 patients are afflicted with SMA in the United States[(1)] and Europe[(2)]. It is characterized by the loss of motor neurons, atrophy of the voluntary muscles of the limbs and trunk and progressive muscle weakness. The underlying pathology of SMA is caused by insufficient production of the SMN (survival of motor neuron) protein, essential for the survival of motor neurons, and is encoded by two genes, SMN1 and SMN2[(3)]. While there has been progress in the development of therapeutics that address the underlying SMA genetic defect, there continues to be a high unmet need for therapeutics that directly address muscle atrophy.

(1) Lally, C. et al. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet Journal of Rare Diseases. (2017) 12:175.
(2) Briefing Document to the Clinical Trial Readiness in Spinal Muscular Atrophy (SMA) SMA Europe, TREAT-NMD and European Medicines Agency meeting. Prepared by SMA Europe and TREAT-NMD. November 11, 2016.
(3) Parente, V. and Corti, S. Advances in spinal muscular atrophy therapeutics. Therapeutic Advances in Neurological Disorders. (2018) 11:1.

About Apitegromab
Apitegromab (SRK-015) is a selective inhibitor of the activation of latent myostatin and is an investigational product candidate for the treatment of patients with 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. Scholar Rock believes the inhibition of the activation of latent myostatin with apitegromab may promote a clinically meaningful improvement in motor function.

The TOPAZ Phase 2 clinical trial in patients with Type 2 and Type 3 SMA is ongoing in the extension phase (NCT03921528). The U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation (ODD) and Rare Pediatric Disease (RPD) designation, and the European Medicines Agency (EMA) has granted Priority Medicines (PRIME) Designation and Orphan Medicinal Product Designation, 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 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, fibrosis and anemia. 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 https://scholarrock.com/ or follow Scholar Rock on Twitter (@ScholarRock) and LinkedIn (https://www.linkedin.com/company/scholar-rock/).

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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 the potential of apitegromab, 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, the potential of its proprietary platform, and its intellectual property protection. The use of words such as "may," "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. 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 the possibility that preclinical and clinical data, including the 12-month top-line results from the Phase 2 trial of apitegromab, are not predictive of, are inconsistent with, or more favorable than, data generated from future clinical trials of the same product candidate, including the planned Phase 3 registrational 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 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 such as COVID-19 on business operations including its clinical trials, as well as those risks more fully discussed in the section entitled "Risk Factors" in Scholar Rock's Annual Report on Form 10-K for the year ended December 31, 2020, 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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