Scholar Rock Announces Positive Proof-of-Concept Data from TOPAZ Phase 2 Trial Interim Analysis of SRK-015 in Patients with Type 2 and Type 3 Spinal Muscular Atrophy

October 27, 2020

- Motor function improvements were observed for all three SRK-015 treatment cohorts in the primary efficacy endpoints (Hammersmith scale scores) at six-months; top-line data from the 12-month treatment period are anticipated in 2Q21

- SRK-015 dose response in the primary efficacy endpoint was observed in the randomized, double-blind cohort, with high dose attaining a 5.6 point mean improvement at six-months over baseline compared to low dose attaining a 2.4 point mean improvement over baseline

- First clinical data showing the potential therapeutic benefits of Scholar Rock's innovative scientific platform of inhibiting the activation of latent myostatin

- First demonstration of the therapeutic potential of the Company's proprietary approach of targeting the latent forms of growth factors

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

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 27, 2020-- 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 six-month interim analysis results from the TOPAZ Phase 2 clinical trial. Treatment with SRK-015 led to improvements in Hammersmith scale scores (primary efficacy endpoint) in all three cohorts of patients with Type 2 and Type 3 Spinal Muscular Atrophy (SMA). Dose response in the primary efficacy endpoint was observed across all evaluated timepoints in the double-blind, randomized portion of the trial (Cohort 3). The high-dose arm of Cohort 3 attained a 5.6 point mean improvement from baseline in the Hammersmith Functional Motor Scale Expanded (HFMSE) as compared to the low dose arm, which attained a 2.4 point mean improvement at the six-month interim analysis timepoint. No safety signals were identified from the interim analysis.

"These interim results are important because they demonstrate the potential of this muscle-directed approach to improve motor function of individuals with Type 2 and Type 3 SMA," said Thomas Crawford, M.D., Professor of Neurology at the Johns Hopkins University School of Medicine and Lead Investigator of the TOPAZ trial. "In the last few years, we've celebrated the remarkable success in treating SMA with SMN-upregulating approaches that stabilize against neurodegeneration. These findings highlight the potential for a whole new approach to SMA therapy, used in conjunction with the SMN-enhancing therapies, to address the persistent and significant unmet needs of individuals weakened by SMA."

"This is an exciting and important step towards establishing SRK-015 as the potential first muscle-directed therapy for patients with SMA, while also providing important validation of our scientific approach of targeting the latent forms of growth factors," said Yung Chyung, M.D., Chief Medical Officer of Scholar Rock. "These interim data support the continuation of the TOPAZ trial and we look forward to engaging with regulatory authorities regarding our registrational trial plans."

TOPAZ Phase 2 Six-Month Interim Results

SRK-015 is a highly 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 U.S. and Europe. The trial is evaluating the safety and efficacy of intravenous SRK-015 dosed every four weeks (Q4W) over a 12-month treatment period. A pre-planned interim analysis was conducted following a six-month treatment period across all three study cohorts. Three patients (one in Cohort 2 and two in Cohort 3) each missed three doses of SRK-015 and the six-month interim analysis timepoint due to COVID-19-related site access restrictions; the six-month timepoint from these patients was not included in the interim analysis.

At the six-month interim analysis timepoint:

- Mean increases from baseline in Hammersmith scale scores were observed in all three cohorts.

  - 67% of total patients achieved ≥1 point improvement in Hammersmith scores.

- Substantial proportion of patients in each cohort achieved a ≥3 point increase in Hammersmith scores.

  - 35% of total patients achieved ≥3 point increase in Hammersmith scores.

Dose response in the primary efficacy endpoint was observed in the randomized, double-blind cohort; numerically greater improvements in HFMSE scores were observed for high-dose (20 mg/kg) arm across all evaluated timepoints.

Detailed Summary of Interim Results by Cohort

Cohort 1: This open-label, single-arm cohort enrolled 23 patients with ambulatory Type 3 SMA. Patients are being treated with 20 mg/kg of SRK-015 Q4W either as a monotherapy or in conjunction with an approved SMN upregulator therapy (nusinersen). The primary objectives of the cohort are to assess safety and the mean change from baseline in Revised Hammersmith Scale (RHS).

At baseline, patients across both subgroups of patients had a mean age of 12.6 years (range 7-21 years) and a RHS score of 49.6 (range 26-63) out of a total possible score of 69. Patients in the SRK-015 monotherapy group had a mean age of 12.1 years (range 7-19 years) and a mean RHS score of 47.6 (range 26-63). Patients in the group treated with SRK-015 and receiving an SMN upregulator (nusinersen) had a mean age of 13.1 years (range

7-21 years) and a mean RHS score of 51.3 (range 43-62). One patient discontinued from the trial for reasons that were assessed to be unrelated to SRK-015 but was included in the intent-to-treat interim analysis.

At the six-month interim analysis timepoint:

- Mean change from baseline in RHS score:

- SRK-015 pooled (n = 23): +0.5 points (95% CI of -1.1, +2.2)

- SRK-015 monotherapy (n = 11): +0.7 points (95% CI of -2.5, +4.0)

- SRK-015 + nusinersen (n = 12): +0.3 points (95% CI of -1.4, +2.0)

- Proportion of patients attaining ≥1 point increase in RHS score:

- SRK-015 pooled: 52% (12/23)

- SRK-015 monotherapy: 64% (7/11)

- SRK-015 + nusinersen: 42% (5/12)

- Proportion of patients attaining ≥3 point increase in RHS score:

- SRK-015 pooled: 26% (6/23)

- SRK-015 monotherapy: 36% (4/11)

- SRK-015 + nusinersen: 17% (2/12)

- Proportion of patients attaining ≥5 point increase in RHS score:

- SRK-015 pooled: 9% (2/23)

- SRK-015 monotherapy: 9% (1/11)

- SRK-015 + nusinersen: 8% (1/12)

Cohort 2: This open-label, single-arm cohort enrolled 15 patients with a mean age of 11.7 years (range 8-19 years) with Type 2 or non-ambulatory Type 3 SMA and who are already receiving treatment with an approved SMN upregulator. Patients are being treated with 20 mg/kg of SRK-015 Q4W in conjunction with an approved SMN upregulator therapy (nusinersen). At baseline, patients had a mean HFMSE score of 22.7 (range 13-39) out of a total possible score of 66. One patient missed three doses of SRK-015 and the six-month interim analysis timepoint due to COVID-19-related site access restrictions; the six-month timepoint from this patient was not included in the interim analysis. The primary objectives of the cohort are to assess safety and the mean change from baseline in HFMSE.

At the six-month interim analysis timepoint:

- Mean change from baseline in HFMSE score (n = 14): +1.4 points (95% CI of +0.1, +2.7)
- Proportion of patients attaining ≥1 point increase in HFMSE score: 71% (10/14)
- Proportion of patients attaining ≥3 point increase in HFMSE score: 21% (3/14)
- Proportion of patients attaining ≥5 point increase in HFMSE score: 14% (2/14)
- Improvements in HFMSE scores progressively increased over the six-month treatment period, and a plateau in improvement appears to not have yet been reached. Twelve-month data may provide additional insights evaluating the potential for durability of effect and for further motor function gains.

Cohort 3: This randomized**,** double-blind, 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 (2 mg /kg SRK-015 Q4W) or high dose (20 mg/kg SRK-015 Q4W); both treatment arms are in conjunction with an approved SMN upregulator therapy (nusinersen). Two patients (one in high-dose arm and one in low-dose arm) each missed three doses of SRK-015 and the six-month interim analysis timepoint due to COVID-19-related site access restrictions; the six-month timepoint from these patients was not included in the interim analysis. The primary objectives of the cohort are to assess safety and the mean change from baseline in HFMSE.

At baseline, patients in the high-dose arm had a mean age of 3.8 years (range 2-6 years) and mean HFMSE score of 23.5 (range 14-42) out of a total possible score of 66 points, while patients in the low dose arm had a mean age of 4.1 years (range 2-6 years) and a mean HFMSE score of 26.1 (range 12-44).

At the six-month interim analysis timepoint:

- Mean change from baseline in HFMSE score:

- 20 mg/kg dose (n = 9): +5.6 points (95% CI of +2.5, +8.7)

- 2 mg/kg dose (n = 9): +2.4 points (95% CI of -0.9, +5.8)

- Proportion of patients attaining ≥1 point increase in HFMSE score:

- 20 mg/kg dose: 100% (9/9)

- 2 mg/kg dose: 67% (6/9)

- Proportion of patients attaining ≥3 point increase in HFMSE score:

- 20 mg/kg dose: 67% (6/9)

- 2 mg/kg dose: 44% (4/9)

- Proportion of patients attaining ≥5 point increase in RHS score:

- 20 mg/kg dose: 56% (5/9)

- 2 mg/kg dose: 33% (3/9)

Greater improvement achieved with high dose: Patients treated with high dose (20 mg/kg) achieved numerically greater improvements from baseline in HFMSE scores as compared to the low dose (2 mg/kg) at all assessed timepoints (week 8, week 16, and the six-month interim analysis timepoint).

- Numerically greater improvements with high dose were observed both in terms of mean change from baseline and in proportions of patients attaining ≥3 point increase in HFMSE score.

Plateau in improvement appears to not have yet been reached: Improvements in HFMSE scores progressively increased over the six-month treatment period. Twelve-month data may provide additional insights evaluating the potential for durability of effect and for further motor function gains.

PK and PD results are supportive of the observed dose response in efficacy:

- Treatment with the high dose led to higher levels of drug exposure than with the low dose.
- Treatment with high dose achieved higher levels of target engagement, and treatment with low dose did not attain full target saturation.

Overall Safety and Tolerability: No safety signals were identified during the interim analysis.

- Incidence and severity of adverse events were consistent with underlying patient population and background therapy.
- Five most frequently reported TEAEs: Headache, upper respiratory tract infection, pyrexia, nasopharyngitis, and cough.
- No grade 3 (severe) or higher adverse events were reported.
- One patient (Cohort 1) experienced a serious treatment-emergent adverse event (TEAE) of Grade 2 viral upper respiratory tract infection leading to hospitalization. The event was resolved without sequelae and was assessed by the trial investigator as unrelated to study drug.
- 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 study drug.

Top-line data from the 12-month treatment are expected in the second quarter of 2021. Twelve-month data may provide additional insights evaluating the potential for durability of effect and for further motor function gains.

As of October 23, 2020, 39 of 39 patients who have completed the 12-month treatment period have opted into the extension period.

Conference Call/Webcast:
Scholar Rock will host a conference call and audio webcast to discuss the SRK-015 TOPAZ Phase 2 clinical trial interim data 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: 1856917. 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 90 days following the presentation.

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 SRK-015
SRK-015 is a selective inhibitor of the activation of 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 myostatin with SRK-015 may promote a clinically meaningful increase in muscle strength. A Phase 2 clinical trial in patients with Type 2 and Type 3 SMA is ongoing. The U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation (ODD) and Rare Pediatric Disease (RPD) designation, and the European Commission (EC) has granted Orphan Medicinal Product Designation, to SRK-015 for the treatment of SMA. The effectiveness and safety of SRK-015 have not been established and SRK-015 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 www.ScholarRock.com or follow Scholar Rock on Twitter (@ScholarRock) and LinkedIn (https://www.linkedin.com/company/scholar-rock/).

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 SRK-015, 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 SRK-015, , 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 data from the TOPAZ final analysis will be inconsistent with the data observed in the interim analysis, 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, 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 TOPAZ clinical trial, 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 June 30, 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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