Scholar Rock Announces Positive Interim Results from Phase 1 Trial of SRK-015 in Healthy Volunteers and Updates on Future Development Plans

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- *Favorable Safety Profile Across All Tested Doses Supports Initiation of a Phase 2 Trial in Patients with Spinal Muscular Atrophy (SMA)*
- *Pharmacodynamic Results Demonstrate Robust and Sustained Target Engagement of Latent Myostatin*
- *Phase 2 Trial Initiation Expected by the End of 1Q19 with Interim Safety and Efficacy Analysis Following Six Months of Treatment Expected in 1H20*
- *Company to Host Conference Call and Webcast on February 26, 2019 at 8:00 a.m. ET*

CAMBRIDGE, Mass., Feb. 26, 2019 (GLOBE NEWSWIRE) -- Scholar Rock Holding Corporation (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 interim results from the ongoing Phase 1 single- and multiple-ascending dose clinical trial of SRK-015 in healthy adult volunteers. SRK-015, a highly specific inhibitor of myostatin activation, was observed to be well tolerated with no apparent safety signals. By demonstrating robust and sustained target engagement in humans, pharmacologic effects on serum concentrations of latent myostatin show initial proof-of-mechanism for this unique therapeutic approach. The favorable interim safety and tolerability, pharmacodynamic (PD), and pharmacokinetic (PK) data support the advancement of SRK-015 to a Phase 2 proof-of-concept clinical trial in patients with spinal muscular atrophy (SMA), evaluating a once every four-week dosing regimen.

“We are very excited with the progress to date in the Phase 1 trial of SRK-015 as we continue to work towards developing our lead antibody candidate as a potential first muscle-directed therapy for the treatment of SMA,” said Yung Chyung, M.D., Chief Medical Officer of Scholar Rock. “We look forward to initiating the Phase 2 proof-of-concept trial to evaluate SRK-015’s potential to address the functional deficits that continue to represent a significant unmet need in SMA.”

Phase 1 Trial Design and Interim Results

Trial Design. The randomized, double-blind, placebo-controlled Phase 1 clinical trial was designed to evaluate the safety and tolerability of intravenously administered SRK-015, assess the PK/PD profile, and inform dosing for the Phase 2 trial.

- **Single-Ascending Dose (SAD):** Enrolled 40 adult healthy volunteers, randomized 3:1 to receive a single dose of SRK-015 or placebo, and evaluated doses of 1, 3, 10, 20 and 30 mg/kg.
- **Multiple-Ascending Dose (MAD):** Enrolled 26 adult healthy volunteers, randomized 3:1 to receive SRK-015 or placebo every two weeks for a total of three doses (Day 0, 14 and 28). The MAD portion of the trial evaluated doses of 10, 20 and 30 mg/kg.

The interim analysis was conducted with data from all subjects in the completed SAD portion of the trial and available data for all subjects in the MAD portion of the trial, including through Day 35 for the highest 30 mg/kg dose cohort and longer follow-up for the 10 and 20 mg/kg dose cohorts. Follow-up in the MAD portion of the trial is ongoing and full clinical results from the Phase 1 trial will be presented at a scientific conference this year.

Safety and Immunogenicity Data. SRK-015 was observed to be well tolerated with no dose-limiting toxicities identified up to the highest evaluated dose of 30 mg/kg. There were no deaths, no discontinuations due to a treatment-related adverse event (AE), no treatment-related serious AEs (SAE), and no hypersensitivity reactions. In the SAD portion of the trial, AEs were observed in 30% (9/30) of SRK-015-treated subjects and 50% (5/10) of placebo-treated subjects. In the MAD portion of the trial, AEs were observed in 30% (6/20) of SRK-015-treated subjects and 67% (4/6) of placebo-treated subjects. A single SAE (gallstone-induced pancreatitis) was observed and assessed by the trial investigator as unrelated to SRK-015 treatment. Immunogenicity as evaluated by anti-drug antibody testing was negative for all subjects in the SAD portion of the trial and data for subjects in the MAD portion of the trial are pending completion of the Phase 1 trial.

Biomarker/Pharmacodynamic Data. PD was evaluated through a proprietary, exploratory biomarker assay developed by Scholar Rock that measures serum concentrations of latent myostatin. This assay was used previously to demonstrate target engagement in preclinical studies in

healthy animals and a mouse model of SMA. Following a single dose of SRK-015 in this Phase 1 trial, levels of latent myostatin were markedly increased from baseline, confirming target engagement. The levels of target engagement attained a plateau, suggesting that the target was saturated after a single dose of SRK-015 at 3 mg/kg or greater. Moreover, this plateau was sustained through Day 28 after a single dose at 10 mg/kg and through at least Day 84 after a single dose at 20 mg/kg or 30 mg/kg, indicating durability of this effect. In contrast, no meaningful change was observed in the latent myostatin biomarker concentrations in subjects who received placebo.

Pharmacokinetic Data. Based on data from the SAD, SRK-015 displayed a PK profile consistent with what is generally observed for monoclonal antibodies. Drug exposure was dose-proportional and the serum half-life was 23-33 days across the SRK-015 dose groups, supporting the investigation of a once every four-week dosing regimen in the Phase 2 trial.

"These interim Phase 1 data provide initial proof-of-mechanism for the pharmacologic potential of SRK-015, and more broadly, Scholar Rock's therapeutic approach of specifically targeting the latent forms of growth factors," said Nagesh Mahanthappa, Ph.D, President and CEO of Scholar Rock. "Through our discovery efforts, we have built a robust pipeline of highly specific growth factor modulators across a diverse range of therapeutic areas and are eagerly working to advance these potential therapies to serve patients with unmet medical needs."

Phase 2 (TOPAZ) Trial Overview

Scholar Rock's preclinical data and translational insights highlight the promising potential of myostatin as a drug target in SMA, and positive interim results from the Phase 1 study demonstrate that SRK-015 may have the necessary pharmacologic profile to modulate this pathway.

Scholar Rock plans to initiate a Phase 2 proof-of-concept clinical trial to assess the safety and efficacy of SRK-015 in patients with Type 2 and Type 3 SMA by the end of the first quarter of 2019. The trial will include three cohorts, each representing a distinct subpopulation of patients. A total of 50-60 patients are planned to be enrolled in the Phase 2 trial and all patients will receive SRK-015 dosed once every four weeks (Q4W) either as a monotherapy or in conjunction with an approved SMN upregulator therapy. The primary efficacy endpoints will measure motor function through clinically meaningful outcome measures validated in SMA, such as the Hammersmith Functional Motor Scale Expanded (HFMSE) in non-ambulatory SMA and the Revised Hammersmith Scale (RHS) in ambulatory SMA, over a 12-month treatment period. Scholar Rock plans to provide additional details on the trial design at the time of initiating patient dosing in the second quarter of 2019.

An interim analysis assessing safety and efficacy is planned for each cohort of the Phase 2 trial, encompassing a subset of patients with at least 6 months of treatment exposure. These interim results by cohort are expected in the first half of 2020. Top-line results for the full 12-month treatment period are expected starting in the fourth quarter of 2020 and through the first quarter of 2021. In addition, analyses of preliminary PK and PD data are planned by the end of 2019.

Conference Call Information
Scholar Rock will host a conference call and webcast to review the interim Phase 1 results and the Phase 2 trial design on Tuesday, February 26, 2019 at 8:00 am ET. The call may be accessed by phone by calling 1-866-809-6221 (U.S.) or 1-409-981-0877 (international) using the conference ID 1394467. The webcast may be accessed live by visiting the Investors & Media section of the Scholar Rock website at http://investors.scholarrock.com. An archived replay of the webcast will be available on the Company's website for approximately 90 days following the call.

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 TGF-beta 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 mass and strength. A Phase 1 clinical trial in healthy volunteers is ongoing and a Phase 2 trial is expected to initiate by the end of the first quarter of 2019. The U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation (ODD), 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 by the FDA or any other regulatory agency.

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 and Europe. 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. 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.

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 newly elucidated understanding of 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 Scholar Rock's future expectations, plans and prospects, including without limitation, Scholar Rock's expectations

regarding the potential of SRK-015 as a therapy in SMA and the timeline for and progress in developing SRK-015. 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 those risks more fully discussed in the section entitled "Risk Factors" in Scholar Rock's Quarterly Report on Form 10-Q for the quarter ended September 30, 2018, 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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