Scholar Rock Announces Publication of Preclinical Pharmacology, Pharmacokinetics, and Safety Profile of SRK-181 in the International Journal of Toxicology

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CAMBRIDGE, Mass.--(BUSINESS WIRE)--Mar. 22, 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 the publication of preclinical development data for SRK-181 in the peer-reviewed journal *International Journal of Toxicology.* SRK-181 is a product candidate that has been shown to be a potent and highly specific inhibitor of latent growth factor-beta 1 (TGFβ1) activation in preclinical studies. SRK-181 is being developed to overcome primary resistance to checkpoint inhibitor therapy and is currently being studied in the two-part DRAGON Phase 1 trial in patients with locally advanced or metastatic solid tumors exhibiting primary resistance to anti-PD-(L)1 therapy.

“This publication provides a comprehensive preclinical assessment of the pharmacology, pharmacokinetics, and safety of SRK-181, which support its evaluation in the DRAGON Phase 1 trial,” said Gregory Carven, Ph.D., Chief Scientific Officer of Scholar Rock. “The initial clinical response and safety data from the DRAGON trial, which we anticipate by end of year, will provide an early look into SRK-181’s safety and tolerability profile and the potential for a specific inhibitor of latent TGFβ1 to overcome the immune exclusion that we believe, for many patients, is responsible for primary resistance to checkpoint inhibitor therapies.”

Targeting the TGFβ1 Pathway

Greater understanding of the role of TGFβ signaling in promoting cancer progression has led to heightened interest in the development of therapies that inhibit the TGFβ pathway. However, most of the approaches to date have been non-selective and target at least two of the three TGFβ isoforms, which may limit the therapeutic window and potentially result in a lack of efficacy, an unfavorable safety profile, or a combination of the two. Examples of dose-limiting toxicities observed nonclinically for nonselective anti-TGFβ therapies include cardiovascular abnormalities, skin lesions, epithelial oral hyperplasia, and gingival bleeding.

Scholar Rock’s approach to targeting the TGFβ pathway is fundamentally different. SRK-181 is a highly specific inhibitor of the latent TGFβ1 isoform with minimal or no binding to latent TGFβ2, latent TGFβ3, or any of the active TGFβ growth factors based on in vitro studies. Based on preclinical evaluations of SRK-181’s pharmacologic and safety profiles across multiple animal species, SRK-181 may offer an improved safety profile and a wider therapeutic window than non-selective TGFβ inhibitors.

About the Preclinical Data

The *International Journal of Toxicology* publication, “Nonclinical Development of SRK-181: An Anti-latent TGFβ1 Monoclonal Antibody for the Treatment of Locally Advanced or Metastatic Solid Tumors,” provides a comprehensive preclinical assessment of the pharmacology, pharmacokinetics, and safety of SRK-181. (Welsh et al., Int J. Tox, March 19, 2021). Key findings include:

- Selective inhibition of latent TGFβ1 activation by SRK-181 was shown to avoid dose-limiting toxicities associated with pan-TGFβ inhibitors in preclinical pharmacology studies.
    - In-vitro studies showed that SRK-181 had no effect on human platelet aggregation, activation, or binding and that SRK-181 does not trigger a proinflammatory cytokine response in peripheral blood mononuclear cells (PBMC).
    - Four-week toxicology study showed that weekly intravenous administration of SRK-181 achieved sustained serum exposure and was well-tolerated in rats and monkeys with no treatment-related adverse findings.
    - No observed adverse effect level (NOAEL) of 200 mg/kg and 300 mg/kg were achieved in rats and cynomolgus monkeys, respectively.

- Preclinical pharmacologic and pharmacokinetics assessments provided support for the dose-selection strategy for the ongoing DRAGON Phase 1 trial in patients with solid tumors.

About SRK-181

SRK-181 is a selective inhibitor of TGFβ1 activation and is an investigational product candidate being developed to overcome primary resistance to checkpoint inhibitor therapy, such as anti-PD-(L)1 antibodies. TGFβ1 is the predominant TGFβ isoform expressed in many human tumors, particularly for those tumors where checkpoint therapies are currently approved. Based on profiling of human tumors that are resistant to anti-PD-(L)1 therapy, data suggests TGFβ1 is a key contributor to excluding immune cell entry into the tumor microenvironment, thereby preventing normal immune function. Scholar Rock believes SRK-181 has the potential to overcome this immune cell exclusion and induce tumor regression when administered in combination with anti-PD-(L)1 therapy. By specifically targeting the latent TGFβ1 isoform, Scholar Rock hypothesizes that SRK-181 can increase

the therapeutic window by potentially avoiding toxicities associated with non-selective TGFβ inhibition. A Phase 1 proof-of-concept clinical trial in patients with locally advanced or metastatic solid tumors is ongoing. The effectiveness and safety of SRK-181 have not been established and SRK-181 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/).

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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 SRK-181, 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, 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 DRAGON clinical trial will be inconsistent with the data observed in preclinical studies, 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 DRAGON clinical trial, 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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