Scholar Rock Announces Design of Phase 3 SAPPHIRE Clinical Trial Evaluating Apitegromab in Non-Ambulatory Patients with Type 2 and Type 3 Spinal Muscular Atrophy (SMA)

November 30, 2021

– Phase 3 trial is a randomized, double-blind, placebo-controlled trial of apitegromab as add-on to background SMN therapy in non-ambulatory Type 2/3 SMA

– Trial design is informed by the positive results from the prior TOPAZ trial, including a new exploratory analysis of patients 2-12 years old with non-ambulatory Type 2/3 SMA

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 30, 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 study design for SAPPHIRE, a Phase 3 trial of apitegromab, a selective inhibitor of the activation of latent myostatin. This pivotal trial will evaluate the efficacy and safety of apitegromab in patients with non-ambulatory Type 2 and Type 3 spinal muscular atrophy (SMA), which is estimated to represent approximately two-thirds of the overall SMA patient population. Study start-up activities for SAPPHIRE have commenced.

“Despite the important progress in SMA treatment offered by SMN therapies, there continues to be significant unmet medical need, and we believe that apitegromab has the potential to improve motor function as add-on to background SMN therapy and transform the lives of patients with SMA,” said Nagesh Mahanthappa, Ph.D., Interim CEO. “We are excited to advance to the pivotal trial phase of apitegromab development through SAPPHIRE.”

SAPPHIRE Trial Design

SAPPHIRE is a randomized, double-blind, placebo-controlled, phase 3 clinical trial. Approximately 156 patients aged 2-12 years old with non-ambulatory Type 2/3 SMA are anticipated to be enrolled in the main efficacy population. Patients will be randomized 1:1:1 to receive for 12 months either apitegromab 10 mg/kg, apitegromab 20 mg/kg, or placebo by intravenous (IV) infusion every 4 weeks added on top of background SMN treatment. Patients receiving the background SMN treatment of nusinersen as well as patients receiving background SMN treatment of risdiplam will both be eligible for enrollment.

Additional key elements of the study design include the following:

- At baseline, all patients will be required to be in the chronic maintenance phase of SMN treatment, corresponding to ≥ 6 months of prior treatment in the case of risdiplam or ≥ 10 months of prior treatment in the case of nusinersen.
- Randomization will be stratified by both the background SMN treatment (nusinersen vs. risdiplam) as well as the age at which SMN treatment had been initiated (< 5 years vs. ≥ 5 years).
- The primary efficacy endpoint will evaluate the mean change from baseline in the Expanded Hammersmith Functional Motor Scale (HFMSE) total score after 12 months of treatment.
- Additional endpoints will evaluate safety, proportion of patients with ≥3-point HFMSE increase, Revised Upper Limb Module (RULM), and World Health Organization (WHO) motor developmental milestones, pharmacokinetics, pharmacodynamics, anti-drug antibody, and other outcome measures.

In addition, the trial provides the opportunity for an interim analysis when at least 50% of patients in the main efficacy population (age 2-12 years) have completed 12 months of treatment.

Separately from the main efficacy population, an exploratory population of 48 patients aged 13-21 years old with non-ambulatory Type 2/3 SMA will be evaluated. These patients will be randomized 2:1 to receive either apitegromab 20 mg/kg or placebo added to background SMN treatment with nusinersen or risdiplam. In this subpopulation of older individuals with SMA, the safety and tolerability of apitegromab will be characterized, and efficacy will also be evaluated in an exploratory, nonpowered manner.

To further characterize apitegromab in SMA, upon completion of the 12-month treatment period, all patients will be offered the option of enrolling in an open-label extension study. In this open-label extension, the safety and tolerability of apitegromab will be evaluated, along with an exploratory characterization of longer-term efficacy. In addition, the TOPAZ extension continues to follow patients from TOPAZ and evaluate the longer-term efficacy and safety of apitegromab. Among the 57 patients who completed the 12-month TOPAZ treatment period, 55 patients continue to participate in the extension period as of November 30, 2021.

SAPPHIRE is planned to enroll across 55 sites globally, including in the U.S. and Europe, and study start-up activities have commenced. For more information about SAPPHIRE, visit www.clinicaltrials.gov.

“We are encouraged and motivated by the positive results of the TOPAZ Phase 2 proof of concept trial, which informed the design of SAPPHIRE to evaluate the therapeutic potential of apitegromab in SMA,” said Yung Chyung, M.D., CMO. “Building on the solid foundation of TOPAZ, our Phase 3 trial and the broader program are aimed at advancing the development of apitegromab towards our aspiration of transforming the lives of patients with SMA.”

TOPAZ Insights Inform Key Elements of the SAPPHIRE Design

The SAPPHIRE design was informed by results from the TOPAZ phase 2 proof of concept trial of apitegromab in patients with Type 2 and Type 3 SMA. Key features of the SAPPHIRE design include the following:

- SAPPHIRE enrolls patients with non-ambulatory Type 2/3 SMA, which was the population of individuals observed to have the largest HFMSE increases from baseline in TOPAZ.
- Selection of the age 2-12 population in SAPPHIRE was informed by the positive efficacy results of an exploratory post hoc analysis from TOPAZ, as described in further detail below.
- SAPPHIRE will use the same primary efficacy endpoint (mean HFMSE change from baseline) as had been used in TOPAZ.
- SAPPHIRE will use the same treatment duration (12 months) as had been used in TOPAZ.
- SAPPHIRE will evaluate apitegromab at 20 mg/kg, which was observed in TOPAZ to have a greater effect than the 2 mg/kg dose both in terms of efficacy and pharmacodynamics. As it is possible that an intermediate dose of apitegromab between 2 and 20 mg/kg may offer comparable effects as the 20 mg/kg dose, SAPPHIRE will include an apitegromab 10 mg/kg arm. To control type I error caused by multiple comparisons, the efficacy analysis will first compare the apitegromab 20 mg/kg arm against placebo before any testing of apitegromab 10 mg/kg against placebo.

Exploratory Analysis of Age 2-12 Non-Ambulatory Patients from TOPAZ

This exploratory post hoc analysis from TOPAZ pooled together patients from both non-ambulatory cohorts (patients who had initiated their background nusinersen therapy at the age of < 5 years and patients who had initiated their background nusinersen therapy at the age of ≥ 5 years). Patients in this subset of the intent-to-treat population were in the age range of 2-12 years old and had been treated with 20 mg/kg of apitegromab.

The 12-month apitegromab results from this age 2-12 years old exploratory analysis of the pooled non-ambulatory cohorts in TOPAZ include the following:

- N= 16 total, with 50% of these patients being from the cohort of background nusinersen initiated at age < 5 years and 50% of these patients being from the cohort of background nusinersen initiated at age ≥ 5 years
- All patients were in the chronic maintenance phase of nusinersen treatment. Data from the SHINE study suggest that the effects of nusinersen upon HFMSE generally plateau after initial increases.[1]
- Mean HFMSE change from baseline was 4.4-point increase (95% CI of 1.3, 7.4)
- 81% (13/16) of patients had ≥ 1-point increase in HFMSE
- 56% (9/16) of patients had ≥ 3-point increase in HFMSE
- Among the older subset of patients (individuals who had started their background nusinersen at the age of ≥ 5 years) in this analysis, 75% (6/8) of patients had ≥ 1-point increase in HFMSE and 50% (4/8) of patients had ≥ 3-point increase in HFMSE

About Apitegromab

Apitegromab is a selective inhibitor of the activation of myostatin and is an investigational product candidate for the treatment of patients with 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, including humans. Scholar Rock believes that inhibiting myostatin activation with apitegromab may promote a clinically meaningful improvement in motor function in patients with SMA. The U.S. Food and Drug Administration (FDA) has granted Fast Track (FTD), Orphan Drug (ODD) and Rare Pediatric Disease (RPD) designations, and the European Medicines Agency (EMA) has granted Priority Medicines (PRIME) and Orphan Medicinal Product designations, 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 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, via SMN-dependent pathways, there continues to be a high unmet need for therapeutics that directly address muscle function.

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, and fibrosis. 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 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, SRK-181, and other product candidates and indication selection and development timing, the ability of any product candidate to perform in humans in a manner consistent with earlier nonclinical, preclinical or clinical trial data, and the potential of its product candidates and proprietary platform. 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 preclinical and clinical data, including the 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 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 and expectations, 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 September 30, 2021, 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.

[1] This information from a third-party study is provided for background purposes only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results.

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