Scholar Rock Announces New SRK-439 Preclinical Data Showing Significant Lean Mass Preservation and Attenuation of Fat Mass Rebound Following GLP-1 Receptor Agonist Withdrawal

June 24, 2024

- SRK-439, a myostatin inhibitor, is part of Scholar Rock's industry-leading anti-myostatin portfolio

- Obesity program continues to progress, with first participants dosed in Phase 2 EMBRAZE trial of apitegromab in obesity

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 24, 2024-- Scholar Rock (NASDAQ: SRRK), a late-stage biopharmaceutical company focused on advancing innovative treatments for spinal muscular atrophy (SMA), cardiometabolic disorders, and other serious diseases where protein growth factors play a fundamental role, today announced that the first participants were dosed in the Phase 2 EMBRAZE proof-of-concept trial, designed to assess the safety and efficacy of apitegromab, an investigational, highly selective myostatin inhibitor, to preserve lean muscle mass in individuals living with obesity and on background therapy of a GLP-1 receptor agonist (GLP-1 RA). The trial will also evaluate the effects of apitegromab on the durability of weight loss upon withdrawal of GLP-1 RA therapy. The results from this trial will inform the development of SRK-439, a novel investigational selective myostatin inhibitor optimized for the treatment of cardiometabolic disorders, including obesity.

The Company also presented new preclinical data that support the potential of SRK-439 to increase lean mass and contribute to a favorable body composition following withdrawal from GLP-1 RA treatment. These data were presented by Melissa Fulham, PhD, of Scholar Rock, at the American Diabetes Association's 84 th Scientific Sessions on June 23rd in Orlando, Florida.

"We are happy to share the exciting news that we've dosed the first participants in our EMBRAZE clinical trial ahead of schedule and to have new preclinical data with SRK-439, our highly selective anti-myostatin, featured at the American Diabetes Association Scientific Sessions," said Jay Backstrom, M.D., MPH, President and Chief Executive Officer at Scholar Rock. "SRK-439 preclinical data to date have demonstrated preservation of lean mass with GLP-1 RA-induced weight loss, attenuation of fat mass regain following GLP-1 RA withdrawal, and greater potency compared to an anti-ACTRII antibody. Together, these data continue to support a best-in-class potential for healthy weight loss management and could be transformative for the management of weight loss. We are looking forward to providing additional updates on our cardiometabolic program as we advance SRK-439, as well as the EMBRAZE trial."

Preclinical experimental design

For the preclinical research study, the Company tested a murine equivalent of SRK-439 in a diet-induced obesity (DIO) mouse model. Mice were given either a high-fat diet plus semaglutide (0.04 mg/kg, daily) and an IgG control antibody (weekly, 10 mg/kg), or a high-fat diet plus semaglutide (0.04 mg/kg, daily) in combination with weekly injections of SRK-439 (10 mg/kg). Following four weeks of treatment, semaglutide was withdrawn from both treatment groups and mice remained on either the IgG control antibody weekly or on SRK-439. Treatment continued for another four weeks, for a total of eight weeks in the study. Quantitative nuclear magnetic resonance (qNMR) was used to analyze change in lean mass at two weeks and again at four weeks of semaglutide treatment, and every two weeks after that until the end of the subsequent four-week withdrawal period.

Changes in body composition after semaglutide withdrawal

The group that received SRK-439 maintained more favorable body composition than the group receiving IgG antibody. Key findings supporting the potential for SRK-439 in advancing healthier weight management include:

- Administration with SRK-439 attenuated the loss of lean mass during semaglutide treatment and significantly increased lean mass after semaglutide discontinuation as compared to IgG control;
- SRK-439 administration also attenuated the fat mass rebound after semaglutide discontinuation as compared to that in IgG control + semaglutide mice; and
- Body composition, i.e. proportion of lean mass or fat mass to total body weight, was more favorable in mice receiving SRK-439 as compared to IgG control: Mice administered SRK-439 had higher relative lean mass (65.8%) and lower relative fat mass (18.0%) at the end of the withdrawal period compared to IgG control (57.1% lean mass and 28.7% fat mass).

Shown below are results for body composition at baseline (6 days before semaglutide treatment), the end of semaglutide treatment (at 4 weeks), and at the end of the semaglutide withdrawal period (at 8 weeks):

Endpoint (units)	IgG control + semaglutide	SRK-439 + semaglutide	P value
Absolute lean mass (g) at baseline	24.8	25.5	n.s.
Absolute lean mass (g) at 4 weeks	22.3	26.4	P<0.001
Absolute lean mass (g) at 8 weeks	25.1	29.4	P<0.0001
Absolute fat mass (g) at baseline	11.8	10.3	n.s.
Absolute fat mass (g) at 4 weeks	5.9	3.8	n.s.
Absolute fat mass (g) at 8 weeks	12.7	8.3	n.s.
Relative lean mass (%) at 8 weeks	57.1%	65.8%	P<0.001
Relative fat mass (%) at 8 weeks	28.7%	18.0%	P<0.01

“These new preclinical data provide compelling evidence that SRK-439 contributed to lean muscle preservation during GLP-1 RA-induced weight loss and attenuated fat mass rebound following discontinuation of semaglutide,” said Mo Qatanani, PhD, Chief Scientific Officer at Scholar Rock. “Mice receiving SRK-439 treatment had significantly more lean mass at the end of the semaglutide withdrawal period. These exciting data continue to support the differentiated profile of SRK-439 and its potential to contribute to healthier weight management and long-term metabolic benefits during and after GLP-1 RA treatment.”

For conference information, visit https://professional.diabetes.org/scientific-sessions.

The slides from the presentation are available in the Publications & Posters section of Scholar Rock’s website.

About EMBRAZE

EMBRAZE is a randomized, double-blind, placebo-controlled, Phase 2 proof-of-concept trial evaluating the efficacy, safety and pharmacokinetics of apitegromab in adults with a body mass index (BMI) of >27 (overweight) or a BMI of >30 (obese) and taking a GLP-1 RA (tirzepatide or semaglutide). The target enrollment of EMBRAZE is 100 subjects aged 18-65 who are overweight or obese without diabetes. As part of the study design, the treatment period is 24 weeks, and all subjects will receive a GLP-1 RA. In addition, all subjects will be randomized 1:1 to receive either apitegromab or placebo by intravenous (IV) infusion every four weeks during the 24-week treatment period. The primary endpoint is change from baseline at Week 24 in lean mass assessed by dual-energy X-ray absorptiometry. Secondary endpoints include additional weight loss measures, safety and tolerability, and pharmacokinetic outcomes. Exploratory endpoints at Weeks 24 and 32 include cardiometabolic parameters (e.g. HbA1c), body composition, and physical function.

About SRK-439

SRK-439 is a novel, preclinical, investigational myostatin inhibitor that binds to pro- and latent myostatin with high affinity and is selective for myostatin (i.e., no GDF11 or Activin-A binding), and is initially being developed for the treatment of cardiometabolic disorders, including obesity. Based on preclinical data, SRK-439 has the potential to support healthier weight management by preserving lean mass during weight loss. The efficacy and safety of SRK-439 have not been established and SRK-439 has not been approved for any use by the FDA or any other regulatory agency.

About Apitegromab

Apitegromab is an investigational fully human monoclonal antibody inhibiting myostatin activation by selectively binding the pro- and latent forms of myostatin in the skeletal muscle. It is the first muscle-targeted treatment candidate to demonstrate clinical proof-of-concept in 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, including humans. Scholar Rock believes that its highly selective targeting of pro- and latent forms of myostatin with apitegromab may lead to a clinically meaningful improvement in motor function in patients with SMA. The U.S. Food and Drug Administration (FDA) has granted Fast Track, Orphan Drug and Rare Pediatric Disease 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 Scholar Rock

Scholar Rock is a biopharmaceutical company that discovers, develops, and delivers life-changing therapies for people with serious diseases that have high unmet need. As a global leader in the biology of the transforming growth factor beta (TGFβ) superfamily of cell proteins and named for the visual resemblance of a scholar rock to protein structures, the clinical-stage company is focused on advancing innovative treatments where protein growth factors are fundamental. Over the past decade, Scholar Rock has created a pipeline with the potential to advance the standard of care for neuromuscular disease, cardiometabolic disorders, cancer, and other conditions where growth factor-targeted drugs can play a transformational role.

Scholar Rock is the only company to show clinical proof-of-concept for a muscle-targeted treatment in spinal muscular atrophy (SMA). This commitment to unlocking fundamentally different therapeutic approaches is powered by broad application of a

proprietary platform, which has developed novel monoclonal antibodies to modulate protein growth factors with extraordinary selectivity. By harnessing cutting-edge science in disease spaces that are historically under-addressed through traditional therapies, Scholar Rock works every day to create new possibilities for patients. Learn more about our approach at ScholarRock.com and follow @ScholarRock and on LinkedIn.

Availability of Other Information About Scholar Rock

Investors and others should note that we communicate with our investors and the public using our company website www.scholarrock.com, including, but not limited to, company disclosures, investor presentations and FAQs, Securities and Exchange Commission filings, press releases, public conference call transcripts and webcast transcripts, as well as on Twitter and LinkedIn. The information that we post on our website or on Twitter or LinkedIn could be deemed to be material information. As a result, we encourage investors, the media and others interested to review the information that we post there on a regular basis. The contents of our website or social media shall not be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended.
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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 and its preclinical programs, including SRK-439, and indication selection and development timing, including the therapeutic potential, clinical benefits and safety thereof, expectations regarding timing, success and data announcements of current ongoing preclinical and clinical trials, 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," "could," "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, without limitation, that preclinical and clinical data, including the results from the Phase 2a clinical trial of apitegromab, or its preclinical data with respect to SRK-439, are not predictive of, may be inconsistent with, or more favorable than, data generated from future or ongoing clinical trials of the same product candidates, including, without limitation, the Phase 3 clinical trial of apitegromab in SMA or the Phase 2a EMBRAZE clinical trial; 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, without limitation, to supply any clinical trials; and 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; 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 March 31, 2024, 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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