SRK-439, a Selective Anti-Pro and Latent Myostatin Antibody, Maintains Lean Mass and Enhances Fat Mass Loss in Models of Pharmacologically-Induced Weight Loss

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Abstract

As obesity and its related comorbidities increase in prevalence worldwide, there is an urgent need for safe and durable pharmacologic therapies. The family of glaucon-like peptide-1 receptor agonists (GLP-1RAs) has emerged as effective treatments with rapid implementation. They mimic human GLP-1 and increase insulin production, lower glucagon production, and control appetite. Each new iteration improves weight loss and glucose control; however none have successfully circumvented the undesirable negative impact on lean mass during weight loss.

We hypothesized that selectively inhibiting myostatin signaling during GLP-1RA-induced weight loss may maintain lean mass and facilitate healthier weight management with improved long-term metabolic health. Myostatin is a negative regulator of muscle mass that belongs to the transforming growth factor-β (TGF-β) superfamily. Produced locally in muscle tissue, myostatin signaling through activin receptor type 2 (Act-RII) receptors inhibits muscle growth and promotes muscle breakdown. Similar to other family members, myostatin is produced as a pro-protein and requires two proteolytic steps for activation to produce latent myostatin and finally active, mature myostatin.

We have developed an exquisitely selective anti-pro and latent myostatin antibody, SRK-439, which locks myostatin into its inactive, latent form. SRK-439 binds specifically to myostatin with 0.579 nM affinity and does not bind to the closely related TGF-β family members (GDF11, Activin A). This selectivity and high affinity, along with favorable developability and pharmacokinetics suggests that SRK-439 is a suitable candidate to enable healthy weight management, specifically in the obese patient population.

To test the impact of SRK-439 on lean mass during GLP-1RA-driven weight loss, we used the GLP-1RA liraglutide to induce weight loss in a mouse model of diet-induced obesity (DIO). Total body weight, lean mass, and fat mass were assessed. As expected, liraglutide reduced body weight in DIO mice. Quantitative nuclear magnetic resonance (qNMR) was used to analyze body composition, which confirmed liraglutide reduced both lean mass and fat mass. Mice that received SRK-439 had increased lean mass, even in the presence of liraglutide. Additionally, SRK-439 further reduced fat mass.

Next, we used semaglutide, a more potent GLP-1RA family member, semaglutide treatment lowered body weight, lean mass, and fat mass -17.4%, -11.3%, and -36.6% from baseline, respectively. SRK-439 diminished the semaglutide-driven lean mass loss in a dose-dependent manner (ranging from -7.5% to -1.4% from baseline). Consistent with improved body composition, SRK-439 also enhanced fat mass loss (-46.3% from baseline). Finally, SRK-439 lowered fasting glucose in a dose-dependent manner in combination with semaglutide. Altogether, these results have demonstrated that in the context of GLP-1RA-driven weight loss SRK-439 maintains lean mass and improves fat mass loss. This promotes a better metabolic profile and healthier weight loss.

In summary, SRK-439 is a highly selective, potent inhibitor of myostatin that has been developed specifically to target patients with obesity.

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References