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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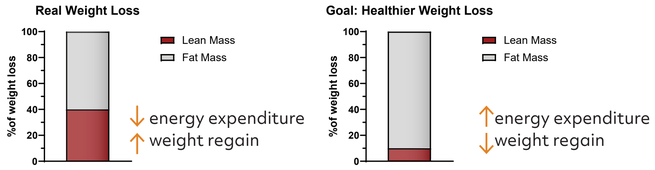
Abstract

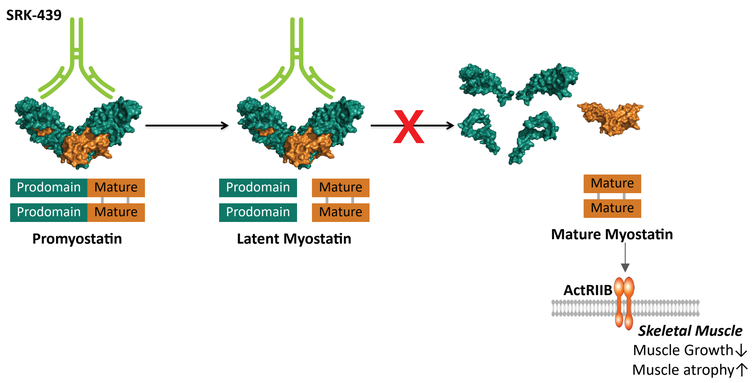
As obesity and its related comorbidities increase in prevalence worldwide, there is an urgent need for safe and durable pharmacologic therapies. The family of glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as effective treatments with rapid implementation. They mimic human GLP-1 and 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.

- Challenge: up to 40% of weight lost is lean mass. This contributes to lower energy expenditure and makes reaching and maintaining a healthy weight difficult
- Solution: maintain 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 (ActRII) 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 characteristics and durable pharmacokinetics suggests that SRK-439 is a suitable candidate to enable healthy weight management, specifically in the obese patient population.



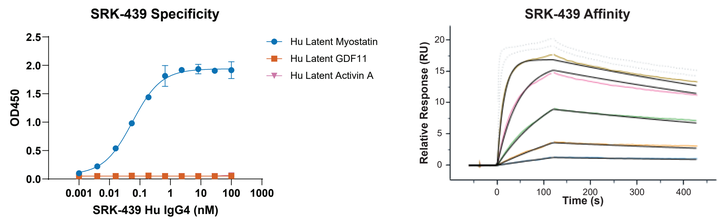
To test the impact of SRK-439 on lean mass during GLP-1RA-driven weight loss, we used the GLP-1RA liraglutide to induce weight loss in a mouse model of diet-induced obesity (DIO). Total body weight, lean mass, and fat mass were assessed. As expected, liraglutide reduced body weight in DIO mice. Quantitative 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, with SRK-439 in weight-stable DIO mice. Similar to other GLP-1RA family members, 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. SRK-439 represents a highly selective, potent inhibitor of myostatin that has been developed specifically to target patients with obesity.

SRK-439 selectively binds to myostatin with high affinity

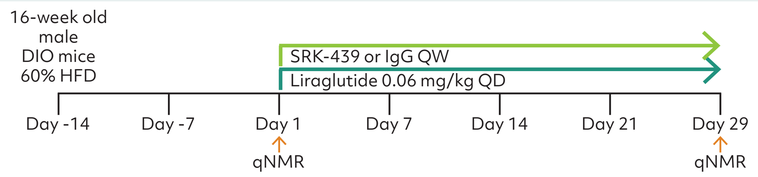
SRK-439 Specificity: an ELISA was performed with plate-immobilized human (hu) latent forms of myostatin, GDF11, and Activin A. SRK-439 bound to myostatin and there was no detectable binding to GDF 11 or Activin A.

SRK-439 Affinity: biotinylated hu latent myostatin was immobilized to a Biacore CAPture chip (Cytiva) and SRK-439 was flowed at 10, 3.2, 1, 0.3, and 0.1 nM to evaluate the kinetics of binding. SRK-439 binds to latent myostatin with a K_D of 0.579 nM.

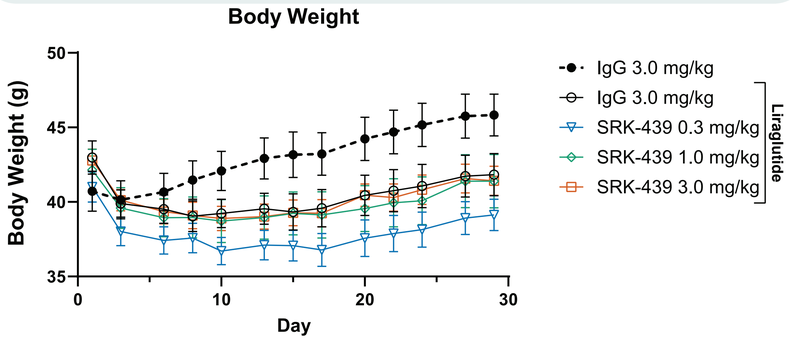


SRK-439 maintains lean mass during liraglutide induced weight loss

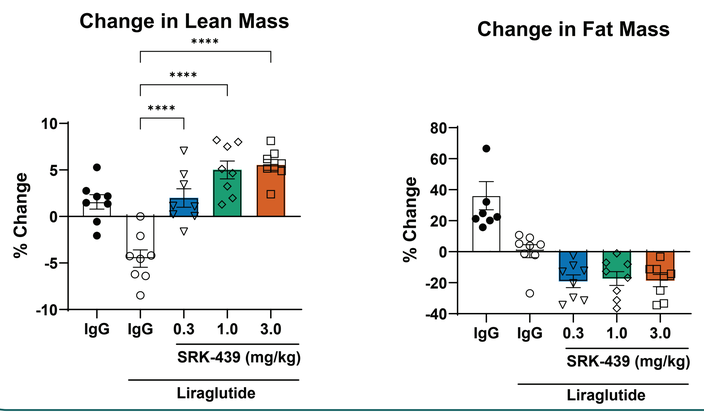
Male, DIO mice were treated with liraglutide daily and SRK-439 or IgG control weekly. Body composition was measured via qNMR on Day 1 and Day 29.



Liraglutide treatment reduced body weight.



Liraglutide treatment reduced lean mass and fat mass. SRK-439 increased lean mass and reduced fat mass in combination with liraglutide.



In vitro data are mean ± SD; *in vivo* data are mean ± SEM
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, one-way ANOVA with Dunnett's multiple comparison test within the GLP-1RA treated groups, compared to the IgG+GLP-1RA control

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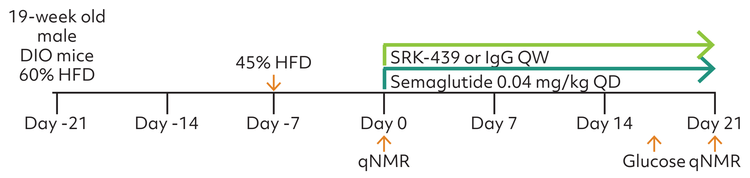
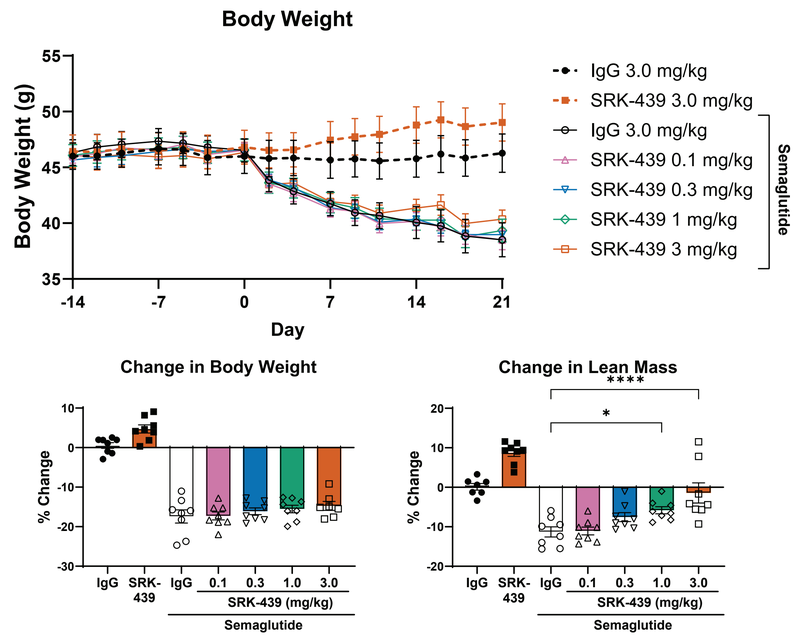
SRK-439 maintains lean mass and reduces fat mass during semaglutide induced weight loss

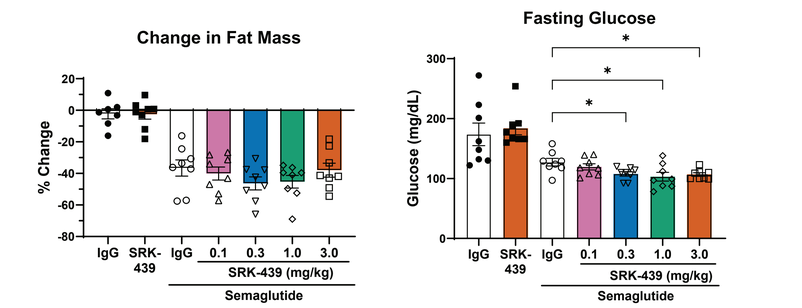
Male, DIO mice were switched to a 45% HFD to generate weight-stable mice one week prior to treatment with semaglutide daily and SRK-439 or IgG control weekly. Body composition was measured via qNMR on Day 0 and Day 21. Fasted blood glucose was measured at Day 18.



Semaglutide treatment reduced body weight and lean mass. SRK-439 preserved lean mass in a dose-dependent manner.



Semaglutide treatment reduced fat mass and fasting glucose. SRK-439 enhanced fat mass loss and lowered fasting glucose in combination with semaglutide.



Summary

SRK-439 is a selective anti-pro and latent myostatin antibody that maintains lean mass and improves fat mass loss during GLP-1RA-driven weight loss, which promotes an improved metabolic profile and healthier weight management.

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