SRK-439 Selectively Inhibits Myostatin to Promote Healthy Body Composition During Metformin Therapy

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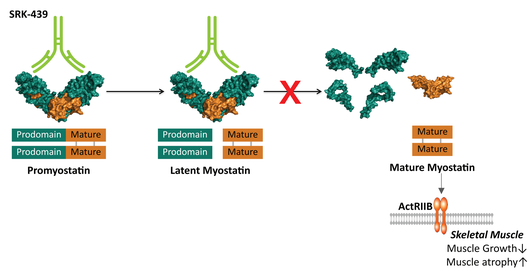
Hypothesis

The increase in the use of pharmacological weight loss interventions highlights the need to maintain a healthy body composition. Up to 40% of total weight lost is lean mass which may diminish long-term health benefits and make maintaining weight loss challenging. Safe and durable complementary therapies are needed to preserve lean mass. Myostatin is a growth factor expressed in skeletal muscle which restricts muscle mass. SRK-439 is a highly selective anti-pro and latent myostatin antibody that increases lean mass in mice. We have previously shown that a mouse chimera of SRK-439 administered with GLP-1 receptor agonists preserves lean mass and enhances fat mass loss in diet-induced obesity (DIO) mice. Clinical work using a related, less-specific mechanism demonstrated weight loss in participants with type 2 diabetes and obesity who were on metformin. We hypothesized that inhibiting myostatin during metformin treatment would maintain lean mass and improve body composition, which may have long-term metabolic benefits.

Background

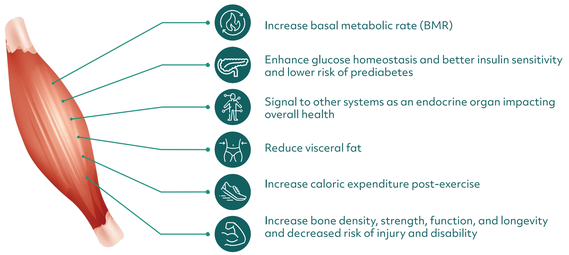
Metformin is a commonly prescribed anti-diabetic drug which has been suggested to have both positive and deleterious effects on skeletal muscle. A clinical trial evaluating an ActRIIA/B-specific antibody in participants with type 2 diabetes and obesity demonstrated increased lean mass during weight loss; 87% of the total participants were taking metformin (Heymsfield 2021). However, non-selective targeting of the receptor has many potential safety liabilities and we believe selectively targeting myostatin is the preferred strategy.

SRK-439 binds to pro- and latent myostatin to prevent activation and enable muscle growth



- SRK-439 binds to pro- and latent myostatin and blocks the conversion of the latent form to mature myostatin
- By inhibiting the release of mature myostatin, SRK-439 prevents myostatin from interacting with receptors which results in the inhibition of signaling and promotes muscle growth

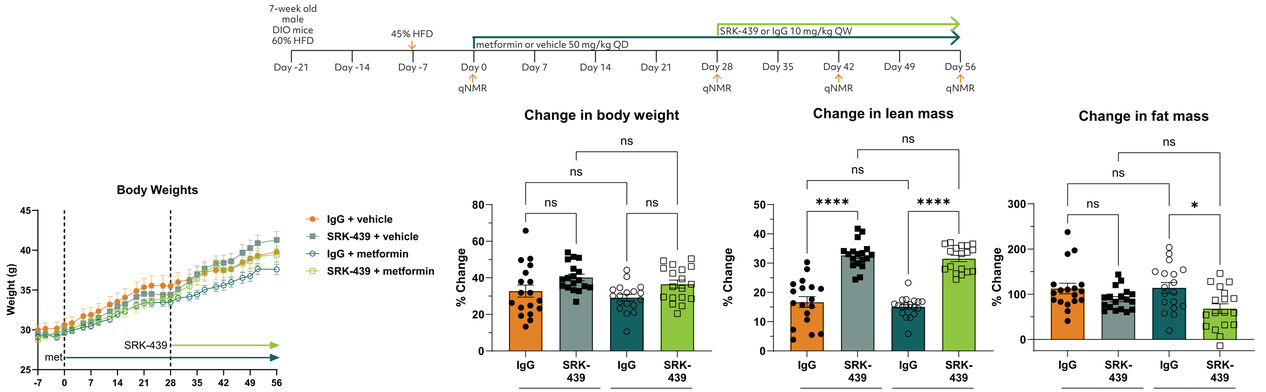
Muscle is critical for overall health



Methods

DIO mice were treated with metformin or vehicle for four weeks and then concurrently with the mouse chimera of SRK-439 or IgG control for an additional four weeks. Body composition via quantitative nuclear magnetic resonance imaging was assessed throughout the study.

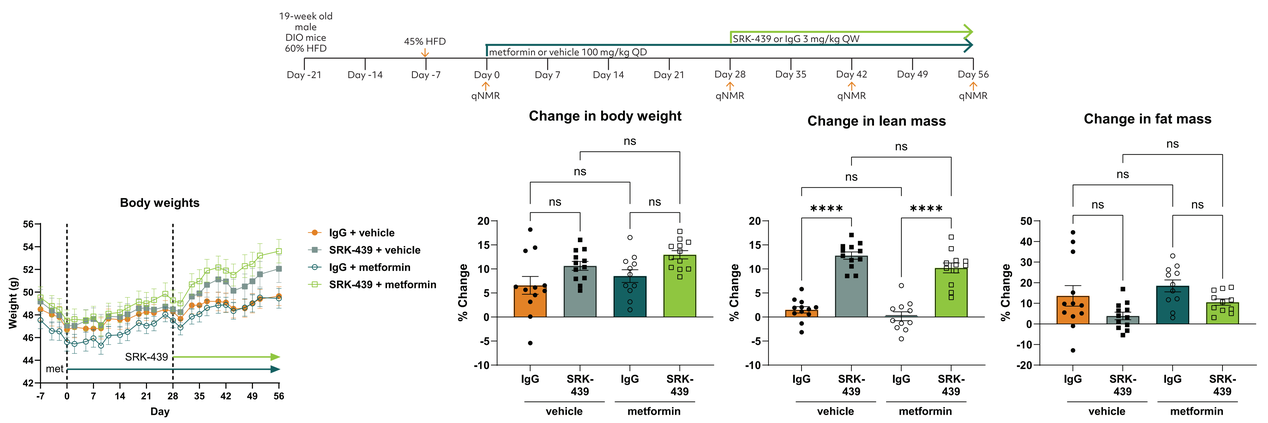
SRK-439 and metformin administration have a synergistic effect on fat mass in young DIO mice



Results

SRK-439 increased lean mass in vehicle and metformin groups when compared to IgG (vehicle: 32.7% increase from baseline vs 16.7% p<0.0001; metformin: 31.6% vs 15.1% p<0.0001). Consistent with previous data, SRK-439 improved fat mass; mice that received metformin+SRK-439 had less fat mass gain when compared to metformin+IgG (68.2% increase from baseline vs 114% p<0.05).

SRK-439 increases lean mass and reduces fat mass regardless of metformin administration in mature DIO mice

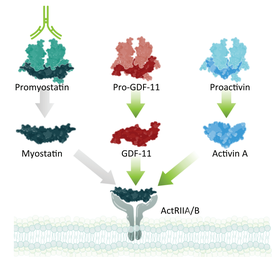


Results

SRK-439 increased lean mass in vehicle and metformin groups when compared to IgG (vehicle: 12.8% increase from baseline vs 1.5% p<0.0001; metformin: 10.2% vs 0.2% p<0.0001). There was a trend of improved fat mass loss; mice that received SRK-439 had lower fat mass gain when compared to IgG (vehicle: 3.9% increase from baseline vs 13.6% ns; metformin: 10.6% vs 18.4%; ns).

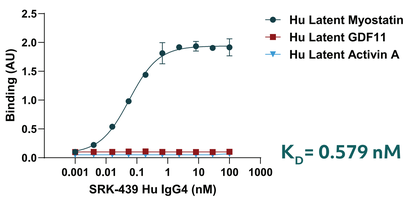
Data are mean ± SEM pooled from two independent experiments in the first study and a single experiment in the second study. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, ns, not significant. one-way ANOVA with Tukey's multiple comparison test.

SRK-439 selectively binds to myostatin and not related growth factors that have potential health risks



- ActRIIB/Activin A/GDF11 KO mice all have perinatal lethality due to developmental defects in multiple organ systems
- GDF11 LOF variants are associated with severe craniofacial, neurological, and skeletal phenotypes in humans
- Inhibition of ActRII or Activin A in adult humans is associated with several health risks, including significant reduction in follicle-stimulating hormone levels

SRK-439 Specificity



Summary

- In younger DIO mice, SRK-439 increased lean mass in the presence and absence of metformin. SRK-439 and metformin had a synergistic effect on fat mass.
- In older DIO mice, SRK-439 increased lean mass in the presence and absence of metformin. SRK-439 reduced fat mass gain regardless of metformin administration.

Conclusion
Selectively inhibiting myostatin in combination with metformin administration increases lean mass and reduces fat mass in DIO mice. This supports the use of SRK-439 to promote healthy body composition during treatment for obesity and type 2 diabetes.

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References

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