The Anti-Myostatin Antibody SRK-439 Promotes Healthy Body Composition in Combination with GLP-1RAs in a Mouse Model of Obesity

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Presenter disclosure

Melissa Fulham

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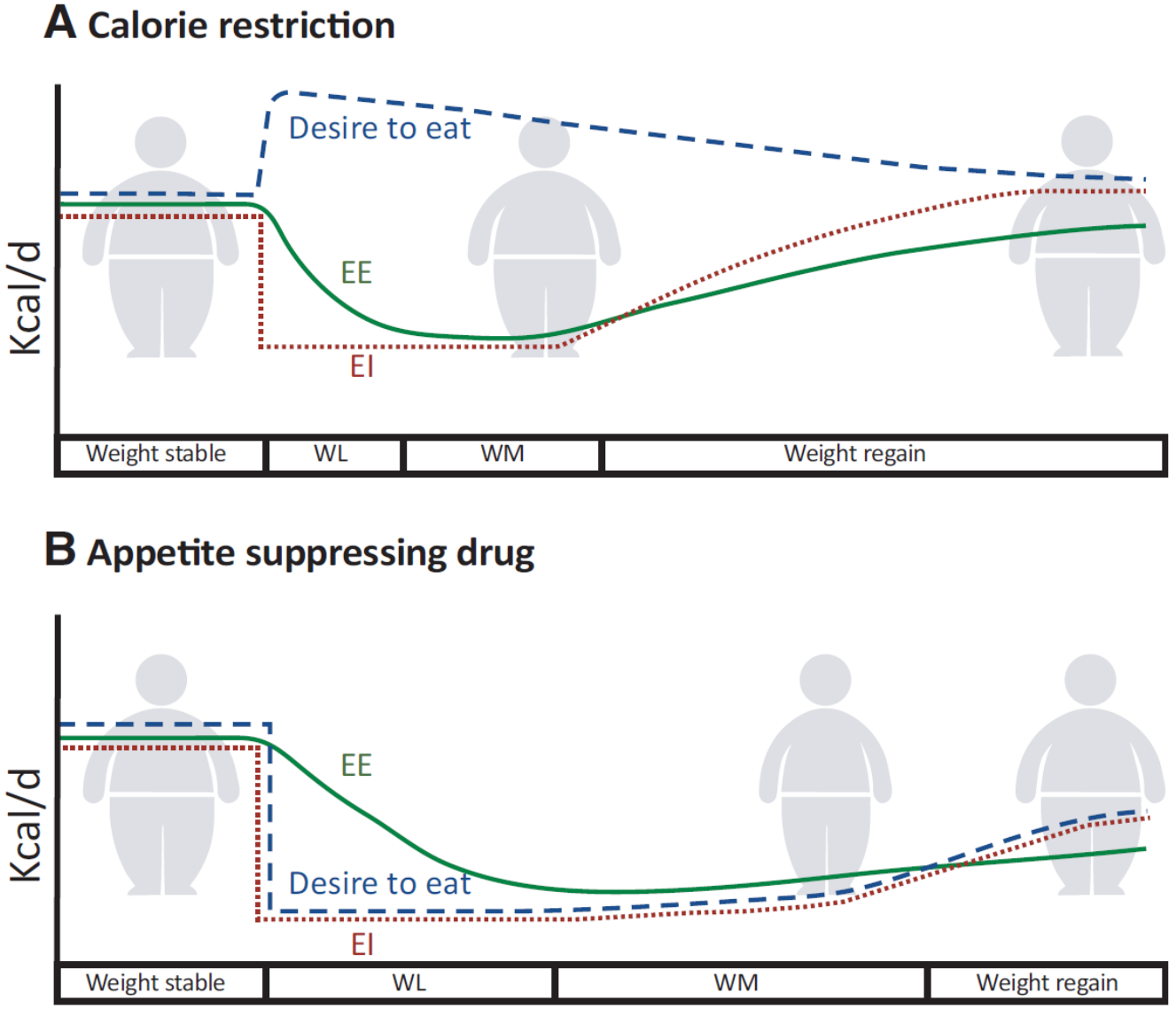
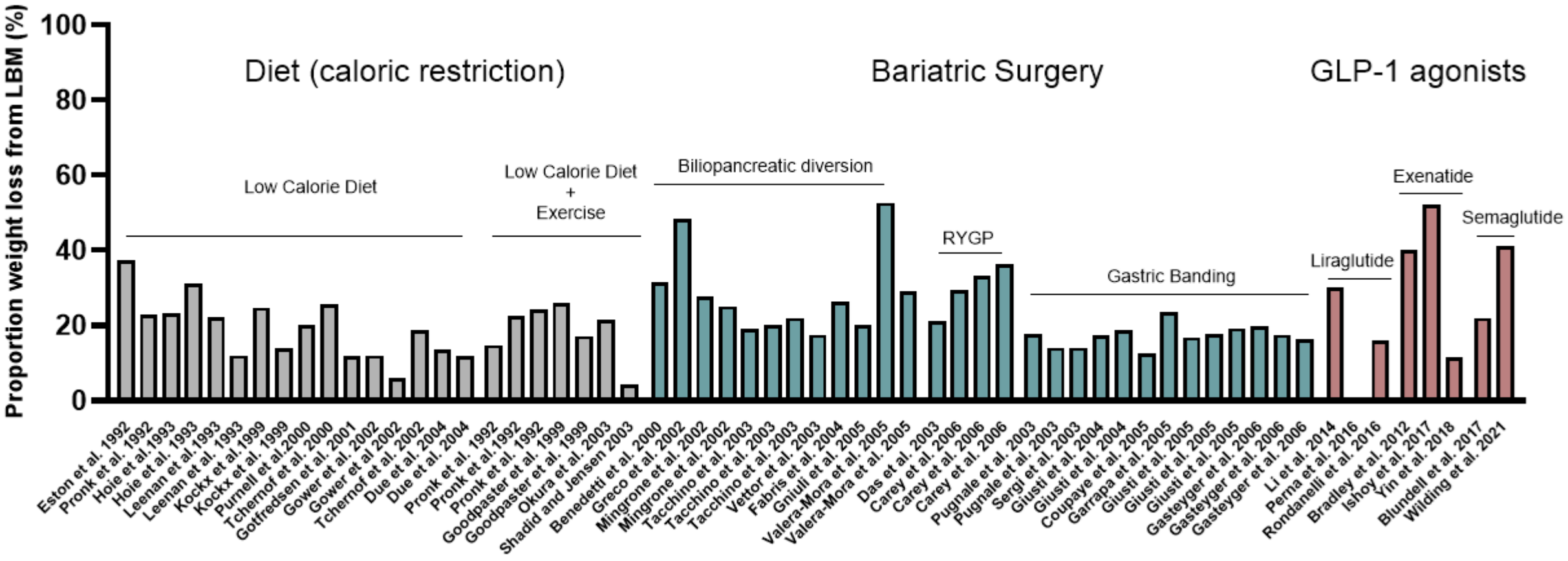
Maintaining weight loss is challenging



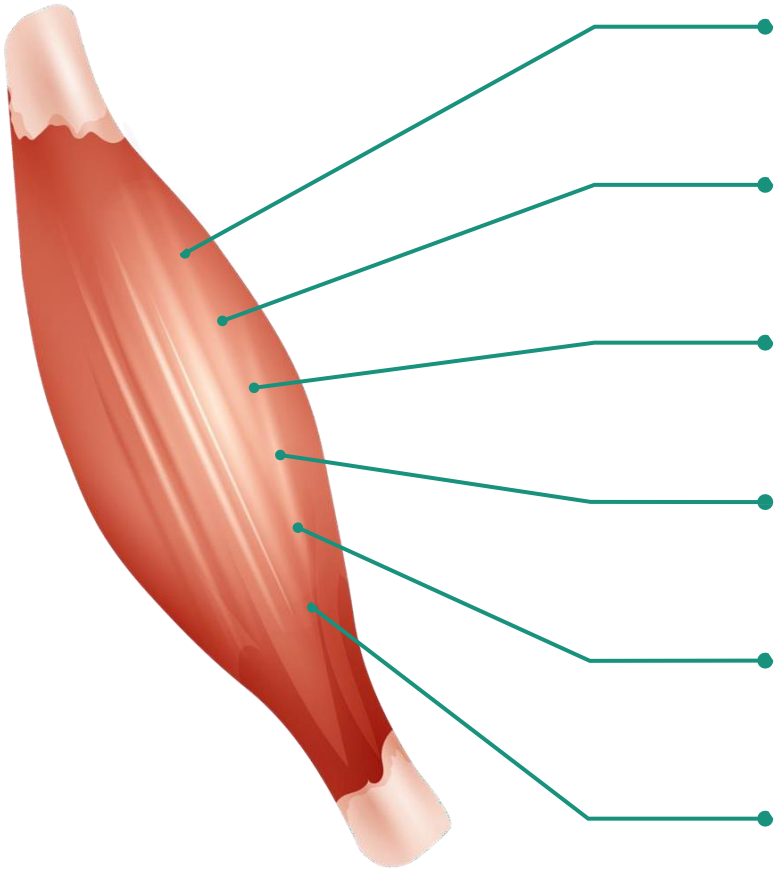
Christoffersen, B.Ø., *et al*. *Obesity (Silver Spring)*. 2022. PMID: 35333444

Lean mass is reduced during weight loss regardless of intervention



Chaston, T. B., *et al*. *Int J Obes*. 2007. PMID: 17075583
Sargeant, J. A., *et al. Endocrinol Metab*. 2019. PMID: 31565876
Wilding J.P.H., *et al*. *Diabetes Obes Metab*. 2022. PMID: 35441470

Muscle is critical for overall health

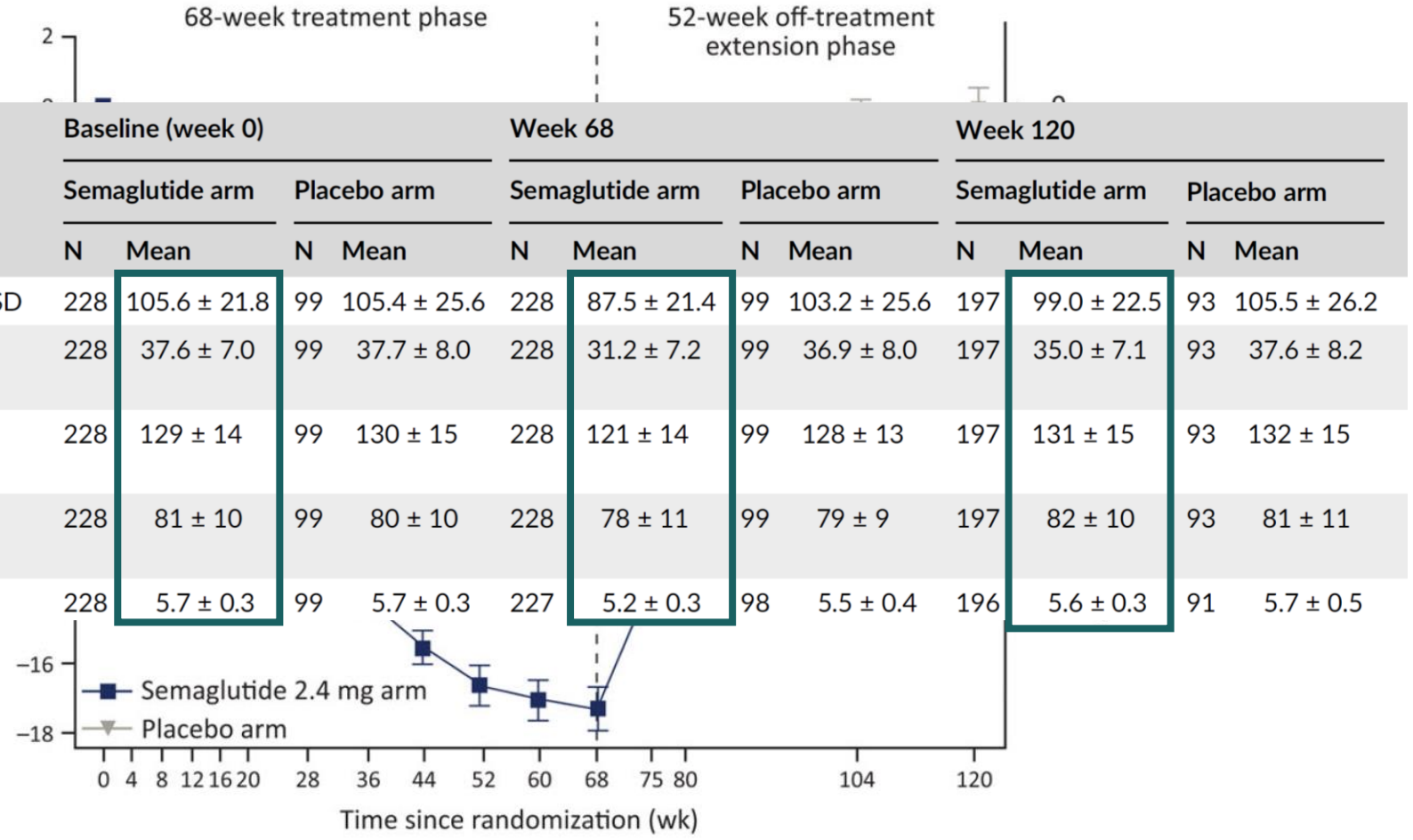


- Increase basal metabolic rate (BMR)[1]
- Enhance glucose homeostasis[2] and better insulin sensitivity and lower risk of prediabetes[3]
- Signal to other systems as an endocrine organ impacting overall health[4]
- Reduce visceral fat[5]
- Increase caloric expenditure post-exercise[6]
- Increase bone density, strength, function, and longevity and decreased risk of injury and disability[7-9]

1. Aristizabal, J.C., *et al*. *Eur J Clin Nutr*. 2015. 2. Lindegaard, B., *et al*. *J Clin Endocrinol Metab*. 2008. 3. Srikanthan, P. and Karlamangla, A.S. *J Clin Endocrinol Metab*. 2011. 4. Severinsen, M.C.K. and Pedersen, B.K. *Endocr Rev*. 2020. 5. Wewege, M.A., *et al*. *Sport Med*. 2022. 6. Zurlo, F., *et al*. *J Clin InvestI*. 1990. 7. Fukushima, Y., *et al*. *Diabetes Metab J*. 2016. 8. Roh, E. and Choi, K.M. *Front. Endocrinol (Lausanne)*. 2020. 9. Volpi, E., *et al*. *Curr Opin Clin Nutr Metab Care*. 2004.

GLP-1RA withdrawal leads to weight regain and loss of cardiometabolic benefits

STEP 1 trial extension: Participants regained weight after semaglutide withdrawal



	Baseline (week 0)				Week 68				Week 120			
	Semaglutide arm		Placebo arm		Semaglutide arm		Placebo arm		Semaglutide arm		Placebo arm	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Body weight (kg), mean ± SD	228	105.6 ± 21.8	99	105.4 ± 25.6	228	87.5 ± 21.4	99	103.2 ± 25.6	197	99.0 ± 22.5	93	105.5 ± 26.2
Body mass index (kg/m^2), mean ± SD	228	37.6 ± 7.0	99	37.7 ± 8.0	228	31.2 ± 7.2	99	36.9 ± 8.0	197	35.0 ± 7.1	93	37.6 ± 8.2
Systolic blood pressure (mmHg), mean ± SD	228	129 ± 14	99	130 ± 15	228	121 ± 14	99	128 ± 13	197	131 ± 15	93	132 ± 15
Diastolic blood pressure (mmHg), mean ± SD	228	81 ± 10	99	80 ± 10	228	78 ± 11	99	79 ± 9	197	82 ± 10	93	81 ± 11
HbA1c (%), mean ± SD	228	5.7 ± 0.3	99	5.7 ± 0.3	227	5.2 ± 0.3	98	5.5 ± 0.4	196	5.6 ± 0.3	91	5.7 ± 0.5

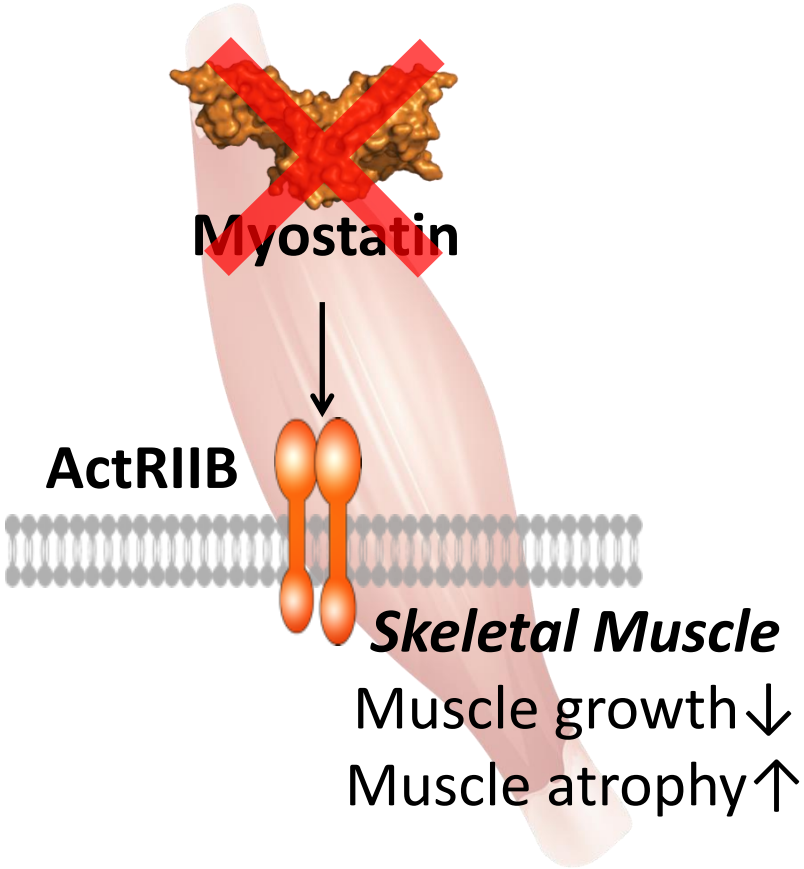
Wilding J.P.H., *et al*. *Diabetes Obes Metab*. 2022. PMID: 35441470

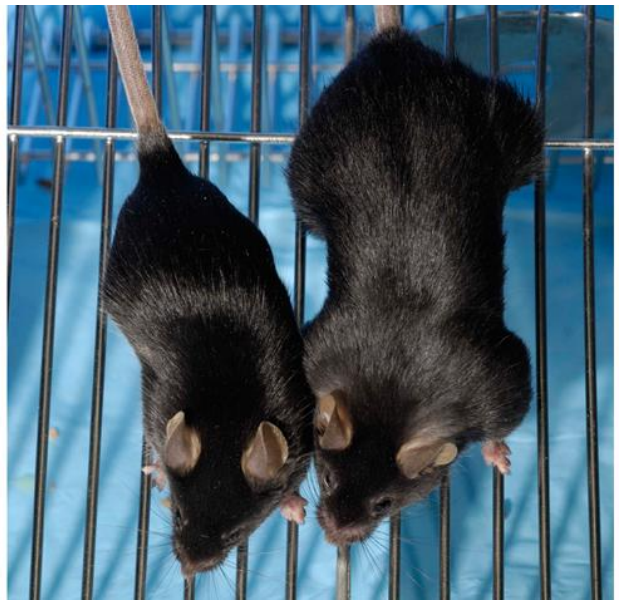
Can we mitigate weight regain and loss of metabolic benefit?

- This is not unique to GLP-1RAs; weight is regained with all weight loss methods

- How can we maintain or increase lean mass during weight loss?

Belgian blue cattle;
MSTN-null



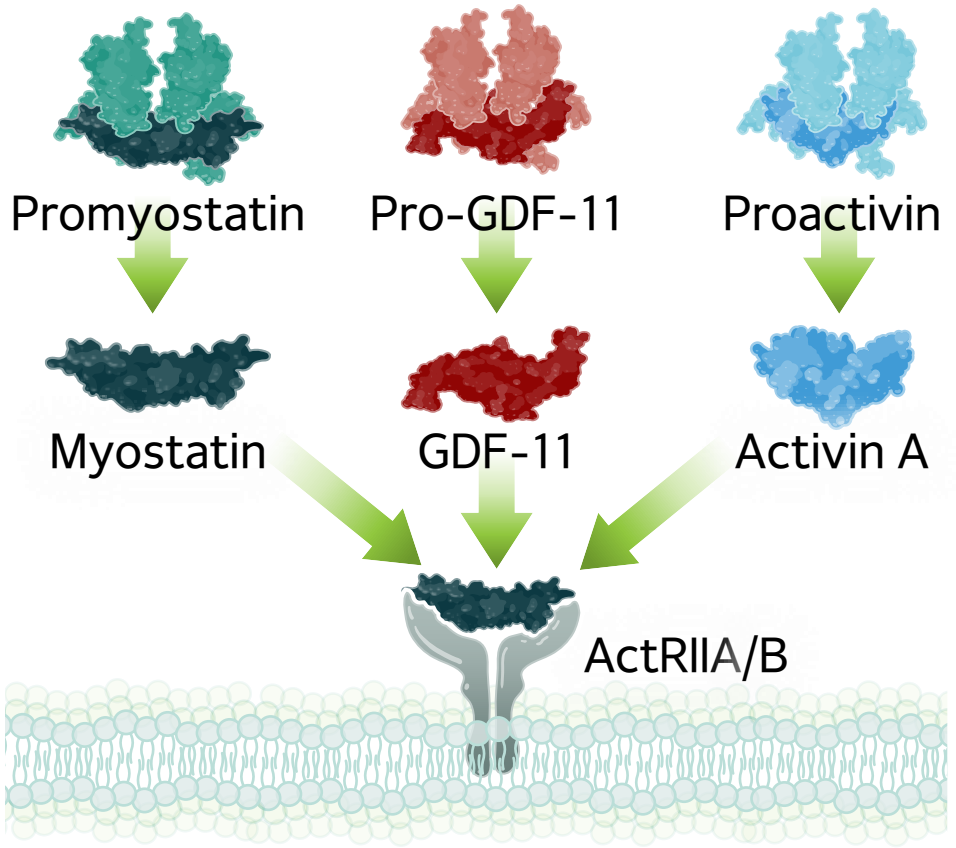


Mstn$^{-/-}$ mice

Lee, S.J. *PLoS One*. 2007. PMID: 17726519

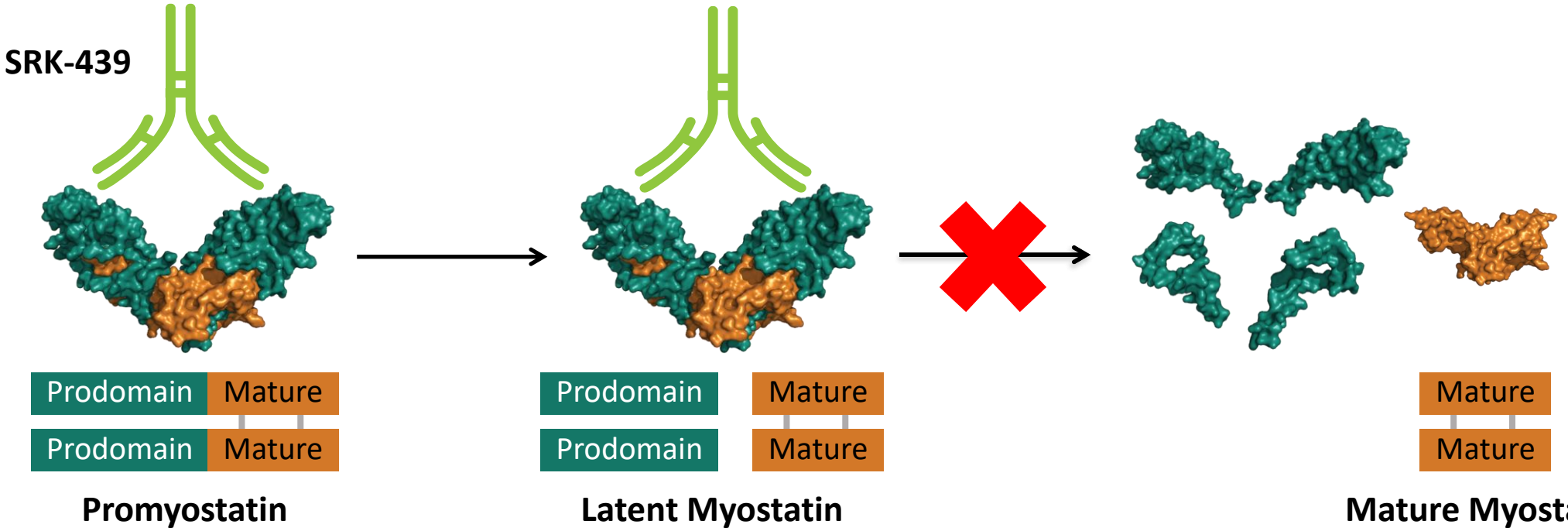
Selectively targeting myostatin is challenging but critical

- Developing an anti-myostatin agent is difficult due to a high degree of similarity with Activin A and GDF-11
- Selectively targeting myostatin is important:
  - 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



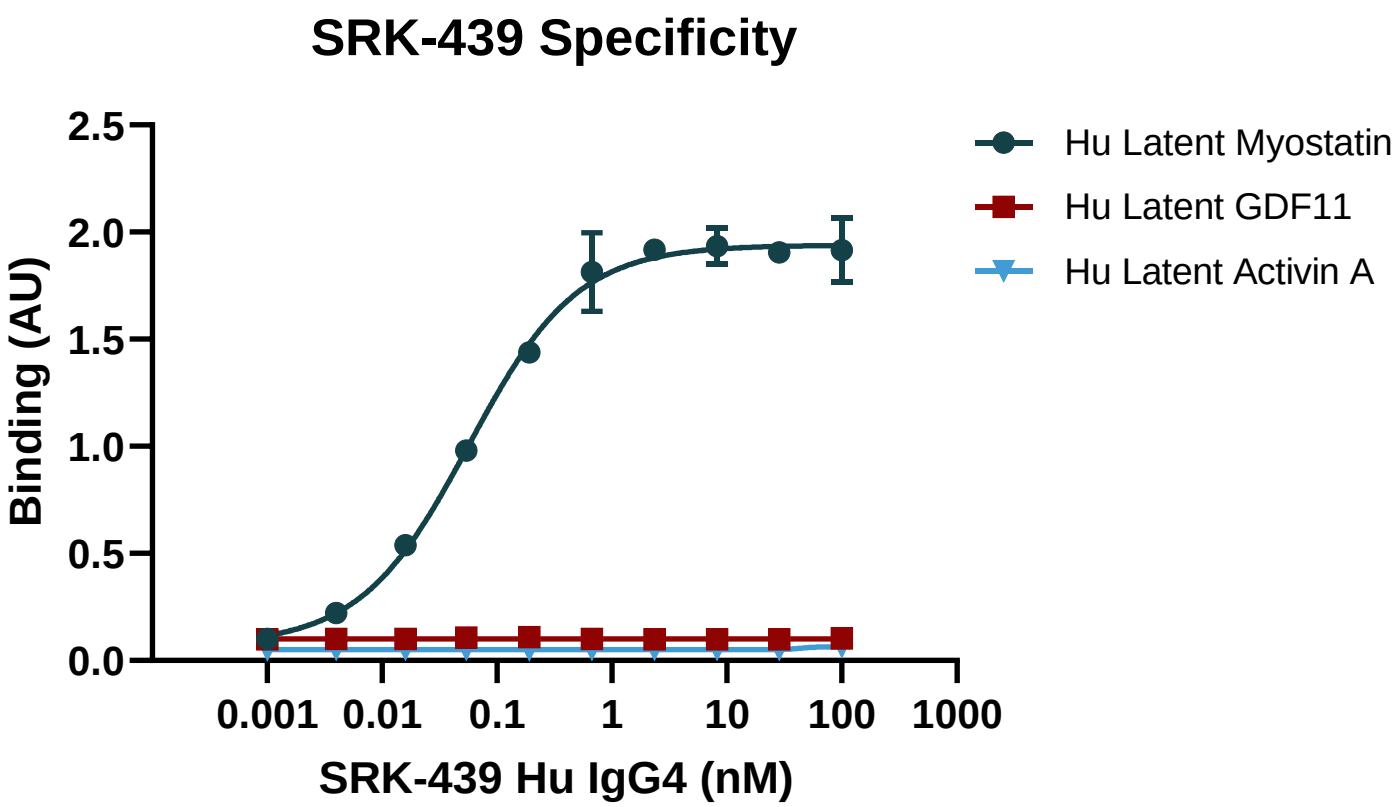
Oh, S.P. and Li, E. *Genes Dev*. 1997.; Matzuk, M. M., *et al*. *Nature*. 1995.; McPherron, A.C., *et al*. *Nat Genet*. 1999.; Garito, T., *et al*. *Clin Endocrinol (Oxf)*. 2018.; Bloise, E. *et al*. *Physiol Rev*. 2019.; Ravenscroft, T.A., *et al*. Genet Med. 2021.

SRK-439 binds to pro- and latent myostatin and enables muscle growth

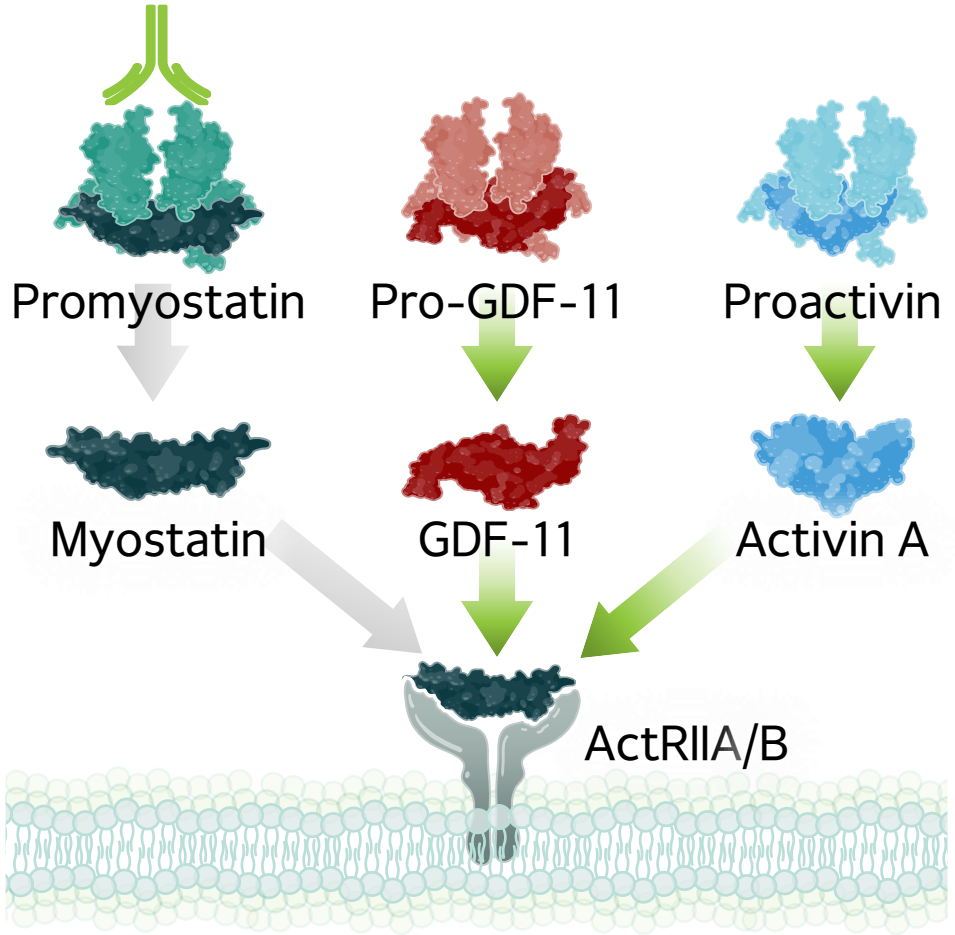


- SRK-439 binds to pro- and latent myostatin and blocks the conversion of the latent form to mature myostatin
- By inhibiting the release of mature myostatin, SRK-439 prevents myostatin from interacting with receptors which results in the inhibition of signaling and promotes muscle growth

SRK-439 is exquisitely selective for pro-and latent-myostatin



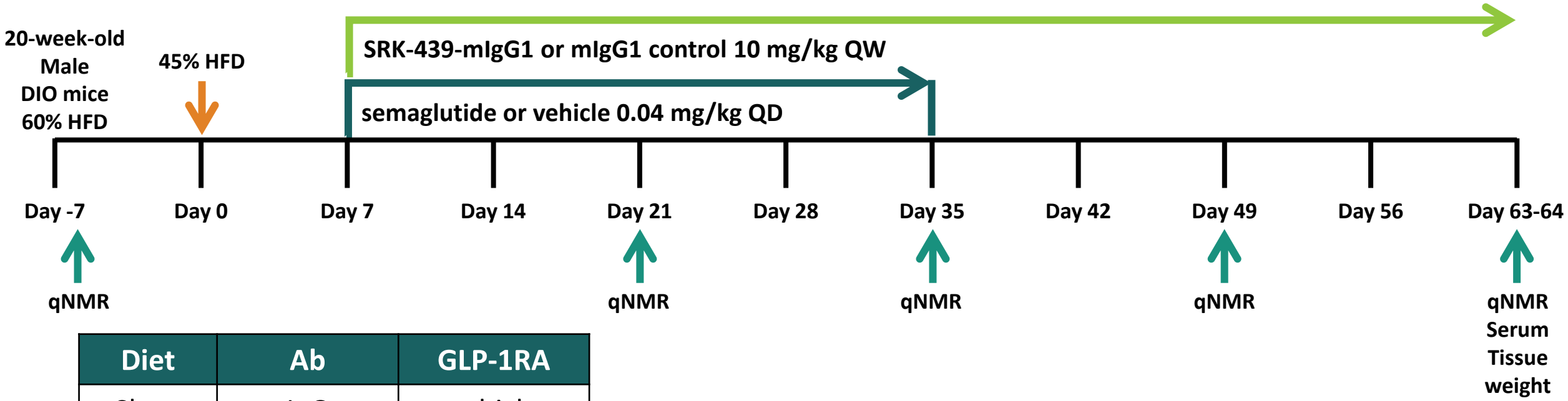
K_D = 0.579 nM



Therapeutic hypothesis

Inhibiting myostatin, a negative regulator of muscle mass, during GLP-1RA-induced weight loss will maintain lean mass and result in a favorable body composition after GLP-1RA withdrawal

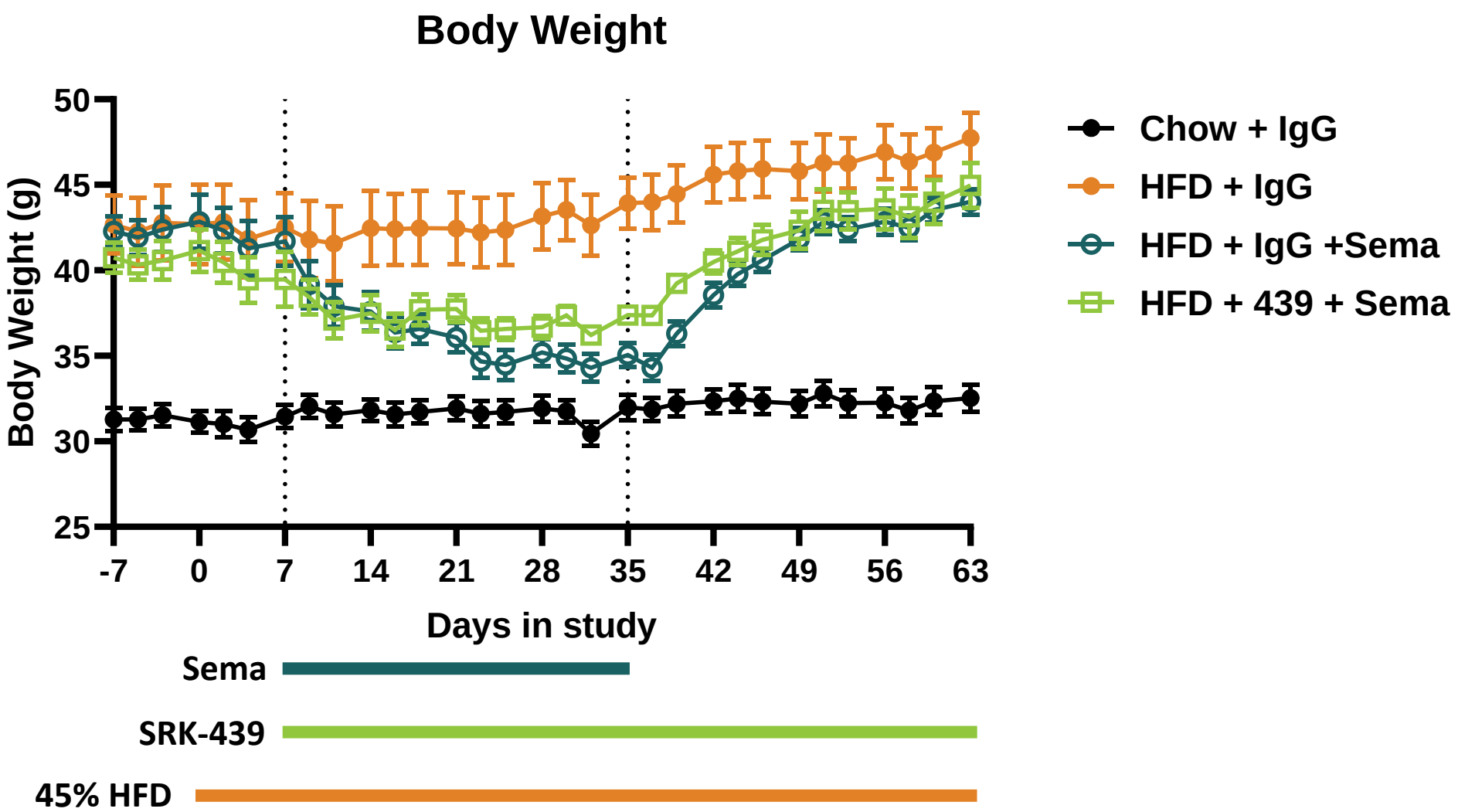
Administering SRK-439-mIgG1 to DIO mice during semaglutide treatment and after discontinuation



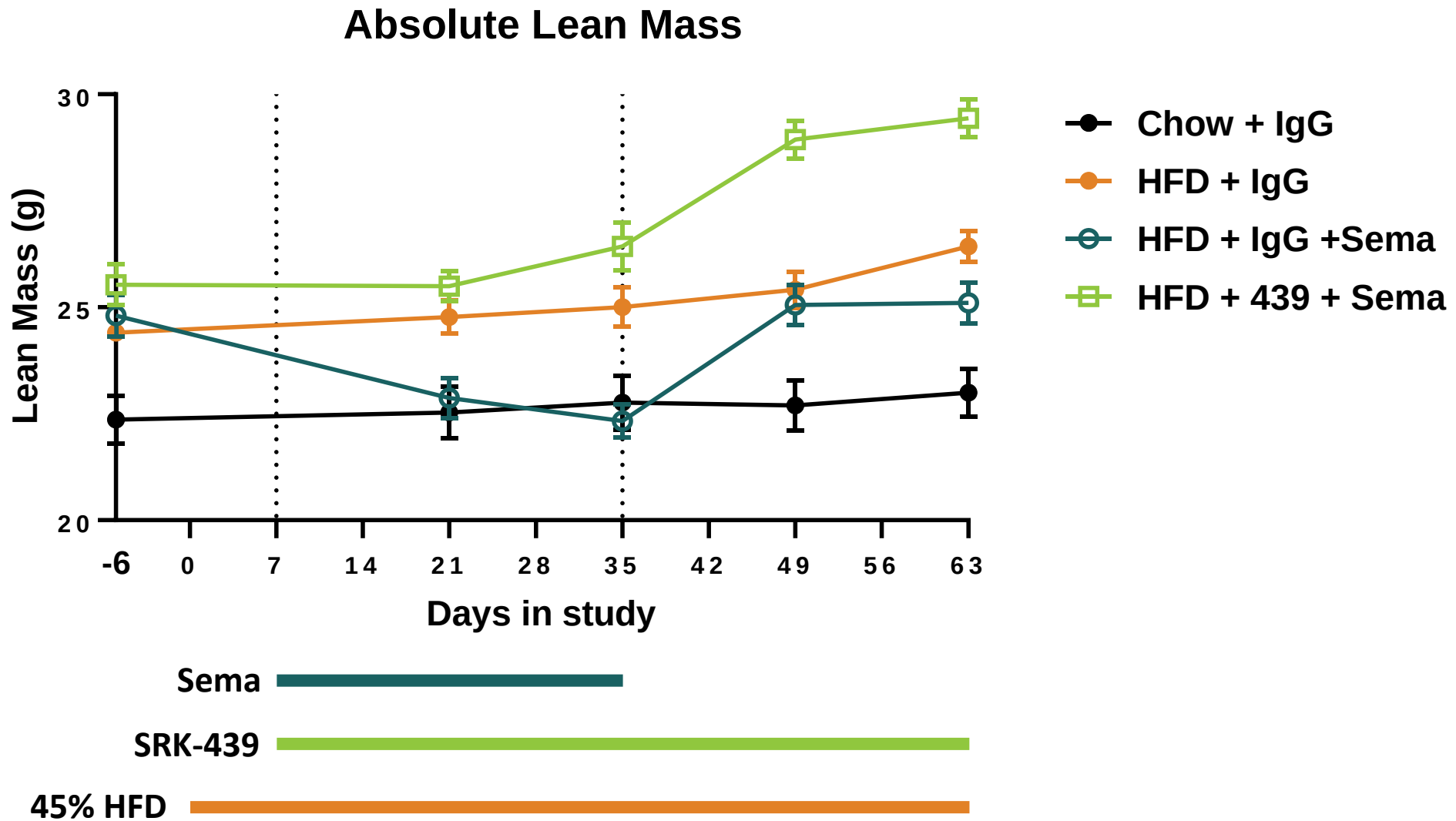
Diet	Ab	GLP-1RA
Chow	IgG	vehicle
HFD	IgG	vehicle
HFD	IgG	sema
HFD	SRK-439	sema

*IgG = mIgG1
*SRK-439 or 439 = SRK-439-mIgG1

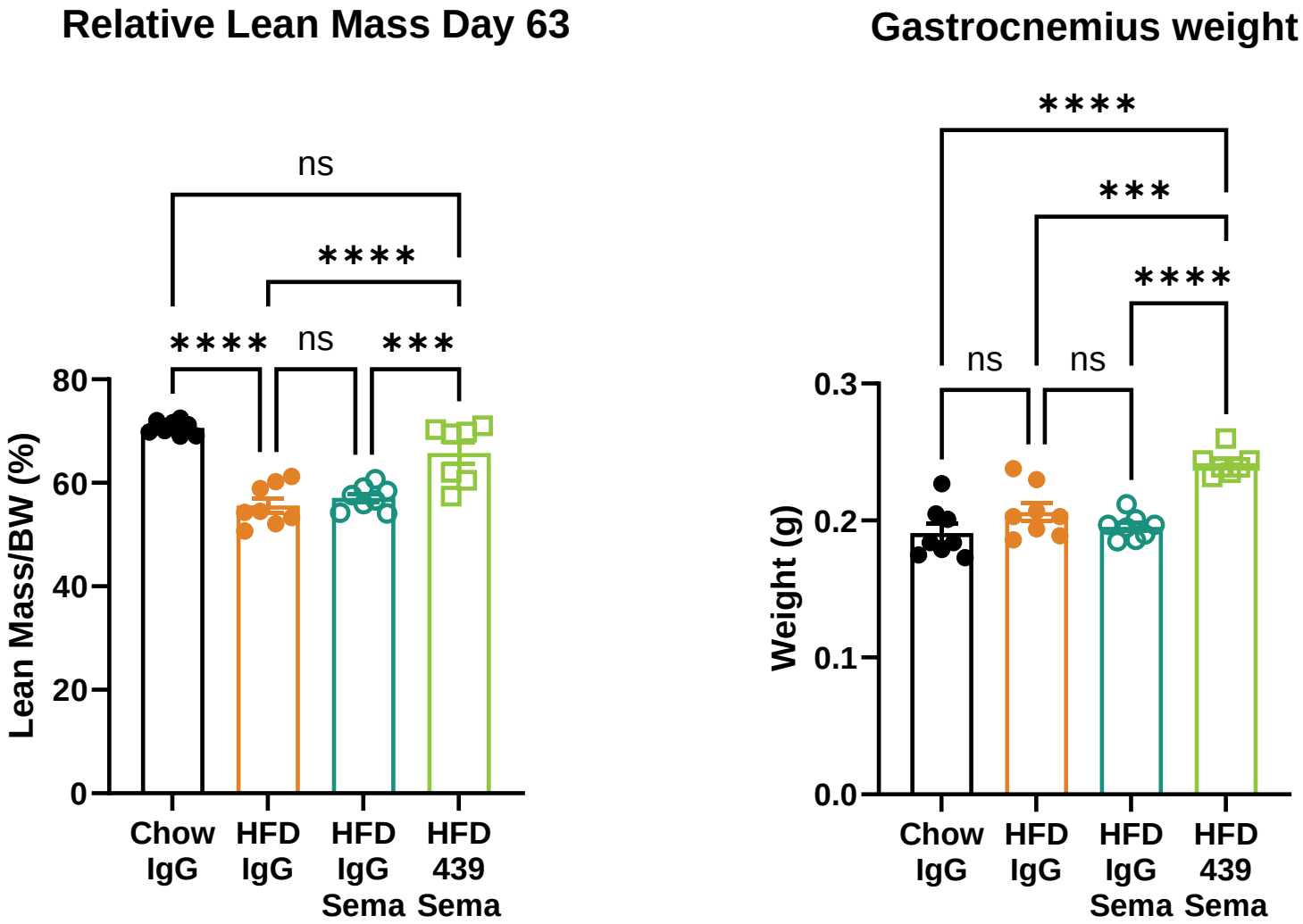
Semaglutide discontinuation caused weight regain



SRK-439 maintained lean mass in combination with semaglutide administration

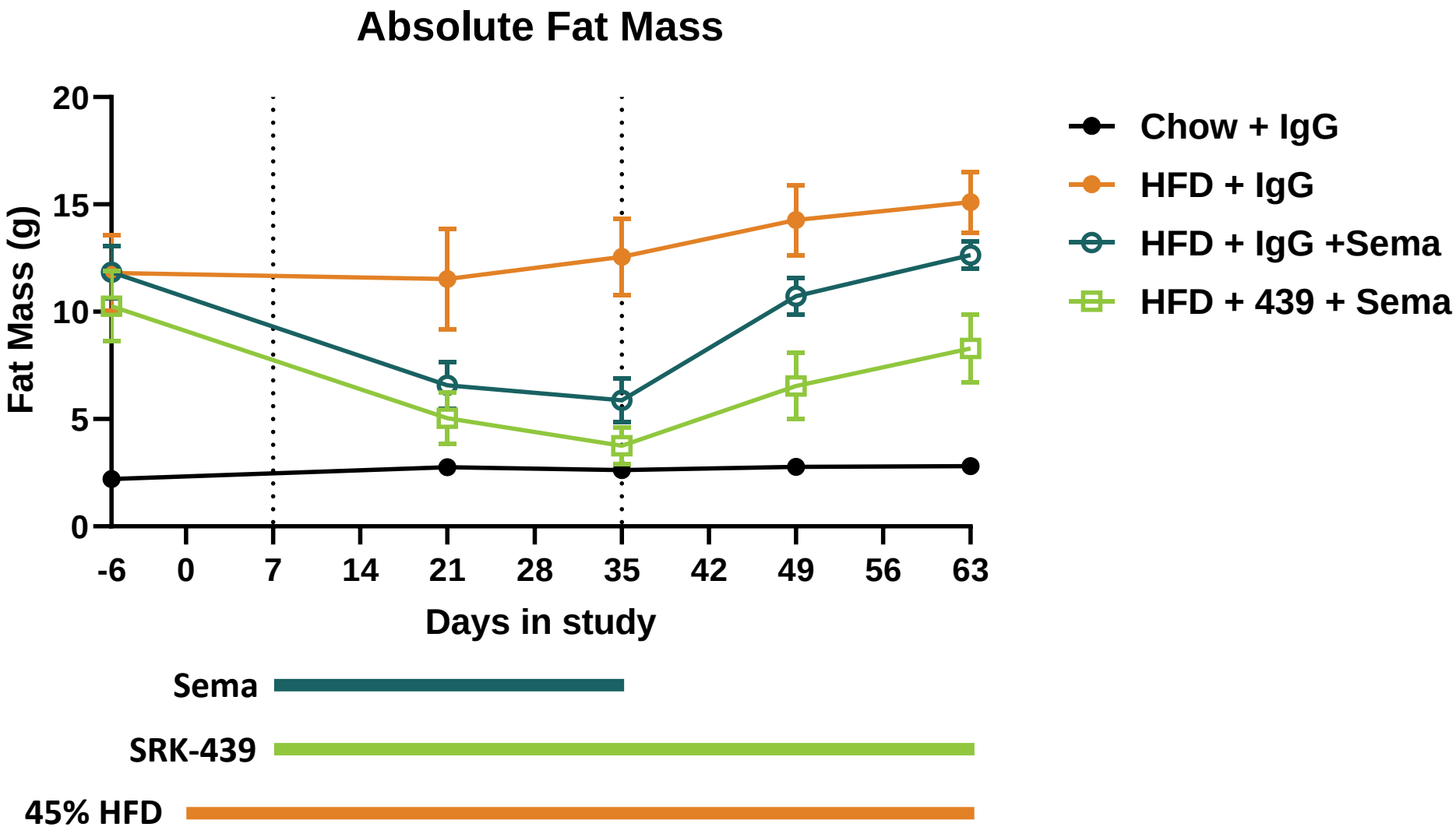


SRK-439 increased relative lean mass and skeletal muscle weight

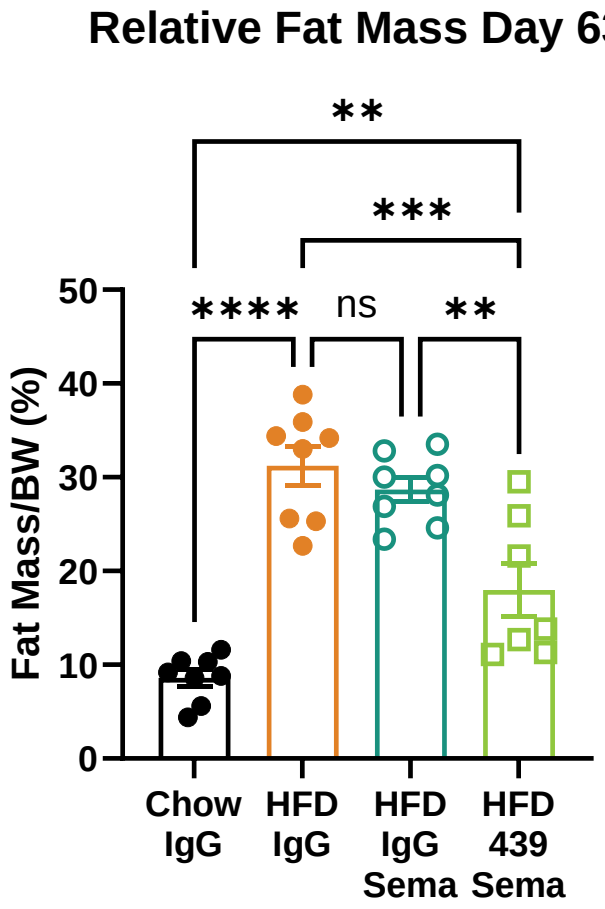


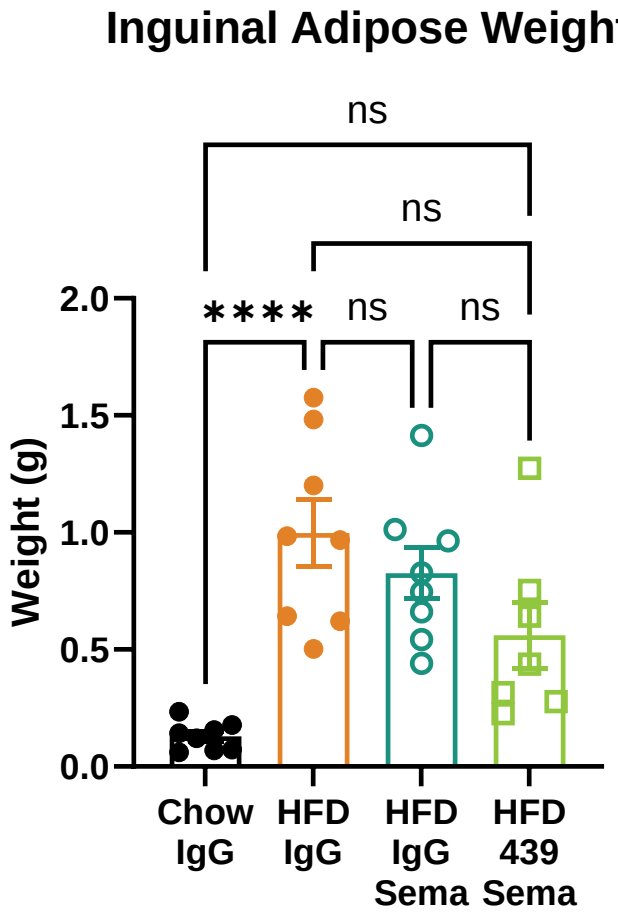
SRK-439 administration in combination with and after withdrawal of semaglutide results in lean mass composition similar to chow-fed animals

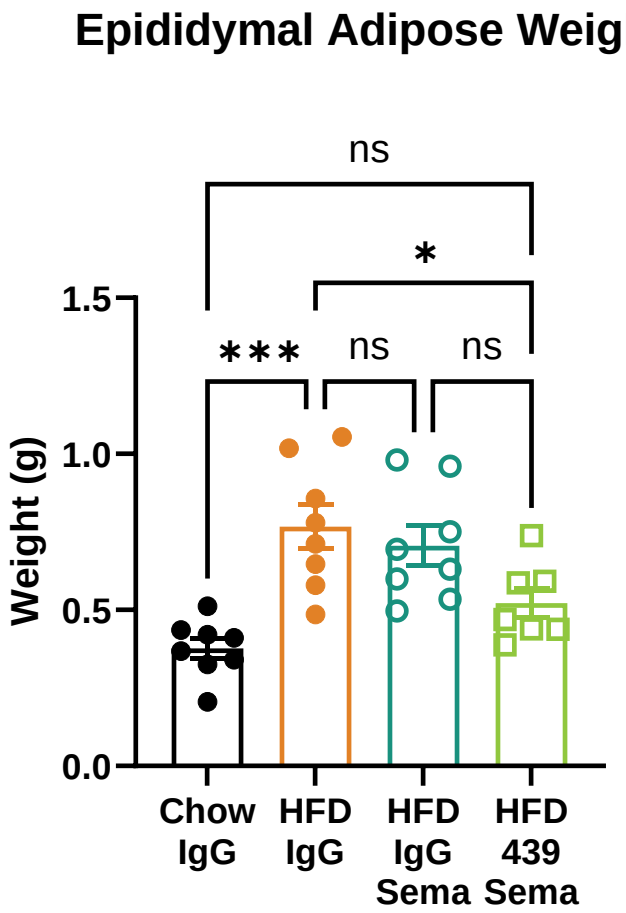
SRK-439 attenuated fat mass regain after discontinuation of semaglutide



SRK-439 treatment improved body composition

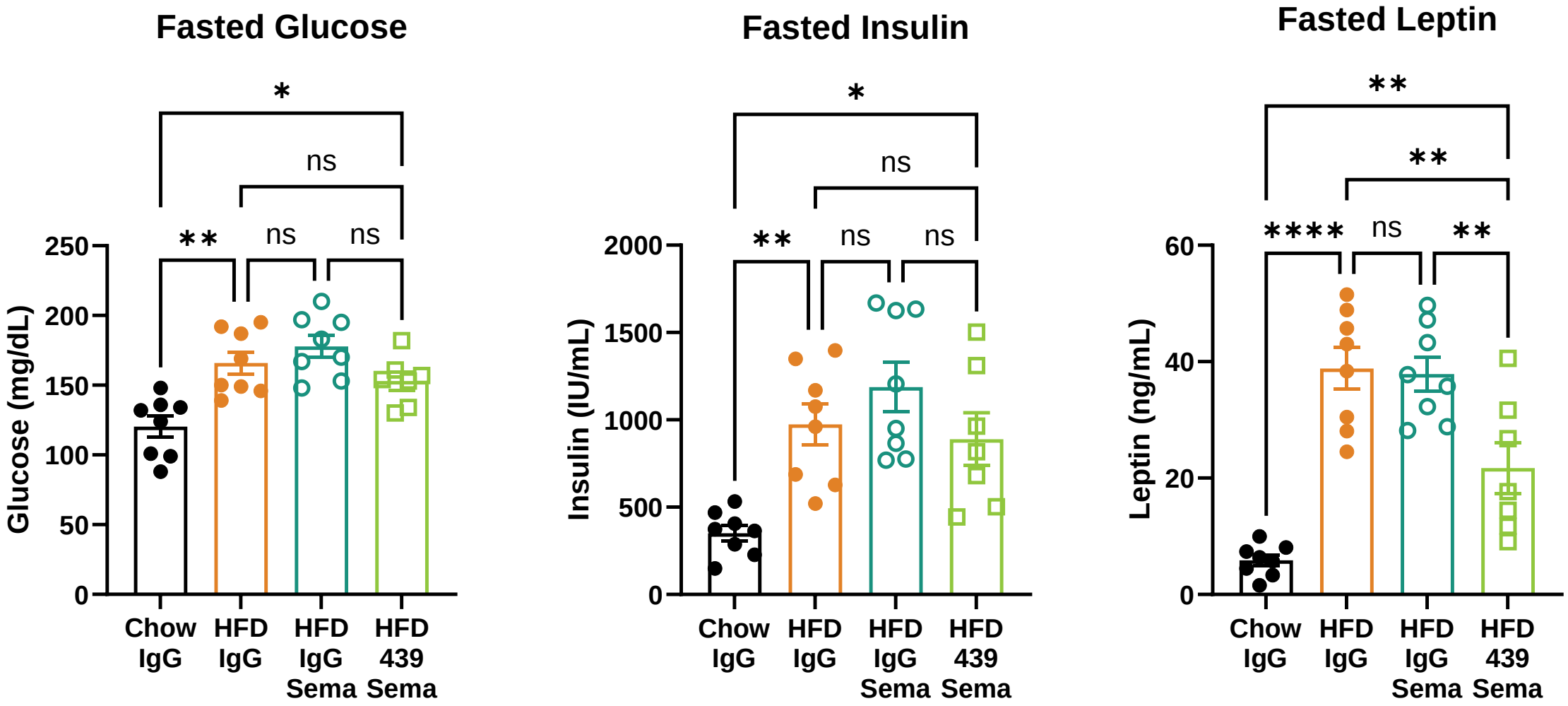






SRK-439 administration in combination with and after withdrawal of semaglutide lowers percent fat mass and reduces adipose depot size

SRK-439 improved circulating metabolic biomarkers



SRK-439 administration in combination with and after withdrawal of semaglutide reduces circulating leptin which confirms reduced adiposity

Summary

- Lean mass decreases during weight loss, regardless of the intervention
- Selectively inhibiting myostatin increases lean mass without the potential liabilities of non-selective targeting of the broader family
- SRK-439-mIgG1 administration prevented lean mass loss during semaglutide-induced weight loss and increased lean mass after semaglutide discontinuation
- SRK-439-mIgG1 administration resulted in lower body fat composition and lower circulating leptin during weight regain

SRK-439-mIgG1 maintains a healthy body composition during GLP-1RA-induced weight loss and subsequent regain following discontinuation

Acknowledgements

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Thank you!

ScholarRock