

# Taldefgrobe Alfa Reduces Fat and Increases Muscle in an Obese Mouse Model

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## CONCLUSIONS

- In an era of unprecedented reductions in total body weight (TBW) with anti-obesity medications (AOMs), careful consideration of changes in body composition, including implications of loss of lean muscle mass, is increasingly important
- In this diet-induced obese mouse model, taldefgrobe monotherapy significantly reduced adipose tissue while increasing lean muscle relative to vehicle
- These data support further development of taldefgrobe as a drug candidate with the potential for differentiated benefit in individuals living with overweight and obesity

**References**  
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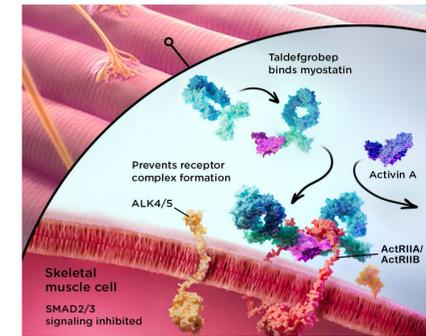
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## INTRODUCTION

- Obesity is a disease of excess or abnormal adipose tissue, the key driver of its pathogenic process<sup>1-3</sup>
- Currently approved AOMs achieve reductions in TBW based on a composite loss of fat mass and loss of lean muscle mass; however, the loss of lean muscle mass with AOMs may have adverse long-term health consequences<sup>4-6</sup>
- Preclinically and in the clinic, anti-myostatin therapies have demonstrated the ability to increase lean mass, reduce fat mass, and improve metabolic parameters<sup>7,8</sup>
  - Taldefgrobe is a novel anti-myostatin fusion protein that blocks signaling through activin IIA and IIB receptors (**Figure 1**)

Figure 1. Taldefgrobe Mechanism of Action



## OBJECTIVE and METHODS

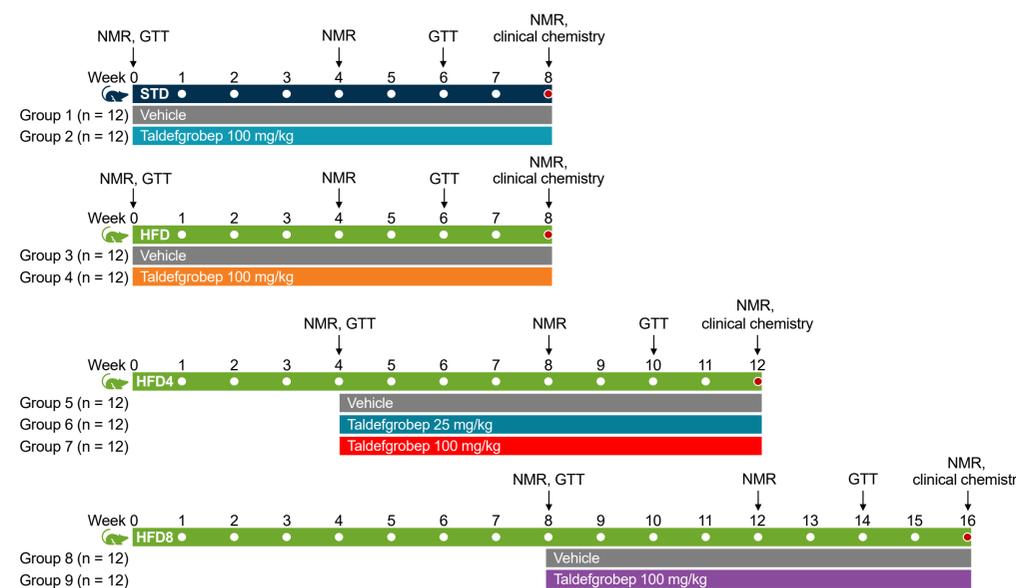
### Objective

- Evaluate taldefgrobe's ability to improve body composition in a high-fat diet (HFD)-induced obese mouse model

### Methods

- 8-week-old C57BL/6J male mice were assigned into groups based on diet – standard (STD) or HFD – and timing of intervention for mice on HFD – 0 weeks (HFD), 4 weeks (HFD4), or 8 weeks (HFD8) into HFD (**Figure 2**)
- Taldefgrobe (100 mg/kg) or vehicle was administered subcutaneously (SC) twice weekly for 8 weeks across all dose groups
- Assessments at baseline and posttreatment included:
  - Body composition with EchoMRI™
  - Metabolic markers, including glucose tolerance test (GTT), insulin, and leptin levels

Figure 2. Study Schematic



NMR, nuclear magnetic resonance.

## RESULTS

- Consistent differences were observed in fat mass and lean mass change (**Table 1**) over time between vehicle and taldefgrobe arms
  - After 8 weeks of treatment, all taldefgrobe dose groups demonstrated lower fat mass and greater lean mass relative to vehicle
- Change in TBW was generally similar over time between vehicle and taldefgrobe arms (**Table 1**)
- Food intake remained generally consistent between taldefgrobe- and vehicle-treated mice over time (data not shown)
- 8-week-old black mice are in late adolescence/early adulthood and not fully grown. Therefore, some increases in TBW, fat mass, and lean mass over time can be attributed to the normal maturation process, as illustrated by TBW and body composition changes seen in Group 1 (STD on vehicle) (**Table 1**)
- At 8 weeks of dosing, HFD8 mice in Group 9 (taldefgrobe) had significantly reduced fat mass and significantly increased lean mass relative to mice in Group 8 (HFD8 on vehicle)
  - Specifically, after 8 weeks of treatment, Group 9 mice achieved an 11% reduction in baseline fat mass and a 25% increase in lean mass, significantly greater than body composition changes in Group 8 mice (+31% and +8%, respectively;  $P \leq 0.001$ ) (**Table 1, Figure 3, and Figure 4**)
- Insulin and leptin levels were consistently reduced more in taldefgrobe-treated mice than vehicle-treated mice (**Figure 5**)
- Glucose tolerance was not improved in the intervention arms relative to vehicle after 7 weeks of dosing (data not shown)

Table 1. Change in Baseline TBW and Body Composition at Week 8: C57BL/6J Mice on Taldefgrobe vs Vehicle

Demography		Baseline <sup>a</sup> Values			Absolute Change Week 8			% Change Week 8		
Group	Diet/ Arm	BL TBW (g)	BL FM (g)	BL LM (g)	ΔTBW (g)	ΔFM (g)	ΔLM (g)	%ΔTBW (%)	%ΔFM (%)	%ΔLM (%)
1 (n = 12)	STD/ Veh	23.77	1.97	20.68	4.04	1.41	2.49	17.03	80.90	12.09
2 (n = 12)	STD/ Tal 100	24.72	1.95	21.54	8.77	0.60	8.12	35.37	29.74	37.64
3 (n = 12)	HFD/ Veh	24.83	2.43	21.29	12.07	8.39	3.85	48.67	353.77	18.33
4 (n = 12)	HFD/ Tal 100	26.09	2.63	22.30	12.04	3.46	8.78	45.87	122.54	39.76
5 (n = 12)	HFD4/ Veh	32.24	7.52	23.67	9.05	6.77	1.93	27.87	102.01	8.15
6 (n = 12)	HFD4/ Tal 25	31.87	6.31	24.47	8.89	2.88	5.99	27.44	38.69	24.68
7 (n = 12)	HFD4/ Tal 100	32.48	7.29	24.07	8.73	1.60	7.20	26.63	14.16	30.04
8 (n = 12)	HFD8/ Veh	40.34	14.39	24.73	5.75	4.06	2.02	14.70	31.43	8.33
9 (n = 12)	HFD8/ Tal 100	39.49	13.29	25.06	4.87	-1.24	6.26	12.09	-11.08	25.02

<sup>a</sup>Baseline was the start of treatment with vehicle or taldefgrobe. Δ, change; BL, baseline; FM, fat mass; LM, lean mass; Tal, taldefgrobe (25, 25 mg/kg; 100, 100 mg/kg); Veh, vehicle.

Figure 3. Change in Fat Mass From Baseline

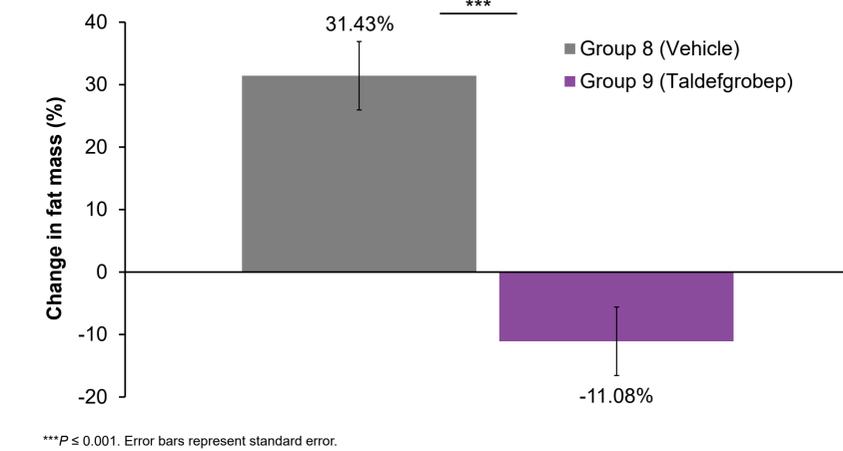


Figure 4. Change in Lean Mass From Baseline

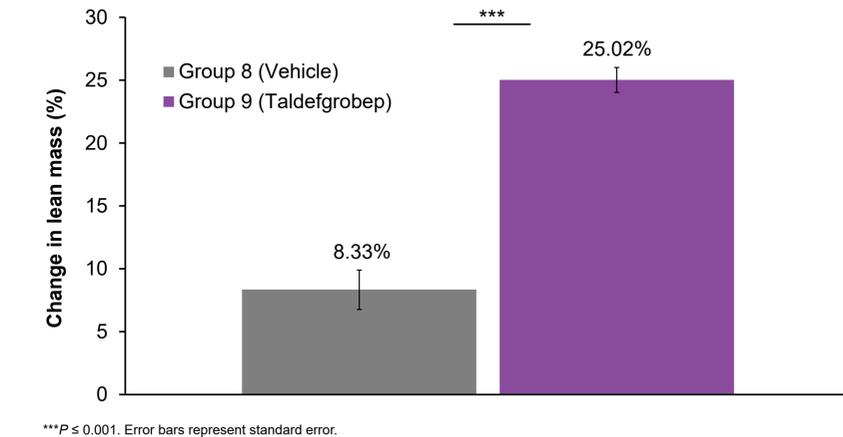
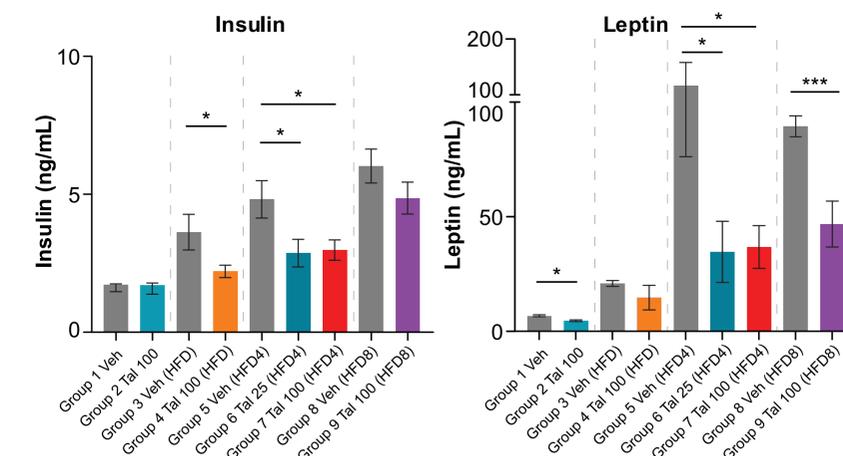


Figure 5. Insulin and Leptin Levels After 8 Weeks of Vehicle or Taldefgrobe Treatment



\* $P \leq 0.05$ . \*\*\* $P \leq 0.001$ .