INTRODUCTION

1. Obesity is a disease of excess or abnormal adipose tissue, the key driver of its pathogenic process. 
2. Currently, approved AOMs achieve reductions in TBM on the basis of a composite loss of fat mass and lean mass, but risk of loss of lean muscle mass with AOMs may have adverse long-term health consequences. 
3. Precipitously in the clinic, anti-myostatin therapies have demonstrated the ability to increase lean mass, reduce fat mass, and improve metabolic parameters. 

Taldefgrobep is a novel anti-myostatin fusion protein that blocks signaling through ActRIIA / ActRIIB receptors (Figure 1). 

OBJECTIVE and METHODS

Objective: Evaluate taldefgrobep’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). Mice were treated with taldefgrobep (0 mg/kg, 25 mg/kg, or 100 mg/kg) or vehicle (0.5% gum arabic) intraperitoneally for 8 weeks. Body composition was measured using EchoMRI™ NMR, GTT NMR, and clinical chemistry. 

RESULTS

1. Consistent differences were observed in fat mass and lean mass change (Table 3) over time between vehicle and taldefgrobep arms.
2. After 8 weeks of treatment, all taldefgrobep dose groups demonstrated lower fat mass and greater lean mass relative to vehicle.
3. Change in TBW was generally similar over time between vehicle and taldefgrobep arms (Table 1).
4. Food intake remained generally consistent between taldefgrobep- and vehicle-treated mice over time (data not shown).
5. A week-old black mice are in late adolescent/acclimatization 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) (Figure 1).

CONCLUSIONS

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

Figure 1. Taldefgrobep Mechanism of Action

Figure 2. Study Schematic

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

REFERENCES

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7. Biohaven Pharmaceuticals, New Haven, CT; The Jackson Laboratory, Bar Harbor, ME.

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