Poster
350

Taldefgrobep Alfa Improves Body Composition as Monotherapy and in Combination With Semaglutide in a DIO Mouse Model

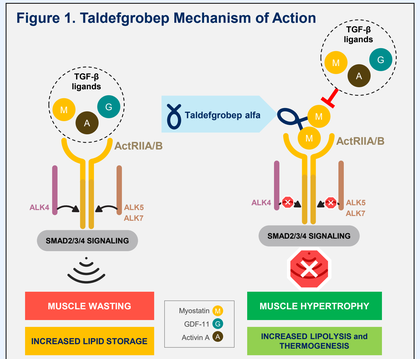
Clifford Bechtold, MS[1]; Ansarullah, PhD[2]; Christopher Brynczka, PhD[1]; Volkan Granit, MD, MSc[1]; Bruce Car, DVM, PhD, DACVP[1]; Christopher Jensen, PharmD[1]; Peter Ackerman, MD[1]; Vlad Coric, MD[1]; Se-Jin Lee, MD, PhD[3,4]

[1]Biohaven Pharmaceuticals, New Haven, CT; [2]The Jackson Laboratory, Bar Harbor, ME; [3]The Jackson Laboratory, Farmington, CT; [4]University of Connecticut School of Medicine, Farmington, CT

INTRODUCTION

- Obesity is a disease of excess or abnormal adipose tissue, the key driver of its pathogenic process[1-3]
- Incretin-based obesity treatments (glucagon-like peptide-1 [GLP-1] analogs) demonstrate significant weight reduction and metabolic benefits[4,5]
- Currently approved antiobesity medications, including GLP-1 receptor agonists, achieve reductions in total body weight based on a composite loss of fat mass and loss of lean muscle mass; however, the loss of lean muscle mass with these therapeutic agents may have long-term adverse health consequences[4-7]
- Inhibition of myostatin and activin A signaling induces significant fat loss and increase in lean mass,[8,9] an ideal combination with GLP-1 receptor agonist therapy
- Taldefgrobep alfa is a novel myostatin inhibitor that selectively blocks signaling through activin II receptors and has demonstrated improvements in lean mass and loss of fat[10] (**Figure 1**)
- Taldefgrobep binds myostatin, and the taldefgrobep/myostatin complex blocks activin A and myostatin signaling
- Results from validated diet-induced obesity (DIO) mouse models have generally paralleled outcomes observed in human studies conducted in adults with obesity[11,12]

Figure 1. Taldefgrobep Mechanism of Action



ActRIIA/B, myostatin/activin type IIA/B receptor; ALK, activin-like kinase; GDF-11, growth differentiation factor 11; TGF-β, transforming growth factor-beta.

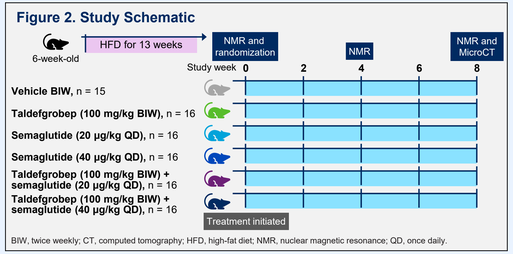
OBJECTIVE

- This high-fat diet (HFD)-induced obese mouse study was designed to evaluate the ability of taldefgrobep to impact body composition as monotherapy and in combination with semaglutide, a GLP-1 receptor agonist

METHODS

- Six-week-old C57BL/6J male mice received a HFD (60% fat; Research Diets D12492) for 13 weeks prior to their subcutaneous treatment assignment: vehicle twice weekly (BIW), taldefgrobep 100 mg/kg BIW, semaglutide 20 µg/kg once daily (QD), semaglutide 40 µg/kg QD, taldefgrobep 100 mg/kg BIW with semaglutide 20 µg/kg QD or 40 µg/kg QD (**Figure 2**)
- Body composition (EchoMRI™) and metabolic markers were assessed at baseline, posttreatment, and study end. MicroCT was performed at the end of the study
- Insulin tolerance tested (1.5 U/kg body weight; human insulin, intraperitoneal) in mice fasted for 4 hours and blood glucose levels were measured at 0, 15, 30, 60, and 120 minutes
- Histopathology of adipose tissue, muscle, and the liver was performed
- Results from 8 weeks of dosing are presented

Figure 2. Study Schematic



BIW, twice weekly; CT, computed tomography; HFD, high-fat diet; NMR, nuclear magnetic resonance; QD, once daily.

RESULTS

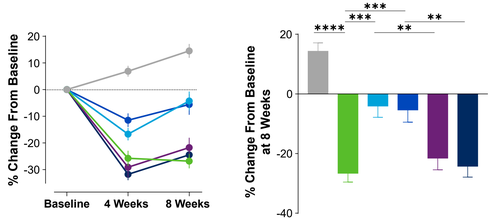
- Through 8 weeks of treatment, all taldefgrobep groups demonstrated significant and durable reductions in fat mass and increased lean mass (**Table 1; Figures 3** and **4**)
- The addition of taldefgrobep to semaglutide resulted in greater reductions in fat mass and increases in lean mass relative to semaglutide alone
- Taldefgrobep demonstrated significant improvement in insulin sensitivity either alone or in combination with semaglutide (**Figure 5**)
- MicroCT images show that after 8 weeks, taldefgrobep treatment significantly increased lean mass (blue) while reducing fat mass (green and red), observed both in monotherapy and in combination with semaglutide (**Figure 6**)

Table 1. Change in Fat Mass and Lean Mass With Taldefgrobep ± Semaglutide in a DIO Mouse Model at Week 8

Treatment (dose)	Δ FM (g)	Δ FM (%)	Δ LM (g)	Δ LM (%)
Vehicle	2.6	14.5	1.5	5.6
Taldefgrobep (100 mg/kg BIW)	-5.0	-26.8	5.5	20.2
Semaglutide (20 µg/kg QD)	-0.8	-4.3	0.0	0.0
Semaglutide (40 µg/kg QD)	-1.1	-5.6	-0.3	-1.2
Taldefgrobep + semaglutide (20 µg/kg QD)	-4.1	-21.8	5.3	19.5
Taldefgrobep + semaglutide (40 µg/kg QD)	-4.6	-24.5	4.5	16.6

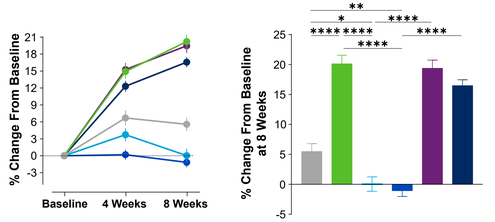
Δ, change; BIW, twice weekly; DIO, diet-induced obesity; FM, fat mass; LM, lean mass; QD, once daily.

Figure 3. Taldefgrobep Monotherapy and Combination Therapy Resulted in Greater Reductions in Fat Mass Than Semaglutide Alone



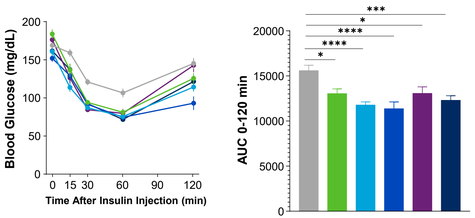
Error bars represent standard error of the mean. Significance evaluated using Tukey's multiple comparisons test. $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$.

Figure 4. Taldefgrobep Monotherapy Increased Lean Muscle Mass and Combination Therapy Prevented Muscle Loss Observed With Semaglutide Alone



Error bars represent standard error of the mean. Significance evaluated using Tukey's multiple comparisons test. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{****}P < 0.0001$.

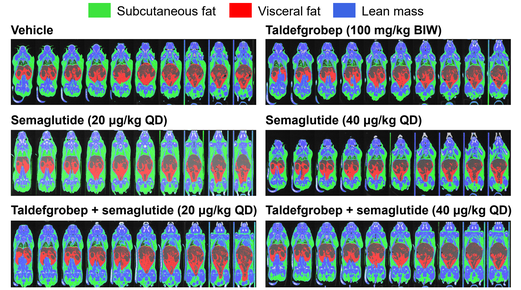
Figure 5. Insulin Tolerance Test After 8 Weeks of Treatment



Error bars represent standard error of the mean. Significance evaluated using Tukey's multiple comparisons test. $^{*}P < 0.05$; $^{***}P < 0.001$; $^{****}P < 0.0001$.
AUC, area under the curve.

- Vehicle
- Taldefgrobep (100 mg/kg BIW)
- Semaglutide (20 µg/kg QD)
- Semaglutide (40 µg/kg QD)
- Taldefgrobep + semaglutide (20 µg/kg QD)
- Taldefgrobep + semaglutide (40 µg/kg QD)

Figure 6. MicroCT Images Showing Fat Mass and Lean Mass



Whole-body scan was performed using Quantum GX (Perkin Elmer). Mice were anesthetized with isoflurane and placed on a platform with the detector. Settings: 50 kV, 160 µA, 72 mm field of view, 0.5 aluminum filter, standard 18-second stitched scan (total of three 18-second scans stitched together, 72 voxel resolution). MicroCT images were exported into DICOM formats. Adipose tissue depots were differentiated using the muscular abdominal wall based on density. The visceral and subcutaneous adipose depots were manually outlined after thresholding, and image processing was performed using Image-J software.
BIW, twice weekly; CT, computed tomography; QD, once daily.

CONCLUSIONS

- In an obese mouse model, taldefgrobep demonstrated significant reductions in fat mass and body weight while increasing lean mass
- In combination with a GLP-1 receptor agonist, taldefgrobep yielded an additive effect in fat loss while maintaining its efficacy in promoting significant lean mass gain
- Taldefgrobep improved insulin sensitivity as a monotherapy and when combined with semaglutide
- The study supports the development of taldefgrobep as a monotherapy and in combination with GLP-1 receptor agonists to reduce fat while maintaining lean mass in individuals living with overweight and obesity

Presented at ObesityWeek 2024, the annual meeting of The Obesity Society
November 3-6, 2024 | San Antonio, TX

DISCLOSURES: CBechtold, **CBrynczka**, **VG**, **BC**, **CJ**, **PA**, and **VC** are employed by and hold stock/stock options in Biohaven Pharmaceuticals. **A** and **SJL** have nothing to disclose.

ACKNOWLEDGMENTS: This study was funded by Biohaven Pharmaceuticals. Medical writing and editorial support were provided by James Banigan, PhD, and Dena McWain of Apollo Medical Communications, part of Helios Global Group, and funded by Biohaven Pharmaceuticals.

REFERENCES: 1. WHO. Accessed May 6, 2024. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. **2.** Panuganti KK, et al. In: *StatPearls*. StatPearls Publishing; 2023. **3.** Shuster A, et al. *Br J Radiol*. 2012;85(1009):1-10. **4.** Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. **5.** Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002. **6.** Locatelli JC, et al. *Diabetes Care*. 2024;47(10):1718-1730. **7.** Wilding JPH, et al. *J Endocr Soc*. 2021;5(suppl 1):A16-A17. **8.** Lee SJ, et al. *J Gerontol A Biol Sci Med Sci*. 2023;78(suppl 1):32-37. **9.** Suh J, et al. *J Bone Metab*. 2020;27(3):151-165. **10.** Ackerman P, et al. Presented at: ObesityWeek 2023; Oct 14-17, 2023; Dallas, TX. Poster 211. **11.** Vickers SP, et al. *Br J Pharmacol*. 2011;164(4):1248-1262. **12.** Wang CY, et al. *Methods Mol Biol*. 2012;821:421-433.

To download a copy of this poster, scan QR code.

biohaven