Taldefgrobep/Myostatin Complex Inhibits TGF-ß Ligand Signaling Reducing Lipid Storage in Adipocytes

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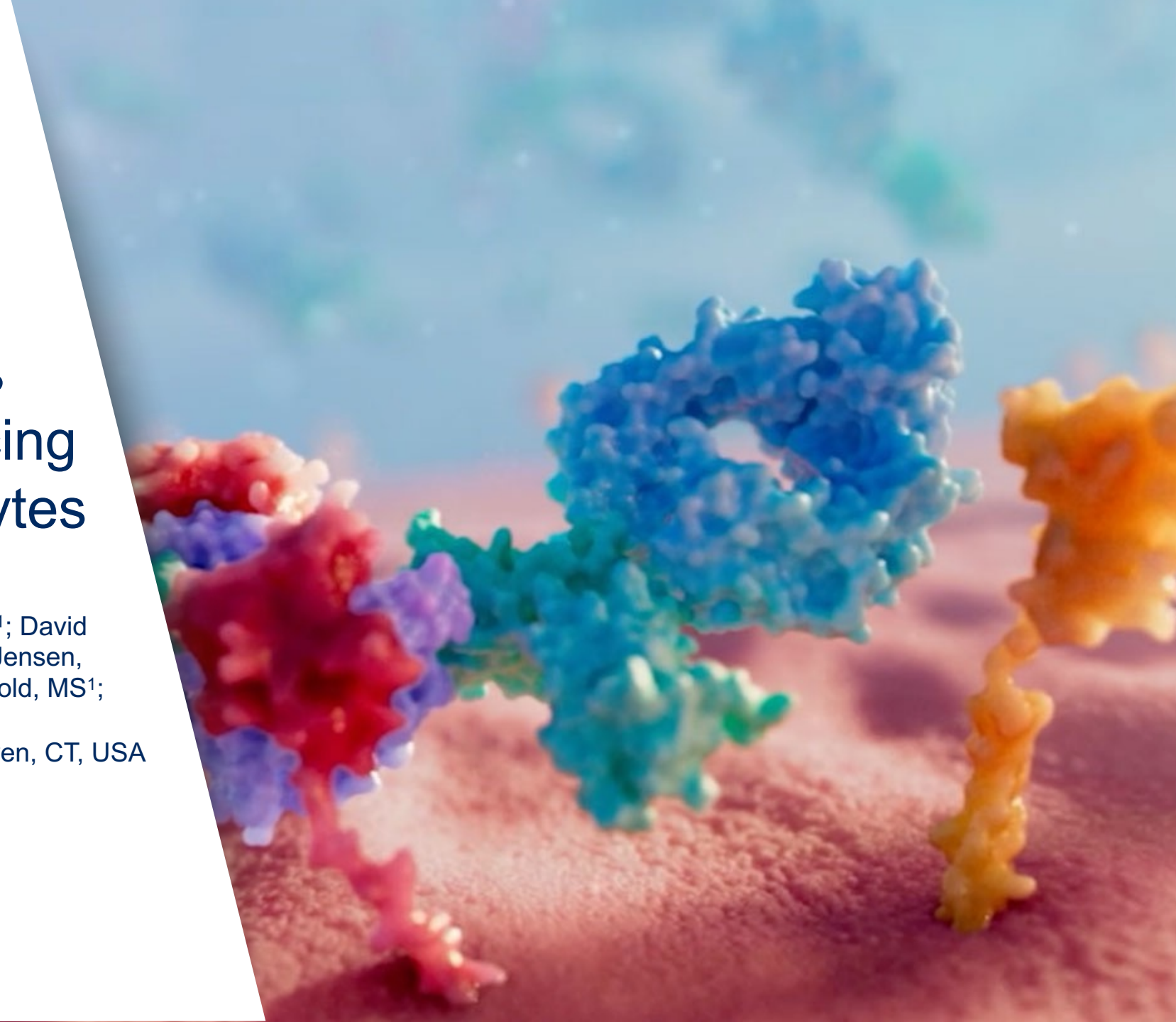
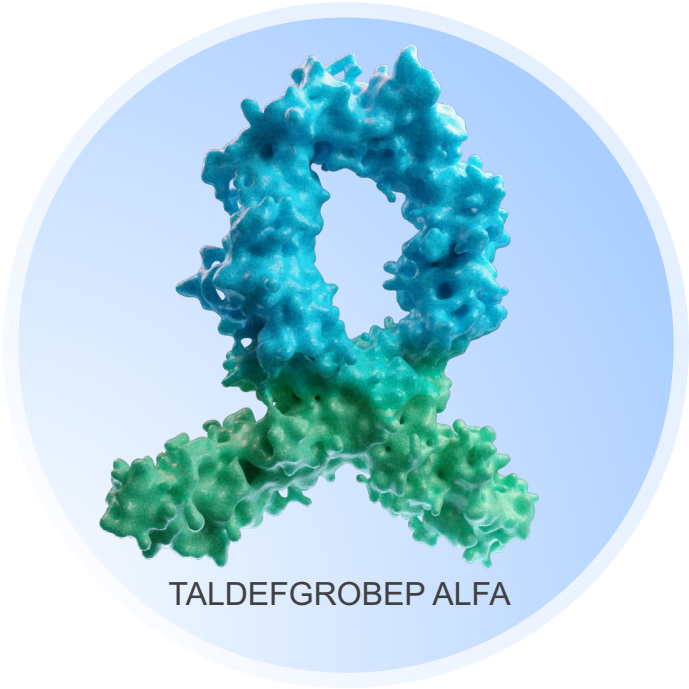


Taldefgrobep Alfa: A Novel Myostatin-Activin Pathway Inhibitor (MAPI) in Development for the Treatment of Overweight and Obesity

MAPIs with varied mechanisms of action have demonstrated beneficial body composition changes in people living with obesity[1-4]

Taldefgrobep is an investigational drug with a favorable safety profile established across diverse clinical populations (N >700 treated)[5]

Taldefgrobep's differentiated pharmacology offers the potential to optimize weight loss quality (reducing fat mass and increasing lean mass) with favorable safety and tolerability



Taldefgrobep is being evaluated as both a monotherapy and in combination with nutrient-stimulated hormone therapies in the treatment of overweight and obesity

1. Heymsfield SB. BELIEVE Study Efficacy and Safety Results—Weight Loss and Body Composition. ADA 85th Scientific Sessions 2025. 2. Heymsfield SB, et al. JAMA Netw Open. 2021;4(1):e2033457. 3. Mosenzon O, et al. EASD 2025. LBA 17. 4. Scholar Rock press release. June 18, 2025. Available at: https://investors.scholarrock.com/news-releases/news-release-details/scholar-rock-reports-positive-phase-2-embraze-trial-results. 5. Biohaven R&D Day. May 29, 2025. Available at: https://ir.biohaven.com/static-files/d11b4f2a-09d4-461b-a7cf-f1df8fc7e555. 6. Bechtold C, et al. ObesityWeek 2024. Poster 350.

In preclinical obesity models, and in the clinic, taldefgrobep demonstrated beneficial effects on body composition (fat mass, lean muscle mass, and bone density)[5,6]

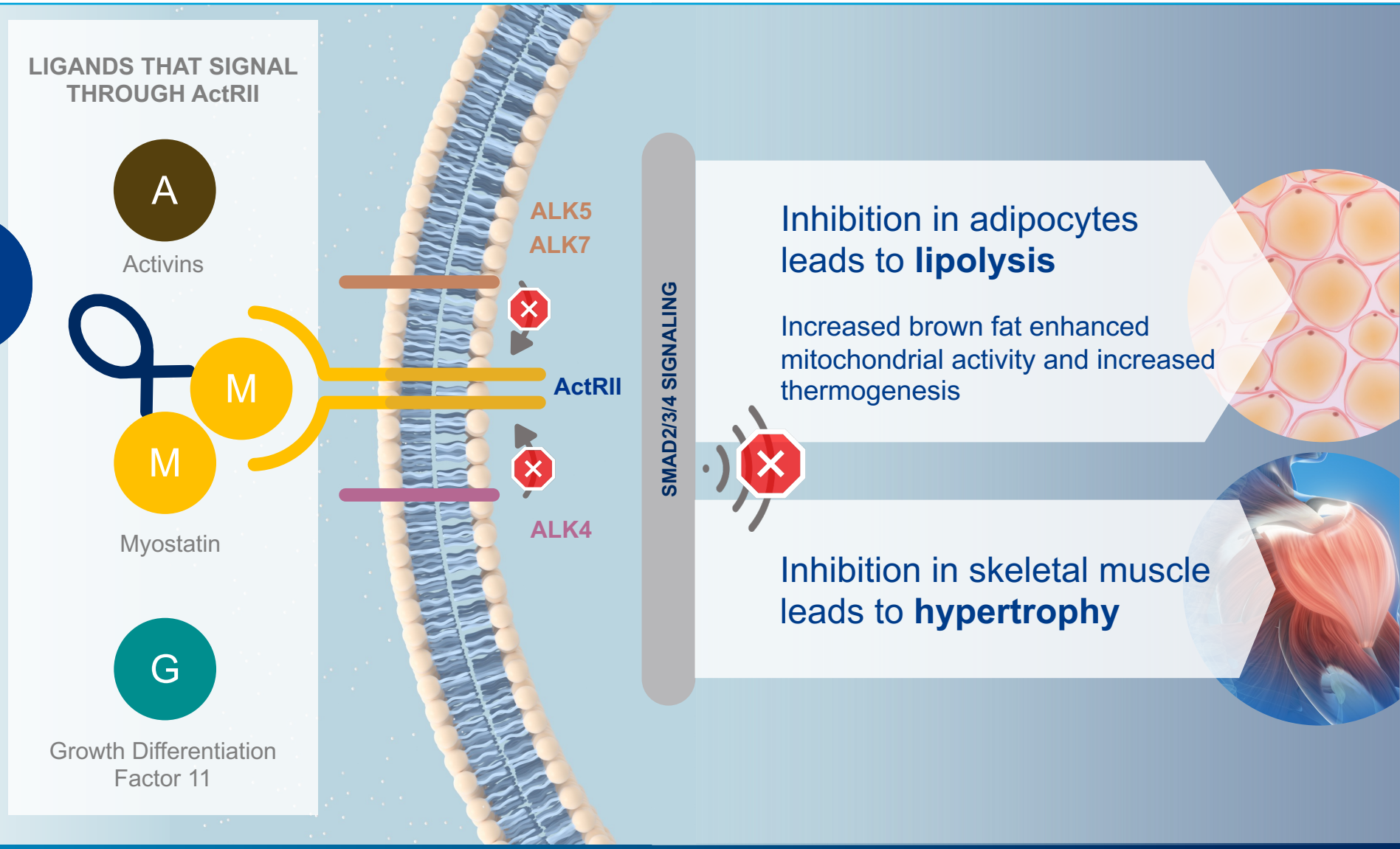
Taldefgrobep Has Direct Effects on Fat and Muscle, Potentially Optimizing the Quality of Weight Loss

Taldefgrobep alfa
Biohaven

Taldefgrobep BINDS
to active myostatin (GDF-8) and growth differentiation factor (GDF-11)

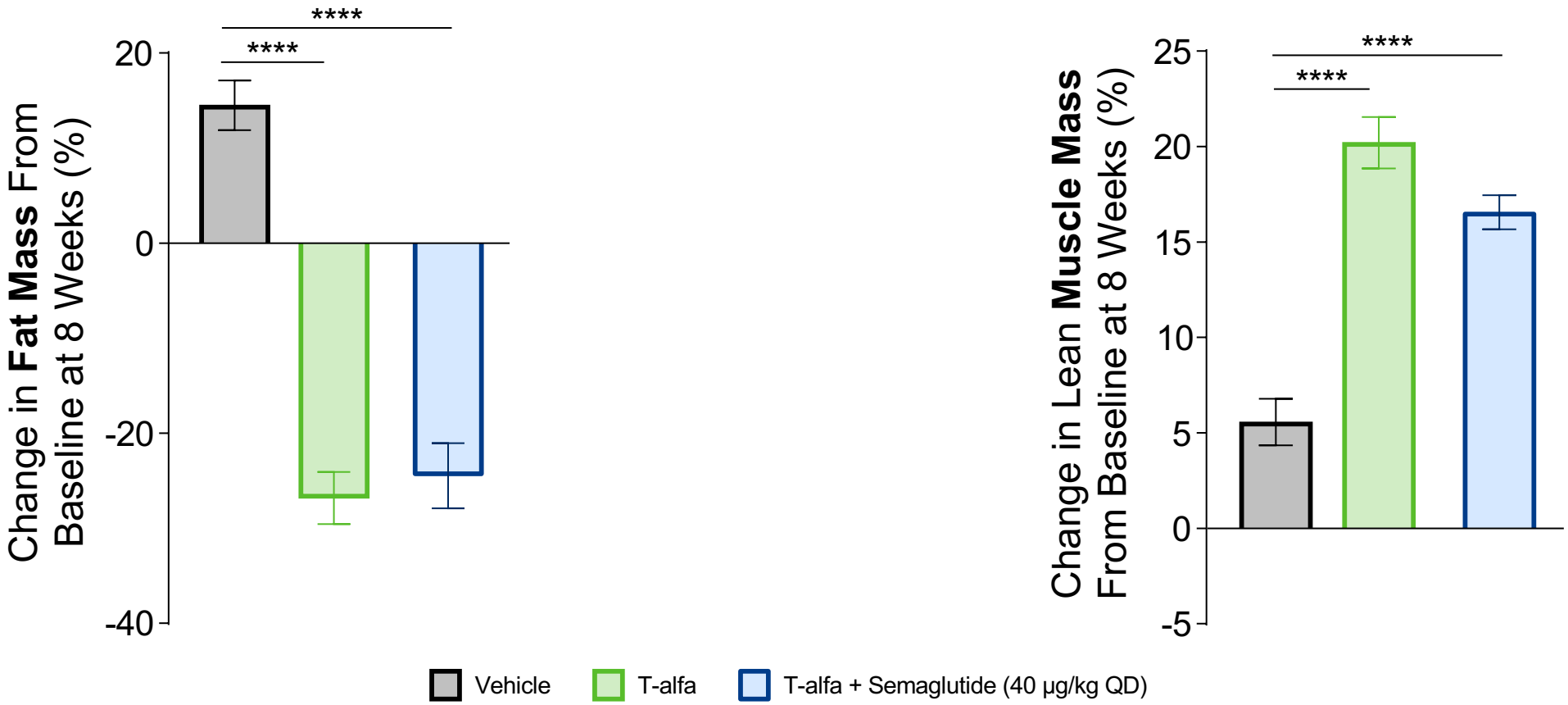
FORMS COMPLEX
that binds to ActRII which prevents recruitment of ALK4,5,7

INHIBITS
ActRII signaling by key ligands including activins



Taldefgrobep/Myostatin Complex Inhibits TGF-ß Ligand Signaling Reducing Lipid Storage in Adipocytes

In an Obese Mouse Model, Taldefgrobep Demonstrated Significant Reductions in Fat Mass While Increasing Lean Mass

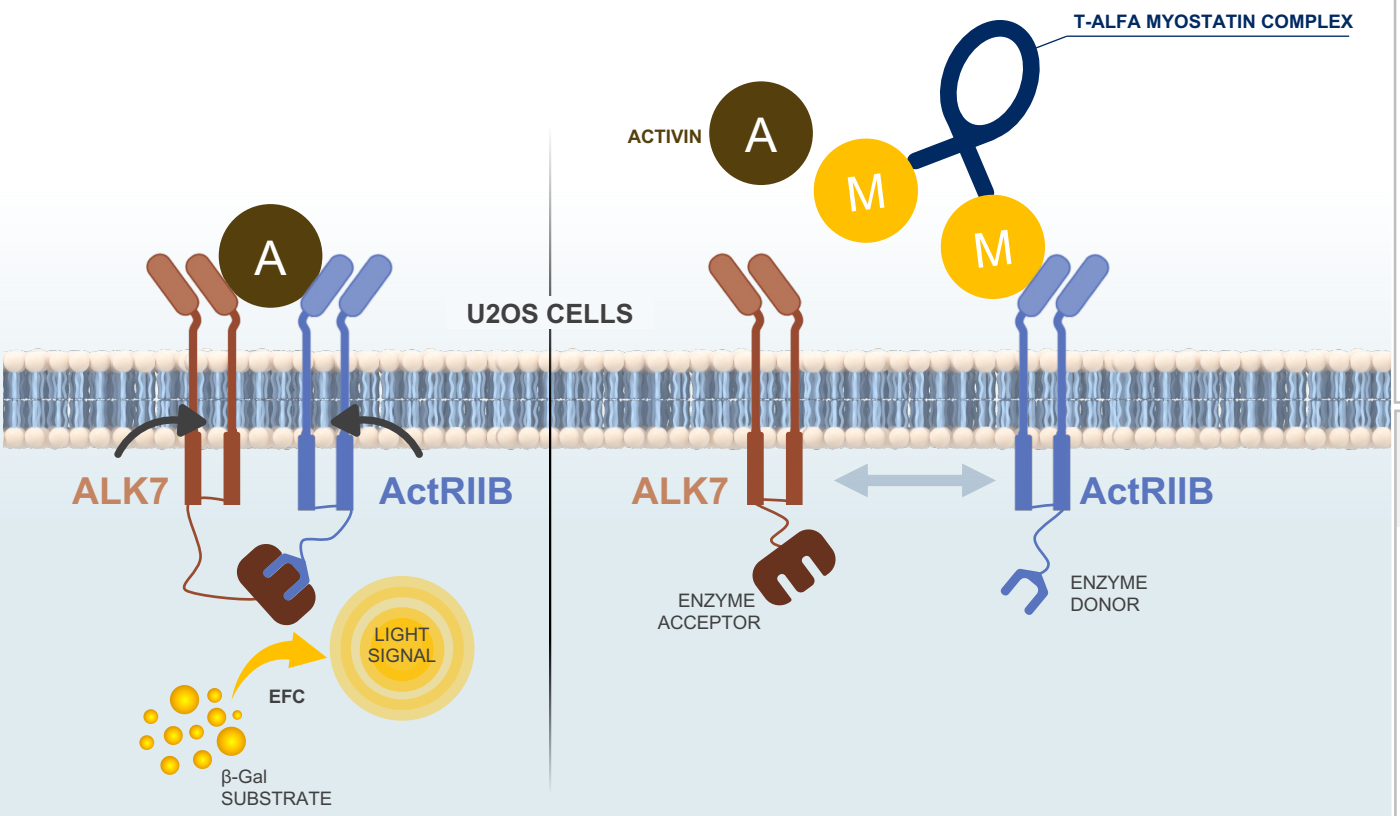


n = 15 for vehicle; n = 16 for all other groups. Error bars represent standard error of the mean. Significance evaluated using Tukey's multiple comparisons test. ****P < 0.0001.
QD, once daily; **T-alfa,** taldefgrobep alfa.
Bechtold C, et al. ObesityWeek 2024. Poster 350.

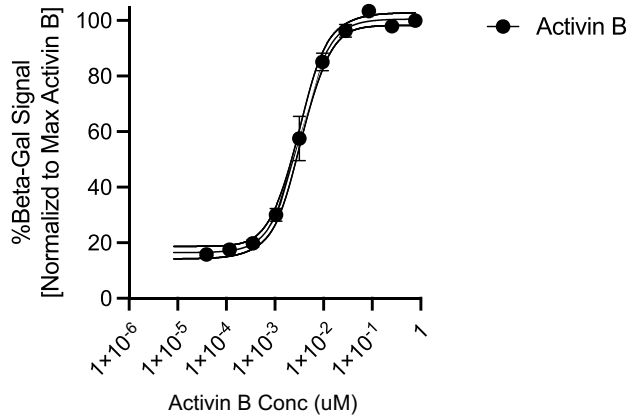
Taldefgrobep demonstrated reductions in fat mass and increases in lean mass as monotherapy and in combination with a GLP-1 receptor agonist

Taldefgrobep-Myostatin Complex Blocks Activin B Induced Dimerization of ActRIIB-ALK7

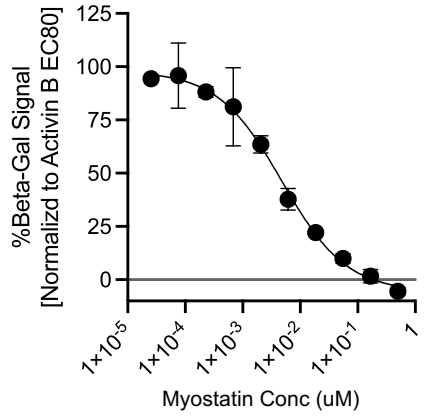
Assay Demonstrates Taldefgrobep-Myostatin Complex Inhibits Activin B–Mediated ActRIIB-ALK7 Dimerization



Chemiluminescent Signal Dose Curve (%)



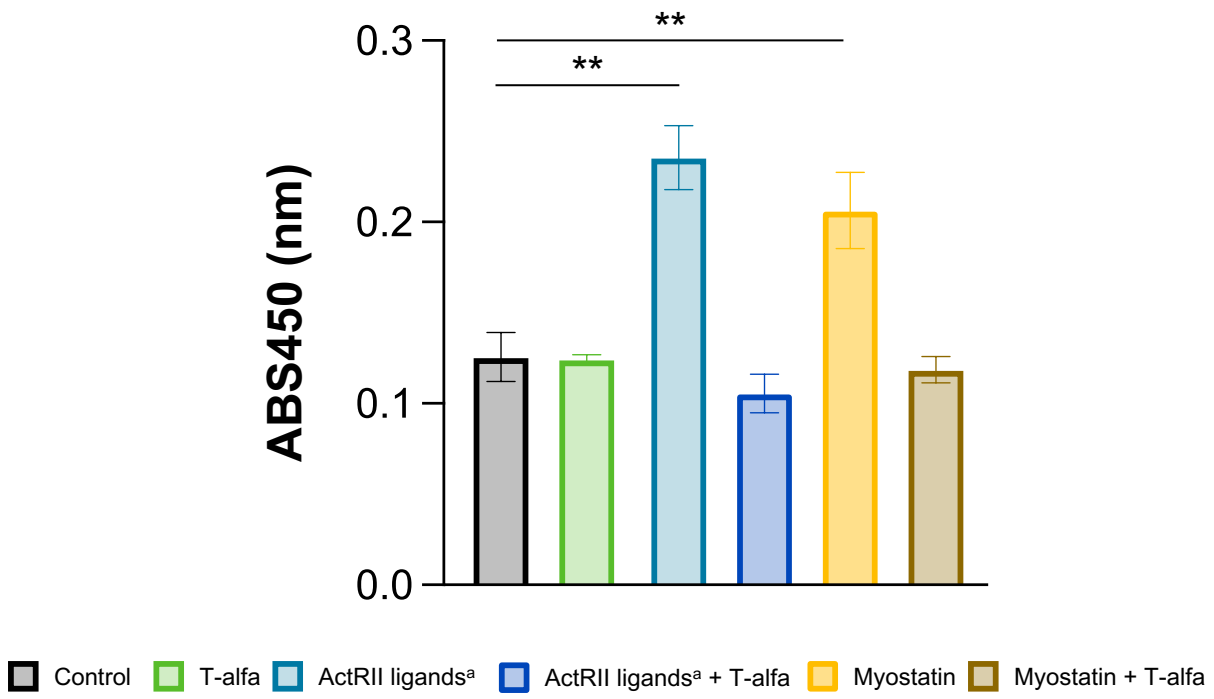
ActRIIB-ALK7 Signaling in the Presence of Taldefgrobep/Myostatin Complex (%)



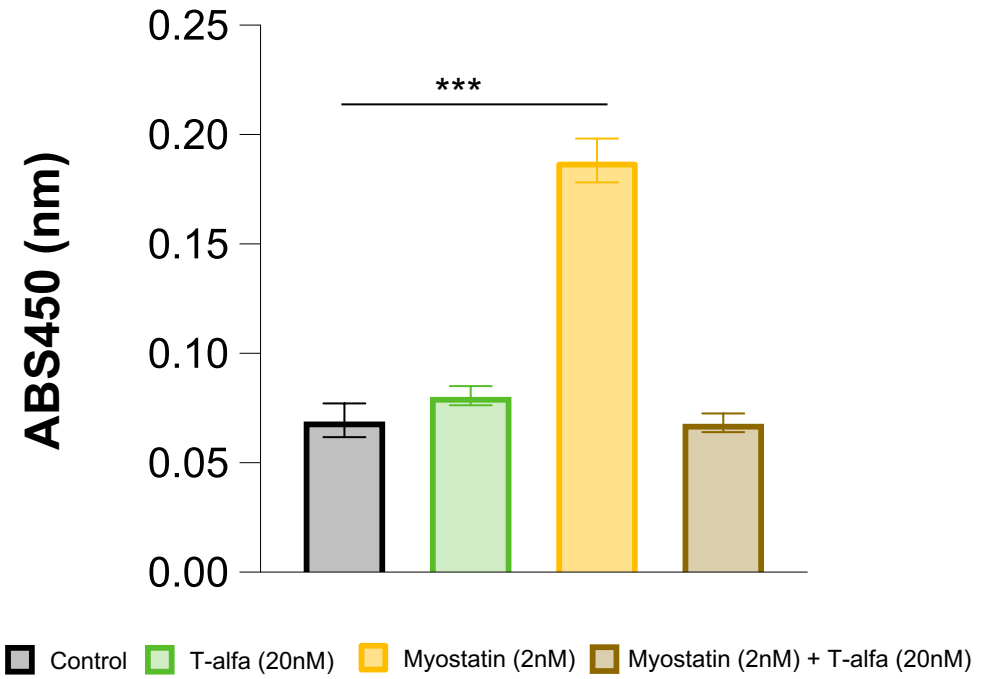
EC80 Activin B: 0.69nM
T-alfa: 1uM

Taldefgrobep Decreases Phospho-SMAD2/3 Signaling in Adipocytes

Taldefgrobep Decreases Phospho-SMAD2/3 Signaling in Mouse 3T3-L1 Adipocytes[1]

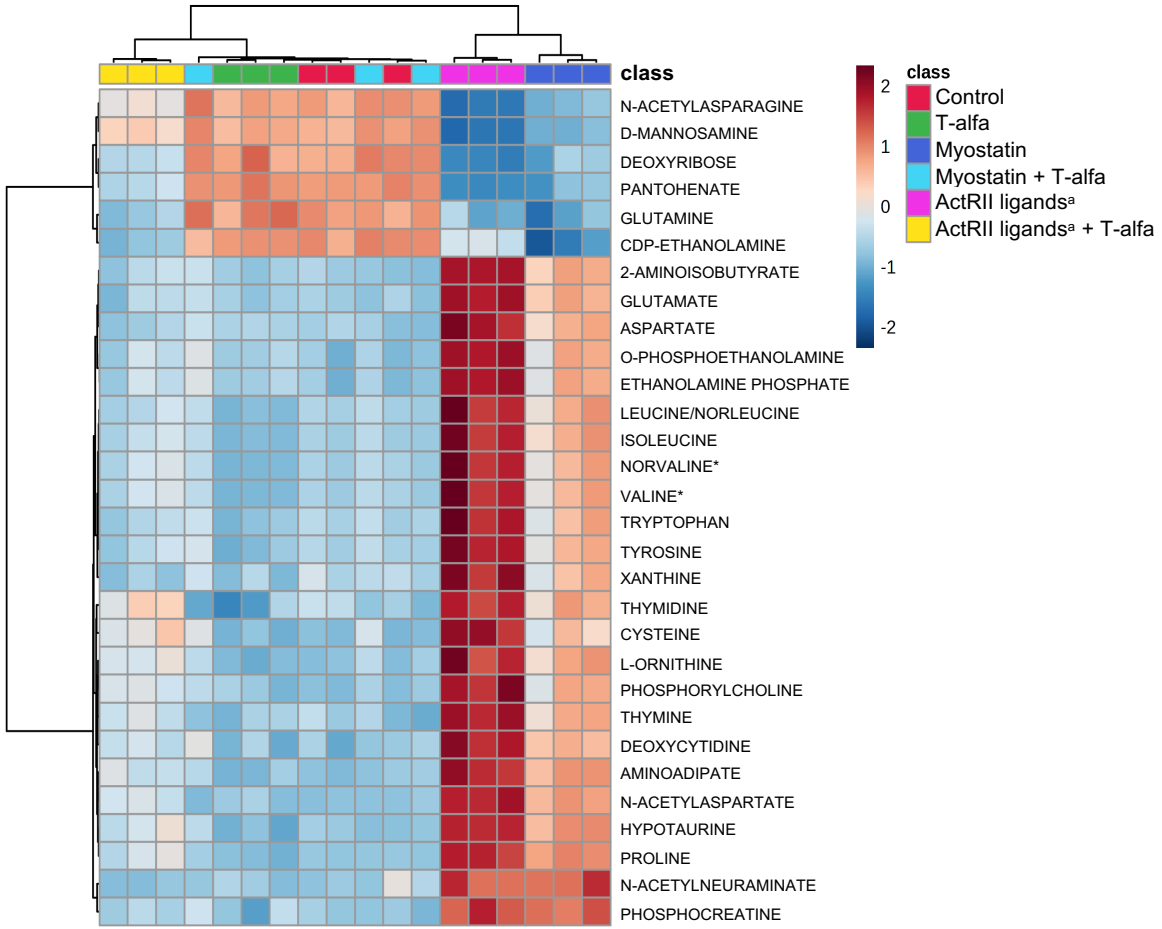


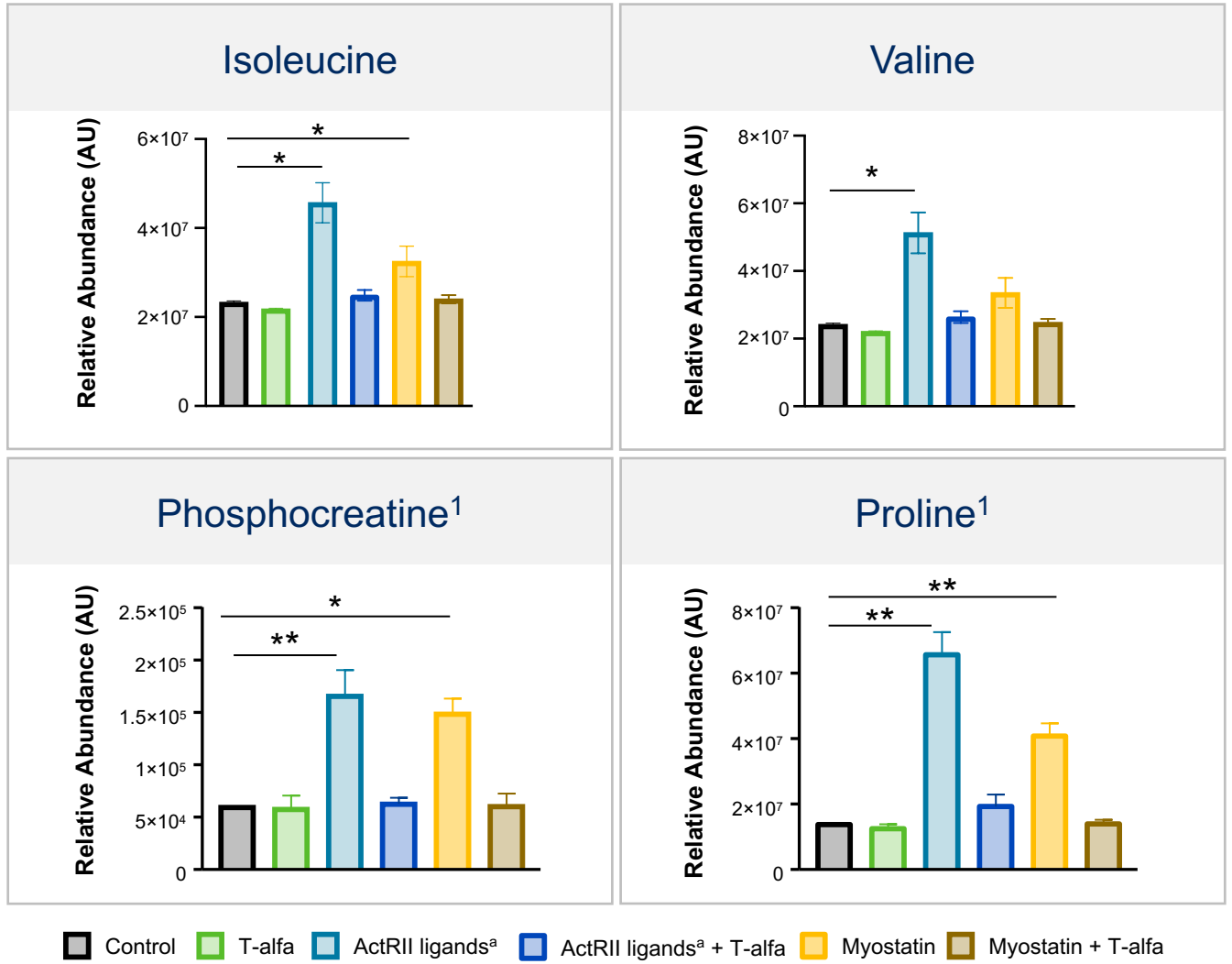
Taldefgrobep Decreases Phospho-SMAD2/3 Signaling in Primary Human Adipocytes



a. Myostatin, GDF11, and activin A. ***P < 0.001, ****P < 0.0001
ABS450, absorbance at 450 nm; **ActRII,** activin II receptor; **T-alfa**, taldefgrobep alfa
1. Ma E, et al. ObesityWeek 2024. Poster 323.

Taldefgrobep Reversed ActRII Ligand-Induced Alterations in Intracellular Metabolite Levels in Adipocytes

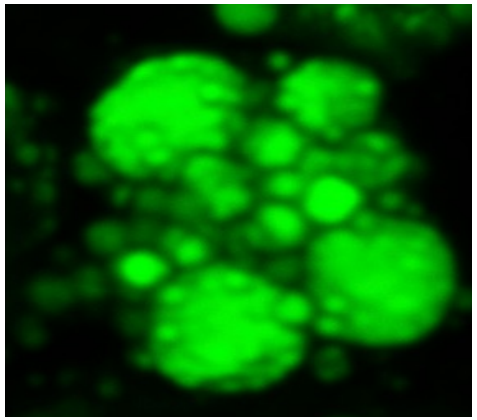




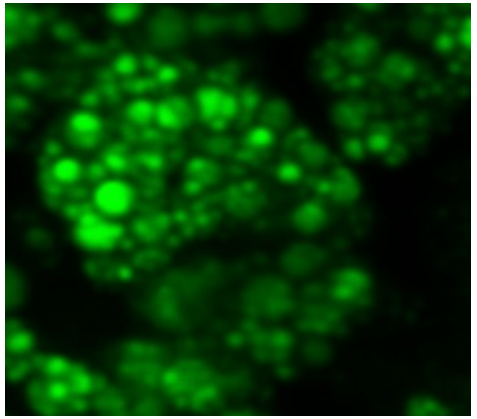
a. Myostatin, GDF11, and activin A. *P < 0.05, **P < 0.01
ActRII, activin II receptor; **AU,** arbitrary units; **T-alfa,** taldefgrobep alfa
1. Pirman D, et al. Keystone Symposia: Obesity and Adipose Tissue 2024. Poster 3005.

Taldefgrobep Treatment Reduces Fat Storage in Adipocytes

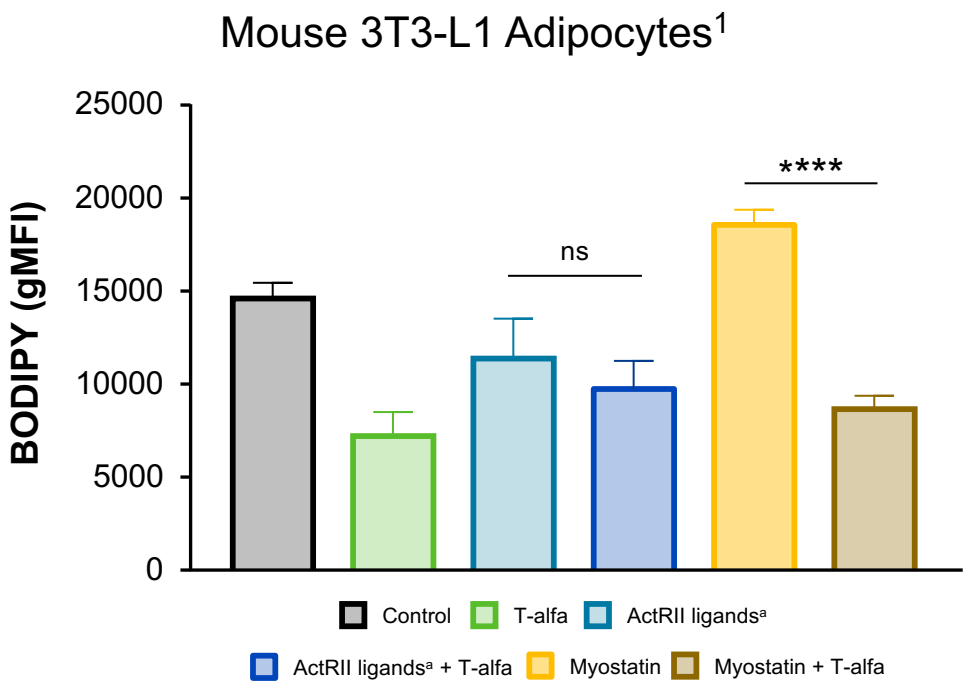
Myostatin drives fat storage

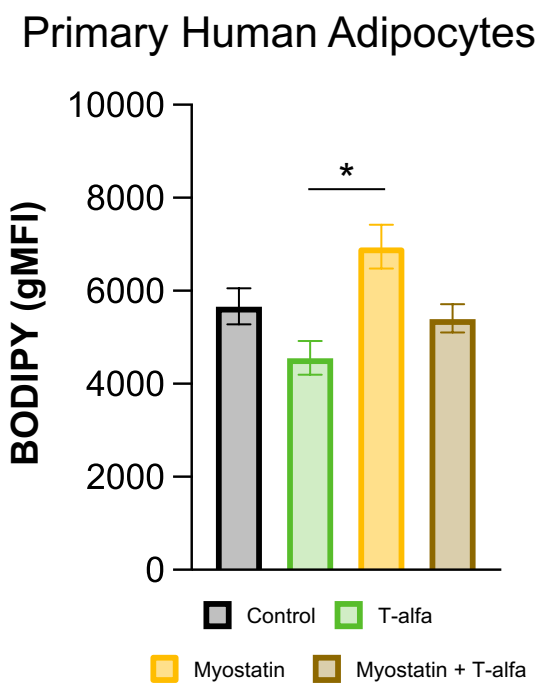


Taldefgrobep reduces this increased storage



Lipid Storage



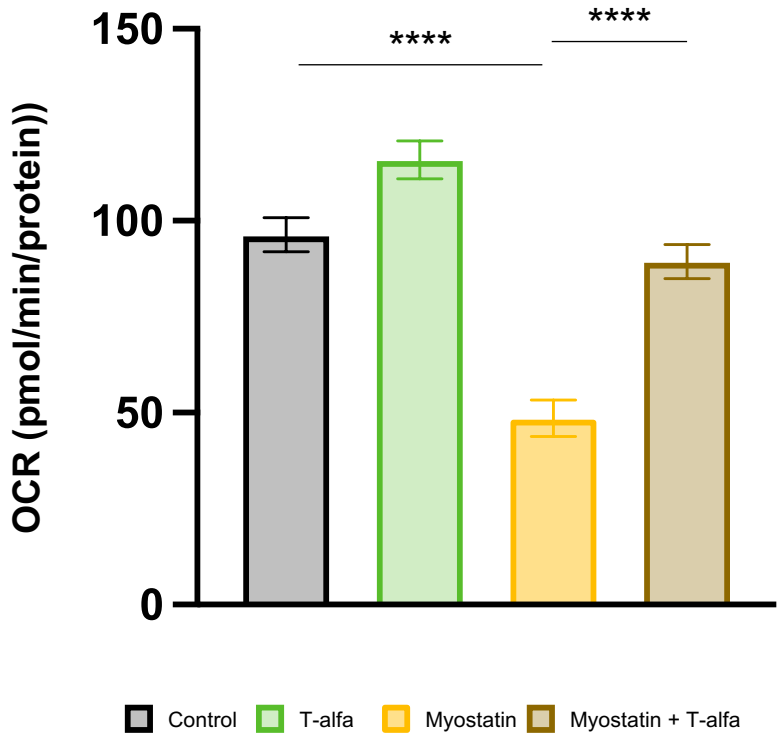


Lower fat storage and smaller intracellular lipid droplets with addition of taldefgrobep

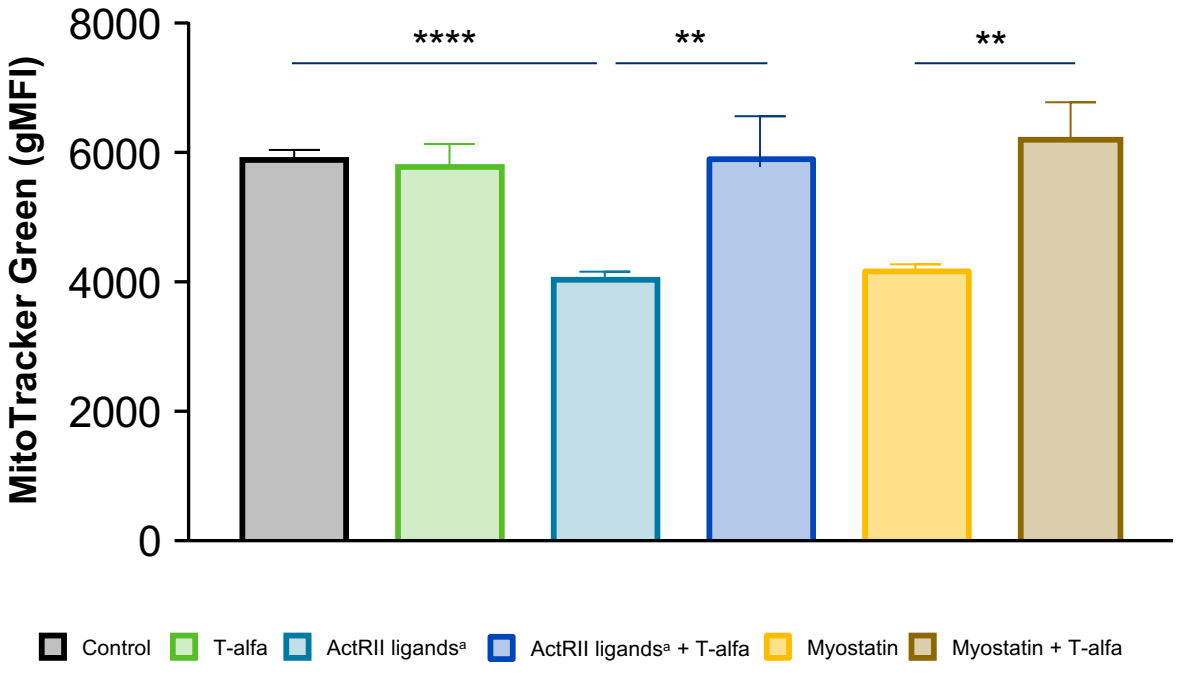
a. Myostatin, GDF11, and activin A.
Significance tested with two-tailed t test. *P < 0.05; ****P < 0.0001.
ActRII, activin II receptor; **BODIPY,** 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene; **gMFI,** geographic mean fluorescence intensity; **ns,** not significant; **T-alfa,** taldefgrobep alfa
1. Ma E, et al. ObesityWeek 2024. Poster 323.

Taldefgrobep Increases Mitochondrial Mass in Adipocytes

Basal Mitochondrial Oxygen Consumption



Mitochondrial Mass[1]



a. Myostatin, GDF11, and activin A. Significance tested with two-tailed t test. **P < 0.01; ****P < 0.0001.
ActRII, activin II receptor; **gMFI,** geographic mean fluorescence intensity; **T-alfa**, taldefgrobep alfa
1. Pirman D, et al. Keystone Symposia: Obesity and Adipose Tissue 2024. Poster 3005.

Conclusions

Taldefgrobep alfa is a novel myostatin-activin pathway inhibitor (MAPI) being developed for the treatment of overweight and obesity

- ActRII-mediated signaling, and downstream SMAD2/3 phosphorylation, leads to muscle wasting and the accumulation of fat mass
- The taldefgrobep-myostatin complex inhibits ActRII signaling that is induced by TGF-β ligands including myostatin and activins
- Inhibition of ActRII signaling leads to enhanced muscle growth, increased lipolysis, and a reduction in fat mass
- In an obese mouse model, taldefgrobep, as monotherapy and in combination with a GLP-1 agonist, demonstrated significant reductions in fat mass and body weight, while increasing lean mass
- These data support the development of taldefgrobep for optimizing the quality of weight loss in people living with overweight and obesity; a Phase 2 clinical trial is planned for 4Q 2025