TERN-501 ENHANCES WEIGHT LOSS EFFICACY OF A GLP-1R AGONIST IN OBESE MICE VIA INCREASED FAT MASS LOSS WITHOUT ADDITIONAL LOSS OF LEAN MASS

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SCAN ME!

Poster No. 760-P

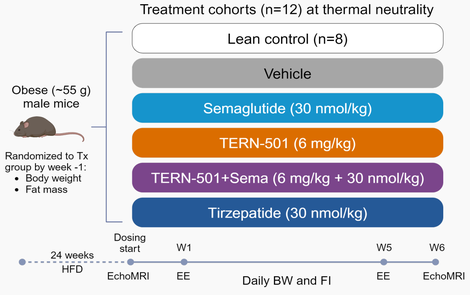
1 INTRODUCTION

GLP-1R agonists suppress food intake resulting in weight loss but efficacy is limited by metabolic adaptation, a compensatory process that lowers energy expenditure (EE). Thyroid hormone receptor-beta (THR-β) regulates EE providing a potential mechanism to mitigate metabolic adaptation. TERN-501, a highly selective THR-β agonist, has shown excellent safety and significant liver fat reduction in a Ph2a study in patients with metabolic dysfunction-associated steatohepatitis. The combined effects of TERN-501 and GLP-1R agonism may offer broader metabolic benefits over either agent alone in people living with obesity.

2 METHODS

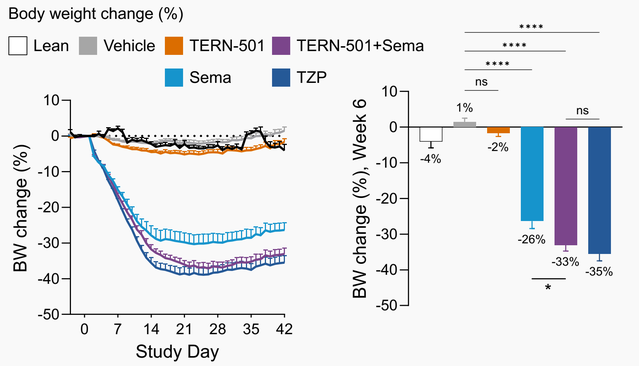
Male C57BL/6JRj mice were fed high fat diet (60% HFD) for 24 weeks prior to study start. Mice were treated once daily with vehicle, TERN-501 (6 mg/kg PO), semaglutide (Sema, 30 nmol/kg SQ), TERN-501+Sema, or tirzepatide (TZP, 30 nmol/kg SQ) for 6-weeks at thermal neutrality. Body weight (BW) and food intake (FI) were measured daily. Body composition was assessed by EchoMRI and EE was measured in metabolic chambers (PhenoMaster). Uncoupling Protein-1 (UCP-1) was measured by immunohistochemistry (IHC) staining of terminal subcutaneous white adipose tissue. One-way ANOVA with Tukey's multiple comparison correction was used to assess statistical significance between treatment groups. *p-value <0.05, **p-value <0.01, ***p-value <0.001, ****p-value <0.0001 vs vehicle unless noted otherwise.

Study schema:



3 RESULTS

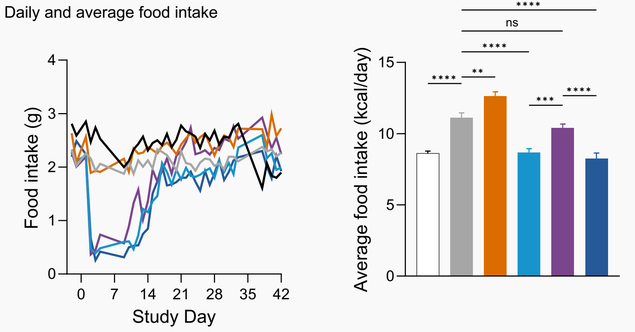
TERN-501+Sema Induces Greater Weight Loss vs Sema Alone



- TERN-501 significantly enhanced BW loss efficacy of Sema (-26% vs -33%, p <0.05). In contrast, BW loss was similar between TERN-501 alone and vehicle (-1.7% vs 1.5%, p >0.05). Percent change in BW at Week 6 was comparable between 501+Sema and TZP (-33% vs 35%, p>0.05).

TERN-501+Sema Enhanced BW Loss Not Driven by Reduced Food Intake

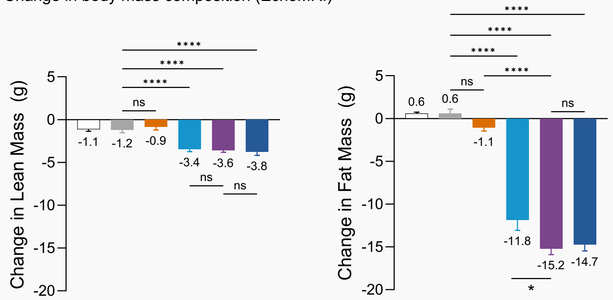
Daily and average food intake



- TERN-501+Sema mice showed higher food consumption compared to Sema alone indicating that enhanced BW loss was not driven by changes in caloric intake. The average food intake for TERN-501+Sema was comparable to vehicle (p>0.05) and significantly higher than Sema alone (p<0.001).

TERN-501+Sema Induces Greater Loss of Fat Mass vs Sema Alone

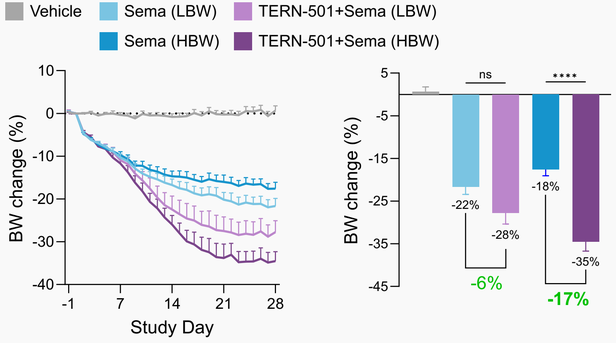
Change in body mass composition (EchoMRI)



- TERN-501+Sema showed greater fat mass loss (-15.2 g vs -11.8 g, p <0.05) without additional loss of lean mass compared to Sema alone (-3.6 g vs -3.4 g, p >0.05).

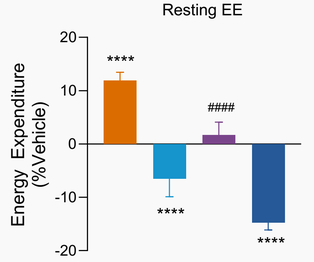
TERN-501+Sema has Even Greater Efficacy in More Obese Mice

Body weight change (%) in Lower (LBW) and Higher Body Weight mice (HBW)

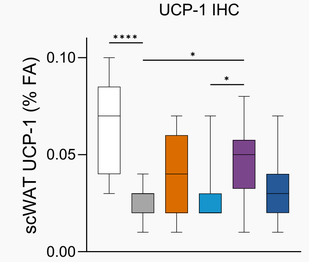


- In mice with higher initial body weight (>55 g), TERN-501+Sema resulted in an additional 17% body weight loss vs Sema alone. Data represents a post-hoc analysis of DIO mice treated for 28 days (n=6 per group).

TERN-501 Protects Against EE Decrease Induced by Weight Loss…



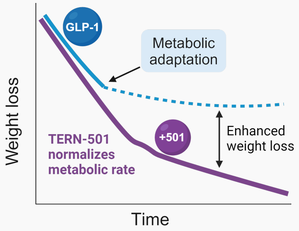
…and partially restores UCP-1 Expression in Fat Tissue



- Decreased EE in Sema-treated mice is consistent with metabolic adaptation induced by weight loss. TERN-501 mitigated EE decrease and partially restored levels of UCP-1 expression in adipose tissue. #### p-value <0.0001 vs. Sema alone.

4 SUMMARY & CONCLUSIONS

Weight Loss and Metabolic Adaptation



- Metabolic adaptation is a counter regulatory process that helps conserve energy but limits the magnitude and sustainability of weight loss induced by calorie restriction or pharmacological intervention (e.g., GLP-1).
- TERN-501 may attenuate metabolic adaptation, which can enhance the weight loss efficacy of GLP-1 therapies.
- In obese mice, TERN-501 significantly improved the efficacy of a GLP-1R agonist by normalizing EE, resulting in greater weight loss, increased fat mass loss, and relative preservation of lean mass.
- These results suggest that TERN-501, a potent and highly selective THR-β agonist, may be an ideal combination partner for GLP-1 therapies and may offer broader metabolic benefits compared to either treatment alone.

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