TERN-501 ENHANCES WEIGHT LOSS OF LOW DOSE ORAL GLP-1R AGONIST IN OBESE MICE

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SCAN ME!

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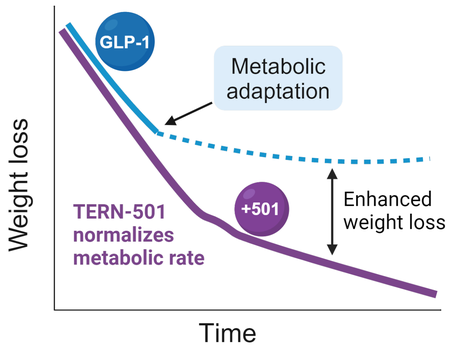
1 INTRODUCTION

To achieve clinically meaningful weight loss, higher doses of GLP-1 receptor agonists (GLP-1RAs) are often necessary, which can result in more gastrointestinal side effects. Mechanisms to enhance GLP-1RA efficacy at lower doses could improve GI tolerability and outcomes. Previous research on diet-induced obese (DIO) mice demonstrated that TERN-501, an oral agonist of thyroid hormone receptor-β (THR-β), when combined with semaglutide (a peptide-based GLP-1RA), resulted in:

- Enhanced weight loss, with greater effects in mice with higher initial body weight
- Improved quality of weight loss, with a greater reduction in fat mass compared to lean mass

This combination may work by mitigating metabolic adaptation, a compensatory response that occurs during weight loss to decrease energy expenditure.

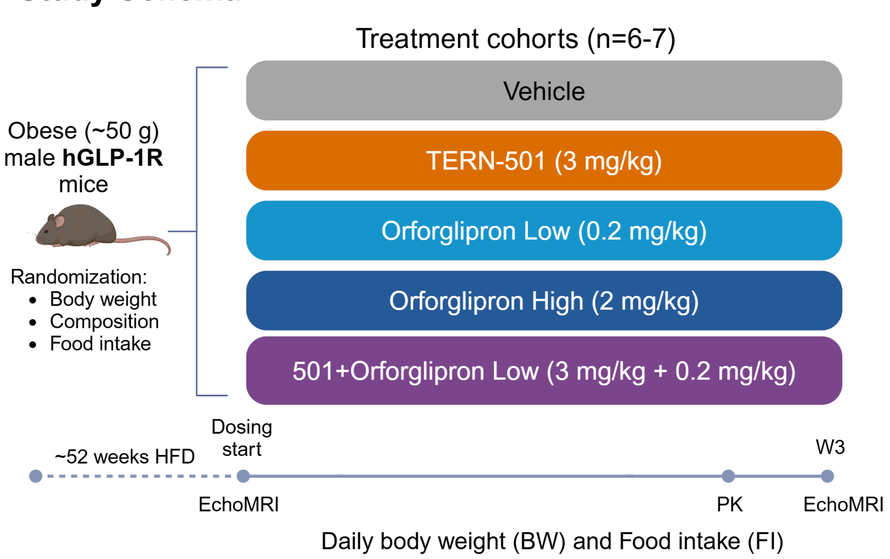


In the current study, we investigated whether TERN-501 could further enhance weight loss when combined with a low dose of orforglipron, an oral, small molecule GLP-1RA.

2 METHODS

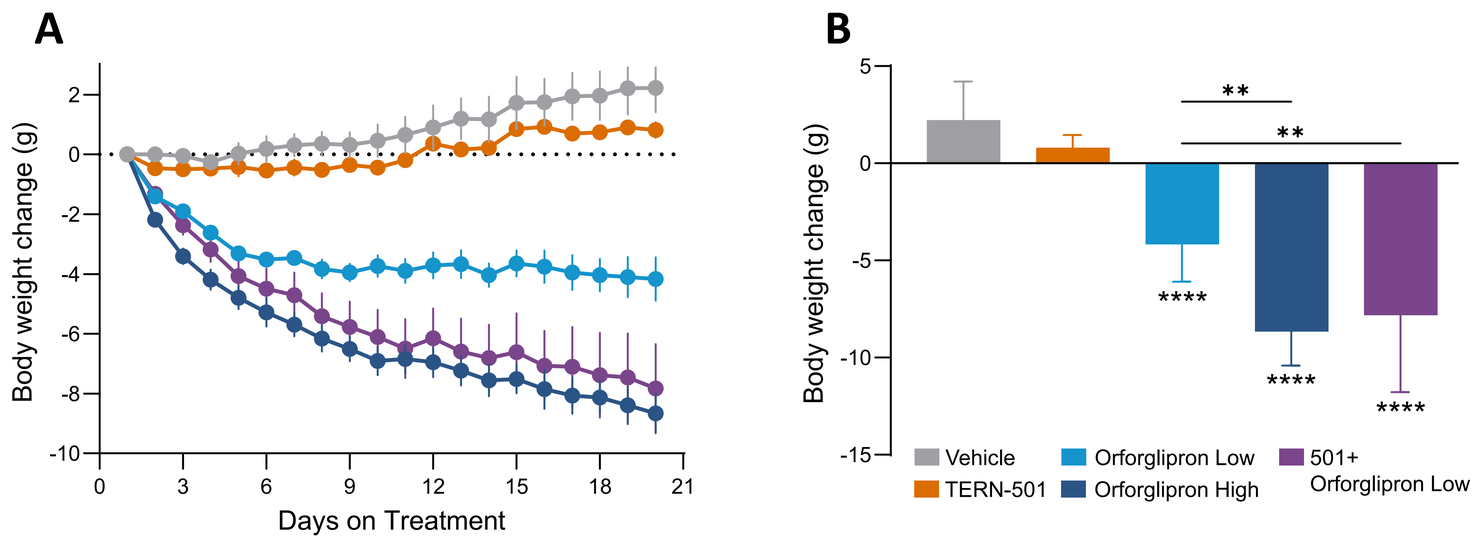
Knock-in mice expressing human GLP-1R (hGLP-1R) were fed a high-fat diet to induce obesity. They were then treated once-daily for 21 days with either vehicle (10% Solutol in saline), TERN-501 (3 mg/kg), orforglipron (0.2 and 2 mg/kg), or a combination of TERN-501 (3 mg/kg) + orforglipron (0.2 mg/kg). Body weight and food intake were measured daily, and body composition was assessed by EchoMRI at the beginning and end of the study. Statistical significance between treatment groups was determined using one-way ANOVA, with significance levels indicated as follows: *p-value <0.05; **p-value <0.01; ***p-value <0.001; and ****p-value <0.001.

Study Schema



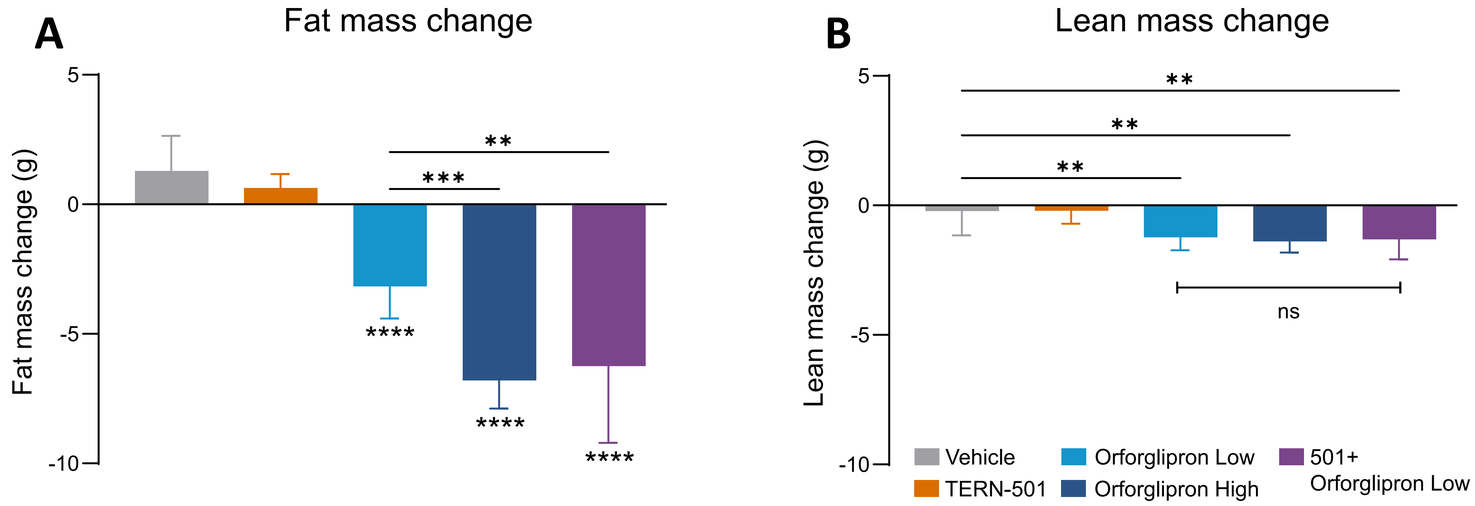
3 RESULTS

TERN-501+Orforglipron Achieves Weight Loss Comparable to 10x Orforglipron Dose Alone



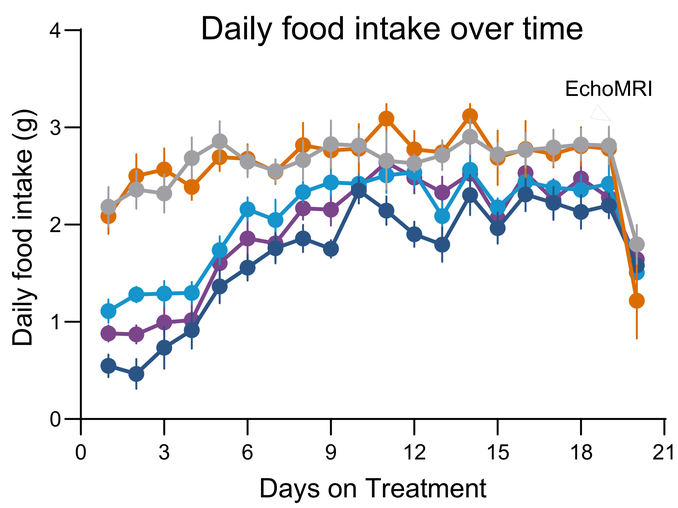
Changes in body weight from baseline over time (**A**) and on Day 20 (**B**) are shown. Data in (**A**) represented as mean ±SEM body weight change (g) from baseline. Data in (**B**) represented as mean ±SD body weight change (g) from baseline to Day 20. SEM = standard error of the mean; SD = standard deviation.

TERN-501 Enhances Weight Loss by Promoting Fat Reduction



Body mass composition change from baseline to Day 19 as measured by EchoMRI. Data represented as mean ±SD fat mass (**A**) and lean mass (**B**) change from baseline. ns = not significant; SD = standard deviation.

TERN-501 Did Not Significantly Affect Food Intake



Daily food intake during treatment. Data represents as mean ±SEM. Decreased food intake was observed on Day 19 following body mass composition measurement (EchoMRI) denoted by triangle. SEM = standard error of the mean.

4 SUMMARY & CONCLUSIONS

- TERN-501 increased the weight loss effect of low-dose orforglipron to a level comparable to a 10-fold higher dose of orforglipron as monotherapy, without additional loss of lean mass.
- TERN-501 and low-dose GLP-1R agonist combination therapy may lead to improved gastrointestinal tolerability and patient outcomes.
- These preclinical results indicate that TERN-501 could be an effective combination partner with GLP-1 therapies for promoting weight loss and preserving lean body mass.

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