Metabolic Effects of ECC4703, a Liver-targeting THRβ Full Agonist, in Combination with Semaglutide and Tirzepatide in Diet-induced Obese Mice

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Introduction and objectives

- GLP-1R agonism is clinically validated mechanism for treatment of obesity. The body weight lowering effects are largely mediated by appetite suppression. However, it's associated with energy expenditure reduction and lean mass loss which may lead to lack of sustained efficacy and refractory weight gain[1].
- ECC4703 is a small molecule liver-targeting THRβ full agonist with desired safety, tolerability, and PD profiles demonstrated in Phase 1 trial[2,3].
- The current study aims to explore the metabolic effects by combination of ECC4703 with Semaglutide and Tirzepatide in the preclinical obesity model.

Methods

- Diet-induced obesity mice received ECC4703, Semaglutide or Tirzepatide monotherapy, or combinatory therapy of ECC4703 with Semaglutide or Tirzepatide for 6 weeks.
- Body weight and food intake were monitored during the treatment.
- Body composition was measured by qNMR at pretreatment and day 28.
- Indirect calorimetry by metabolic cage was conducted during day 28 to day 38.
- At the end of study, fasting glucose, insulin, plasma lipids were measurand. Liver, representative adipose tissue and skeletal muscles were collected and weighed.
- Data are presented as Mean±Sem. N=10 for each group unless otherwise indicated.
- Statistical analyses were performed using one-way ANOVA with Tukey's test.

References

1. Obesity Reviews. 2025;26:e13841
2. Hepatology 76: S638, October 2022
3. AASLD 2024, poster# 5019

Results

In combination with Semaglutide or Tirzepatide, ECC4703 treatment resulted in greater weight loss without further food intake suppression

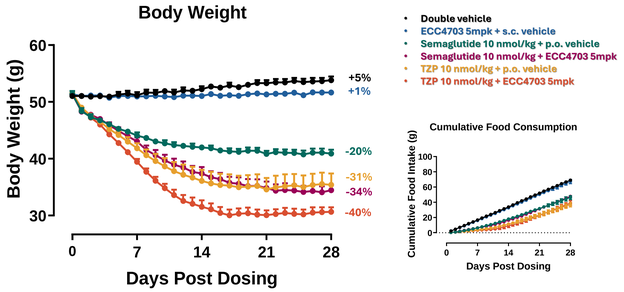

Figure 1. Absolute body weight and cumulative food intake during treatment.

Combo treatment resulted in greater fat loss, lean mass preservation and increase of lean mass percentage

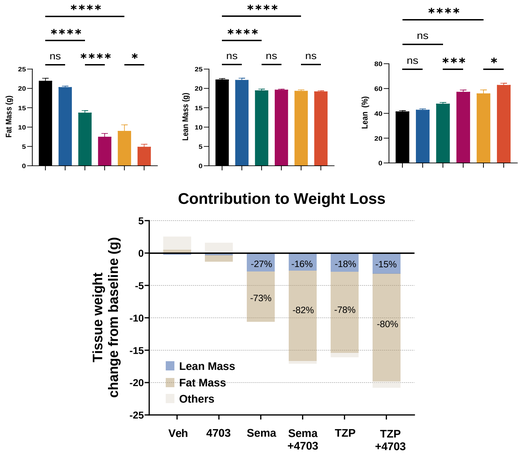

Figure 2. Body composition measured by qNMR. Absolute fat mass, lean mass and lean mass% at day 28 are shown at top. Changes from baseline of lean mass and fat mass are shown at bottom, with %change labeled in the column.

Combo treatment resulted in preserved energy expenditure and elevation of RER in late dark phase

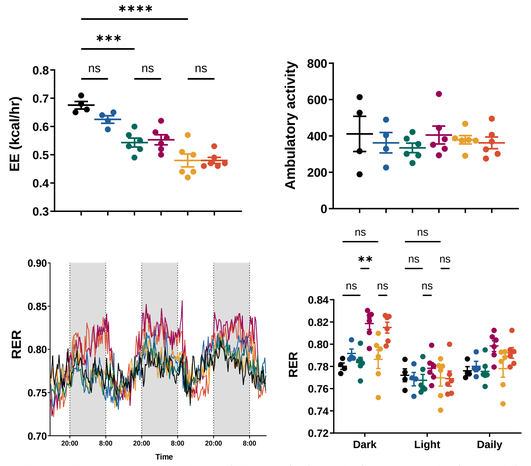

Figure 3. Energy expenditure (EE, top left), ambulatory activity (top right) and diurnal RER pattern (bottom) measured by metabolic cage study. N=4~6 for each group..

Combo treatment improved glycemic and lipid profiles

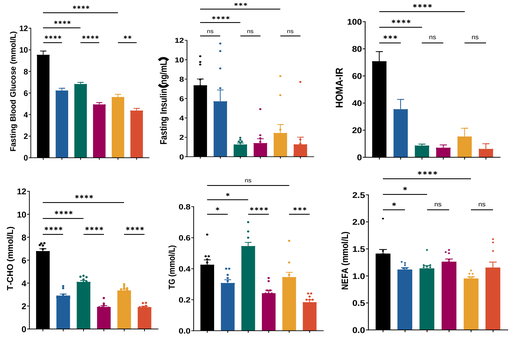

Figure 4. Fasting glucose, insulin and HOMA-IR were showed on top. Plasma total cholesterol (T-CHO), triglyceride (TG) and non-esterified fatty acids (NEFA) were showed on bottom.

Tissue weight confirmed muscle sparing, fat specific weight loss by the combo treatment

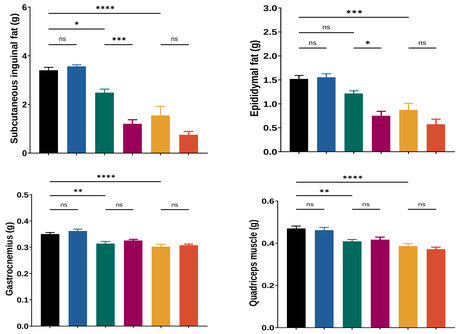

Figure 5. Representative adipose tissue weight (Subcutaneous inguinal fat and Epididymal fat, top) and skeletal muscle weight (Gastrocnemius and Quadriceps muscle, bottom).

Conclusions

- In combination with Semaglutide or Tirzepatide (TZP), ECC4703 resulted in greater weight loss.
- Consistent with findings in humans, the weight loss by Semaglutide or TZP was associated with suppression of food consumption and reduction of lean mass.
- The additional weight loss by combo treatment was independent of food consumption, and was mainly driven by fat mass loss leading to an improved lean mass percentage.
- Weight loss by Semaglutide or TZP was associated with substantial decrease of energy expenditure, while the additional weight loss by combo treatment maintained energy expenditure.
- Additional improvement of glycemic and lipid profiles were observed by the combo treatment.
- ECC4703 in combination with GLP-1R agonists holds therapeutic potential to treat obesity and related comorbidities.

Acknowledgement

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