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Synergistic fat mass loss in diet-induced obese mice when thyroid hormone receptor-β agonist ALG-055009 was administered in combination with incretin receptor agonists

POSTER #6

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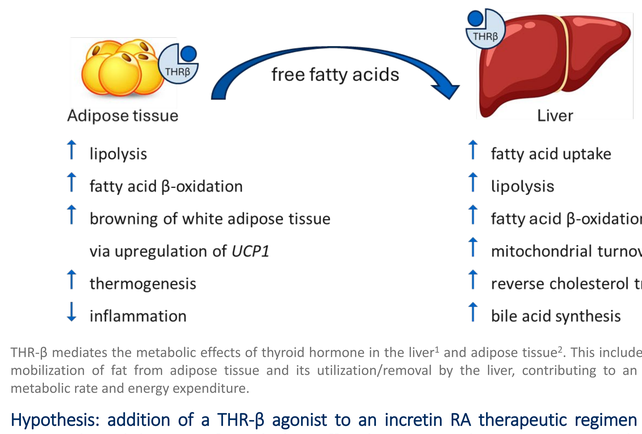
BACKGROUND

ALG-055009 is a potent and selective thyroid hormone receptor-β (THR-β) agonist that has demonstrated significant reductions in liver fat (placebo-adjusted median relative reductions up to 46.2%) and atherogenic lipids in patients with presumed metabolic dysfunction-associated steatohepatitis (MASH) and stage 1-3 liver fibrosis. In addition, THR-β is known to play a critical role in regulating metabolism in adipose tissue and the liver, and its activation has been shown to enhance energy expenditure and promote weight loss. Here, the ability of the THRβ agonist ALG-055009 to augment the weight loss effects of approved incretin receptor agonists (RAs) was assessed in diet-induced obese (DIO) mice.

Fig. 1 Key Role of Thyroid Hormone in Metabolism



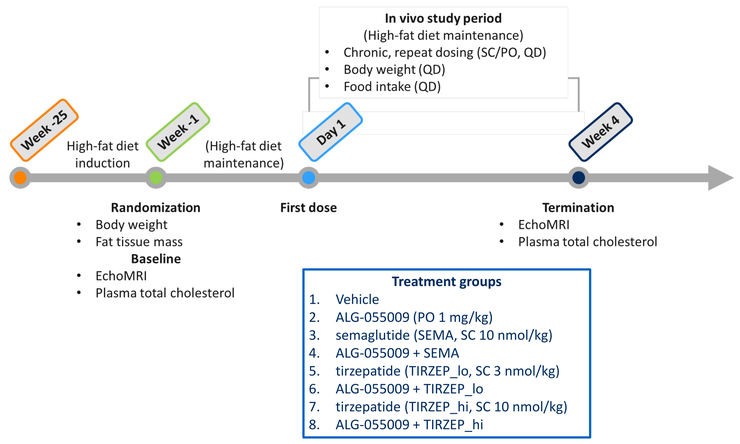
THR-β mediates the metabolic effects of thyroid hormone in the liver[1] and adipose tissue[2]. This includes accelerating the mobilization of fat from adipose tissue and its utilization/removal by the liver, contributing to an increase in basal metabolic rate and energy expenditure.

Hypothesis: addition of a THR-β agonist to an incretin RA therapeutic regimen enhances the magnitude and duration of weight loss effect by GLP-1 RA by attenuating metabolic adaptation response via normalizing metabolic rate

METHODS

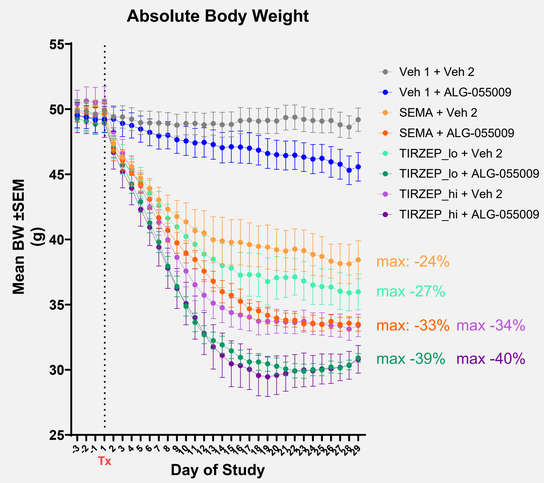
Animals: Male, C57BL/6JRj diet-induced obese (DIO) mice; n =10 animals/group

Diet: 60%-kcal high-fat diet (D12492)



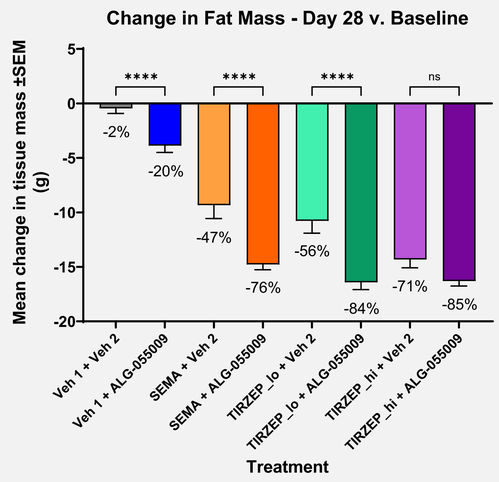
RESULTS

Fig. 2 Combination Therapy Enhances Body Weight Loss



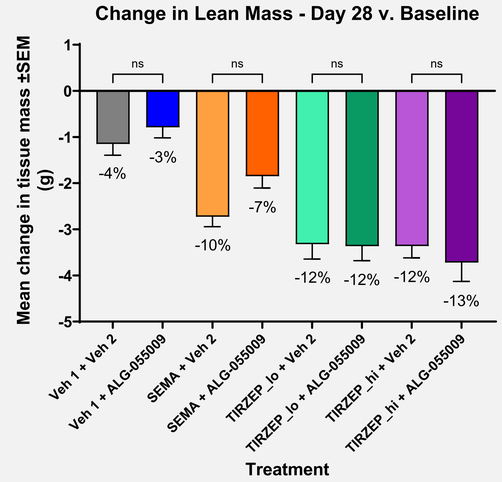
BW = body weight; Tx = start of therapeutic; percentages reported correspond to percent changes in weight as compared to baseline measurements (nadir)

Fig. 3 Combination Therapy Enhances Loss of Fat Mass



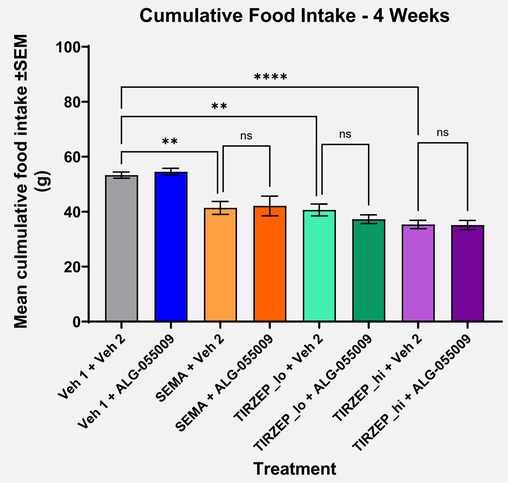
One-way ANOVA with Tukey's multiple comparisons test; percentages displayed below each bar correspond to percent changes in tissue mass as compared to baseline measurements; **** = p-value <0.0001; ns = not statistically significant

Fig. 4 Combination Therapy Does Not Affect Changes in Lean Mass



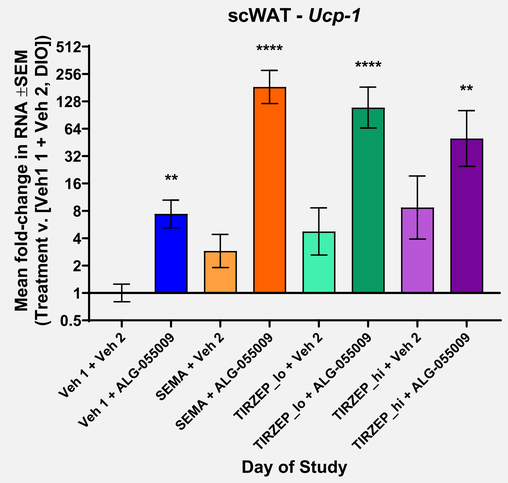
One-way ANOVA with Tukey's multiple comparisons test; percentages displayed below each bar correspond to percent changes in tissue mass as compared to baseline measurements; ns = not statistically significant

Fig. 5 Weight Loss Effects of ALG-055009 are Not Due to Changes in Food Intake



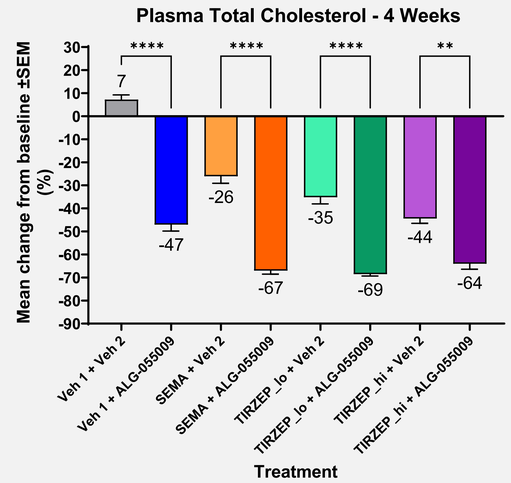
One-way ANOVA with Tukey's multiple comparisons test; ** = p-value <0.01; **** = p-value <0.0001; ns = not statistically significant

Fig. 6 Combination Therapy Synergistically Upregulates *Ucp1* Expression in White Adipose Tissue



Ucp1 = uncoupling protein 1, thermogenin; scWAT = subcutaneous white adipose tissue; Brown-Forsythe and Welch ANOVA test; ** = p-value <0.01; **** = p-value <0.0001; ns = not statistically significant

Fig. 7 Combination Therapy Offers Enhanced Antihyperlipidemic Effects



Ucp1 = uncoupling protein 1, thermogenin; scWAT = subcutaneous white adipose tissue; Brown-Forsythe and Welch ANOVA test; ** = p-value <0.01; **** = p-value <0.0001; ns = not statistically significant

CONCLUSIONS

- DIO mice treated with ALG-055009 in combination with semaglutide or tirzepatide (low or high dose) experience greater weight loss for longer durations compared to animals treated only with incretin RA
  - The additional weight loss conferred by ALG-055009 is mainly due to decrease in fat tissue mass and not due to changes in lean tissue mass or food intake
  - ALG-055009 + SEMA reaches similar weight loss as TIRZEP_hi monotherapy
  - ALG-055009 + TIRZEP_lo has greater weight loss than TIRZEP_hi only, indicating a possible dose-sparing regimen
- We provide evidence that the synergism is a result of ALG-055009's ability, as a THRβ agonist, to increase overall metabolism and overcome the metabolic adaptation that emerges after a period of weight loss
- Furthermore, combination therapy exhibited enhanced antihyperlipidemic effects as compared to monotherapy

REFERENCES

1. https://doi.org/10.2337/db22-0656
2. https://doi.org/10.1038/s41575-024-00991-4

FINANCIAL DISCLOSURES

All authors are employees of Aligos Therapeutics, Inc. or Aligos Belgium BV and may own stock or stock options in the company.

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