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

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ALG-055009 Discovery and Early Development

Executive Summary

- **ALG-055009, is a proprietary, potent, purpose-built, orally administered THR-β agonist**
  - Optimization of the molecule for pharmacological properties, including linear and low variability pharmacokinetics, no DDI potential, and substantially increased potency that resulted in very low doses that are well-tolerated
- **Demonstrated a significant decrease in liver fat (met primary endpoint) in a Phase 2 study in MASH patients[1]**
- **Clinical safety database includes 179 subjects with 80 subjects up to 12 weeks of dosing**
  - Demonstrates favorable GI tolerability when compared to resmetirom
- **ALG-055009 is ready for continued clinical development in MASH as monotherapy and in combination with both GLP-1 mono- or dual-agonists for obesity treatment**

1) HERALD (NCT06342947) is a randomized, double-blind, placebo-controlled trial that enrolled 102 subjects with presumed MASH and stage 1-3 liver fibrosis (F1-F3).

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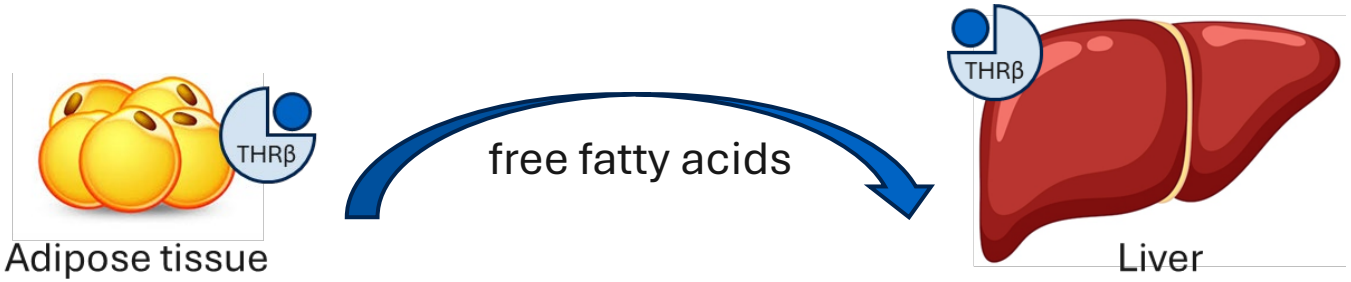
Key Role of Thyroid Hormone in Metabolism

- **Thyroid hormones regulate key metabolic pathways that control energy balance**
- **In adipose tissue[1] and the liver[2], THR-β mediates the metabolic effects of thyroid hormone**
- **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**



- ↑ lipolysis
- ↑ fatty acid β-oxidation
- ↑ browning of white adipose tissue via upregulation of *UCP1*
- ↑ thermogenesis
- ↓ inflammation

- ↑ fatty acid uptake
- ↑ lipolysis
- ↑ fatty acid β-oxidation
- ↑ mitochondrial turnover
- ↑ reverse cholesterol transport
- ↑ bile acid synthesis

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

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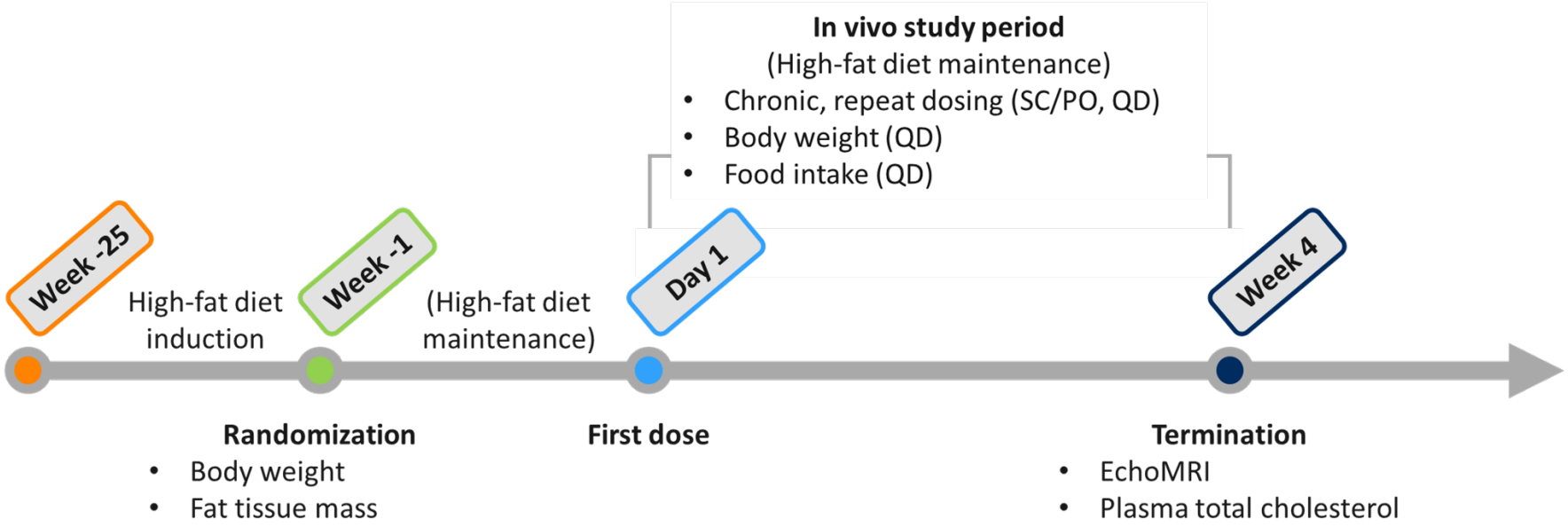
THR-β Agonist (ALG-055009) + Incretin Receptor Agonists

Study Design

- Hypothesis: addition of a THR-β agonist will enhance the magnitude and duration of weight loss effect by GLP-1 RA by attenuating the metabolic adaptation response via normalizing metabolic rate



Treatment groups

1. Vehicle
2. ALG-055009 (PO 1 mg/kg)
3. semaglutide (SEMA, SC 10 nmol/kg)
4. ALG-055009 + SEMA
5. tirzepatide (TIRZEP_lo, SC 3 nmol/kg)
6. ALG-055009 + TIRZEP_lo
7. tirzepatide (TIRZEP_hi, SC 10 nmol/kg)
8. ALG-055009 + TIRZEP_hi

PO =oral; QD =once daily; SC =subcutaneous; RA =receptor agonist.

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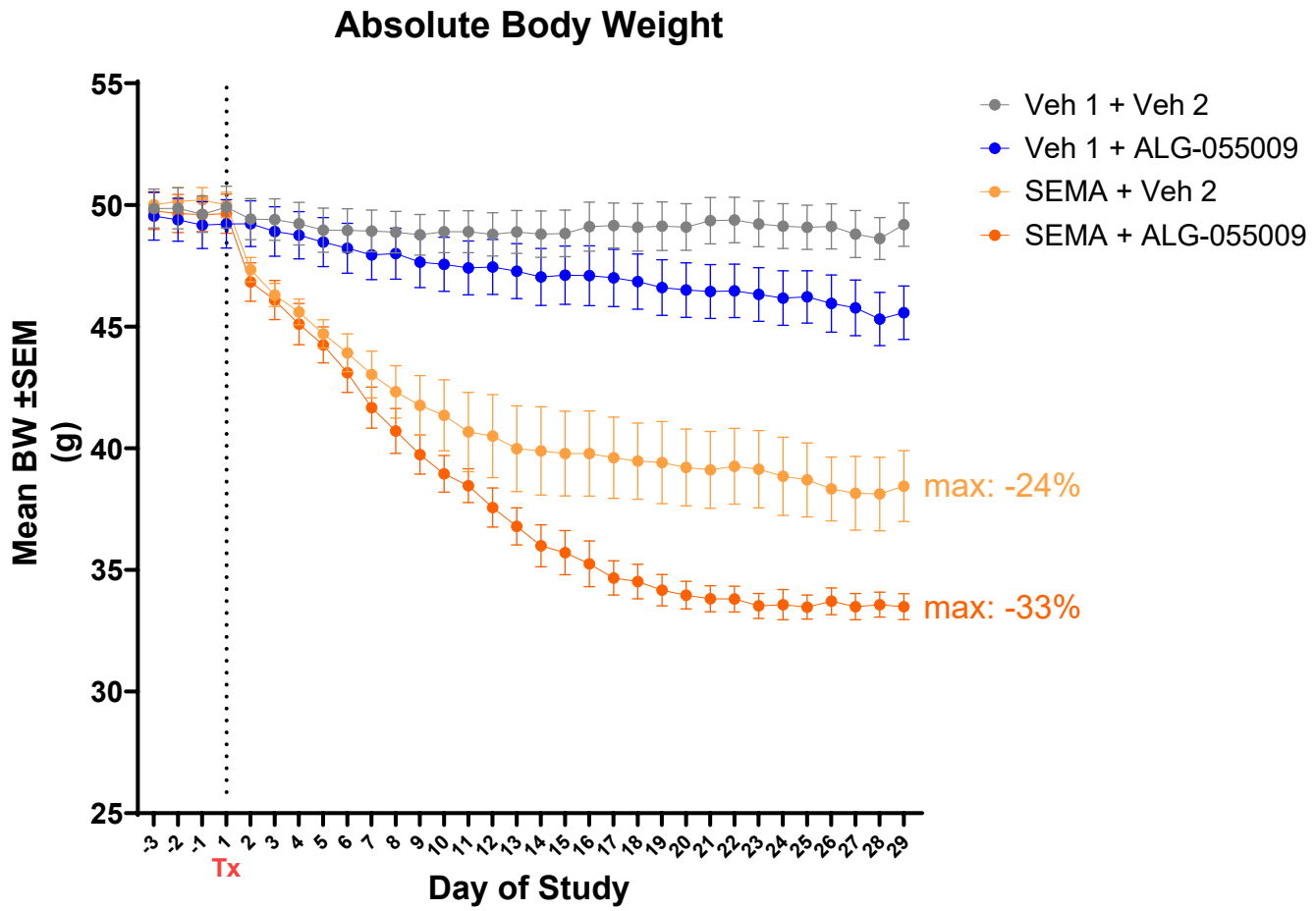
THR-β Agonist (ALG-055009) + Semaglutide

Combination Therapy Enhances Body Weight Loss in Diet-Induced Obese (DIO) Mice



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

ALG-055009 has profound synergistic effects on BW loss when combined with semaglutide, with as much as 33% decrease in BW within 28 days

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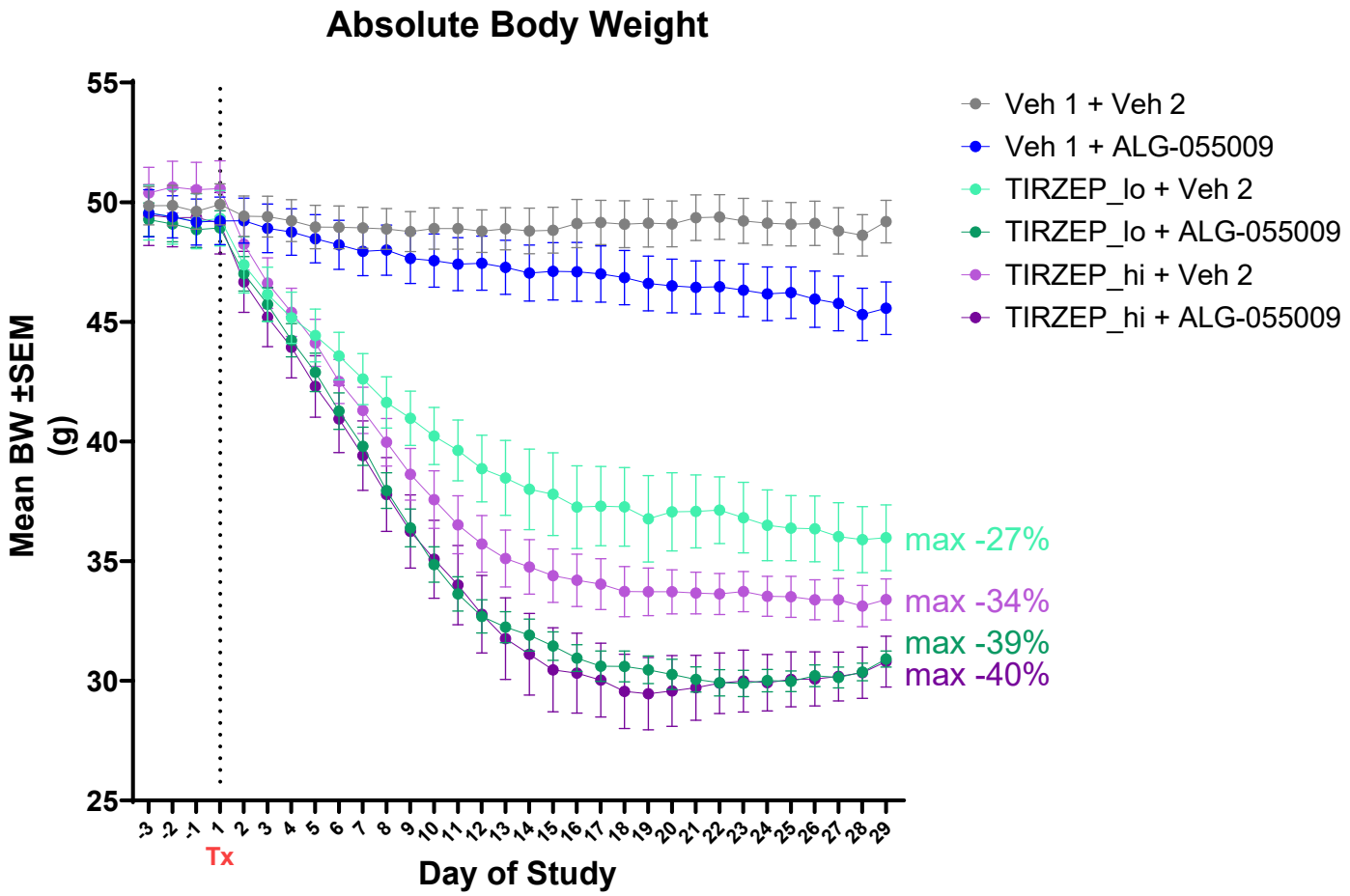
THR-β Agonist (ALG-055009) + Tirzepatide

Combination Therapy Enhances Body Weight Loss in Diet-Induced Obese (DIO) Mice



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

ALG-055009 has profound synergistic effects on BW loss when combined with both low- and high-dose tirzepatide, with as much as 40% decrease in BW within 28 days

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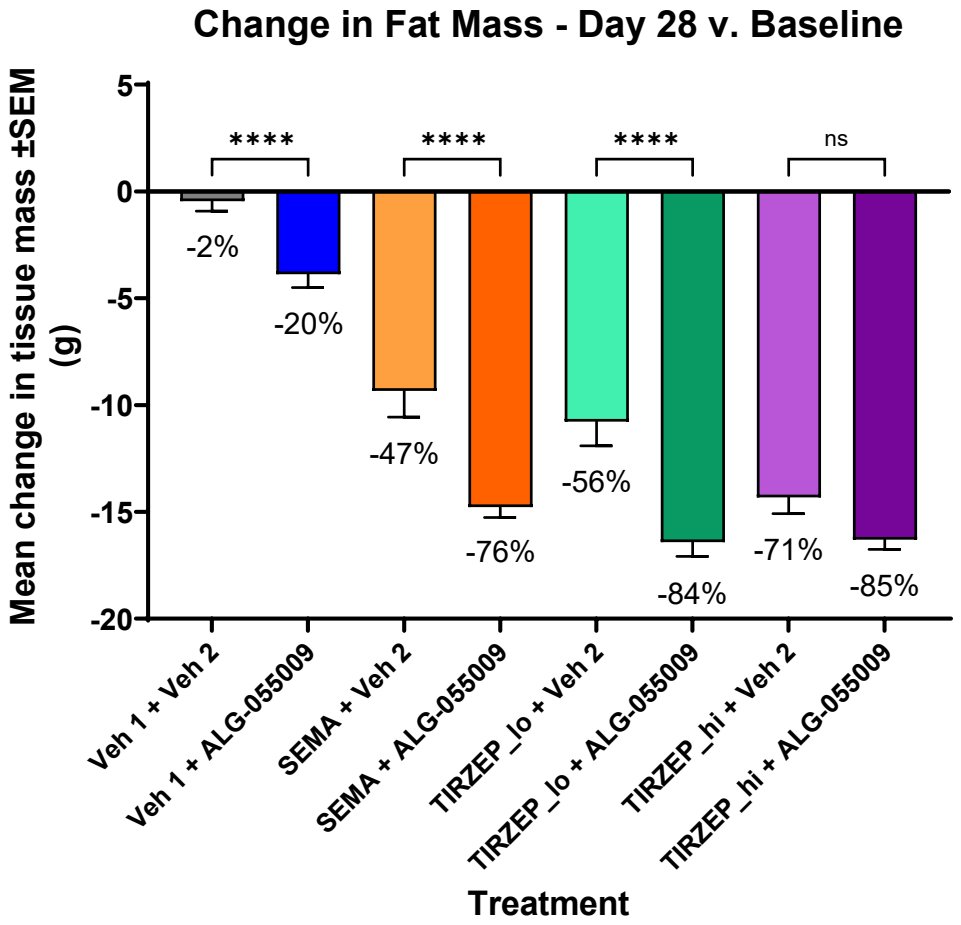
THR-β Agonist (ALG-055009) + Incretin Receptor Agonists

Combination Therapy Enhances Loss of Fat Mass in Diet-Induced Obese (DIO) Mice



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.

The addition of ALG-055009 to incretin RA treatment results in greater decreases in fat mass as compared to incretin RA monotherapy

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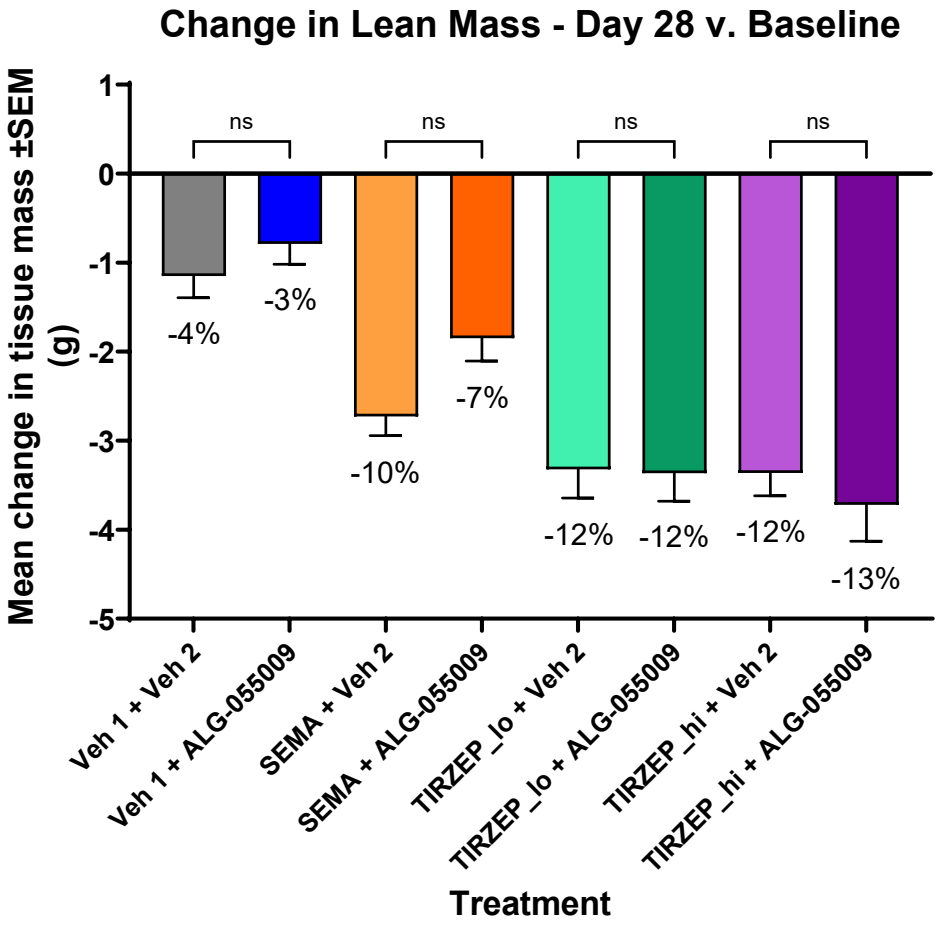
THR-β Agonist (ALG-055009) + Incretin Receptor Agonists

Combination Therapy Does Not Affect Changes in Lean Mass in Diet-Induced Obese (DIO) Mice



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.

The addition of ALG-055009 to incretin RA treatment had no significant effects on changes in lean mass as compared to incretin RA monotherapy

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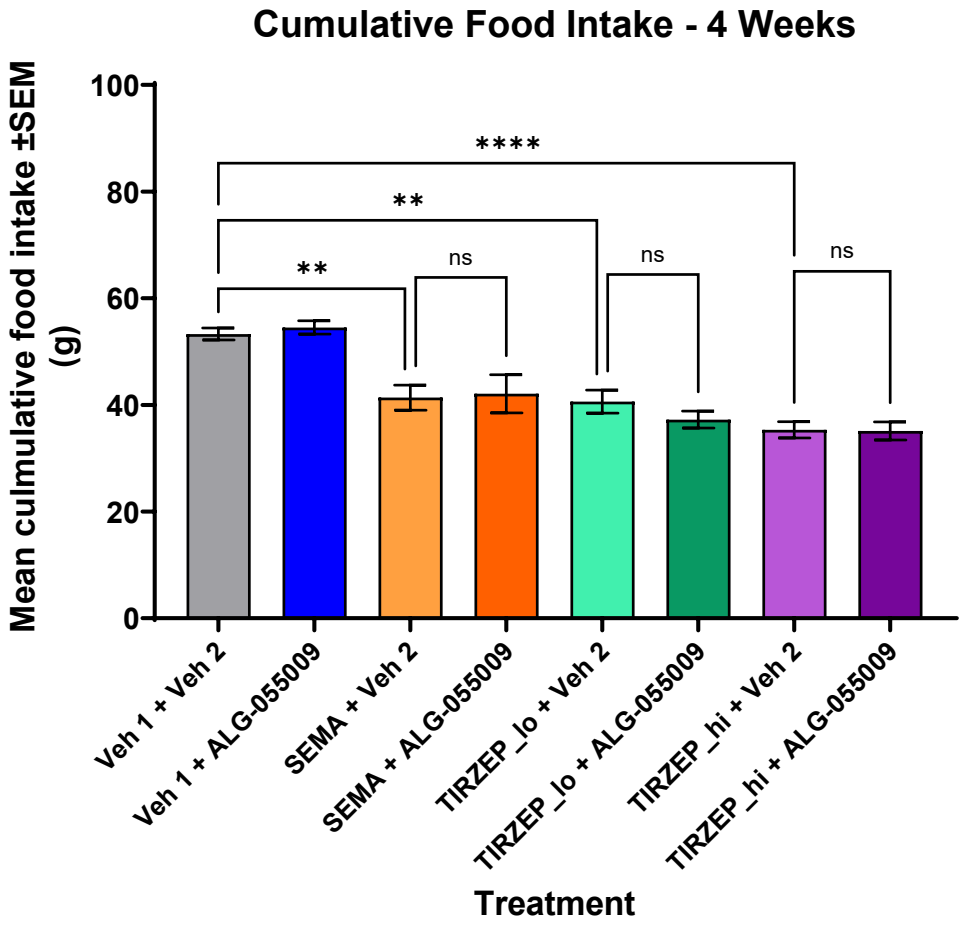
THR-β Agonist (ALG-055009) + Incretin Receptor Agonists

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.

The addition of ALG-055009 to incretin RA treatment had no significant effects on food intake as compared to incretin RA monotherapy

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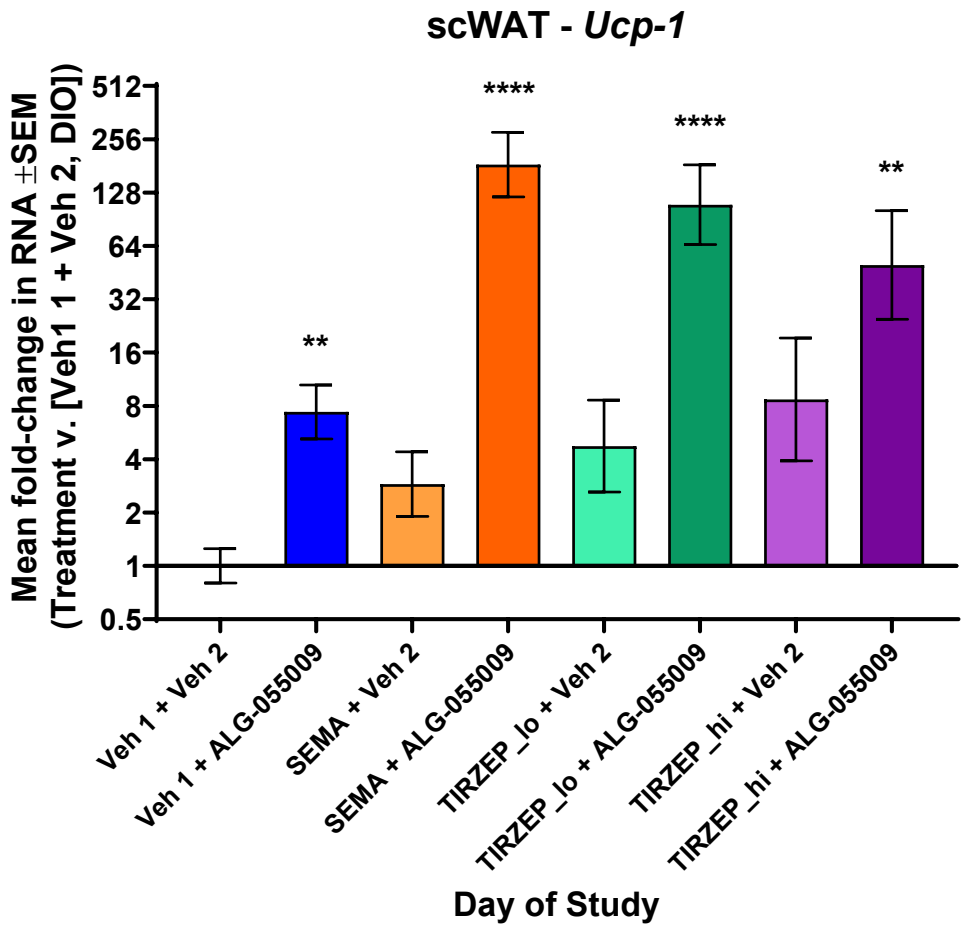
THR-β Agonist (ALG-055009) + Incretin Receptor Agonists

Combination Therapy Synergistically Upregulates *Ucp1* Expression in White Adipose Tissue of (DIO) Mice



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.

Upregulation of *Ucp1* expression in scWAT indicates induction of "brown/beige" adipocytes and increased energy expenditure

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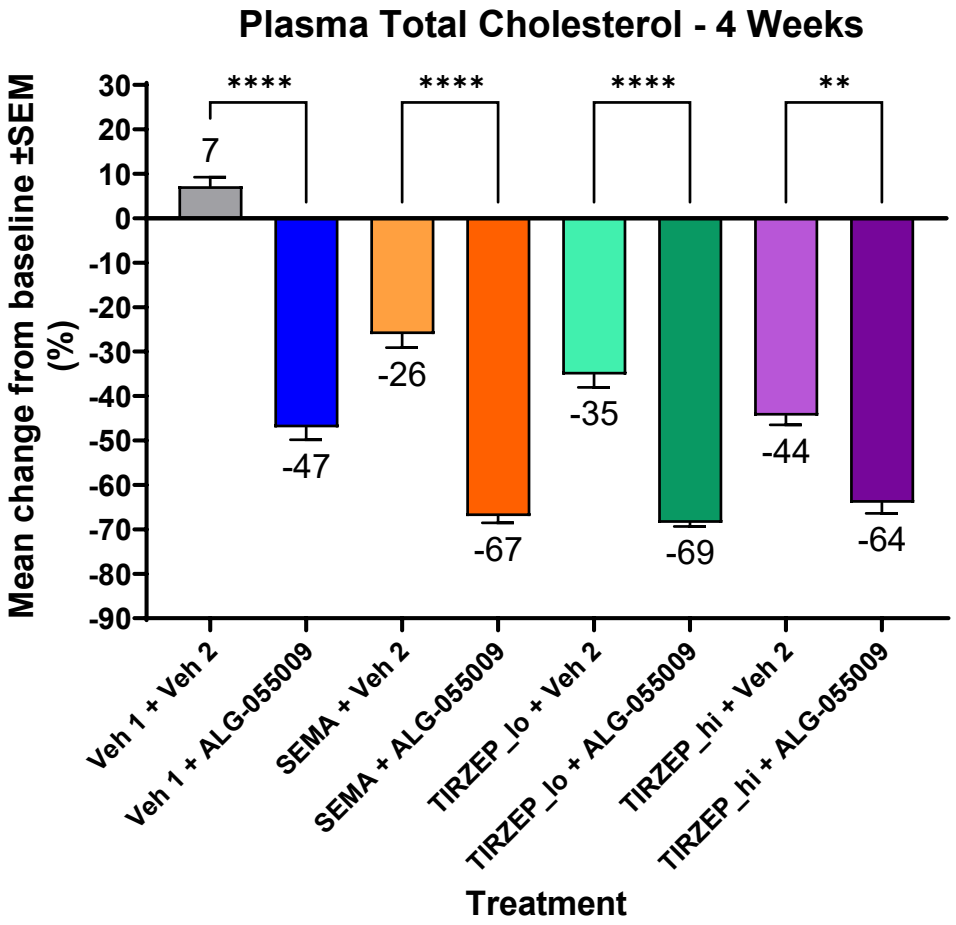
THR-β Agonist (ALG-055009) + Incretin Receptor Agonists

Combination Therapy Offers Enhanced Antihyperlipidemic Effects



One-way ANOVA with Tukey's multiple comparisons test; percentages displayed below each bar correspond to percent changes in total cholesterol as compared to baseline measurements; ** = p-value <0.01; **** = p-value <0.0001.

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ALG-055009 monotherapy has greater lipid-lowering effects than incretin RA monotherapy and combination therapy offers enhanced antihyperlipidemic effects

THR-β Agonist (ALG-055009) + Incretin Receptor Agonists

Summary

- 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 compared to TIRZEP_hi monotherapy indicating a possible dose-sparing regimen
- We provide evidence that the synergism is a result of ALG-055009's ability, as a THR-β 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

Acknowledgements

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