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Co-Administration of Thyroid Hormone Receptor-beta Agonist ALG-055009 and Incretin Receptor Agonists Leads to Synergistic Weight Loss and Modulation of Molecular Pathways Underlying Adipocyte Dysfunction in Diet-Induced Obese Mice

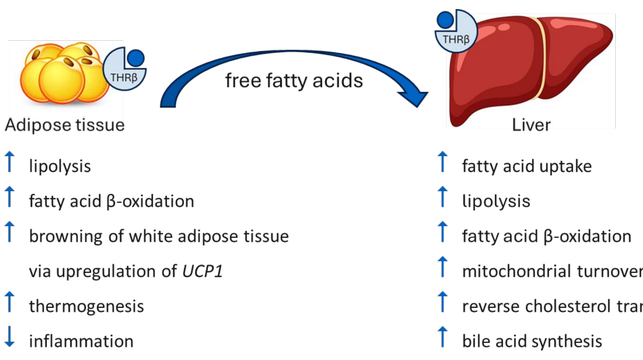
Jieun Song[1], Kusum Gupta[1], Peter J. Althoff[1], Lillian C. Adame[1], Dinah L. Misner[1], Tse-I Lin[2], Lawrence M. Blatt[1], Julian A. Symons[1], Sushmita Chanda[1], Xuan (Susan) G. Luong[1]

[1]Aligos Therapeutics, Inc., South San Francisco, CA, United States of America; [2]Aligos Belgium BV, Leuven, Belgium

INTRODUCTION

ALG-055009 is a potent and selective investigational thyroid hormone receptor-β (THR-β) agonist. In a Phase 2a clinical trial[1], ALG-055009 demonstrated significant reductions in liver fat (placebo-adjusted median relative reductions up to 46.2%) and atherogenic lipids in subjects with presumed metabolic dysfunction-associated steatohepatitis (MASH) and stage 1-3 liver fibrosis. Furthermore, THR-β plays 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 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[2] and adipose tissue[3]. 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 (HFD, D12492).

Fig. 2 Design of Study A

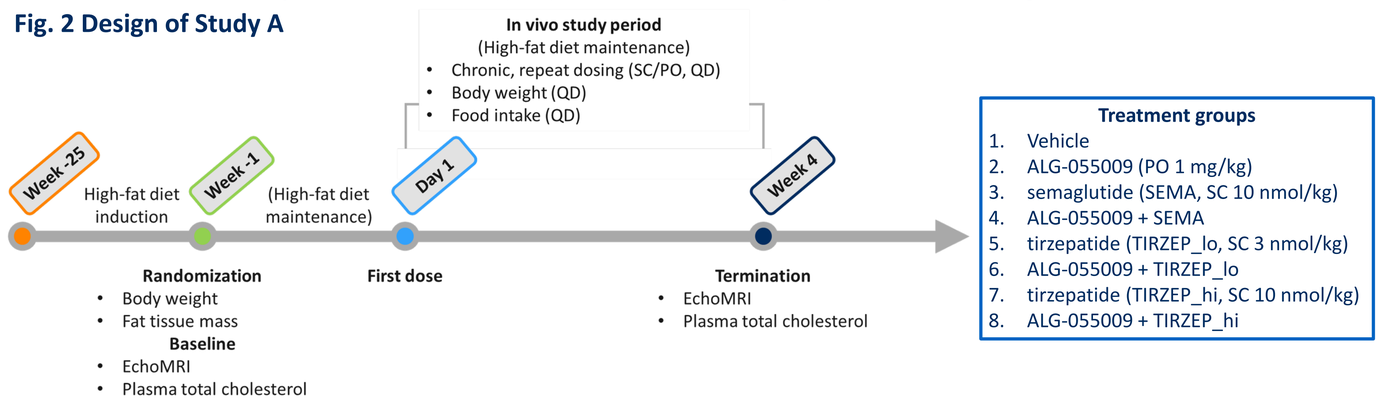
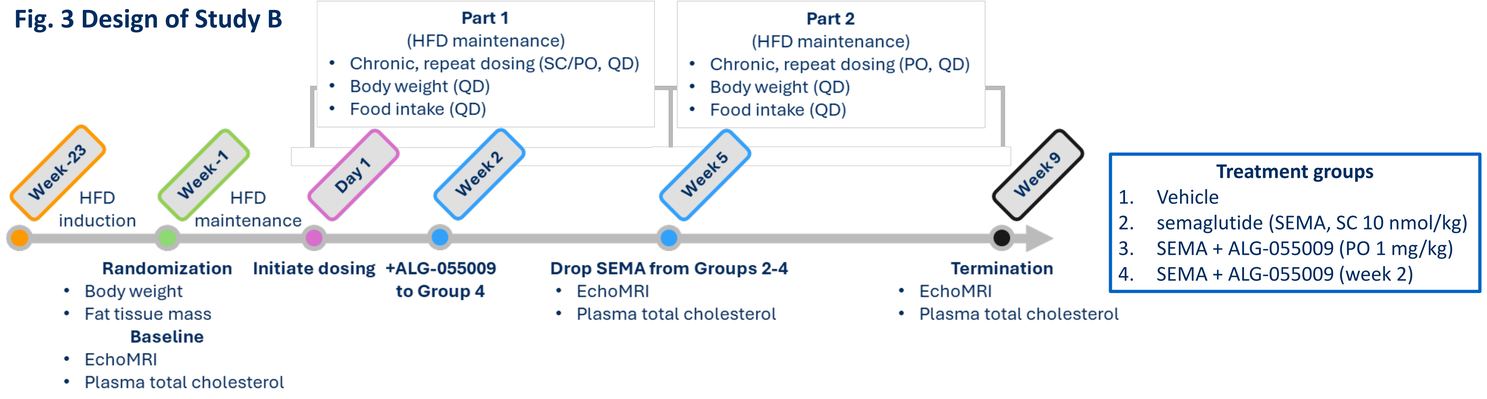


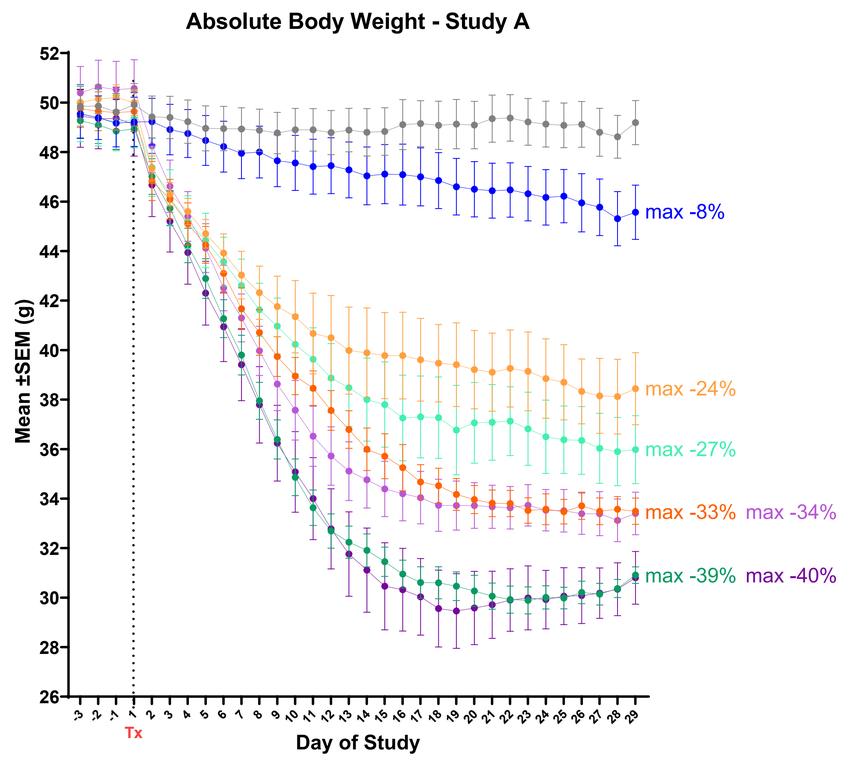
Fig. 3 Design of Study B



RESULTS

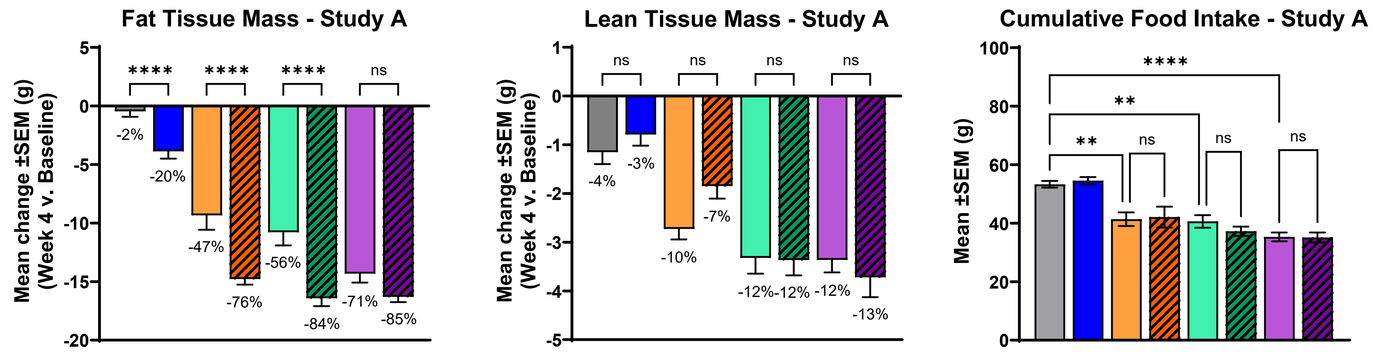
Veh 1 + Veh 2 | Veh 1 + ALG-055009 | SEMA + Veh 2 | SEMA + ALG-055009
TIRZEP_lo + Veh 2 | TIRZEP_lo + ALG-055009 | TIRZEP_hi + Veh 2 | TIRZEP_hi + ALG-055009

Fig. 4 Combination Therapy Enhances Body Weight Loss



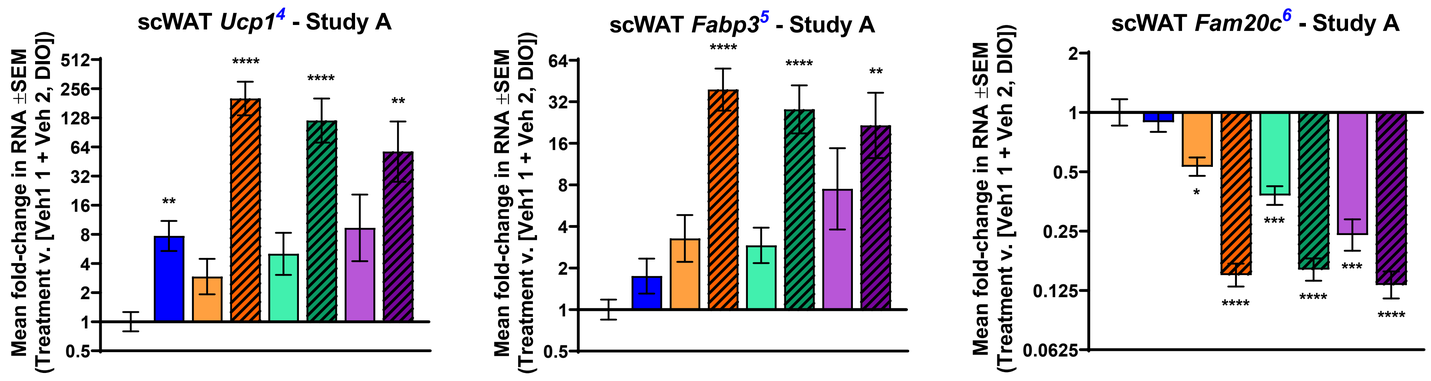
Tx =start of treatment; percentages displayed correspond to % changes compared to baseline (nadir).

Fig. 5 Additional Weight Loss by ALG-055009 is Due to Enhanced Fat Tissue Mass Loss and Not Changes in Lean Mass or Food Intake



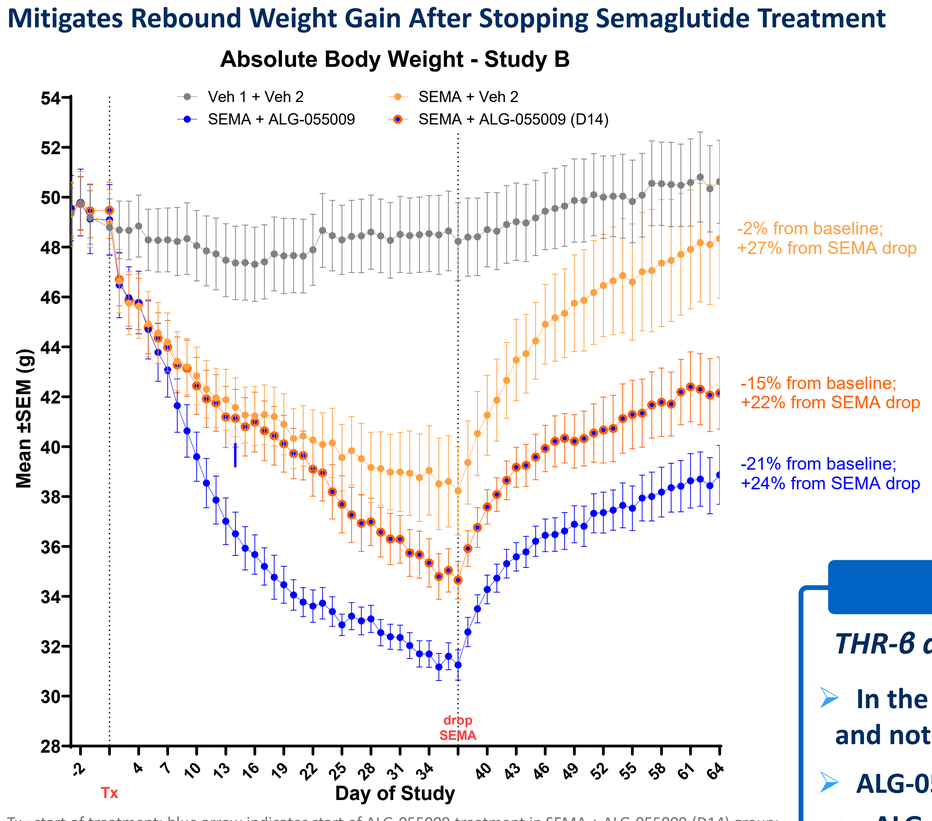
Percentages displayed correspond to % changes compared to baseline. Two-way ANOVA (left, middle) or one-way ANOVA (right) with Tukey's multiple comparisons test; **** =p-value <0.0001; ** =p-value <0.01; ns =not statistically significant.

Fig. 6 Combination Therapy Synergistically Modulates Molecular Pathways Underlying Adipose Metabolism and Health



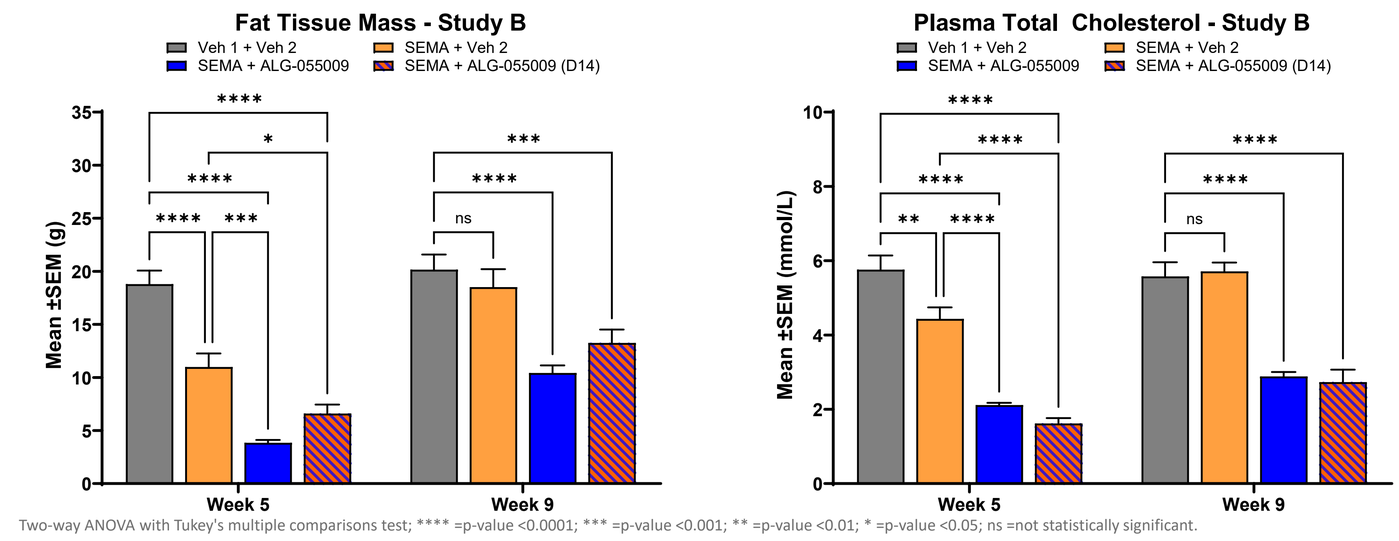
RT-qPCR results. scWAT =subcutaneous white adipose tissue; *Ucp1* (uncoupling protein 1) promotes browning of adipocytes and thermogenesis; *Fabp3* (fatty acid binding protein 3) is induced during adipocyte browning and regulates fatty acid oxidation; *Fam20c* (FAM20C golgi associated secretory pathway kinase) is a driver of adipose inflammation and insulin resistance. Brown-Forsythe and Welch ANOVA tests with Dunnett's T3 multiple comparisons test; **** =p-value <0.0001; *** =p-value <0.001; ** =p-value <0.01; * =p-value <0.05.

Fig. 7 ALG-055009 Enhances Body Weight Loss When Administered to an Existing Incretin RA Regimen and ALG-055009 Maintenance Dosing Mitigates Rebound Weight Gain After Stopping Semaglutide Treatment



Tx =start of treatment; blue arrow indicates start of ALG-055009 treatment in SEMA + ALG-055009 (D14) group; semaglutide dosing was suspended for all treatment groups on day 37.

Fig. 8 ALG-055009 Maintenance Dosing Preserves Fat Mass Reductions and Maintains Lowered Circulating Lipid Levels



Two-way ANOVA with Tukey's multiple comparisons test; **** =p-value <0.0001; *** =p-value <0.001; ** =p-value <0.01; * =p-value <0.05; ns =not statistically significant.

CONCLUSION

THR-β agonism is potentially a powerful mechanism complementary to incretin receptor agonists in combating obesity

- **In the DIO mouse model, the additional weight loss conferred by ALG-055009 was mainly due to decrease in fat tissue mass and not due to changes in lean tissue mass or food intake**
- **ALG-055009 + SEMA reached similar weight loss as TIRZEP_hi monotherapy**
  - **ALG-055009 boosted the efficacy of a mono incretin RA to match that of a highly-dosed dual incretin RA**
- **ALG-055009 + TIRZEP_lo had greater weight loss than TIRZEP_hi monotherapy, indicating a possible dose-sparing regimen**
- **ALG-055009 can enhance weight/fat tissue mass loss when added to an existing incretin RA regimen for weight loss**
- **ALG-055009 can mitigate rebound weight/fat tissue mass gain after withdrawal of incretin RA therapy**
- **We provide evidence that the synergism is a result of ALG-055009's ability to increase adipocyte metabolism, improve adipocyte insulin resistance and inflammation, and overcome the metabolic adaptation that emerges after a period of weight loss when combined with incretin receptor agonists**

Contact Xuan (Susan) Luong, PhD: xluong@aligos.com

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Conflict of Interest

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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