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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

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ALIGOS THERAPEUTICS

BACKGROUND AND AIMS

ALG-055009 is a potent and selective investigational thyroid hormone receptor-β (THR-β) agonist. In a Phase 2a clinical trial[1], ALG-055009 has 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.

METHOD

Animals: Male, C57BL/6JRj diet-induced obese (DIO) mice; n =10 animals/group
Diet: 60%-kcal high-fat diet (HFD, D12492)

Figure 2. Design of Study A

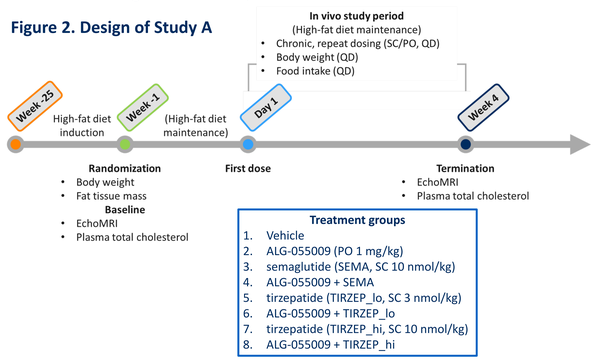
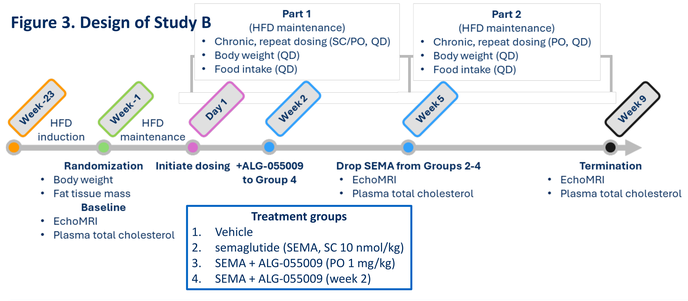


Figure 3. Design of Study B



RESULTS

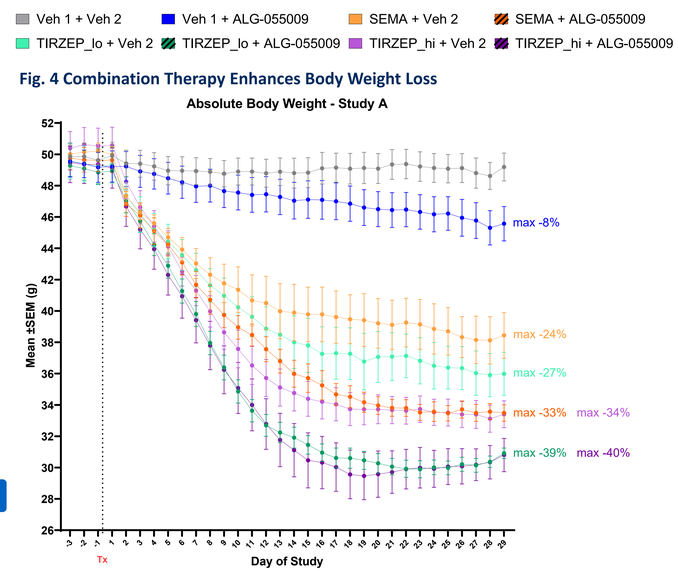


Fig. 4 Combination Therapy Enhances Body Weight Loss

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

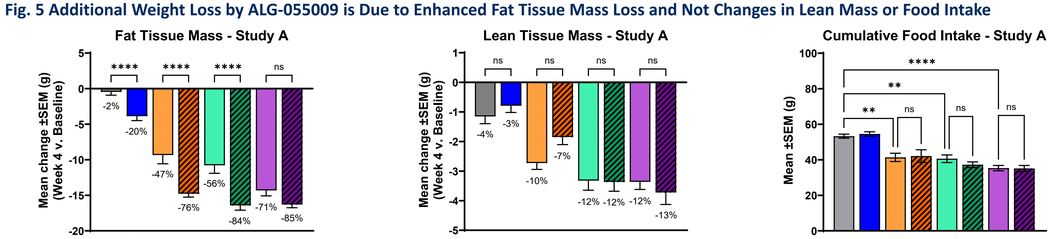


Fig. 5 Additional Weight Loss by ALG-055009 is Due to Enhanced Fat Tissue Mass Loss and Not Changes in Lean Mass or Food Intake

Percentages displayed below each bar correspond to % changes in tissue mass compared to baseline. One-way ANOVA with Tukey's multiple comparisons test; **** =p-value <0.0001; ** =p-value <0.01; ns =not statistically significant.

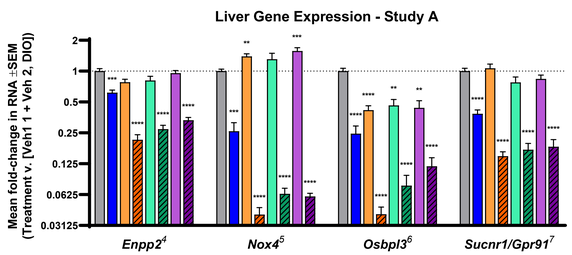


Fig. 6 Combination Therapy Synergistically Modulates Key Genes in the Liver to Restore Hepatic Heath and Function

Enpp2 (autotaxin) induces liver inflammation and fibrosis via LPA signaling; *Nox4* (NADPH oxidase 4) drives oxidative stress leading to cell damage; *Osbpl3* (oxysterol-binding protein-like 3) promotes lipid accumulation and inflammation; *Sucnr1* (succinate receptor 1) activates hepatic stellate cells. 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.

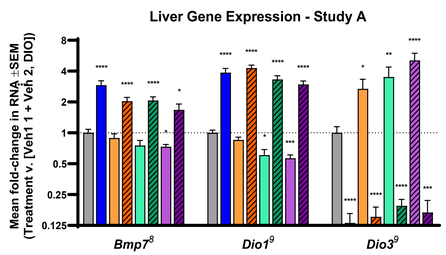


Fig. 7 ALG-055009 Can Uniquely Shift the Liver Towards a Less Fibrotic and More Metabolically Functional State

Bmp7 (bone morphogenic protein 7) inhibits hepatic stellate cell activation; *Dio1* (deiodinase, iodothyronine, type I) activates thyroid hormone & promotes lipid metabolism; *Dio3* (deiodinase, iodothyronine, type III) deactivates thyroid hormone & linked to liver injury. 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.

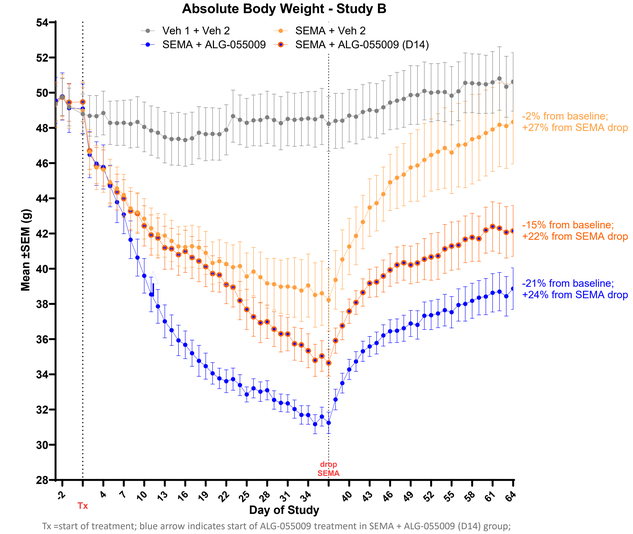


Fig. 8 ALG-055009 Enhances Body Weight Loss When Administered to an Existing Incretin RA Regimen and ALG-055009 Maintenance Dosing Mitigates Rebound Weight Gain After Stopping Semaglutide Treatment

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.

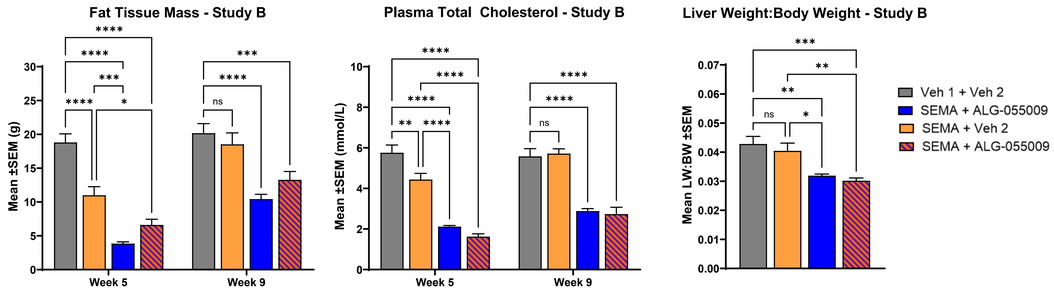


Fig. 9 ALG-055009 Maintenance Dosing Preserves Fat Mass Reductions and Maintains Lowered Circulating Lipid Levels

One-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.

Fig. 10 Combination Treatment and ALG-055009 Maintenance Leads to Reduced Liver Weights

One-way ANOVA with Tukey's multiple comparisons test; *** =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 MASH and 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 only, 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
- The benefits of ALG-055009 combination therapy & maintenance dosing on hepatic steatosis and inflammation/injury was confirmed by significantly decreased mouse liver weights
- In the mouse liver, the combination of ALG-055009 and incretin RA synergistically modulated select genes involved in hepatic metabolism, inflammation, and fibrosis, supporting the benefits of combination therapy for the treatment of metabolic diseases
- Furthermore, ALG-055009 also independently and uniquely regulated the expression of key genes associated with liver health, highlighting its distinct mechanism of action and contribution as a potential therapy for MASH

Acknowledgements

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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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