Combination of MS 001 with GLP-1R Agonist Semaglutide Induces Further Weight Loss While Supporting Muscle Health in Mice

Poster 3059-LB

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Introduction and Objectives

GLP-1R agonists have reshaped the obesity and diabetes care, with approximately 12.4% of Americans (43 million) currently using them.

Despite remarkable success, GLP-1R agonist do have certain limitations:

- Major limitation is loss of muscle health (25-45%)
- 65% of weight regained (mostly fat) within 1 year after stopping
- Weight loss plateaus around 15 – 20%

MS 001 (ulodesine hemiglutarate) is an orally bioavailable, highly potent, and selective inhibitor of purine nucleoside phosphorylase (PNP).

We hypothesized that Combination of MS 001 with GLP-1R agonist, semaglutide (sema) or tirzepatide (tirze), could potentially address these limitations based on the effects of MS 001 on inosine (1, 2) and NAD+ (3, 4) that can increase energy expenditure, enhance GLP-1 efficacy and improve overall metabolic health.

To confirm this hypothesis we evaluated MS 001, MS 001 with sema (combo) and MS 001 with tirze in the mouse model of diet induced obesity (DIO).

Methodology

DIO Model: C57BL/6J or C57BL/6N mice are fed an obesogenic diet from the age of 6 weeks. Approximately 18 or 30-week-old mice are either treated with vehicle, MS 001, sema, MS 001 with sema (combo), tirze or MS001 with tirze.

RNA-sequencing: RNA-sequencing (RNA-seq) was performed using NGS system following manufacturer provided protocols.

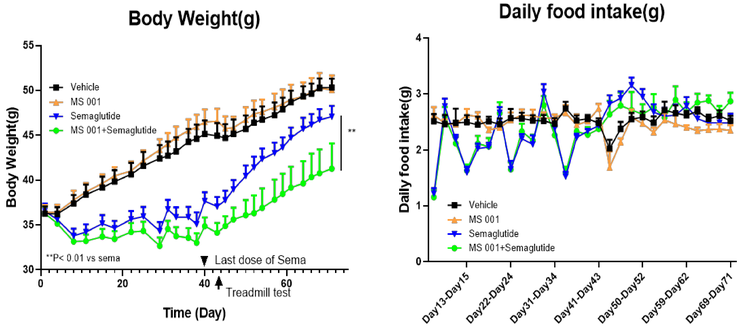
Energy Expenditure studies: Oxygen consumption was recorded for 24 hours using the Oxymax/CLAMS metabolic monitoring system.

Thermal Imaging: Thermal imaging was performed using FLUKE iSee Thermal Camera.

Statistical analysis: All results are provided as means ± standard errors of the mean (SEM). For comparison between two independent groups, a two-tailed Student's paired t-test was applied. Significance was accepted at a P value of <0.05.

Results

Figure 1. MS 001 enhances GLP-1 efficacy and control weight rebound after semaglutide discontinuation with no reduction in food intake



Study design - C57Bl/6J; 18-week-old mice; 7 mice/group; semaglutide – 10 nmole/kg Q3d; MS 001-1 mg/kg 3 days/week; last dose of sema-day 40 and treadmill test day 43. Day 71 (end of study) tissue weights, cholesterol and triglyceride levels were determined.

Results Cont'd

Figure 2. Combo treatment decreases fat tissue and preserves muscle mass and muscle health

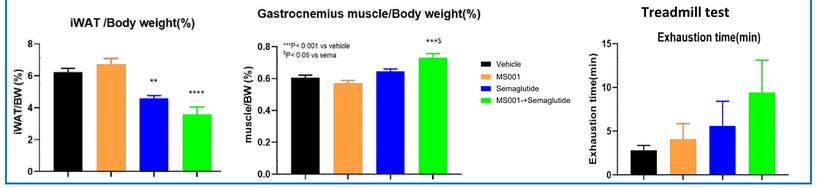


Figure 3. Combo treatment improves lipid and liver profile

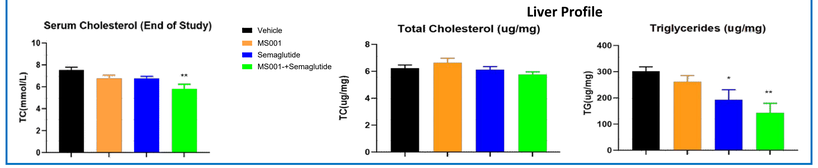


Figure 4. Comparison of RNA seq analysis of combo vs semaglutide.

Differentially expressed genes observed mainly in white adipose tissue (iWAT) and is related to increased thermogenesis through glucagon and futile calcium signaling. Improved mitochondrial function and fatty acid metabolism

Tissue	Upregulated	Downregulated
BAT	0	0
GM	2	23
iWAT	573	52

BAT -brown adipose tissue; GM – Gastrocnemius muscle

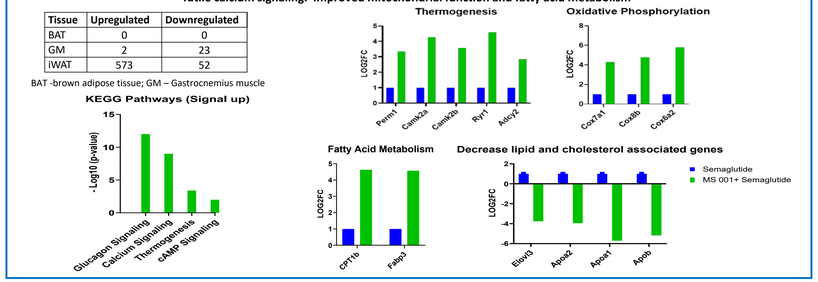
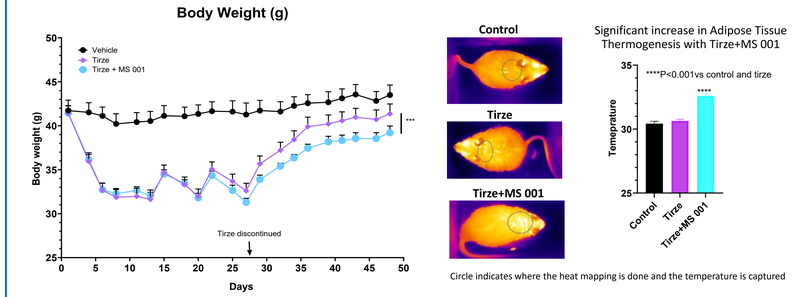


Figure 5. MS 001 Boosts Tirzepatide Efficacy via Enhanced Energy Expenditure

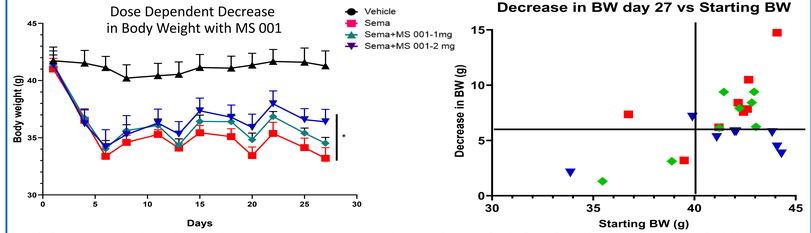


Circle indicates where the heat mapping is done and the temperature is captured

Study design: C57BL/6N; 30-week-old; 8 mice/gp. Tirze was given twice a week 0.05 mg/kg except for the first 2 doses (0.3 mg/kg; first week) and MS 001 was given orally 3 days/week at 1mg/kg dose. Thermal imaging performed day 45

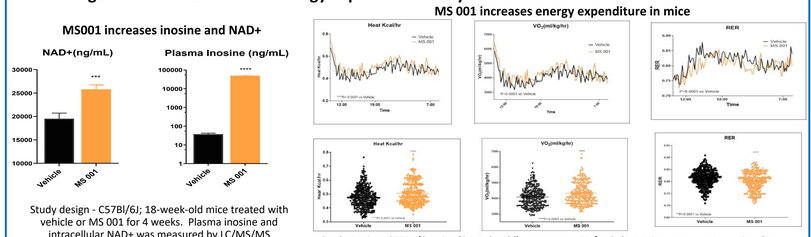
Results Cont'd

Figure 6. Heavier mice experienced greater weight loss with combo treatment.



Study design: C57BL/6N; 30-week-old; 8 mice/gp. Sema was given twice a week 0.05 mg/kg except for the first 2 doses (0.3 mg/kg; first week) and MS 001 was given orally 3 days/wk at 1mg/kg or 2mg/kg dose.

Figure 7. MS 001 increases energy expenditure likely due to increase in inosine and NAD+



Study design - C57Bl/6J; 18-week-old mice treated with vehicle or MS 001 for 4 weeks. Plasma inosine and intracellular NAD+ was measured by LC/MS/MS

Study Design: C57BL/6J mice (8 weeks old) were on a HFD for 3 days prior to treatment. Mice then received MS001 (2 mg/kg) or vehicle once daily for 3 days and O2 consumption measured.

Results Summary

MS 001 significantly enhances the metabolic effects of GLP-1R agonist

- Driving deeper fat loss, more so, in mice with higher baseline body mass, suggesting the combination may be particularly effective in subjects with greater adiposity.
- Reducing weight rebound after GLP-1R agonist discontinuation
- Preserving muscle mass and muscle health
- Improving lipid and liver profiles
- Activating thermogenesis primarily in adipose tissue
- Known Human Safety: Ulodesine has been administered to > 500 subjects with doses ranging from 240 mg daily for 3 weeks to 40 mg daily for 6 months with favorable safety profile and well tolerated (5). In the DIO mouse study, MS-001 was administered at 1-2 mg/kg, corresponding to a human-equivalent dose of about 5mg to 10 mg.

Conclusion

MS 001 enhances GLP-1R agonist efficacy primarily through increased adipose tissue breakdown while preserving muscle health, representing a promising novel combination strategy for treatment of obesity and overall metabolic health.

References

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