Comparative Efficacy of DA-1726, a Novel Oxyntomodulin Analogue, with Semaglutide in a Diet-Induced NASH Mouse Model

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BACKGROUND

- DA-1726 is a novel, balanced, long-acting oxyntomodulin (OXM) analogue acting as a dual agonist of the GLP-1 and glucagon receptors.
- Unlike select GLP-1 receptor agonists which primarily affect food intake, dual GLP-1/glucagon receptor agonists provide the added benefit of glucagon receptor agonism which includes an increase in core energy expenditure and hepatic lipid oxidation.[1]
- Previous animal studies in obesity indicated DA-1726 was superior to semaglutide (SEMA) in terms of weight loss.[2]
- The purpose of this study was to evaluate the therapeutic potential of DA-1726 compared to SEMA for the treatment of nonalcoholic steatohepatitis (NASH).

METHODS

- To induce NASH, male mice were given a diet containing 40% kcal% fat, 20% fructose, and 2% cholesterol for 30-weeks.
- Afterwards the mice were randomly allocated to one of 4 treatment groups (n=8 per group): 1) Control (placebo injection), 2) SEMA 250 nmol/kg, 3) DA-1726 100 nmol/kg, and 4) DA-1726 200 nmol/kg.
- All animals received their assigned treatment as a subcutaneous injection every 3 days for 8 weeks.
- Food consumption and body weight were recorded every 3 days.
- At the end of treatment, plasma liver function tests (LFTs) and liver histology were analyzed.
- Gene expression of inflammation and fibrosis biomarkers were analyzed using quantitative RT-PCR in liver tissue.

RESULTS

- Compared to vehicle control, DA-1726 (100 or 200 nmol/kg) and SEMA (250 nmol/kg) significantly reduced body weight (BW) compared to baseline (Figure 1).
- Furthermore, DA-1726 significantly decreased plasma LFTs, glucose, cholesterol, and the expression of inflammatory and fibrotic genes (Figures 2 and 3).
- In a histopathological analysis of steatosis, lobular inflammation, and ballooning in the liver, DA-1726 showed an excellent improvement in NAFLD Activity Score and overall fibrosis compared to SEMA (Figures 4, 5 and 6).

Figure 1. BWL in DIO-NASH Mouse

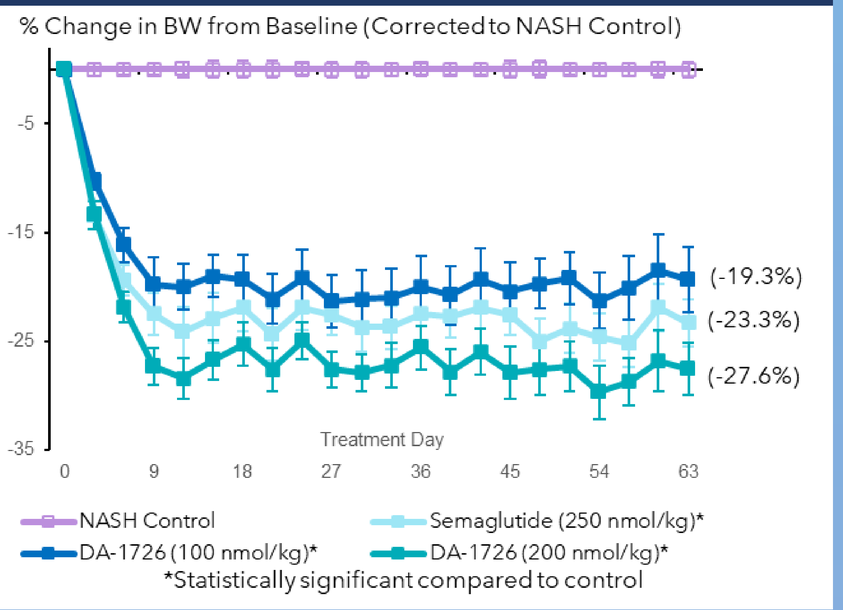


Figure 2. Plasma Biochemistry Analysis

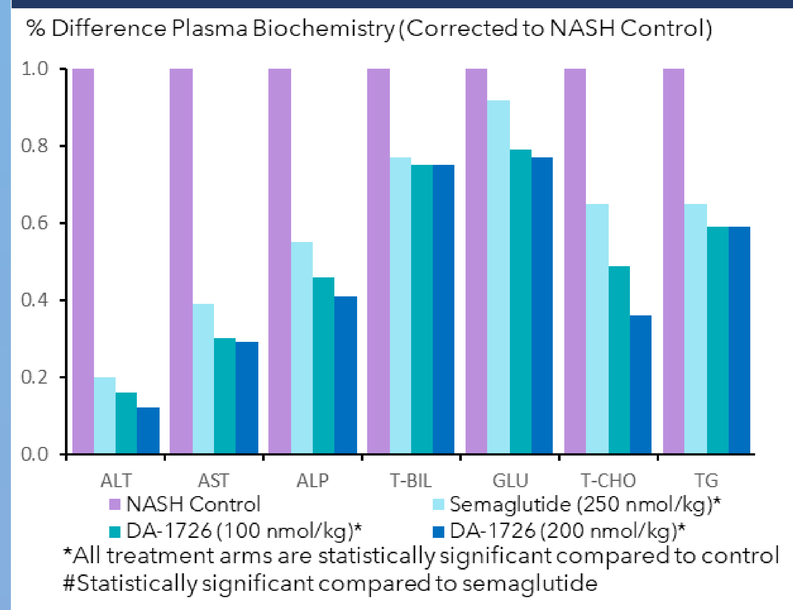


Figure 3. Hepatic Gene Expression

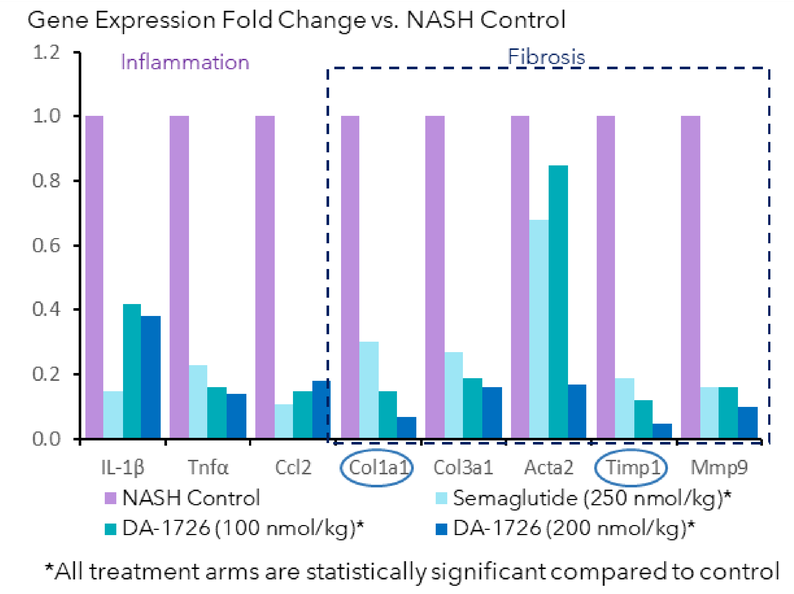


Figure 4. Steatosis & Inflammation (HE Stain)

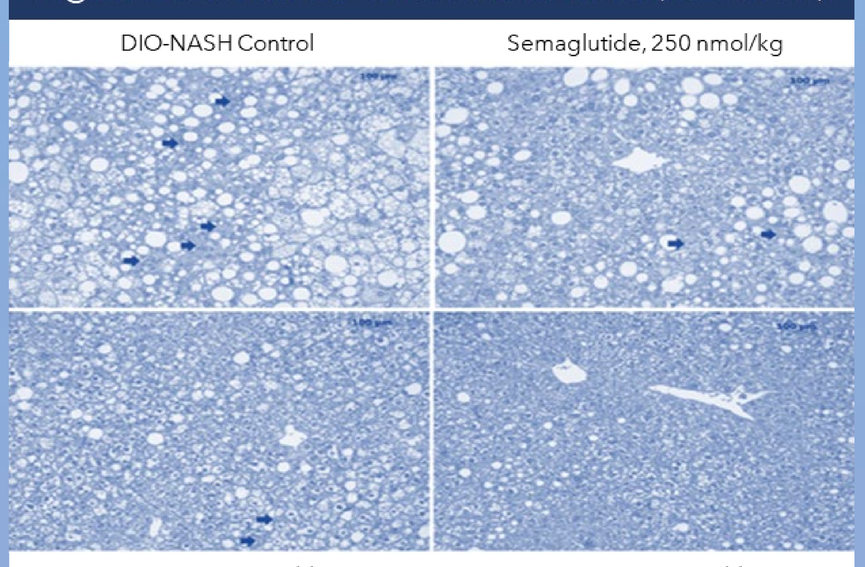
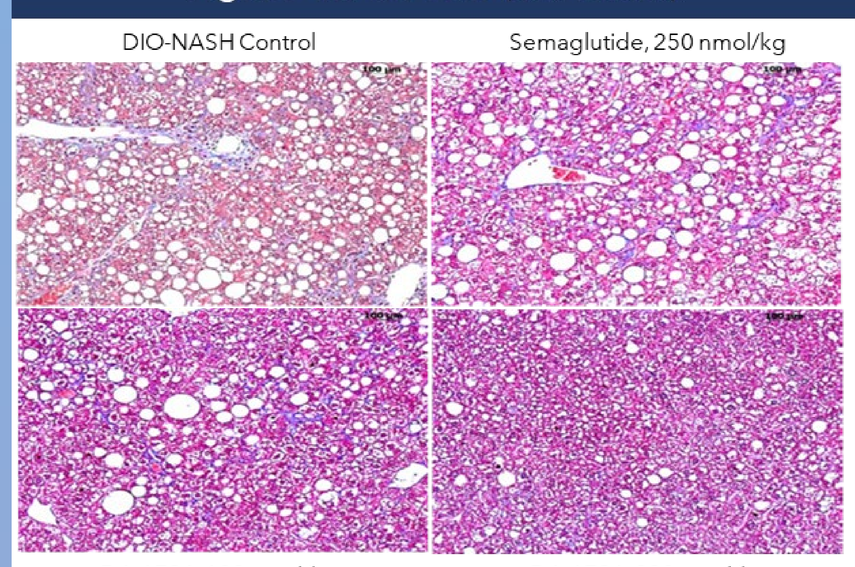
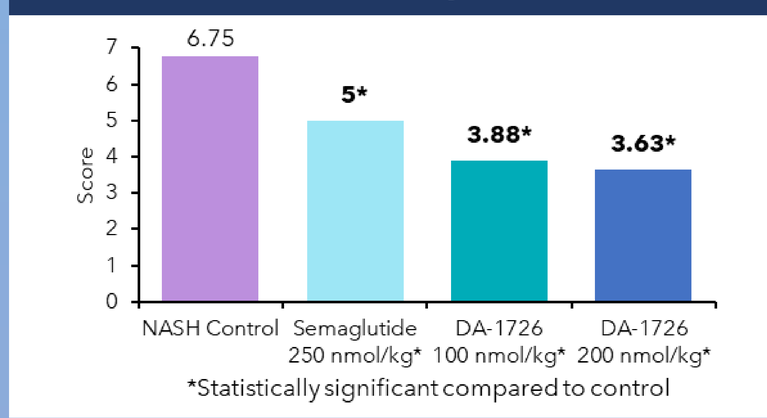


Figure 5. Fibrosis (MT Stain)



NAFLD Activity Score



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1. Pocai A. *Mol Metab* 2014;3:241-51.
2. Kim TH, et al. *American Diabetes Association 82nd Scientific Sessions* 2022. [abstract].

CONCLUSION

- In this study, DA-1726 treatment was associated with significant changes in weight loss, plasma LFTs, and genetic biomarkers of disease as well as significant improvements in hepatic steatosis, inflammation, and fibrosis.
- These effects were often superior to the comparator agent SEMA, a GLP-1 receptor agonist.
- The added therapeutic benefit of DA-1726 is secondary to the dual actions of DA-1726 on GLP-1 and glucagon receptors.
- Taken together, our findings suggest DA-1726 has a therapeutic potential for NASH in addition to obesity and type 2 diabetes.

Data previously presented at the 82nd Meeting of the American Diabetes Association, 2022 [abstract].