GLP-1/Glucagon Dual Receptor Agonist ALT-801 is Superior to Semaglutide in Improving NASH Endpoints in a Biopsy-Confirmed DIO Mouse Model

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Background

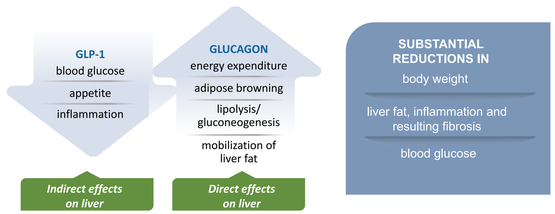
NASH and NAFLD

HEPATIC MANIFESTATIONS OF OBESITY AND METABOLIC SYNDROME

- Body weight loss of 10% or greater improves the metabolic derangements and liver disease in most NASH patients, suggesting metabolic modulators may be effective in the control of the disease (Vilar-Gomez 2015).
- GLP-1 agonists show promise for NASH, but weight loss associated with these agents at approved doses is modest and associated with side effects (Armstrong 2016, Gomez-Peralta 2019, Nauck 2019).
- Glucagon receptor activation has direct effects on lipolysis, basal energy expenditure and liver lipid metabolism and may act synergistically with GLP-1 in the treatment of obesity and NASH (Day 2012).

GLP-1/Glucagon Receptor Dual Agonists

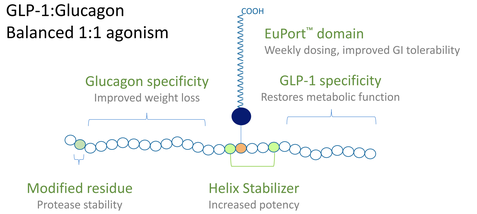
OPTIMIZED FOR NASH AND WEIGHT LOSS



ALT-801

STRUCTURE IS KEY TO DIFFERENTIATION

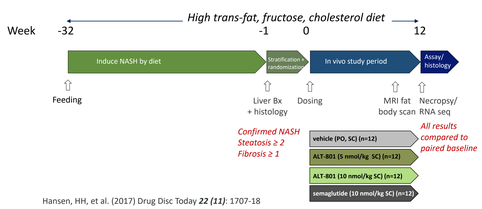
Proprietary EuPort™ domain provides prolonged $t_{1/2}$ and reduced C_{max}



Aim and Methods

- We compared ALT-801, a balanced and long-acting GLP-1/glucagon receptor dual agonist, and semaglutide, a GLP-1 agonist, in a biopsy-confirmed DIO mouse NASH model.

GUBRA AMYLIN NASH MODEL IN MALE C57BL/6JRj MICE

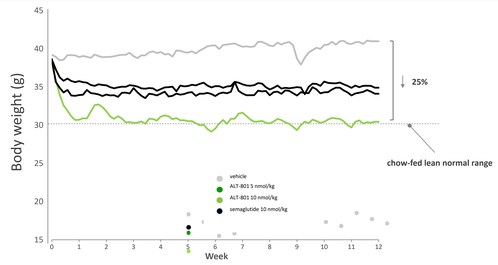


Hansen, HH, et al. (2017) Drug Disc Today ***22 (11)***: 1707-18

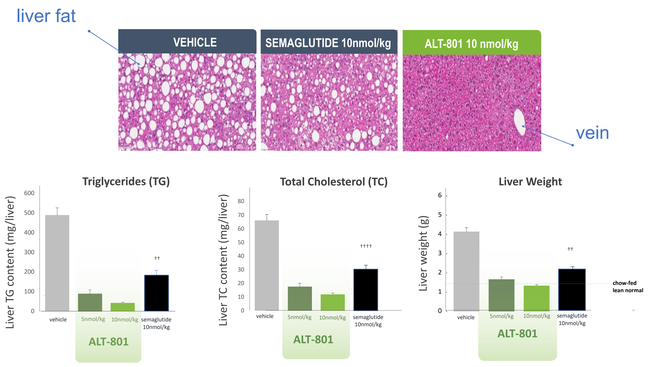
Method: Male C57BL/6J mice were fed an AMLN diet high in trans-fat, fructose and cholesterol for 32 weeks. Animals with biopsy-confirmed steatosis (score ≥2) and fibrosis (stage ≥1) received ALT-801 (10 nmol/kg; SC), semaglutide (10 nmol/kg; SC) or vehicle (SC) for 12 weeks while maintained on the diet. Liver RNA sequencing analysis was performed to evaluate the regulation of genes involved in NASH pathways.

Results

BODY WEIGHT RETURNS TO CHOW-FED LEAN NORMAL RANGE

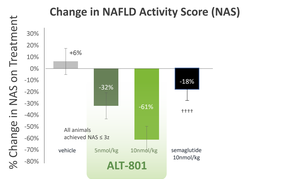


REDUCTION IN LIVER FAT AND LIVER WEIGHT TO LEAN NORMAL RANGE

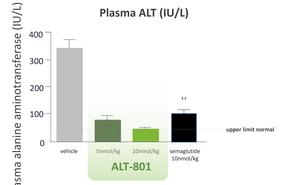


Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity†† p < .01, †††† p < .0001 vs. ALT-801 10 nmol/kg (n=11-12)

IMPROVEMENT IN NAFLD ACTIVITY SCORE (NAS)

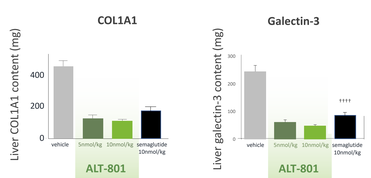


NORMALIZATION OF PLASMA ALT



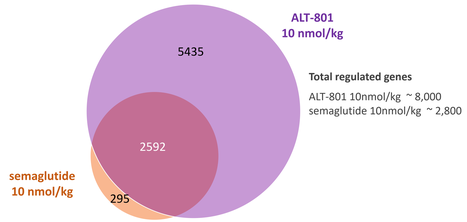
Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity†† p < .01, ††† p < .001, †††† p < .0001 vs. ALT-801 10 nmol/kg (n=11-12)

GREATER EFFECTS ON FIBROSIS

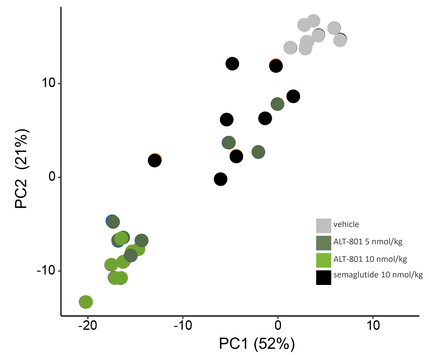


Mean (SE), 1-way ANOVA with Dunnett's adjustment for multiplicity†† p < .01, ††† p < .001, †††† p < .0001 vs. ALT-801 10 nmol/kg (n=11-12)

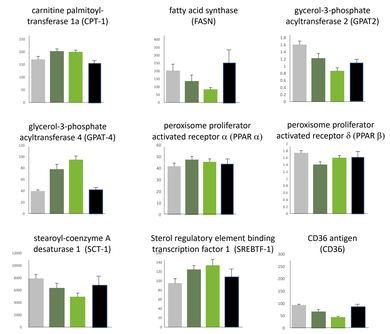
MORE NASH PATHWAYS DIFFERENTIALLY REGULATED



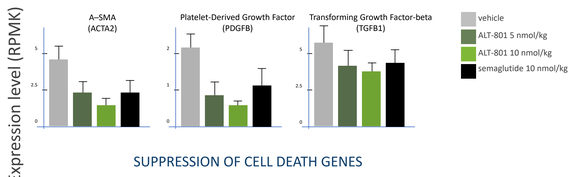
PRINCIPLE COMPONENT ANALYSIS



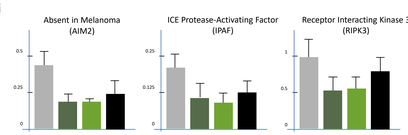
MODULATION OF GENES AFFECTING FAT USAGE AND TRANSPORT



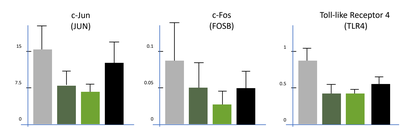
SUPPRESSION OF STELLATE CELL PATHWAY PRO-FIBROSIS GENES



SUPPRESSION OF CELL DEATH GENES



SUPPRESSION OF INFLAMMATION GENES



Summary

- ALT-801 demonstrated superior reductions in body weight, liver weight, plasma ALT, liver TG and TC, and plasma TC compared to semaglutide, with only the ALT-801 group returning to normal lean mouse body weight, liver weight and ALT levels.
- Reduction in the inflammation marker galectin-3 was also superior to semaglutide, with a numerically greater reduction in the fibrosis marker COL1a1.
- All animals treated with ALT-801 improved composite NAS driven by reduction in steatosis, lobular inflammation and hepatocellular ballooning scores.
- Principal component analysis of the 500 most variable genes differentially clustered genes regulated by ALT-801 from those regulated by semaglutide, consistent with a unique gene regulatory signature associated with glucagon receptor activation.
- ALT-801 suppressed archetypal genes involved in de novo lipogenesis and fatty acid uptake (FASN, GPAT2, CD36), stellate cell activation (ACTA2, PDGFB, TGFB1) and fibrosis (Col1A1, Galectin-3).
- ALT-801 also suppressed genes associated with hepatocellular death (AIM2, CASP1, IPAF, RIPK3), and inflammation (JUN, FOSB, TLR4).

Conclusions

- This study provides evidence for the beneficial effects of an optimized GLP-1/Glucagon dual receptor agonist in the therapeutic treatment of NASH. The return of body weight to lean normal and metabolic improvement with improvement of liver pathology highlights ALT-801 as a new candidate for the treatment of NASH.

REFERENCES: Day JW, Peptide Science 2012; 98:443-50; Armstrong MJ, Lancet 2016; 387:679–90; Vilar-Gomez, Gastroenterology 2015;149:367–378; Gomez-Peralta F, Drug Des Dev Ther 2019;13:731–738; Nauck MA, Eur J Endocrinol 2019; 181: R211–R234

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