Combinatory treatment with miR-22 ASO and GLP-1 RA increases positive outcomes on body weight and liver parameters in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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1 INTRODUCTION

miR-22 was identified as a crucial controller of lipid homeostasis, hepatic steatosis and inflammation. Both genetic and pharmacological inhibition are very effective in reducing body weight and increasing liver health in mouse and non-human primate models.

Interestingly, unlike GLP-1 RA, the therapeutic effect of miR-22 inhibition is completely independent from food intake.

We hypothesize that GLP-1 RA and miR-22 inhibition operate through two distinct orthogonal mechanisms of action and that a combination could potentially enhance the positive effects observed with GLP-1 RA monotherapy.

2 MATERIALS & METHODS

Male C57BL/6 mice were fed the GAN diet high in fat, fructose and cholesterol for 38 weeks prior to study start. A liver biopsy was sampled 4 weeks prior to study start. Only animals with biopsy-confirmed NAFLD Activity Score (NAS≥5) and fibrosis stage ≥F1 were included and stratified into treatment groups. Mice were administered vehicle (n=18) or Semaglutide (30 nM/kg, n=18) or Semaglutide and anti-sense oligonucleotide targeting miR-22 (30nM/kg daily; 10mg/kg weekly n=18) for 24 weeks.

Mouse body weight was measured daily and histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed to evaluate the effect of combinatory treatment. Other terminal endpoints in GAN DIO-MASH mice included quantitative liver histology, blood and liver biochemistry.

5 ACKNOWLEDGEMENTS & DISCLOSURES

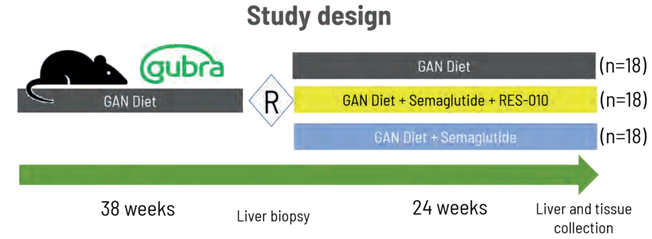
This project is part of an international teamwork supported by Novo Nordisk Foundation, thought the "Challenge Program" NNF18OC0033438; PR, NAM, KS are beneficiaries of this Grant.

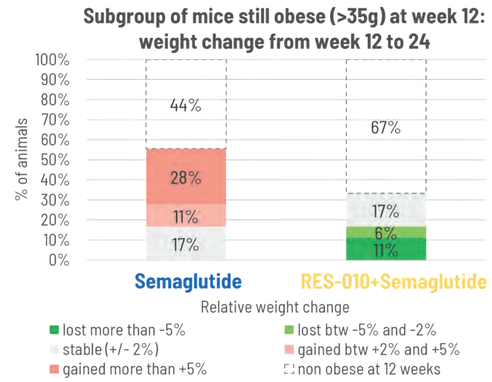
PR and KS are founders and shareholders of "Resalis Therapeutics"; PR is also a Board Member at "Resalis Therapeutics"

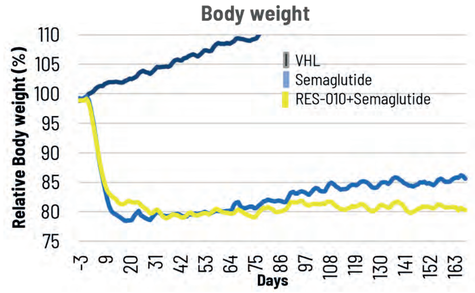
3 RESULTS

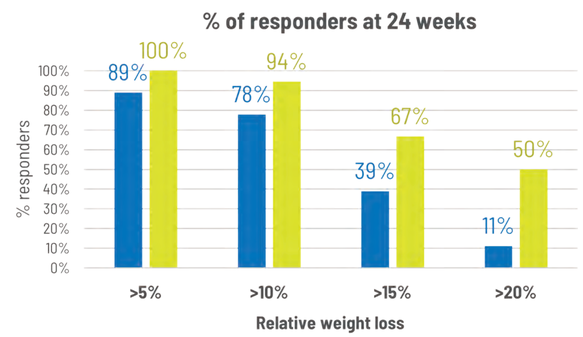
Our combinatory therapeutic approach was able to further improve the positive effect of GLP-1 RA on body weight and liver parameters.

Combination of GLP-1 RA and miR-22 inhibition was able to prevent the rebound in body weight observed in GLP-1 RA monotherapy, improving the overall effect of GLP-1 RA monotherapy on metabolism while being very well tolerated.





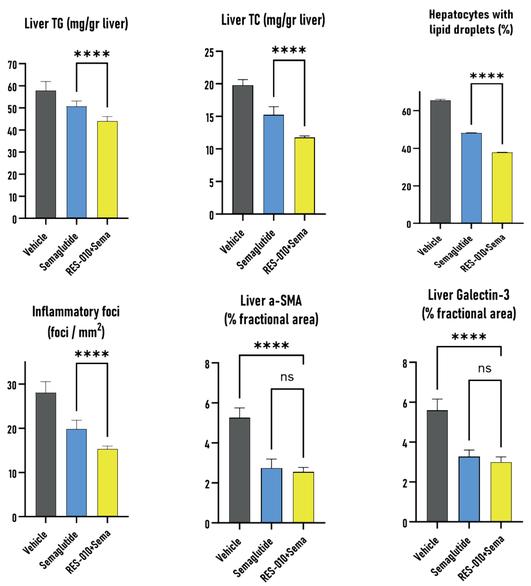




By combining GLP-1 RA and miR-22 pharmacological inhibition, we gathered compelling evidence of a strong synergistic effect, resulting in a 5-fold increase in the number of mice achieving at least a 20% initial body weight reduction.

Moreover, our combinatory treatment prevented the rebound in body weight observed in GLP-1 RA monotherapy.

Importantly, the combinatory group exhibits more significant improvements in certain liver parameters associated with hepatic lipid content when compared to monotherapy. However, the findings pertaining to markers related to inflammation and liver injury are less conclusive.



4 CONCLUSION

This data is paving the way to the first combinatory treatment for obesity and NAFLD based on targeting a non-coding RNA.