PXL770, a Novel Direct AMP-activated Protein Kinase Activator Produces Greater Efficacy when Combined with Other Key Therapeutic Mechanisms Targeting NASH

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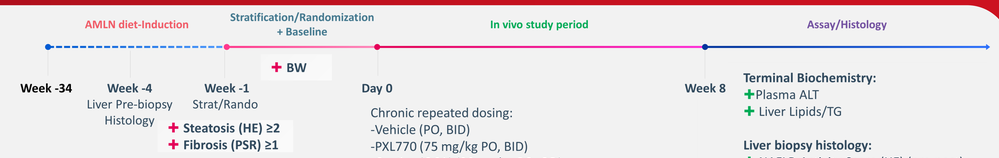
BACKGROUND and OBJECTIVES

Non-Alcoholic SteatoHepatitis (NASH) is a metabolic disease characterized by liver steatosis, inflammation and fibrosis. The complexity of the phenotype supports the need for a combination therapy strategy. Here, we assessed the potential to combine PXL770, a direct AMPK-activator that successfully completed a phase 2a clinical trial in NASH, with other agents in development: a glucagon-like peptide receptor (GLP-1R) agonist (Semaglutide/ SMG), a farsenoid x receptor (FXR) agonist (Obeticholic acid/ OCA) and a thyroid hormone receptor (THR-β agonist (Resmetirom/MGL) in a diet-induced obese and biopsy-confirmed mouse model of NASH.

OBJECTIVES : evaluate PXL770 in NASH *via* combo-therapy strategy in a diet induced obesity biopsy proven-NASH mouse model

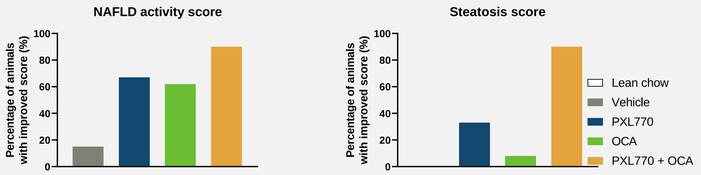
METHODS

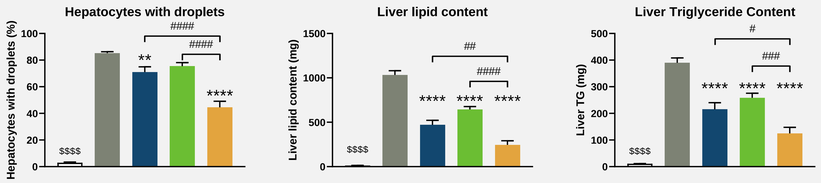


Male C57BL/6J mice were fed Gubra Amylin NAS diet for 34 weeks. NASH biopsy-proven mice were treated for 8 weeks according to the study plan above.

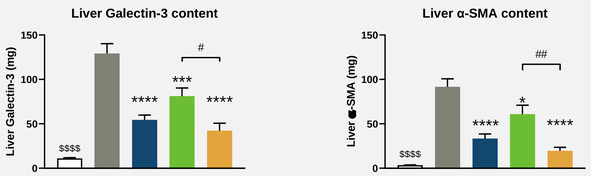
PXL770 + OCA

The combination PXL770 + OCA improved steatosis to a greater extent than monotherapies



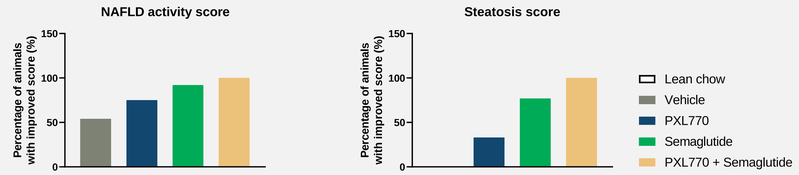


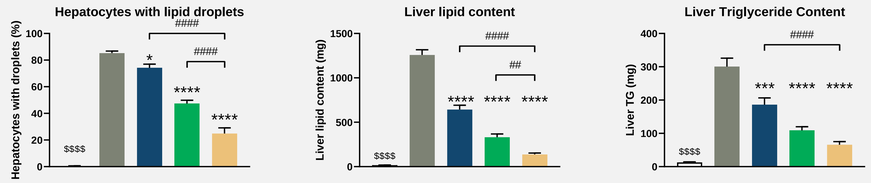
PXL770 + OCA tends to have better efficacy on inflammation (Galectin-3) and fibrogenesis (α-SMA) than monotherapies



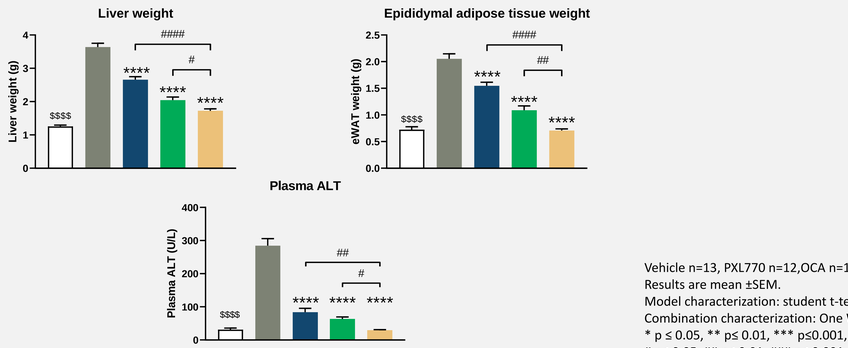
PXL770 + Semaglutide

The combination PXL770 + SMG improved steatosis to a greater extent than monotherapies



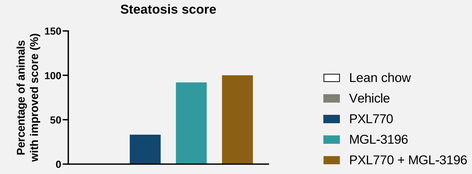


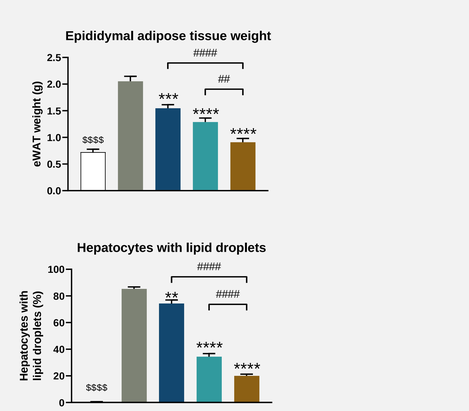
PXL770 + SMG decreased liver and white adipose tissue weight and decreased liver injury



PXL770 + MGL3196

PXL770 + MGL3196 improved liver steatosis, decreased the number of hepatocytes with lipid droplets and epididymal adipose tissue weight





Vehicle n=13, PXL770 n=12,OCA n=13, PXL770 + OCA n=10, Semaglutide n=13, PXL770 + Semaglutide n=12, MGL3196 n=13, PXL770 + MGL3196 n=12
Results are mean ±SEM.
Model characterization: student t-test lean chow *vs* Vehicle with $ p ≤ 0.05, $$ p≤ 0.01, $$$ p≤0.001, $$$$ p≤ 0.0001
Combination characterization: One Way ANOVA – Dunnett's multiple comparison test
* p ≤ 0.05, ** p≤ 0.01, *** p≤0.001, **** p≤ 0.0001 *vs* DIO
# p≤ 0.05, ## p≤ 0.01, ### p≤ 0.001, #### p ≤ 0.0001 *vs* combination

CONCLUSION

- Monotherapies improved NASH hallmarks
- Combinations of PXL770 with OCA, SMG and MGL improved selected NASH hallmarks to a greater extent than monotherapies
- These results highlight the potential benefit of combining PXL770 with FXR, GLP1-R and THRβ agonists