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Additive hepatoprotective effects of DA-1241, a novel GPR119 agonist, in combination with semaglutide in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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Background & Aim

The G protein-coupled receptor 119 (GPR119) and glucagon-like peptide-1 receptor (GLP1R) are promising therapeutic targets for metabolic dysfunction-associated steatohepatitis (MASH).

The aim of this study was to evaluate the metabolic, biochemical, histological and transcriptomic effects of DA-1241 (GPR119 agonist, Phase 2a) and semaglutide (GLP-1R agonist) combination therapy in the GAN diet-induced obese (DIO) and biopsy-confirmed mouse model of MASH with moderate-severe liver fibrosis.

1 Study outline

Group	Animal	Gender	Number of animals	Treatment		Administration route	Dosing Frequency	Dosing concentration
1	DIO-MASH	Male	15	**Vehicle**	**Vehicle**	PO + SC	QD	NA + NA
2	DIO-MASH	Male	15	**DA-1241**	**Vehicle**	PO + SC	QD	100 mg/kg + NA
3	DIO-MASH	Male	15	**Vehicle**	**Semaglutide**	PO + SC	QD	NA + 30 nmol/kg
4	DIO-MASH	Male	15	**DA-1241**	**Semaglutide**	PO + SC	QD	100 mg/kg + 30 nmol/kg

Figure 1. Study outline. PO; per oral, SC; subcutaneous, QD; Once daily, NA; Not applicable, GAN; Gubra Amylin NASH.

2 Metabolic and biochemical parameters

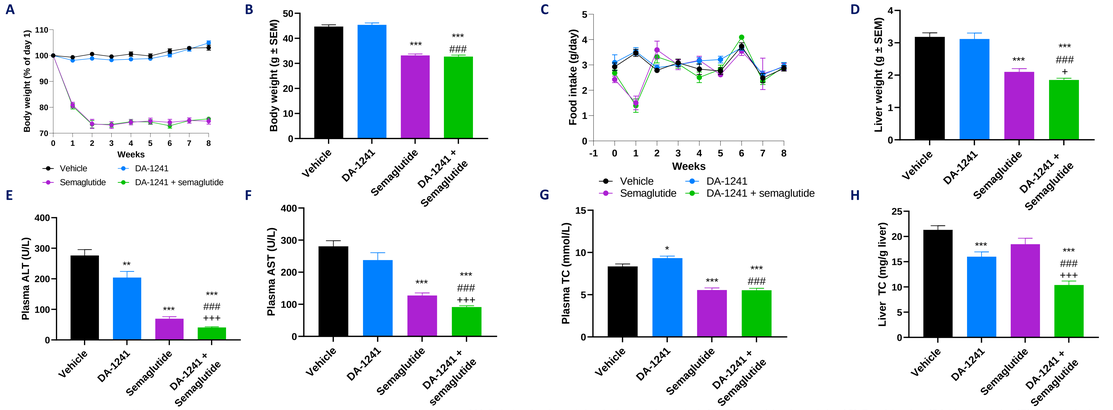

Figure 2. Metabolic and biochemical effects of DA-1241 and semaglutide as mono- and combination therapy. (A) Relative body weight during study period. **(B)** Terminal body weight. **(C)** Food intake. **(D)** Liver weight. **(E)** Terminal plasma alanine aminotransferase (ALT). **(F)** Terminal plasma aspartate aminotransferase (AST). **(G)** Plasma total cholesterol (TC) **(H)** Terminal liver total cholesterol. *p<0.05, ***p<0.001 compared to vehicle control, ###p<0.001 compared to DA-1241, and +p<0.05, +++p<0.001 compared to Semaglutide (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis Stage

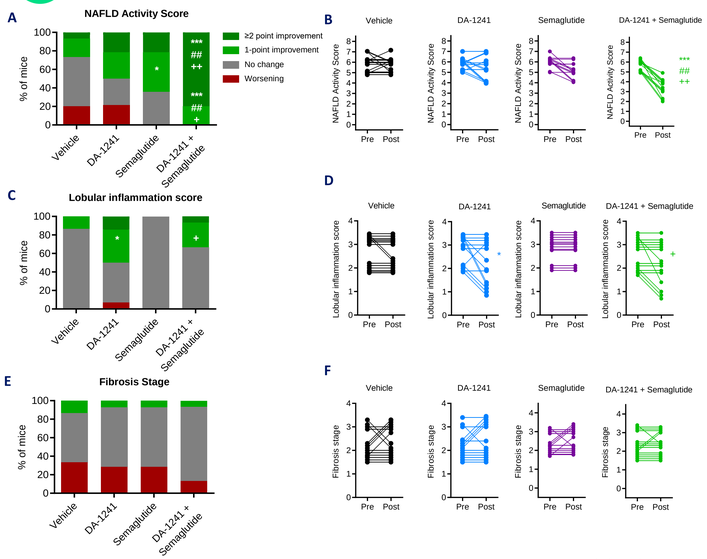

Figure 3. Synergistic therapeutic effects of DA-1241 and semaglutide on NAFLD Activity Score in GAN DIO-MASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Individual pre-post NAS. **(C)** Lobular inflammation score**. (D)** Individual pre-post lobular inflammation score. **(E)** Fibrosis stage. **(F)** Individual pre-post fibrosis stage. *p<0.05, ***p<0.001, ##p<0.01 compared to DA-1241, and +p<0.05, ++p<0.01 compared to Semaglutide (Dunnett's test one-factor linear model). compared to corresponding vehicle control (One-sided Fisher's exact test).

4 Histological markers of steatosis, inflammation and fibrosis

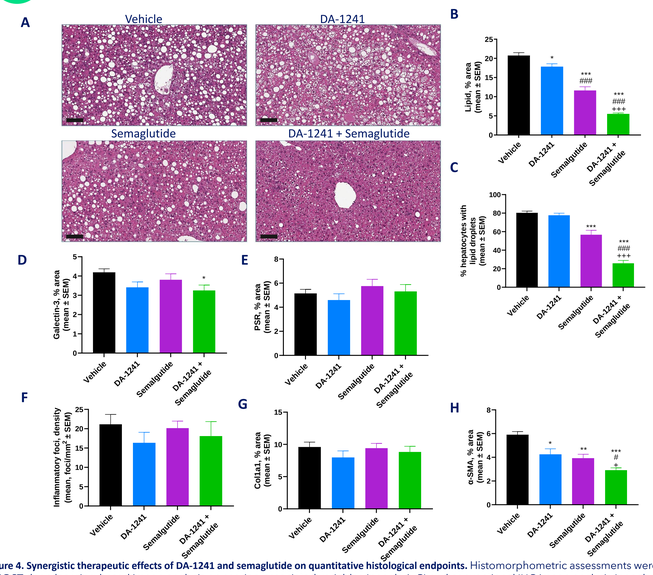

Figure 4. Synergistic therapeutic effects of DA-1241 and semaglutide on quantitative histological endpoints. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-C) and conventional IHC image analysis (panels D-H). **(A)** Representative photomicrographs of H&E staining (scale bar, 100 µm). **(B)** % area of liver lipids. **(C)** % hepatocytes with lipid droplets. **(D)** % area of galectin-3. **(E)** % area of PSR. **(F)** Number of inflammatory foci. **(G)** % area of collagen-1a1 **(H)** % area of alpha-smooth muscle actin (α-SMA, marker of stellate cell activation). Mean ± SEM. *p<0.05, ***p<0.001 to corresponding vehicle group, #p<0.05, ###p<0.001 compared to DA-1241, and +p<0.05, +++p<0.001 compared to Semaglutide (Dunnett's test one-factor linear model). Bottom panels:

5 Liver transcriptome analysis

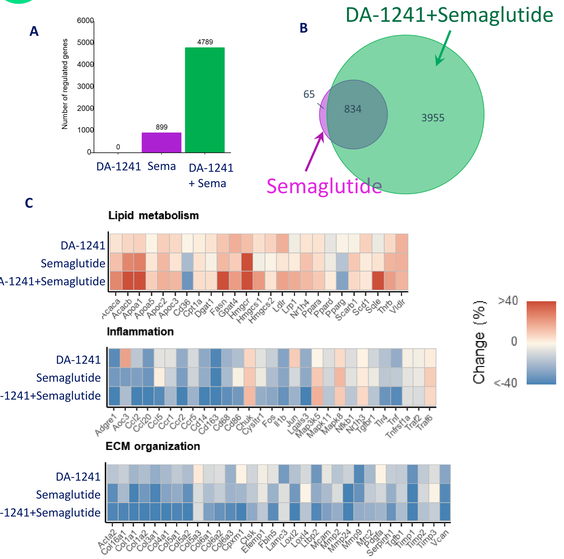

Figure 5. Combination therapy with DA-1241 and semaglutide improves hepatic transcriptome profile. (A) Total number of differentially expressed genes. **(B)** Venn diagram on overlapping gene expression signatures. **(C)** Expression regulation of hepatic lipid metabolism, inflammation and extracellular matrix (ECM). Red and blue colours indicate up- and down-regulation respectively, shown as % change, when compared to Vehicle.

Conclusion

- DA-1241 + semaglutide exhibited only body weight loss caused by semaglutide.
- Combination therapy further improves NAS compared to monotherapy. Driven by anti-inflammatory effects were likely attributed to DA-1241 treatment.
- Benefits on NAS is supported by quantitative histological markers.
- Combination therapy improves hepatic gene expression markers of lipid metabolism, inflammation and fibrogenesis.
- DA-1241 and semaglutide show no effect on fibrosis score after 8-week treatment.
- Combined GPR119 and GLP1R agonist treatment shows promise in MASH.