Metabolic, biochemical, histopathological, and transcriptomic effects of Seladelpar in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH

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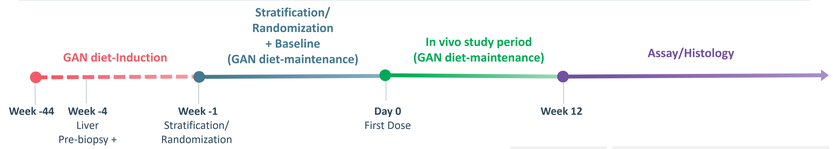
Background & Aim

Seladelpar, a PPAR-delta agonist, is currently in late-stage clinical development for liver disease including non-alcoholic steatohepatitis (NASH). The present study aimed to evaluate the metabolic, biochemical, histopathological and transcriptomic effects of seladelpar treatment in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH.

Study outline



Group #	Animal	Gender	Strain	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	LEAN-CHOW	Male	C57BL/6JRj	10	**Vehicle**	PO	QD	5 ml/kg	-
2	DIO-NASH	Male	C57BL/6JRj	16	**Vehicle**	PO	QD	5 ml/kg	-
3	DIO-NASH	Male	C57BL/6JRj	16	**Seladelpar**	PO	QD	5 ml/kg	**15 mg/kg**

Improvement in metabolic and biochemical parameters

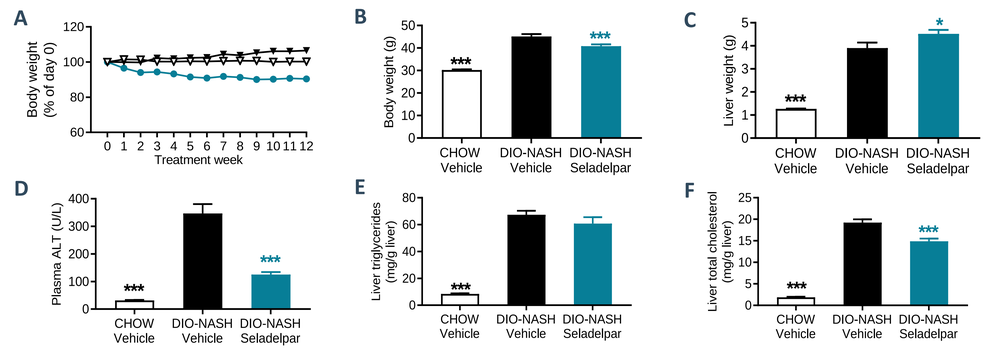


Figure 1. Seladelpar improves body weight and biochemical parameters in GAN DIO-NASH mice. **(A)** Body weight change relative to baseline (day 0). **(B)** Terminal body weight (g). **(C)** Terminal liver weight. **(D)** Terminal plasma alanine aminotransferase (ALT). **(E)** Terminal liver triglycerides. **(F)** Terminal liver total cholesterol. **(H)** **p<0.01, ***p<0.001 compared to corresponding DIO-NASH vehicle control (Dunnett's test one-factor linear model).

Improvement in NAFLD Activity Score

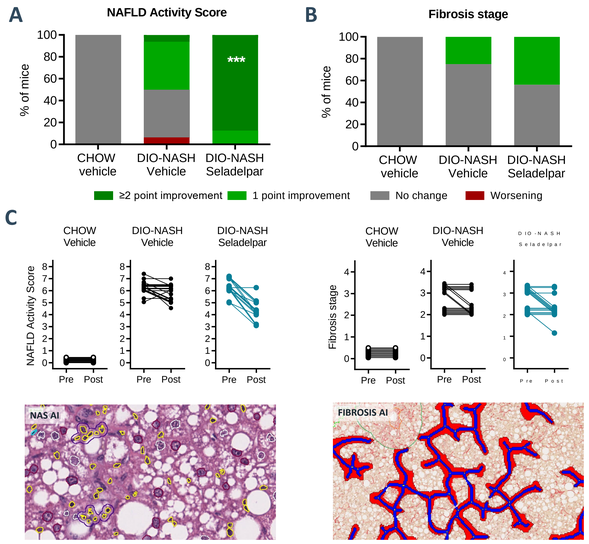


Figure 2. Seladelpar improves liver histopathological scores in GAN DIO-NASH mice.
Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis stage. **(C)** Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. ***p<0.001 to corresponding DIO-NASH vehicle group (One-sided Fisher's exact test with Bonferroni correction). Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

Improvement in quantitative histology of steatosis, inflammation and fibrosis

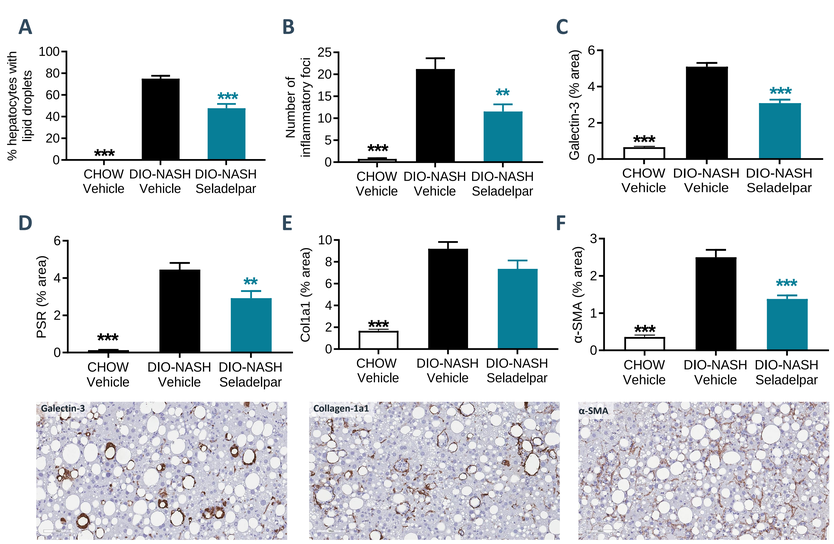


Figure 3. Seladelpar improves quantitative liver histological markers in GAN DIO-NASH mice.
Histomorphometric terminal assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). **(A)** % hepatocytes with lipid droplets. **(B)** Number of inflammatory foci. **(C)** % area of galectin-3. **(D)** % area of PSR. **(E)** % area of collagen-1a1. **(F)** % area of alpha-smooth muscle actin (α-SMA) as marker for stellate cell activation. Mean ± SEM. **p<0.01, ***p<0.001 to corresponding DIO-NASH vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1 and α-SMA photomicrographs (scale bar, 100 µm).

Hepatic transcriptomic profile for fibrosis and inflammation

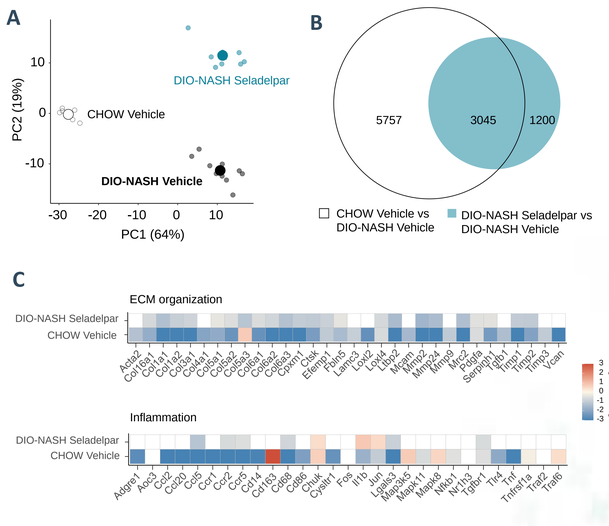


Figure 4. Seladelpar suppress fibrosis-associated genes in GAN DIO-NASH mice.
(A) Principal component analysis (PCA) of samples based on top 500 most variable gene expression levels. **(B)** Venn diagram depicting shared and separate differentially expressed genes in treatment groups. **(C)** Regulation of hepatic extracellular matrix (ECM) and inflammation candidate genes (log2-fold change compared to DIO-NASH vehicle mice). Blue and red colour gradients indicate significantly (p<0.05) down-regulated and up-regulated gene expression, respectively. White boxes indicate genes not significantly regulated (p>0.05) compared to DIO-NASH vehicle mice.

CONCLUSION

+ Seladelpar reduces body weight, plasma ALT and liver total cholesterol levels.
+ Seladelpar promotes ≥2-point significant improvement in NAFLD Activity Score.
+ Fibrosis stage was unaffected by Seladelpar.
+ Seladelpar reduces quantitative histological markers of steatosis, inflammation, fibrosis and stellate cell activation.
+ Seladelpar demonstrated transcriptomic effects on fibrosis-associated gene expression.
+ These findings agree with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model