Preclinical efficacy and clinical translatability of obeticholic acid in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH

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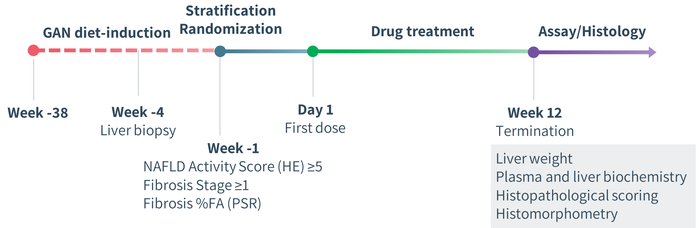
BACKGROUND & AIM

The farnesoid X receptor (FXR) agonist, obeticholic acid (OCA) has recently been reported to improve histological outcomes in a phase-3 clinical trial for NASH (REGENERATE trial; Younossi et al., Lancet, 2019). The present study aimed to (i) evaluate the metabolic, biochemical and histopathological effects of OCA treatment in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH; and (ii) compare preclinical efficacy data to primary endpoints in the REGENERATE trial.

1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dose
1	LEAN-CHOW	Male	10	**Vehicle**	PO	QD	-
2	DIO-NASH	Male	16	**Vehicle**	PO	QD	-
3	DIO-NASH	Male	15	**OCA**	PO	QD	30 mg/kg

2 Metabolic and biochemical markers

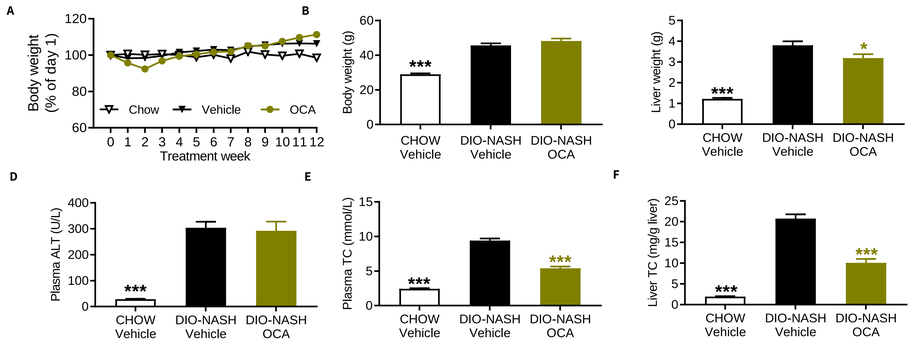


Figure 1. OCA is weight-neutral and improves both hepatomegaly and biochemical markers in GAN DIO-NASH mice. **(A)** Body weight change relative to baseline (day 0). **(B)** Terminal body weight (g). **(C)** Liver weight. **(D)** Plasma alanine aminotransferase (ALT). **(E)** Plasma total cholesterol (TC). **(F)** Liver total cholesterol (TC). *p<0.05, ***p<0.001 compared to corresponding DIO-NASH vehicle control (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis Stage

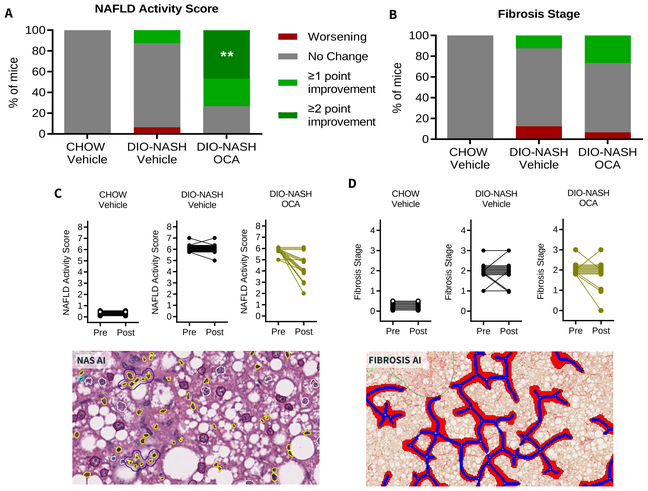


Figure 2. OCA improves liver histopathological scores in GAN DIO-NASH mice.
Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis Stage. **(C)** Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation. ##p<0.01 with 1 point improvement, *p<0.05) ≥1 stage fibrosis improvement, **p<0.001 compared to DIO-NASH vehicle control (One-sided Fisher's exact test with Bonferroni correction). Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

4 Quantitative histological markers of steatosis, inflammation and fibrosis

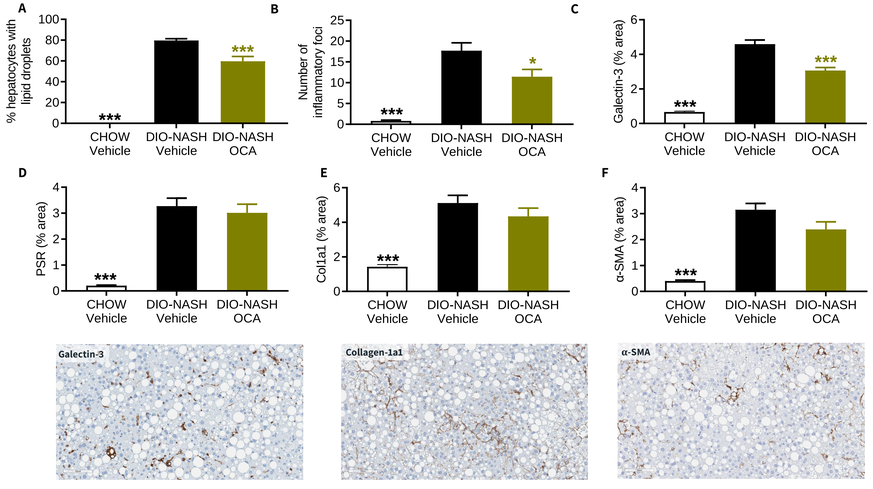


Figure 3. OCA improves quantitative liver histological markers in GAN DIO-NASH mice.
Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). **(A)** % hepatocytes with lipid 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<0.05, ***p<0.001 to DIO-NASH vehicle control (Dunnett's test one-factor linear model). Bottom panels: Representative photomicrographs (scale bar, 100 µm).

5 Clinical translatability

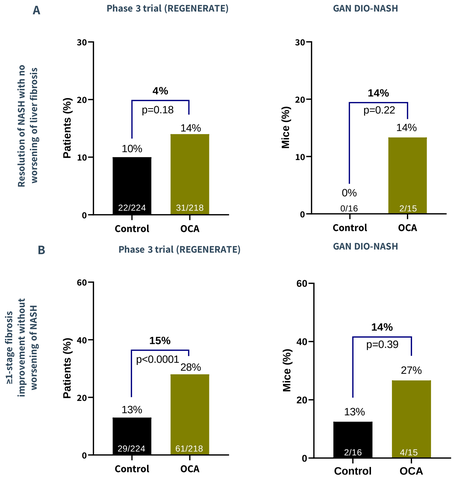


Figure 5. Comparative efficacy of OCA on NASH resolution and Fibrosis Stage improvement in GAN DIO-NASH mice and NASH patients with fibrosis. (A) Resolution of NASH (inflammation score ≤1; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis in GAN DIO-NASH mice (30 mg/kg, PO, 12 weeks) compared to clinical phase-3 trial data (REGENERATE trial; Younossi *et al.*, Lancet, 2019). **(B)** ≥1-stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-3 trial data (REGENERATE trial).

CONCLUSION

- OCA reduces hepatomegaly and plasma/liver total cholesterol levels.
- OCA promotes ≥2-point significant improvement in NAFLD Activity Score.
- Correspondingly, OCA reduces quantitative histological markers of steatosis and inflammation.
- OCA showed no significant effect on Fibrosis Stage and quantitative fibrosis histology.
- Level of efficacy for OCA treatment on histopathological scoring in GAN DIO-NASH mice resembles primary outcomes in the REGENERATE phase-3 trial in NASH patients.

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