

Longitudinal changes in FIB-4 and improvement in fibrosis stage with obeticholic acid: A secondary analysis of FLINT trial

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Disclosure/Disclaimer

- All material is intended for medical information and medical education purposes only. These materials have been produced in response to an unsolicited request for information.
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- Obeticholic acid (OCA) is an investigational drug. It is not approved for use by the FDA, EMA or any other regulatory body. No conclusions can be drawn concerning the safety or efficacy of OCA at this time.

Conflicts of interest

- **Salaried employee: of VCU**
- Member of Board: McGuire VA Research Institute, unpaid member
- Ad hoc consultant:
 - Salix: < \$ 5K
 - Ikaria: < \$ 5K
 - Abbott: \$5-10K
 - Bristol-Myers: < \$ 5K
 - Genfit: \$ 5-10 K
 - Genentech: < \$ 5K
 - Bristol Myers: < \$ 5K
 - Echosens: unpaid consultant
 - Gilead: unpaid consultant
 - Novartis: unpaid consultant
 - Takeda: unpaid consultant
- Royalties:
 - Elsevier- Boyers Textbook of Hepatology: < \$ 5K
 - Uptodate: < \$ 5K
- Grants (awarded to university):
 - NIH: \$ 1.5 million annual direct costs
 - Roche, Gilead, Astellas: \$ 25-50K total
 - Salix, Ikaria: \$ 50-100000 each
 - Gilead: \$ 150 K annual direct costs based on recruitment
 - Genfit: US PI for GFT505 trial
 - Galectin: \$ 30000

Background

- ▶ Nonalcoholic steatohepatitis (NASH) is a common cause of chronic liver disease and can progress to cirrhosis
- ▶ Obeticholic acid (OCA) is a farnesoid X receptor (FXR) agonist that was shown to improve disease activity and fibrosis in patients with NASH in a phase 2B clinical trial (FLINT)
- ▶ Improvement in fibrosis is considered particularly relevant because fibrosis stage is associated with mortality in patients with NASH
- ▶ Thus, there is a need to identify which patients are or are not experiencing an improvement in fibrosis so they can be managed accordingly

Background

- ▶ A liver biopsy is the gold standard for assessment of changes in fibrosis stage but can not be repeated frequently due to its invasive nature and attendant risks
- ▶ Several non-invasive measures of fibrosis have been found to relate the presence of advanced fibrosis in patients with NASH
- ▶ These include the AST: platelet ratio index (APRI)¹, FIB-4² and NAFLD Fibrosis Score (NFS)^{3,4}
- ▶ It is not known whether these indices are sensitive to change and can identify those whose fibrosis stage is improving

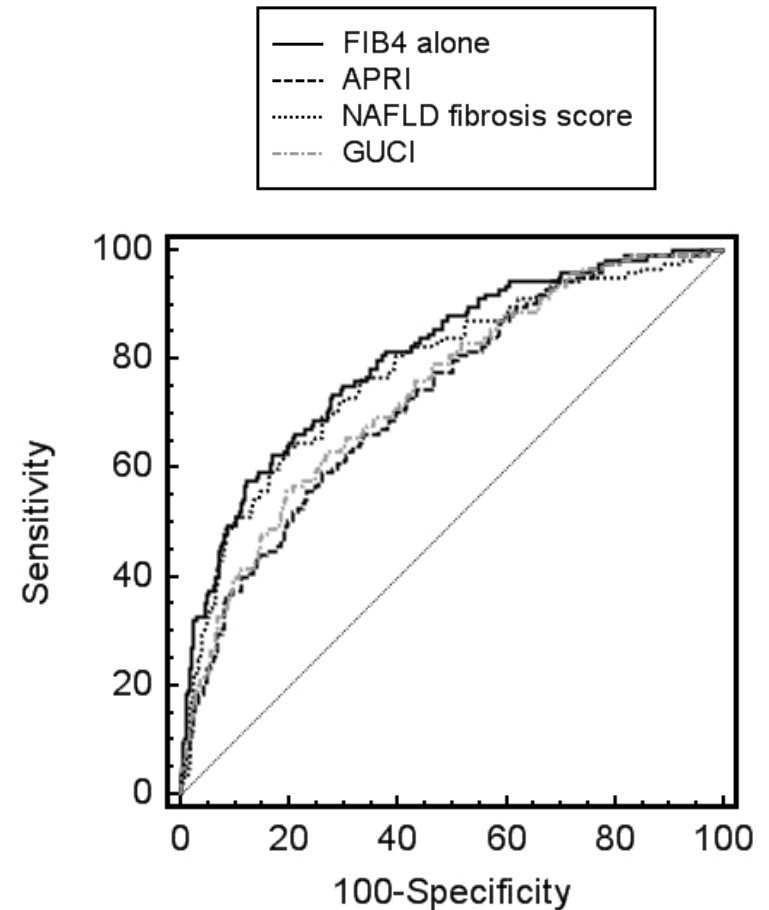
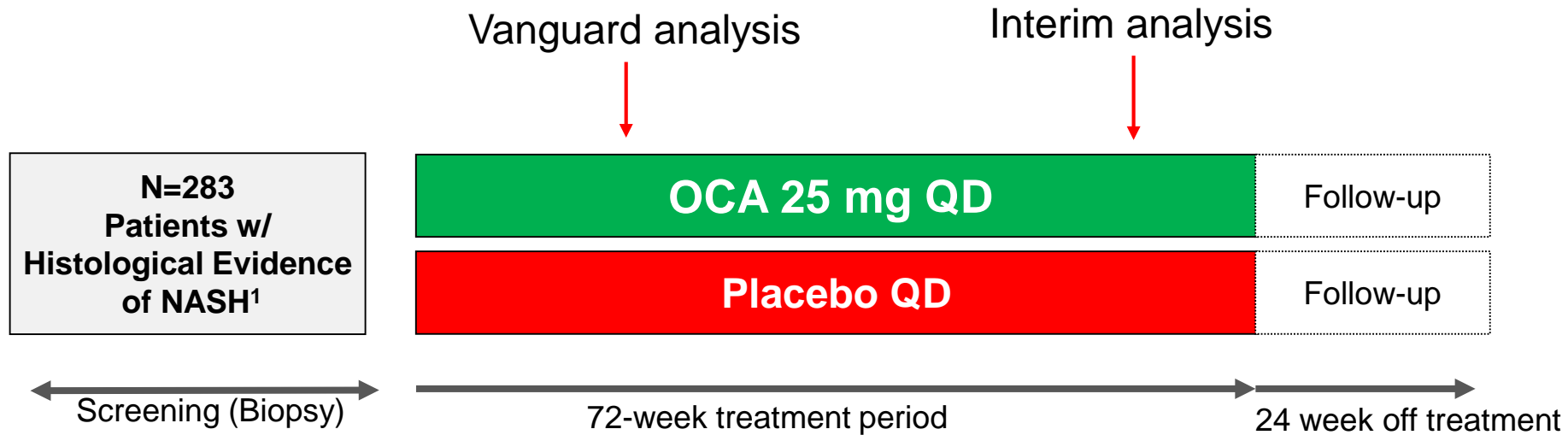


Figure adapted from Shah A, et al. *CGH*. 2009; 1. Cales P, et al. *J Hepatol*. 2009;50:165–73; 2. Shah AG, et al. *Clin Gastroenterol Hepatol*. 2009;7(10):1104-12; 3. Angulo, et al. *Hepatology*. 2007;45:846-854; 4. Angulo, et al. *Gastroenterology*. 2013;145:782-789.

Objective

- ▶ **Hypothesis:** Noninvasive markers of fibrosis improve in those with improvement in fibrosis stage
- ▶ **Specific Aim:** To determine if the APRI, FIB-4 and NFS improved in those whose fibrosis improved with OCA treatment in the FLINT clinical trial
- ▶ *The null hypothesis was that none of the parameters would change with improvement in fibrosis with OCA treatment*

FLINT Trial Design



Primary endpoint: liver histological improvement defined as decrease in NAFLD Activity Score (NAS) of ≥ 2 points with no worsening in fibrosis

1. Neuschwander-Tetri BA, et al. Lancet. 2015;385(9972):956-65.

Methods

- Levels of the three noninvasive markers were computed for baseline, and at 24, 48, 72, and 96 weeks in all patients
 - N=283 (n=141 [OCA]; n=142 [Placebo])
- Comparison of histology data with noninvasive markers was performed in patients who had baseline and end-of-treatment biopsies
 - N=200 (n=102 [OCA]; n=98 [Placebo])
- The specific parameters measured included:
 - FIB-4, APRI and NFS (equations below)
- Changes in markers over time in placebo and OCA treatment were compared in a mixed effects model
- A logistic regression model was used to evaluate early changes (24 wks) in markers as predictors of fibrosis improvement at end of treatment (72 wks)

$$\text{APRI} = \{[(\text{AST level}) / (\text{AST ULN})] / [\text{platelet count } (10^9/\text{L})]\} \times 100$$

$$\text{FIB-4} = \text{age (years)} \times \text{AST [U/L]} / (\text{platelets } [10^9/\text{L}] \times (\text{ALT [U/L]})^{1/2})$$

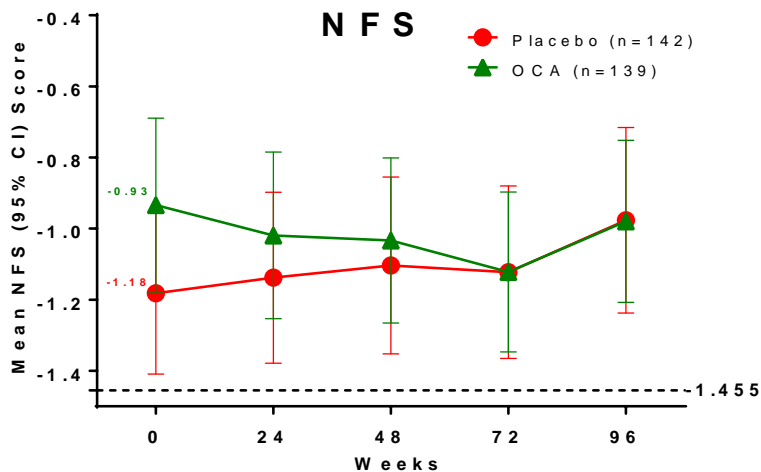
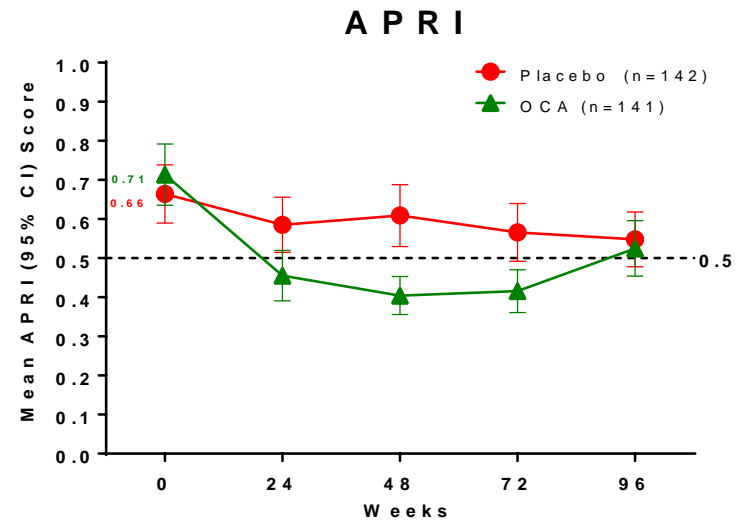
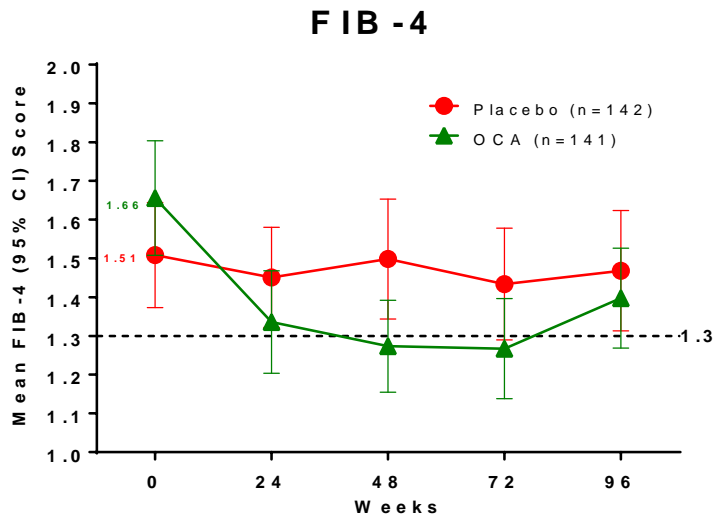
$$\text{NFS} = -1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelets } (\times 10^9/\text{L}) - 0.66 \times \text{albumin (g/dL)}$$

Baseline Characteristics

Parameter	OCA (25 mg/day) N=141	Placebo N=142	P-value†
Age (yrs)	51.9 (0.9)	51.0 (1.0)	0.450
BMI (kg/m ²)	35.2 (0.6)*	33.9 (0.5)	0.086
Diabetics (%)	53.2	52.1	0.911‡
AST (U/L)	64.1 (3.2)	58.0 (2.8)	0.163
ALT (U/L)	82.8 (4.2)	82.4 (4.3)	0.960
Alk Phos (U/L)	82.2 (2.4)	81.5 (2.1)	0.836
Triglycerides (mg/dL)	216.4 (23.4)	177.7 (12.8)	0.157
Platelets (10 ⁹ /L)	237.5 (5.0)	236.8 (5.5)	0.902
Albumin (g/dL)	4.3 (0.0)	4.3 (0.0)	0.859
APRI	0.7 (0.0)	0.7 (0.0)	0.387
FIB-4	1.7 (0.1)	1.5 (0.1)	0.163
NAFLD Fibrosis Score	-0.9 (0.1)*	-1.2 (0.1)	0.120

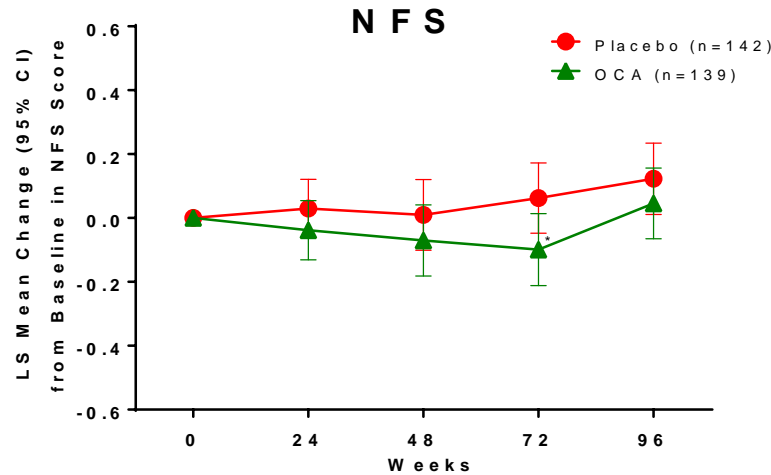
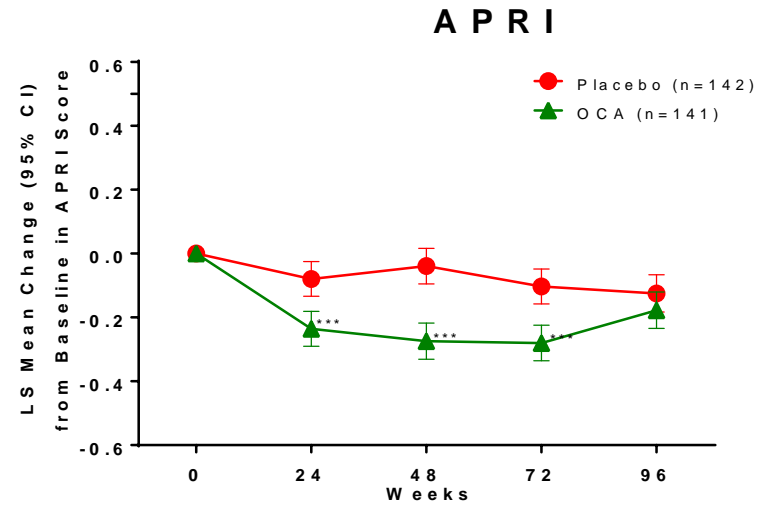
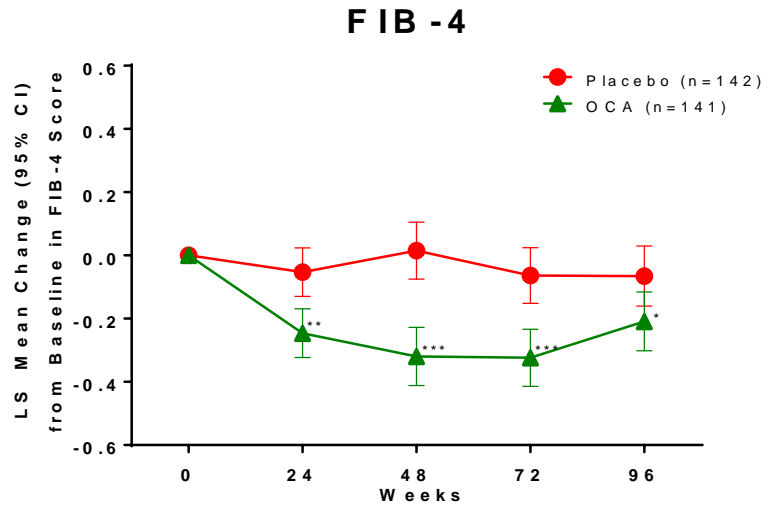
Data are mean (SE) where applicable. *N=139; †Continuous variable p-values from ANOVA with treatment and stratification strata (center, diabetes status) as fixed effects; ‡Diabetes status p-value from CMH chi-square stratified by center; All P-values are based on LS Mean.

FIB-4, APRI and NFS Values Over Time



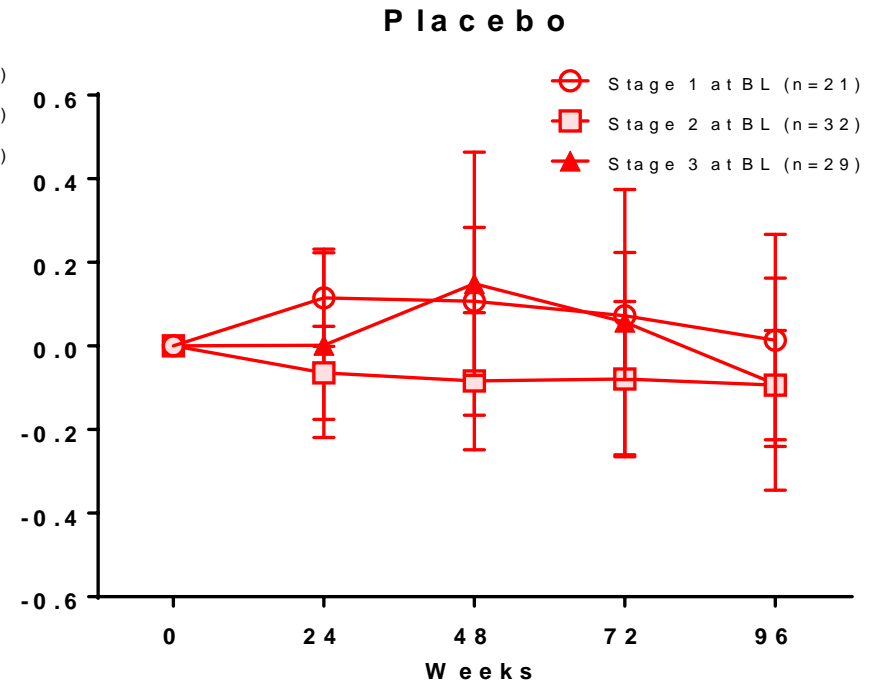
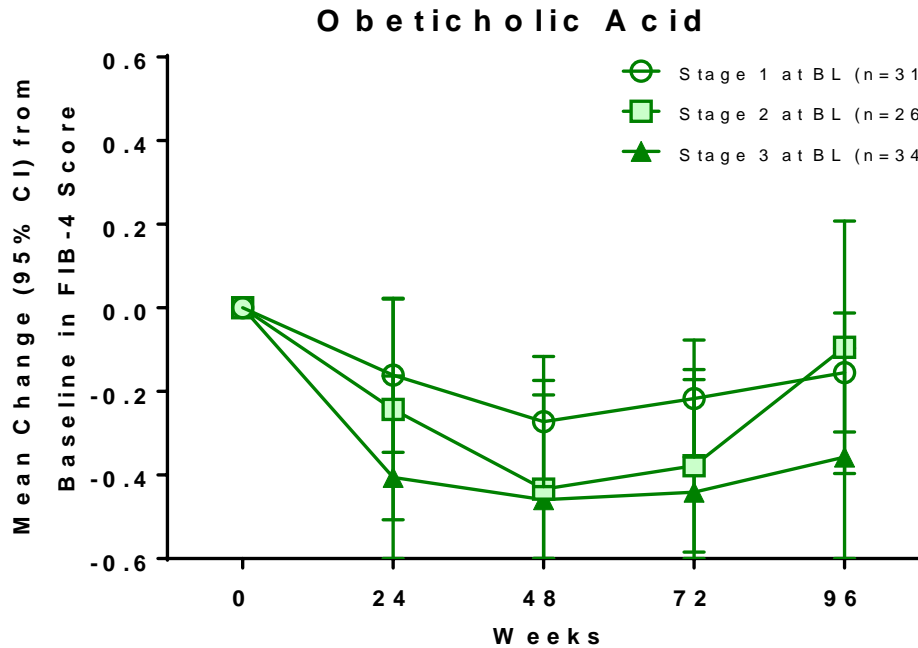
Noninvasive scores below the cut-off value have a low probability of advanced fibrosis

Change from Baseline in FIB-4, APRI and NFS

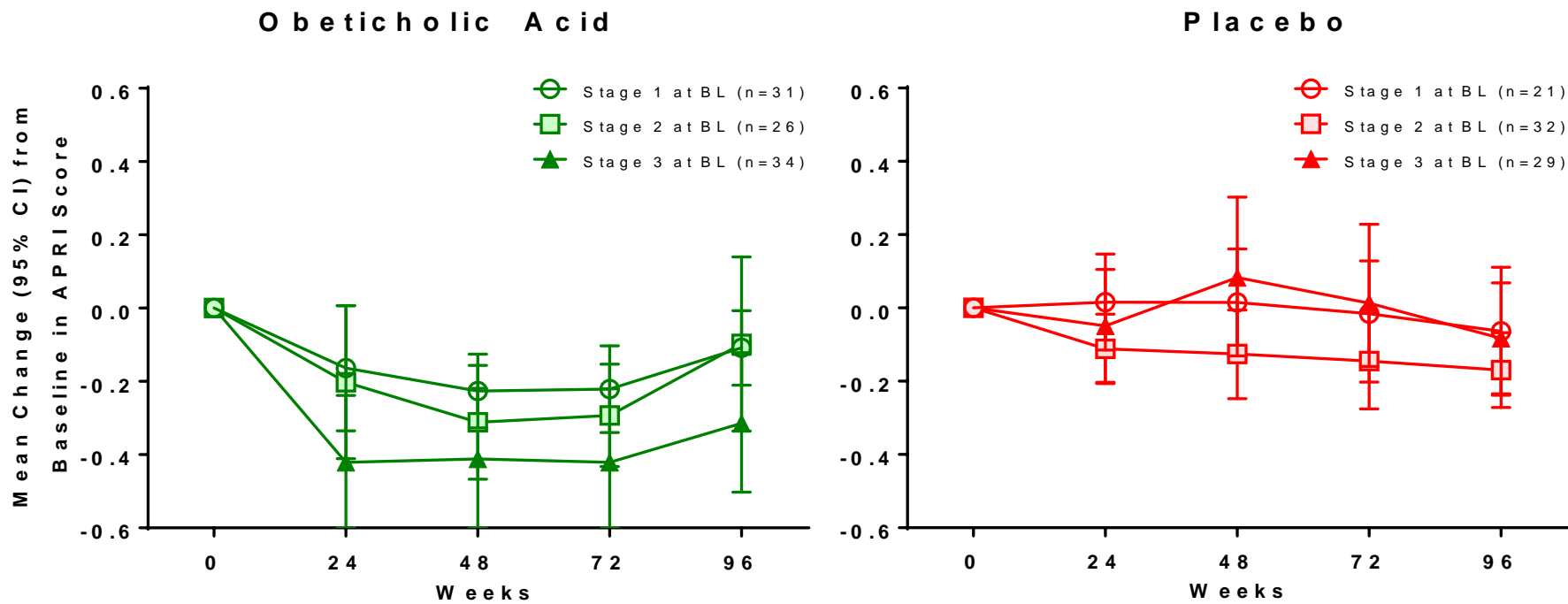


*p<0.05,**p<0.01,***p<0.0001. P-values were calculated using ANCOVA models, regressing change from baseline at each post-baseline visit on treatment group and baseline value of the outcome.

Change from Baseline in FIB-4 by Baseline Fibrosis Stage

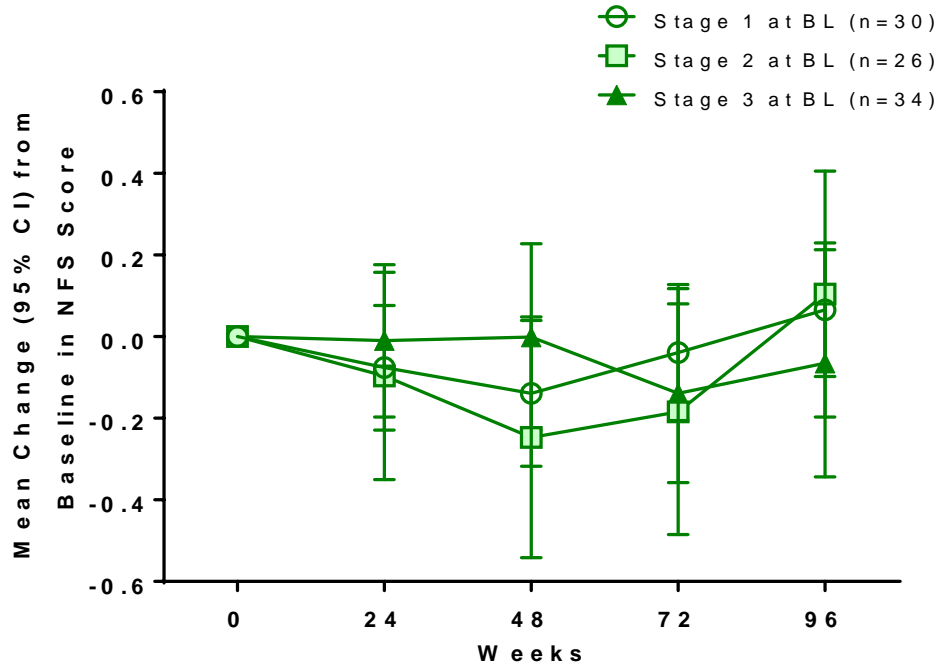


Change from Baseline in APRI by Baseline Fibrosis Stage

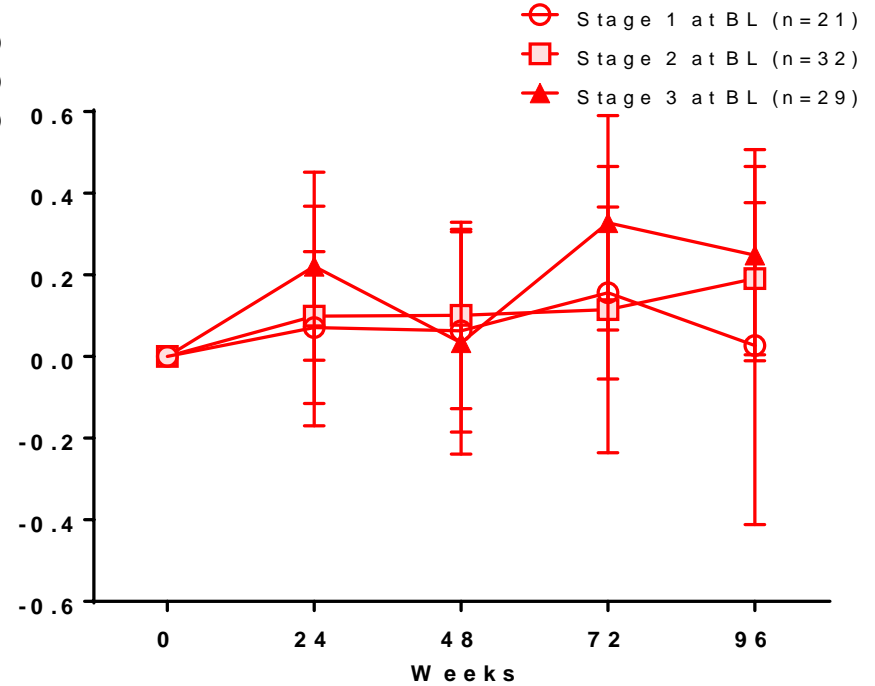


Change from Baseline in NFS by Baseline Fibrosis Stage

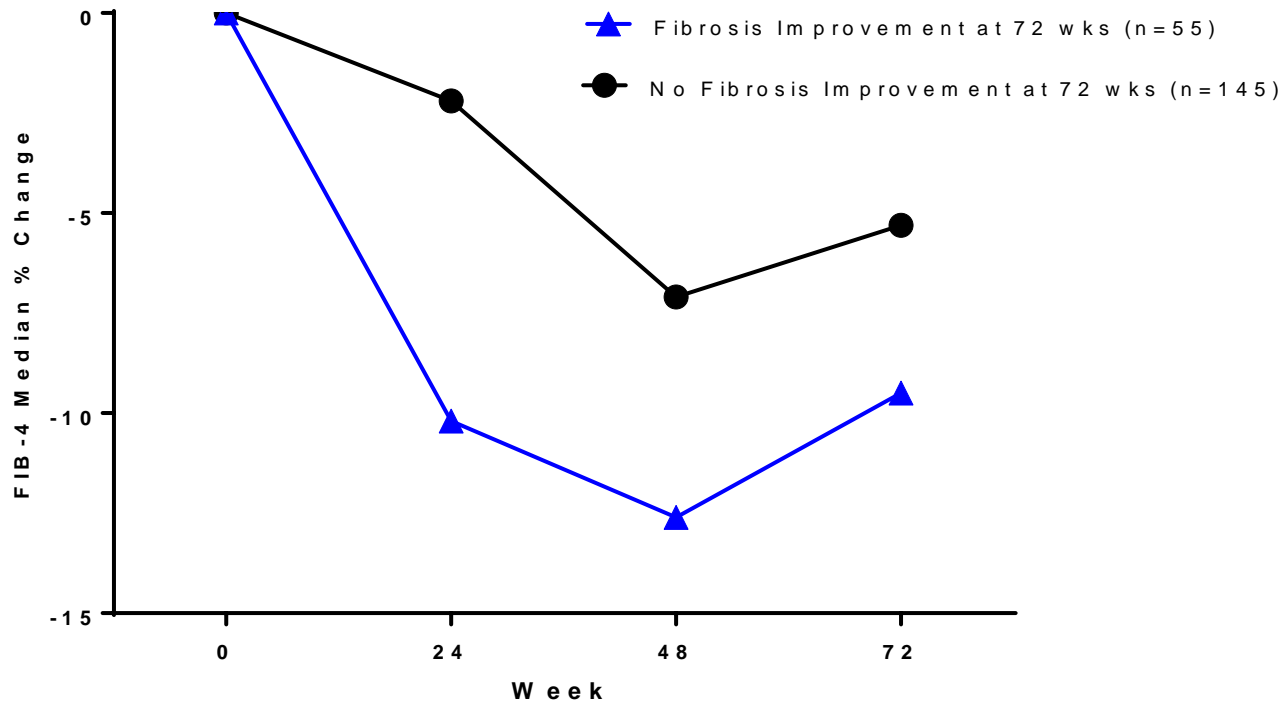
O b e t i c h o l i c A c i d



P l a c e b o

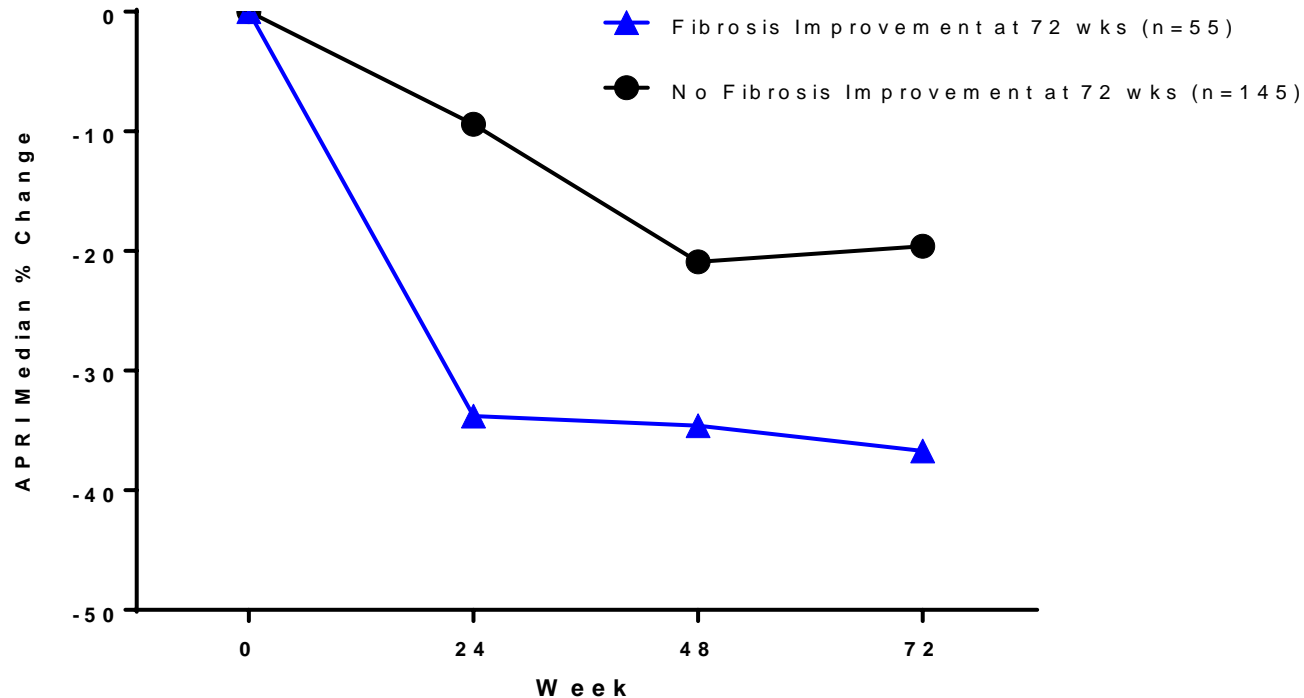


Decrease in FIB-4 Score at 24 Weeks is Associated with Improvement in Histologic Fibrosis Stage at 72 Weeks



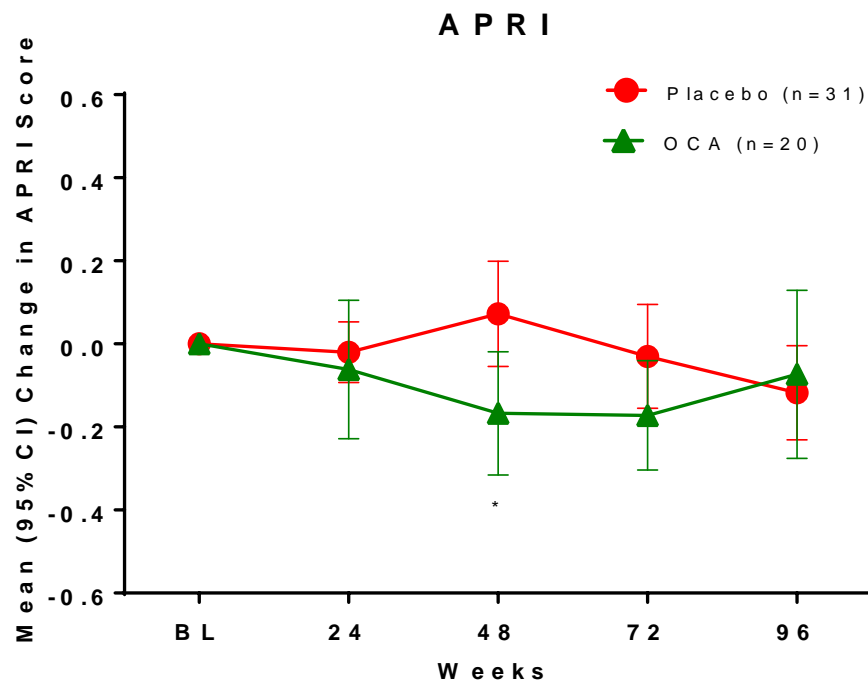
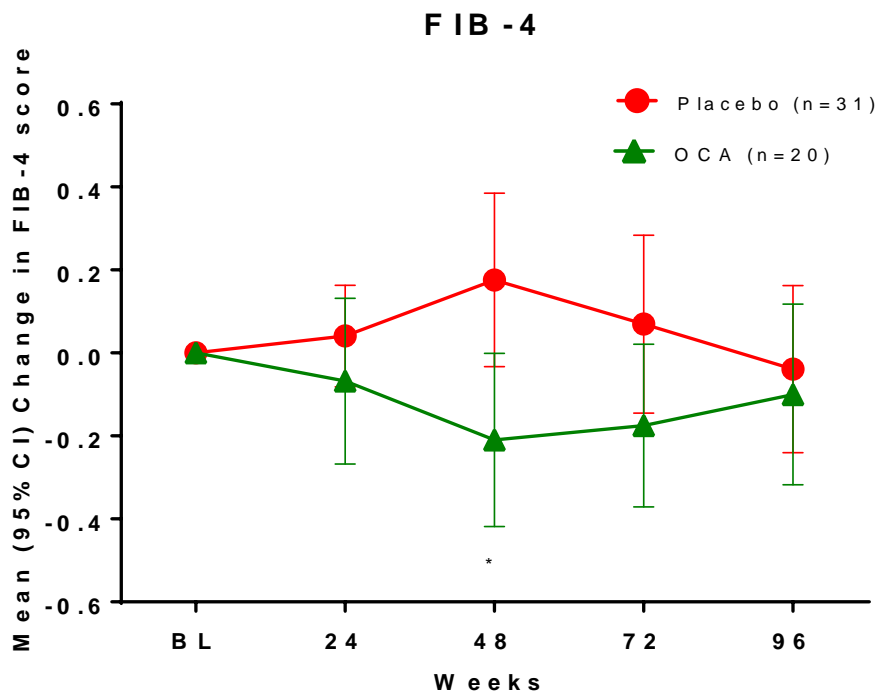
A Wilcoxon Rank Sum analysis showed that a 10% reduction in median FIB-4 values at 24 weeks is associated with a ≥ 1 stage improvement in fibrosis stage at 72 weeks ($p < 0.05$)

Decrease in APRI at 24 Weeks is Associated with Improvement in Histologic Fibrosis Stage at 72 weeks



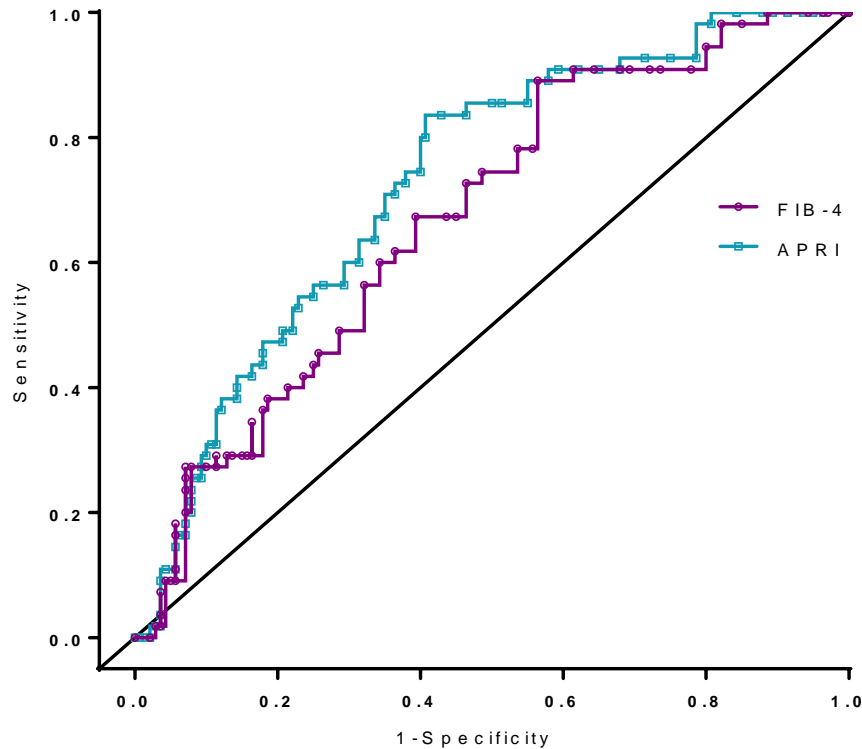
A Wilcoxon Rank Sum analysis showed that a 34% reduction in median APRI values at 24 weeks is associated with a ≥ 1 stage improvement in fibrosis stage at 72 weeks ($p < 0.05$)

Worsening of Histologic Fibrosis was Associated with Little Change in FIB-4 and APRI



*p<0.05. P-values were calculated using ANCOVA models, regressing change from baseline at each post-baseline visit on treatment group and baseline value of the outcome.

ROC Curves for Noninvasive Fibrosis Scores



Parameters

- Fibrosis stage at baseline
- FIB-4/APRI at baseline
- FIB-4/APRI change at 24 weeks
- Treatment

NAME	CUT OFF	AUROC	NPV	PPV	95% CI
FIB-4	0.29	0.6817	80.7%	40.7%	(0.6024, 0.7610)
APRI	0.34	0.7238	80.6%	47.5%	(0.6483, 0.7993)

AUROC: Area under the receiver operator characteristic curve; NPV: negative predictive values; PPV: positive predictive values.

Summary

- ▶ The baseline values of FIB-4, APRI and NFS were similar in patients receiving OCA or placebo
- ▶ APRI and FIB-4 decreased in patients receiving OCA compared to those who received placebo
- ▶ This was related to improvement in fibrosis stage; a 10% and 34% decrease at 24 weeks in FIB-4 and APRI respectively was associated with a ≥ 1 stage improvement in fibrosis at 72 weeks
- ▶ These changes in FIB-4 and APRI were seen across all baseline stages of disease studied
- ▶ NFS was not sensitive to changes in fibrosis in this study

Conclusions

- ▶ APRI and FIB-4 scores improved in patients with improvement in fibrosis stage induced by OCA treatment
- ▶ It provides proof of concept that noninvasive markers of fibrosis can be sensitive to change
- ▶ Improvement in FIB4 or APRI on treatment is encouraging and more studies to refine their diagnostic utility are needed