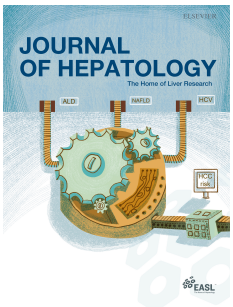

Non-invasive evaluation of response to obeticholic acid in patients with NASH: Results from the REGENERATE study

Mary Rinella, Jean-Francois Dufour, Quentin M. Anstee, Zachary Goodman, Zobair Younossi, Stephen A. Harrison, Rohit Loomba, Arun J. Sanyal, Martin Bonacci, Aldo Trylesinski, Macky Natha, Reshma Shringarpure, Tanya Granston, Aditya Venugopal, Vlad Ratziu

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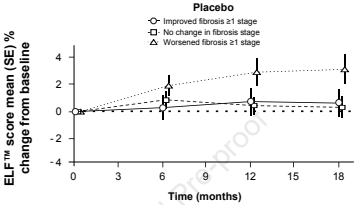
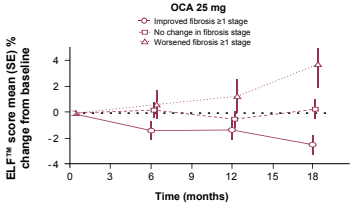
Results from an 18-month interim analysis of the phase 3 REGENERATE study

Changes in various NITs in patients with NASH and fibrosis treated with OCA or placebo reflect histologic changes

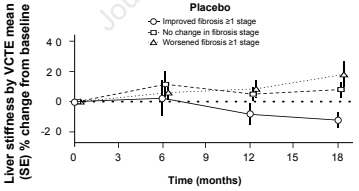
NITs may be useful in assessing histologic response to therapy

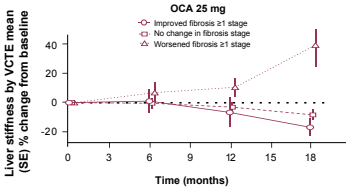
ELF™ changes according to histologic response





Transient elastography changes according to histologic response





ELF, enhanced liver fibrosis; NASH, nonalcoholic steatohepatitis; NIT, noninvasive test; OCA, obeticholic acid; SE, standard error; VCTE, vibration-controlled transient elastography.

Non-invasive evaluation of response to obeticholic acid in patients with NASH: Results from the REGENERATE study

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Declaration of interest

MR was a consultant over the past 36 months for Alnylam, Amgen, AMRA, BMS, Boehringer Ingelheim, Centara, Coherus, Enanta, Galecto, Intercept Pharmaceuticals, Inc., Madrigal, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Fractyl, Gelesis, Siemens, Thetis, Terns, Rivus, 3vbio (Sagimet), 89Bio, and Novartis. She currently has no active consulting contracts.

J-FD reports advisory committee participation for AbbVie, Bayer, Bristol-Myers Squibb, Falk, Genfit, Genkyotex, Gilead Sciences, HepaRegeniX, Intercept Pharmaceuticals, Inc., Lilly, Merck, Novartis; speaking and teaching fees from Bayer, Bristol-Myers Squibb, Intercept Pharmaceuticals, Inc., Genfit, Gilead Sciences, Novartis, Roche.

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ZG has no conflicts to report.

ZY reports consulting fees and research grants from Gilead Sciences, Intercept Pharmaceuticals, Inc., BMS, Novo Nordisk, Viking, Terns, Siemens, Quest, AbbVie, Madrigal, Merck, and Novartis.

SAH reports SH reports consulting/advisory, stock ownership/equity from Akero, Galectin, Genfit, Madrigal, Metacrine, Histoindex and NGM Bio; grants from Axcella, Cirius, CymaBay, Galectin, Galmed, Genfit, Gilead, HighTide, Madrigal, NGM, Novartis, Novo Nordisk, Pfizer, and Second Genome; consulting/advisory for Alentis, Axcella, Bristol-Meyers Squibb, CiVi, CLDF, Corcept, Echosens, , Gilead, HighTide, Medpace, Novartis, Novo Nordisk, Perspectum, Prometric, Viking, Hepagene, Hepion, and Terns

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Novo Nordisk, Pfizer, Sagimet, 89Bio, Viking Therapeutics; advisory committee participation for Intercept Pharmaceuticals, Inc.; co-founder of Liponexus, Inc.

AJS is President of Sanyal Biotechnology; he reports stock options in Sanyal Bio, Exhalenz, Akarna, GenFit, Hemoshear, Durect, Indalo, Tiziana, Rivus; paid consultant to 89Bio, Albireo, Amgen, Ardelyx, Boehringer Ingelheim, Bird Rock, Bristol-Myers, Conatus, Covance, Echosens-Sandhill, ENYO, Genentech, General Electric, Genfit, Gilead, Hemoshear, HistoIndex, Inventiva, Janssen, Lilly, Madrigal, Mallinckrodt, Merck, NGM Bio, Nimbus, NorthSea, Novartis, Novo Nordisk, Owl, PathAI, Perspectum, Pfizer, Poxel, Prosciento, Regeneron, Rivus, Roche, Salix, Sanofi, Second Genome, Servier, Siemens, Takeda, Terns, Tiziana, Zydus; unpaid consultant to Immuron, Intercept Pharmaceuticals, Inc., Galectin, Sequana, Fractyl; Durect, Indalo, Allergan, Chemomab, Affimune, Teva, BASF, AMRA, Perspectum, Biocellvia; advisory board member for Immuron; royalties from Elsevier and UptoDate; grant support from Gilead, Mallinckrodt, Salix, Novartis, Galectin, Bristol-Myers, Sequana; receipt of equipment from Echosens-Sandhill; ongoing research collaboration with Echosens-Sandhill, Owl, Second Genome, Siemens; his institution has received grant support from Conatus, Gilead, Mallinckrodt, Boehringer Ingelheim, Novartis, Bristol-Myers, Merck, Lilly, Novo Nordisk, Fractyl, Madrigal, Inventiva, Covance; his institution has received fees from AstraZeneca.

MB reports employment at and stock ownership in Intercept Pharmaceuticals, Inc. at the time of the study.

AT reports employment at and stock ownership in Intercept Pharmaceuticals, Inc.

MN reports employment at and stock ownership in Intercept Pharmaceuticals, Inc. at the time of the study.

RS reports employment at and stock ownership in Intercept Pharmaceuticals, Inc. at the time of the study.

TG reports employment at and stock ownership in Intercept Pharmaceuticals, Inc. at the time of the study.

AV reports employment at Intercept Pharmaceuticals, Inc. at the time of the study.

VR reports consulting fees from Galmed, Genfit, Madrigal, NGM, Bristol-Myers Squibb, Boehringer Ingelheim, Theratechnologies, Terns; advisory committee participation for Intercept Pharmaceuticals, Inc.

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Author Contributions

Study design: MR, VR, AJS, ZMY, RS

Acquisition of data: MR, JFD, QMA, ZMY, SH, RL, AJS, VR

Statistical analysis: MR, TG

Data analysis and interpretation: All authors

Manuscript preparation: All authors

Manuscript review and revisions: All authors

Final approval of manuscript: All authors

Study investigator: MR, JFD, QMA, ZMY, SH, RL, AJS, VR

Collection and assembly of data: MR, JFD, QMA, ZMY, SH, RL, AJS, VR, ZG, TY

Clinical Trial Registration: ClinicalTrials.gov number NCT02548351

Highlights

- Reduced ALT, AST, GGT, FIB-4, and FibroTest scores were seen with OCA vs placebo
- Reduced liver stiffness by VCTE was observed in OCA vs placebo arms at Month 18
- NIT changes in OCA treatment arms were associated with shifts in fibrosis stage
- The antifibrotic effect of OCA might be measurable with commonly used NITs

ABSTRACT

Background & Aims: Nonalcoholic steatohepatitis (NASH) is a chronic, progressive fibrotic liver disease that can lead to cirrhosis. While liver biopsy is considered the reference standard for histologic diagnosis of NASH and staging of fibrosis, use in clinical practice is limited. Noninvasive tests (NITs) are increasingly being used to identify and stage liver fibrosis in patients with NASH, and several can assess liver-related outcomes. We report changes in various NITs in patients treated with obeticholic acid (OCA) or placebo in the phase 3 REGENERATE study.

Methods: Patients with NASH and fibrosis stage F2 or F3 (N = 931) were randomized (1:1:1) to receive placebo, OCA 10 mg, or OCA 25 mg once daily. Various NITs based on clinical chemistry and/or imaging were evaluated at baseline and throughout the study.

Results: Rapid, sustained reductions from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels, as well as in FIB-4, FibroTest, FibroMeter, and FibroScan-AST scores were observed in OCA-treated patients versus placebo. Reduction in liver stiffness by vibration-controlled transient elastography (VCTE) was observed in the OCA 25 mg group versus placebo group at Month 18. NIT changes were associated with shifts in histologic fibrosis stage. The greatest improvements were observed in patients with ≥1-stage fibrosis improvement; however, improvements in ALT, AST, FIB-4, and FibroTest were also observed in OCA-treated patients whose histologic fibrosis remained stable.

Conclusions: Based on the REGENERATE Month 18 interim analysis, rapid and sustained improvements in various NITs were observed with OCA treatment. Dynamic changes in selected NITs separated histologic responders from non-

responders. These results suggest that NITs may be useful in assessing histologic response to OCA therapy.

Lay Summary

Nonalcoholic steatohepatitis (NASH) is a chronic, progressive liver disease that can lead to cirrhosis. To diagnose and assess liver fibrosis (scarring) in patients with NASH, noninvasive tests (NITs) are increasingly being used rather than liver biopsy, which is invasive, expensive, and can be risky. In the REGENERATE study evaluating the effects of obeticholic acid versus placebo in patients with NASH, various NITs were evaluated as well. This analysis shows that improvements in levels of certain blood components, as well as favorable results of ultrasound imaging and proprietary tests of liver function, were associated with improvements in liver fibrosis after treatment with obeticholic acid, suggesting that NITs may be useful alternatives to liver biopsy in assessing NASH patients' response to therapy.

Introduction

Nonalcoholic steatohepatitis (NASH) is a chronic, progressive liver disease characterized by hepatocellular injury, inflammation, and fibrosis, leading to cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC), and death in a subset of patients.[1-3] NASH is a fast-growing indication for liver transplantation in the United States and the leading indication for liver transplantation in women without HCC.[4, 5] The global prevalence of NASH is projected to increase steadily in the next decade.[6] There are currently no approved drugs in the United States or Europe for nonalcoholic fatty liver disease (NAFLD)/NASH.[7] Weight loss may be effective, but is difficult to achieve and sustain and may have limited antifibrotic effects in advanced fibrosis.[8] Fibrosis is the strongest driver and predictor of disease progression and transplant-free survival in patients with NASH. There is a clear unmet need for new therapies that improve or stabilize fibrosis for patients with advanced fibrosis due to NASH.[9-11]

Obeticholic acid (OCA) is a potent and selective farnesoid X receptor (FXR) agonist.[12-14] Activation of FXR, which plays a central role in metabolism and regulation of bile acids,[15] has beneficial effects on hepatic inflammation and fibrosis.[12, 16] In the phase 3 REGENERATE study (NCT02548351), the primary endpoint of ≥1-stage fibrosis improvement with no worsening of NASH was achieved by 23% of patients with fibrosis stage 2 or 3 who received OCA 25 mg versus 12% of patients who received placebo (p = 0.0002) at the prespecified Month 18 interim analysis.[14] The antifibrotic effect of OCA was dose dependent, consistent across subgroups, and further supported by fibrosis-related secondary endpoints. REGENERATE is ongoing and will continue through clinical outcomes for verification and description of clinical benefits of OCA in the treatment of NASH with fibrosis.

Key fibrosis-related endpoints in REGENERATE were based on histologic assessment.[14] While biopsy remains the reference standard for assessing liver fibrosis, it is invasive, costly, impractical to perform for monitoring in routine clinical practice, and carries risk.[17-19] Because of these limitations, noninvasive tests (NITs) are being studied to reduce the need for liver biopsy and replace it in the monitoring of treatment response. NIT improvements have been associated with improvements in liver histology and, in some conditions, are being adopted as an alternative to biopsy.[7, 20-25] Simple NITs are based on routine biochemical parameters of hepatic inflammation (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), gamma-glutamyl transferase [GGT], composite scores (AST-to-platelet ratio index [APRI],[26] FIB-4 score,[26, 27] and NAFLD fibrosis score [NFS][28]) and proprietary markers (FibroTest™,[19] enhanced liver fibrosis [ELF™] score[29, 30]) in addition to imaging-based methodologies such as ultrasound technology (vibration-controlled transient elastography [FibroScan® VCTE]).[31] Emerging markers include FibroMeter™,[32] FibroMeter™ VCTE,[33] FibroScan®-AST (FAST) score,[34] CK-18 M30 fragment,[35] Pro-C3,[35] and magnetic resonance (MR) imaging-based modalities such as MR elastography and multiparametric MR.[36, 37] Several of these have been shown to predict liver-related outcomes and transplant-free survival.[38] REGENERATE provided an opportunity to examine the correlation of NITs with histologic findings in a large population of patients with NASH. The objective of this analysis was to investigate NIT trends using results from the prespecified 18-month interim analysis.

Patients and methods

Study design and participants

REGENERATE is an international, multicenter, randomized, placebo-controlled, double-blind trial that enrolled patients ≥18 years of age with histologic

evidence of steatohepatitis; NAFLD activity score ≥4 (including ≥1 point for steatosis, lobular inflammation, and hepatocellular ballooning); fibrosis stage F2 or F3 per NASH Clinical Research Network criteria or F1 with ≥1 comorbidity (obesity, type 2 diabetes mellitus, or ALT >1.5 × upper limit of normal). Patients were randomized 1:1:1 to daily placebo or oral OCA 10 or 25 mg. REGENERATE is ongoing and will continue through clinical outcomes for verification and description of clinical benefits of OCA in the treatment of NASH with fibrosis. Detailed methods for REGENERATE have been reported.[14, 39]

Outcomes

The primary objectives of REGENERATE were to evaluate the effects of OCA treatment compared with placebo on 1) histologic improvement assessed at the prespecified Month 18 interim analysis and at end of study and 2) liver-related clinical outcomes to be assessed at the end of the study in patients with NASH with liver fibrosis. The primary endpoints of the Month 18 interim analysis were the proportions of patients with ≥1-stage fibrosis improvement and no worsening of NASH or with NASH resolution and no worsening of fibrosis. Secondary endpoints included histologic improvement in individual features of NASH and liver biochemistry. NITs of fibrosis and steatohepatitis were assessed as exploratory endpoints. A prespecified interim analysis was conducted after ≥750 randomized patients with fibrosis stage F2 or F3 had reached or would have reached their 18-month visit.

Safety results from the REGENERATE 18-month interim analysis, which included patients whose NIT results are reported herein, have been previously described.[14]

Laboratory tests and radiologic markers

Routine biochemical and clinical markers including ALT, AST, GGT, and platelets were measured at baseline and each visit. FIB-4, APRI, and NFS were calculated at Months 1, 3, 6, 9, 12, 15, and 18.[14]

Proprietary serum measures of liver fibrosis (FibroTest™, ELF™), apoptosis markers, and collagenic fibrosis markers (CK-18 M30 fragment, Pro-C3) were evaluated at baseline and Months 6, 12, and 18. Liver stiffness, measured by FibroScan® VCTE imaging (Echosens, Paris, France),[40] was evaluated at baseline and Months 6, 12, and 18 at centers where available. Additional details are reported in **Supplementary Methods**.

Statistical analysis

Least-square (LS) mean, standard error (SE), and 95% confidence intervals (CIs) of percentage change from baseline over time in ALT, AST, GGT, FIB-4, FibroTest™ and ELF™ were analyzed using a mixed-effect repeated-measures (MMRM) model with treatment, baseline, visit, visit by treatment interaction, and stratification factors (baseline diabetes status and use of thiazolidinediones or vitamin E) as fixed effects. For VCTE, change from baseline rather than percentage change from baseline was analyzed.

Univariate logistic regression analysis assessed probability of fibrosis improvement (≥1 stage) at Month 18, reporting odds ratio (OR), 95% CI, and *p* value for every 10% decrease in various NITs at Months 1, 3, 6, 12, and 18. Area under the receiver operating characteristic (AUROC) curves assessed the ability of NITs to predict fibrosis improvement.

Results

The intention-to-treat (ITT) population, defined as patients with fibrosis stage F2 or F3 who received ≥1 dose of study drug, consisted of 931 patients randomized to placebo (n = 311), OCA 10 mg (n = 312), or OCA 25 mg (n = 308). Baseline demographic and clinical characteristics were generally well balanced across groups (**Table 1**). The interim 18-month on-treatment population, defined as patients in the ITT population who had ≥18 months of treatment, consisted of 735 patients (placebo, n = 247; OCA 10 mg, n = 246; OCA 25 mg, n = 242). In the ITT and 18-month on-treatment populations, baseline aminotransferases and fibrosis marker values were consistent with those expected for patients with NASH and significant fibrosis (**Table 2, Table S1**).

Liver biochemistries

Dose-dependent reductions in ALT, AST, and GGT values were persistent through Month 18 in the ITT and 18-month on-treatment populations (**Table 2, Fig. 1, Table S1**). Patients treated with OCA 25 mg achieved rapid ALT reduction; LS mean change (95% CI) from baseline: −20.6% (−23.7, −17.4) at Month 1 versus −14.0% (−17.2, −10.8) with OCA 10 mg and −5.2% (−8.3, −2.0) with placebo. Further dose-dependent ALT reductions were observed in patients treated with OCA through Month 18; LS mean change from baseline (95% CI): −31.9% (−37.7, −26.1) for patients receiving OCA 25 mg and −23.2% (−28.9, −17.4) for patients receiving OCA 10 mg. No additional ALT reductions were observed with placebo beyond Month 1; LS mean change from baseline at Month 18: −4.9% (−10.7, 0.9) (**Fig. 1A**). A similar pattern but smaller reduction from baseline at Month 18 was observed with AST (**Fig. 1B**). Rapid reductions in GGT were observed in the OCA groups, with

levels stable to Month 18 (**Fig. 1C**). In the ITT population, changes from baseline over time in AST and GGT in the placebo group were small (**Table 2**); the 18-month on-treatment population showed similar trends (**Table S1**). Patients receiving OCA versus placebo had improved aminotransferases and GGT over time regardless of baseline status (**Fig. S1**). Relative to placebo, patients receiving OCA with abnormal enzyme levels at baseline had the greatest reductions over time. However, reductions in enzyme levels were also observed in patients with normal baseline values (ALT ≤55 U/L, AST ≤34 U/L), with meaningful differences in those treated with OCA versus placebo (**Fig. S1**).

Composite fibrosis scores based on clinical parameters

Reduction in FIB-4 and APRI scores were observed in patients treated with OCA in the ITT and 18-month on-treatment populations (**Table 2, Table S1**). Reduction of FIB-4 scores was observed as early as Month 1 in the OCA 25 mg treatment group and sustained through Month 18 (**Fig. 1D**). FIB-4 values in the placebo group increased slightly during follow-up and remained above baseline values throughout treatment. Consistent with FIB-4 score changes, dose-dependent decreases in APRI scores were seen in the OCA treatment groups. APRI score reductions were evident as early as Month 1 in patients treated with OCA 25 mg (not shown). In the ITT and 18-month on-treatment populations, APRI values were lower at Month 18 versus baseline in all treatment groups, with the greatest reductions in the OCA arms versus placebo (**Table 2, Table S1**). In contrast, changes in NFS were more variable, with no clear differentiation across treatment groups (not shown).

Proprietary serum fibrosis markers

In the ITT population, dose-dependent reductions in FibroTest™ scores were observed in OCA patients as early as Month 6 and sustained over 18 months compared with a small increase among placebo patients (**Table 2, Fig. 2A**); a similar trend was observed for the 18-month on-treatment population (**Table S1**). There was a modest non–dose-dependent reduction in ELF™ scores in the OCA treatment groups and a slight increase in ELF™ scores with placebo (**Fig. 2B**). When patients were categorized by baseline ELF™ quartile, among patients with baseline ELF™ ≥10.3, 8.6% receiving placebo versus 15.4% receiving OCA 25 mg showed histologic fibrosis improvement with no worsening of NASH (**Fig. S2**).

Imaging-based markers of liver stiffness

At Month 18 in the ITT population, liver stiffness assessed by VCTE demonstrated a dose-dependent decrease in patients treated with OCA (**Table 2**, **Fig. 3**); the 18-month on-treatment population showed a similar trend (**Table S1**). OCA 10 and 25 mg patients showed improvement in liver stiffness values versus baseline (LS mean change [95% CI] −0.56 [−1.65, 0.53] kPa and −1.30 [−2.41, −0.20] kPa, respectively). Conversely, placebo-treated patients had an increase in liver stiffness relative to baseline (LS mean change [95% CI] = 1.11 [0.04, 2.18] kPa). Consistent with OCA-mediated fibrosis improvement, the difference in LS mean (95% CI) change from baseline at Month 18 between OCA- and placebo-treated patients was −1.67 (−3.06, −0.28) kPa for OCA 10 mg and −2.41 (−3.82, −1.00) kPa for OCA 25 mg (**Fig. 3**)**.**

Emerging markers

In the ITT population, FibroMeter™ (N = 419), FibroMeter™ VCTE (N = 415), and FAST scores (N = 310) were evaluated in a subset of patients with available data. Compared with placebo, patients treated with OCA had meaningful reductions in these scores at Month 6 that were sustained through Month 18 (**Table 2, Fig. 4**). Dose-dependent decreases were also observed in FibroMeter™ and FAST values. FibroMeter™ VCTE did not show this pattern. Similar trends were observed for the 18-month on-treatment population (**Table S1**).

Mean levels of procollagen biomarker Pro-C3 were stable throughout the study with little to no change at Month 18 relative to baseline in all groups in both the ITT and 18-month on-treatment populations (**Table 2**; **Table S1**). A robust dose-dependent reduction in caspase-cleaved CK-18 (M30 fragment) was observed at Month 18 in patients in the ITT population receiving OCA versus placebo (**Table 2**).

Individualized changes in ALT, AST, FIB-4, and VCTE

Waterfall plots displaying patient-level changes of these markers from baseline are presented in **Fig. S3**. Compared with placebo, more patients treated with OCA had reductions from baseline in ALT and AST at Months 1, 3, 6, and 18 (**Fig. S3A-D**) and FIB-4 and VCTE score from baseline to Month 18 (**Fig. S3E**). At Month 18, differences were most apparent with ALT; 208 patients had reductions with OCA 25 mg versus 164 patients with placebo. A similar pattern was observed with AST at Month 18 among patients with baseline AST ≥30 U/L (OCA 25 mg, n = 263; placebo, n = 251); 88 (33.5%) and 47 (18.7%) OCA 25 mg and placebo patients, respectively, had AST <30 U/L at Month 18 (**Table S2**). FIB-4 score reductions (OCA 25 mg, n = 157; placebo, n = 137) and VCTE reductions (OCA 25

mg, n = 115; placebo, n = 97) were also more common in patients treated with OCA 25 mg.

NIT changes by change in fibrosis stage

Aminotransferases

Mean percentage changes from baseline for each NIT were evaluated by treatment group and differentiated by change in fibrosis status: improved fibrosis (≥1 stage), stable fibrosis, and worsened fibrosis (≥1 stage).

ALT decreased over time in all patients with a ≥1-stage improvement in histologic fibrosis. This improvement was most pronounced in the OCA 25 mg group (−43.2% at Month 18). ALT reductions were also observed in the OCA 25 mg group in patients either with stable histologic fibrosis (−29.6% at Month 18) or worsened fibrosis ≥1 stage (−24.01% at Month 18) (**Fig. 5A**). A similar pattern was observed with AST (**Fig. 5B**). Consistent AST reductions over time were observed in patients with improved fibrosis, regardless of treatment group. Similarly, OCA 25 mg patients had the greatest AST reductions. In patients with stable fibrosis, AST was unchanged in the placebo group but decreased over time in the OCA groups, with a mean change of −20.9% at Month 18 in OCA 25 mg patients.

Composite fibrosis scores based on clinical parameters

Separation of FIB-4 scores between those with improved fibrosis and those with stable or worsened fibrosis occurred as early as Month 6; FIB-4 score improvement was most pronounced in patients with a ≥1-stage improvement in histologic fibrosis treated with OCA 25 mg (−16.0% at Month 18) (**Fig. 5C**). In patients with stable fibrosis, mean FIB-4 values remained near baseline in all groups.

Mean FIB-4 values increased over time in all treatment groups in patients with ≥1-stage increase in fibrosis (**Fig. 5C**).

Proprietary serum fibrosis markers

While mean FibroTest™ scores increased over time in patients receiving placebo independently of fibrosis improvement, all patients receiving OCA had improved mean FibroTest™ scores (**Fig. 6A**). In the OCA 25 mg group, mean changes of −20.3%, −8.1%, and −4.0% were observed for patients with improved, stable, and worsened fibrosis, respectively, at Month 18. Mean ELF™ scores increased over time in patients with ≥1-stage fibrosis worsening in all treatment groups (**Fig. 6B**). In patients with unchanged fibrosis stage, mean ELF™ scores remained stable over 18 months regardless of treatment allocation. Patients in the OCA treatment groups with ≥1-stage fibrosis improvement had improved ELF™ scores over time. In these patients, mean (percentage change) change from baseline to Month 18 in ELF™ score was 0.03 (0.6%), −0.18 (−1.7%), and −0.25 (−2.4%) with placebo, OCA 10 mg, and OCA 25 mg, respectively. In patients with ≥1-stage increase in fibrosis, mean (percentage change) change from baseline to Month 18 in ELF™ scores was 0.28 (3.1%), 0.28 (3.1%), and 0.33 (3.8%), respectively.

Imaging-based markers of liver stiffness

Liver stiffness assessed by VCTE improved over time among patients with ≥1-stage fibrosis improvement. Mean kPa (percentage change) changes from baseline to Month 18 of −1.89 (−13.2%), −1.83 (−10.9%), and −3.68 (−19.8%) were seen in patients treated with placebo, OCA 10 mg, and OCA 25 mg, respectively. In patients

with stable fibrosis, liver stiffness improved in the OCA 10 and 25 mg groups (mean [mean percentage] change, −1.43 [−7.6%] and −1.73 [−7.6%]) versus placebo (0.00 [19.5%]). Conversely, VCTE results worsened over time in patients with ≥1-stage increase in fibrosis (**Fig. 6C**). Among patients with stable fibrosis, liver stiffness improved in patients receiving OCA 25 mg versus placebo.

Univariate logistic regression analysis

Univariate logistic regression analysis showed significant (OR [95% CI excludes 1], p <0.05) but weak (AUROCs ≤0.62) associations between fibrosis improvement at Month 18 and NIT improvements at all time points, except for AST at Month 1, VCTE at Month 6, and ELF™ at Month 12 (OR [95% CI includes 1], p >0.05; **Table S3**).

Discussion

Histologic improvement in fibrosis is the only validated predictor of clinical outcomes[41, 42] and is required to assess antifibrotic efficacy in NASH trials. Liver biopsy is invasive, prone to sampling and observer variability,[43] and inappropriate for gauging treatment response in routine clinical practice. Establishing NIT options in lieu of biopsy to assess efficacy would represent a major advance in NASH trials that could then be applied clinically upon drug approval. This analysis was restricted to identifying NITs reflecting histologic changes in fibrosis in patients with NASH and, as a prespecified exploratory objective, to determine whether the histologically demonstrated antifibrotic effect of OCA in REGENERATE is identifiable using NITs.

The primary objectives of REGENERATE were to evaluate the effects of OCA treatment compared with placebo on 1) histologic improvement assessed at the

prespecified Month 18 interim analysis and at end of study and 2) liver-related clinical outcomes to be assessed at the end of the study in patients with NASH with liver fibrosis. This analysis was performed to assess the association between NIT changes and histologic improvement at the Month 18 interim analysis; evaluation of a potential association between NIT changes or fibrosis improvement and clinical outcomes is beyond its scope but will be assessed at the end of the study. Since REGENERATE demonstrated histologic fibrosis improvement in patients treated with OCA at Month 18, we determined if treatment allocation resulted in similar changes in NITs. Remarkably, patients receiving OCA showed improved biochemical markers of liver injury (ALT, AST, GGT), serum fibrosis markers, elastography measurements, and imaging biomarkers. Compared with placebo, patients in the OCA arms had reduced ALT, AST, and GGT levels as early as Month 1, with further improvements through Month 18. Patients receiving either dose of OCA showed improved liver stiffness measured by VCTE by Month 18, while stiffness increased in patients taking placebo. Serum fibrosis biomarkers such as FIB-4, FibroTest™, ELF™ FibroMeter™, and FibroMeter™ VCTE (which combines liver stiffness with clinical data) improved in the OCA arms compared with placebo at Month 18. Thus, changes in NITs reflected histologic changes, and the magnitude of effect was larger in patients treated with OCA compared with those treated with placebo in a dose-dependent manner. FAST score also improved in patients receiving OCA versus placebo through Month 18. Collectively, these data show patients who received OCA exhibited improvements in several NITs in parallel with previously demonstrated histologic response.

We determined whether NIT changes were associated with histologic fibrosis changes by analyzing NIT data in patients with improved, stable, or worsened

fibrosis at Month 18. Regardless of treatment, patients with ≥1-stage fibrosis improvement had the greatest improvement in NITs while patients with ≥1-stage fibrosis worsening typically showed no NIT improvement. There was clear separation in values for both FIB-4 and ELF™ during the trial and at Month 18 across treatment groups. However, ELF™ changes were more marked with fibrosis worsening than with improvement, while FIB-4 changes equally reflected fibrosis worsening and improvement. ELF™ scores only improved in the OCA 10 and 25 mg arms in patients with fibrosis improvement, and they worsened in patients who received placebo. In patients whose fibrosis worsened, ELF™ scores increased in all treatment groups. Interestingly, patients who received OCA 25 mg and experienced fibrosis improvement had more pronounced improvements in FIB-4, ELF™, VCTE, and FibroTest™ scores compared with those with histologic improvement in the placebo group. In patients with stable histologic fibrosis, a trend toward improved FIB-4 and FibroTest™ scores was observed with OCA. While this could be due to OCA-induced changes in NIT parameters unrelated to fibrosis, it could also reflect histologic changes in fibrosis or profibrogenic activity pathways not captured by categorical histologic staging at Month 18, as histologic staging is semiquantitative, with rather low sensitivity to change, and is fraught with the previously noted limitations. Improvements in serum-based NITs observed in patients with stable histologic fibrosis in the OCA 25 mg arm were corroborated by reduced liver stiffness by VCTE. Our results suggest these NITs could identify patients with histologic improvement of fibrosis.

We also analyzed aminotransferase changes at Month 18 by histologic improvement. Aminotransferases are not primarily fibrosis markers but rather surrogates of necroinflammatory activity that drives the fibrogenic response. Even

with placebo, ALT reflected changes in histologically assessed fibrosis. Patients with fibrosis improvement had ALT reduction, whereas ALT remained stable in patients with no histologic change and increased in patients with fibrosis progression.

Using univariate logistic regression analysis, statistically significant but weak associations were found between NIT improvements at various time points and fibrosis improvement at Month 18. An OR of 1.09 for every 10% improvement in either ALT or AST at Month 18 was identified, suggesting that the odds of fibrosis improvement increase exponentially for each 10% improvement in ALT or AST. For example, with a 25% improvement in ALT or AST, the OR of a 1-stage fibrosis improvement versus no change would be approximately $1.09^{2.5} = 1.2$. For a 50% improvement in either measure, the OR versus no improvement would be approximately 1.5 ($1.09^{5} = 1.54$). Other NITs also displayed significant associations, at various time points, with Month 18 fibrosis improvement. This is an encouraging result for the prospect of a connection between NIT values and eventual fibrosis changes; however, the AUROC values for each of these were suggestive of only weak associations, indicating that while NIT improvements observed in REGENERATE are associated with fibrosis improvement at Month 18, individual NIT changes are not likely to be effective univariate clinical predictors of fibrosis improvement by Month 18. This is underscored by the fact that individual patient results, as seen in the waterfall plots, show many more patients in all groups had improvements in individual NIT values than ultimately had fibrosis improvement at Month 18. These results suggest that NIT improvements, when considered in combination with other clinical measurements, could also be useful in assessing fibrosis improvement within a multivariate model, a concept that warrants further exploration when additional data from REGENERATE become available.

Our results expand on similar observations in FLINT,[7] a phase 2 trial first demonstrating an antifibrotic effect with OCA in patients with NASH. In FLINT, changes in ALT and AST at Weeks 12 and 24 were significantly associated with histologic response at Week 72 (p <0.05).[23] Further *post hoc* analyses demonstrated that OCA-treated patients had significant reductions in APRI and FIB-4 scores versus placebo-treated patients after 72 weeks (p <0.01). In patients with APRI and FIB-4 score improvement after 24 weeks of OCA 25 mg treatment, those changes significantly correlated with histologic fibrosis improvement (≥1 stage) after 72 weeks (APRI, p = 0.015; FIB-4, p = 0.036).[44]

FIB-4 and NFS have been suggested to provide the best accuracy among simple NITs in identifying advanced fibrosis in fatty liver diseases, and some NITs may be useful in determining the stage of hepatic fibrosis in other diseases (*e.g.*, hepatitis C virus); however, the reliability of NITs may depend on the disease or treatment being assessed.[45-47] In our study, changes in NITs likely reflect both direct and indirect (reduction in inflammatory activity) effects of OCA on fibrogenesis. Some patients treated with OCA were still showing improvement in NITs at Month 18; future analyses may show that they continue to improve as time progresses. Although these results are promising, the use of ALT, AST, other NITs, and/or NIT combinations to assess fibrosis requires further exploration.

Strengths of the REGENERATE study include a large patient population; centralized assessment of serum-based NITs at multiple time points; protocol-driven liver biopsy; and blinded, central liver pathology assessment. Eighteen months is likely sufficient to capture meaningful NIT changes reflecting changes in liver fibrosis. Notable limitations of NITs are that they have limited (although increasing) availability and can be operator dependent. This NIT evaluation was an exploratory

objective of REGENERATE with no prespecified hypothesis testing for treatment effects. These findings are specific to this analysis in patients with NASH with fibrosis and may not be applicable to individual patients with NASH or to other liver diseases. Finally, only the completion of the clinical outcome portion of REGENERATE at end of study will inform whether observed NIT changes correspond with clinical outcomes.[39]

In conclusion, in a large sample of patients with protocolized measurements of histology and NITs, we have confirmed that the antifibrotic effect of OCA demonstrated by liver histology is consistently observed in NITs routinely measured in clinical practice. We have demonstrated that fibrosis improvement or deterioration may be reflected in NIT changes. If confirmed in other studies with similar predesigned methodology, these results could open the field to the use of NITs as measures of treatment response in clinical trials and as indicators of therapeutic efficacy in clinical practice. The REGENERATE study is ongoing and will continue through clinical outcomes for verification and description of clinical benefits of OCA in the treatment of NASH with fibrosis.

Abbreviations

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; ELF, enhanced liver fibrosis; FAST, FibroScan-AST; FIB-4, fibrosis-4; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; INR, international normalized ratio; IQR, interquartile range; ITT, intention-to-treat; LS, least squares; LSM, least squares mean; MMRM, mixed-effect repeated-measures; MR, magnetic resonance; MRI, magnetic resonance imaging; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, nonalcoholic fatty liver disease fibrosis score; NIT, noninvasive test; OCA, obeticholic acid; OR, odds ratio; SD, standard deviation; SE, standard error; SEM, standard error of the mean; VCTE, vibration-controlled transient elastography.

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Data Sharing Statement

All data supporting the findings of this analysis are available within the article and its supplementary materials. The REGENERATE study is ongoing at the time of publication and blinded at the individual study participant level; participant-level data therefore will not be available until completion of the study and the end-of-study

analysis. Questions regarding additional data availability should be directed to the study Sponsor through the corresponding methods author.

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TABLES

Table 1. Baseline demographic and clinical characteristics (intention-to-treat population).

	Placebo (n = 311)	OCA 10 mg (n = 312)	OCA 25 mg (n = 308)
Age, years, mean (SD)	55 (12)	55 (11)	55 (11)
Female, n (%)	187 (60)	177 (57)	175 (57)
White, n/N (%)[a]	264/280 (94)	263/287 (92)	249/286 (87)
Hispanic ethnicity, n/N (%)[a]	52/282 (18)	42/286 (15)	47/282 (17)
BMI, kg/m^2, mean (SD)	34.1 (5.9)	33.6 (5.6)	33.8 (5.4)
Fibrosis stage F3, n (%)	169 (54)	182 (58)	169 (55)
NAFLD activity score ≥6, n/N (%)[a]	215/309 (70)	211 (68)	208 (68)
Type 2 diabetes, n (%)	175 (56)	171 (55)	171 (56)
Lipid-lowering medications, n (%)	175 (56)	170 (54)	160 (52)
Statins, n (%)	144 (46)	142 (46)	127 (41)

[a]Percentages are calculated based on patients for whom information was available.

BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; OCA, obeticholic acid; SD, standard deviation.

Table 2A. Clinical chemistry and markers of inflammation and fibrosis (intention-to-treat population) with placebo.

	Placebo (n = 311)			
	n	Baseline, mean (SD)	Month 18, mean (SD)	Change from baseline to Month 18 (LS mean [95% CI])
Laboratory parameters or liver biochemistry				
ALT, U/L	311	79.6 (56.59)	62.9 (43.56)[a]	−14.8 (−19.7, −10.0)[a]
AST, U/L	311	58.9 (40.51)	47.8 (29.64)[a]	−8.7 (−12.1, −5.2)[a]
GGT, U/L	311	101.8 (128.78)	84.2 (101.78)[a]	−8.7 (−17.8, 0.5)[a]
Total bilirubin, mg/dL	311	0.64 (0.28)	0.68 (0.35)[a]	0.04 (0.01, 0.07)[a]
INR	311	1.07 (0.08)	1.07 (0.10)[a]	0.005 (−0.007, 0.018)[a]
Platelets, 10^9/L	311	241.9 (67.00)	243.8 (74.71)[b]	1.5 (−3.2, 6.1)[b]
Albumin, g/dL	311	4.43 (0.25)	4.34 (0.27)[a]	−0.10 (−0.13, −0.08)[a]
Composite fibrosis scores based on clinical parameters				
FIB-4	311	1.62 (0.89)	1.58 (0.88)[c]	−0.04 (−0.12, 0.05)[c]
APRI	311	0.78 (0.57)	0.65 (0.53)[c]	−0.11 (−0.17, −0.05)[c]
NFS	309	−0.87 (1.33)	−0.80 (1.45)[c]	0.10 (0.001, 0.19)[d]
Proprietary serum fibrosis markers				
FibroTest™ score	302	0.40 (0.22)	0.42 (0.22)[c]	0.02 (−0.001, 0.03)[e]
ELF™ score	295	9.70 (0.94)	9.73 (0.94)[a]	0.03 (−0.07, 0.13)[f]
Imaging-based markers				
FibroScan® VCTE, kPa	225	12.46 (7.54)	11.98 (8.84)[g]	1.09 (0.02, 2.16)[h]
Emerging markers of fibrosis and NASH				
FAST score	100	0.60 (0.21)	0.52 (0.26)[i]	−0.03 (−0.09, 0.03)[j]
FibroMeter™	131	0.53 (0.26)	0.53 (0.25)[h]	0 (−0.04, 0.04)[k]

FibroMeter™ VCTE	129	0.59 (0.29)	0.58 (0.30)[h]	−0.02 (−0.07, 0.02)[l]
CK-18 (M30), U/L	308	776.5 (802.09)	659.8 (658.45)[m]	−54.4 (−117.4, 8.63)[c]
Pro-C3, µg/L	224	17.13 (10.13)	16.66 (7.97)[n]	−0.53 (−1.99, 0.94)[o]

[a]n = 257; [b]n = 254; [c]n = 253; [d]n = 251; [e]n = 246; [f]n = 245; [g]n = 221; [h]n = 183; [i]n = 150; [j]n = 68; [k]n = 91; [l]n = 89; [m]n = 256; [n]n = 146; [o]n = 143.

Table 2B. Clinical chemistry and markers of inflammation and fibrosis (intention-to-treat) with OCA 10 mg.

	OCA 10 mg (n = 312)			
	n	Baseline, mean (SD)	Month 18, mean (SD)	Change from baseline to Month 18 (LS mean [95% CI])
Laboratory parameters or liver biochemistry				
ALT, U/L	312	75.6 (46.96)	51.7 (43.08)[a]	−23.0 (−27.9, −18.1)[a]
AST, U/L	312	56.6 (34.04)	41.8 (32.38)[b]	−13.4 (−16.8, −9.9)[b]
GGT, U/L	312	99.6 (108.33)	77.0 (138.49)[a]	−17.2 (−26.3, −8.0)[a]
Total bilirubin, mg/dL	312	0.65 (0.30)	0.68 (0.36)[a]	0.03 (−0.001, 0.06)[a]
INR	312	1.07 (0.10)	1.06 (0.12)[c]	−0.009 (−0.02, 0.004)[c]
Platelets, 10^9/L	310	238.5 (68.00)	238.6 (71.33)[d]	3.3 (−1.4, 7.9)[b]
Albumin, g/dL	312	4.43 (0.25)	4.35 (0.28)[a]	−0.10 (−0.13, −0.07)[a]
Composite fibrosis scores based on clinical parameters				
FIB-4	310	1.63 (0.88)	1.58 (1.21)[e]	−0.08 (−0.17, 0.01)[f]
APRI	310	0.76 (0.53)	0.59 (0.69)[e]	−0.17 (−0.23, −0.11)[f]
NFS	306	−0.88 (1.35)	−0.69 (1.45)[g]	0.11 (0.02, 0.21)[h]
Proprietary serum fibrosis markers				
FibroTest™ score	305	0.42 (0.21)	0.39 (0.22)[d]	−0.03 (−0.05, −0.02)[e]
ELF™ score	303	9.73 (0.92)	9.71 (1.06)[i]	−0.03 (−0.12, 0.07)[j]
Imaging-based markers				
FibroScan® VCTE, kPa	225	11.94 (5.64)	10.55 (6.69)[k]	−0.58 (−1.67, 0.50)[l]
Emerging markers of fibrosis and NASH				
FAST score	107	0.60 (0.24)	0.42 (0.28)[m]	−0.11 (−0.17, −0.06)[n]
FibroMeter™	155	0.57 (0.24)	0.48 (0.25)[o]	−0.08 (−0.12, −0.04)[p]

FibroMeter™ VCTE	155	0.64 (0.26)	0.50 (0.29)[o]	−0.13 (−0.17, −0.09)[p]
CK-18 (M30), U/L	307	713.6 (617.92)	506.2 (440.97)[q]	−222.9 (−285.4, −160.3)[r]
Pro-C3, µg/L	225	17.54 (12.13)	16.54 (10.60)[s]	−1.16 (−2.66, 0.35)[t]

[a]n = 255; [b]n = 253; [c]n = 256; [d]n = 254; [e]n = 250; [f]n = 249; [g]n = 248; [h]n = 244; [i]n = 261; [j]n = 252; [k]n = 213; [l]n = 182; [m]n = 136; [n]n = 73; [o]n = 180; [p]n = 111; [q]n = 262; [r]n = 258; [s]n = 137; [t]n = 135.

Table 2C. Clinical chemistry and markers of inflammation and fibrosis (intention-to-treat) with OCA 25 mg.

	OCA 25 mg (n = 308)			
	n	Baseline, mean (SD)	Month 18, mean (SD)	Change from baseline to Month 18 (LS mean [95% CI])
Laboratory parameters or liver biochemistry				
ALT, U/L	308	80.2 (56.36)	45.8 (36.72)[a]	−33.5 (−38.4, −28.6)[a]
AST, U/L	308	57.0 (34.09)	36.8 (20.99)[a]	−19.4 (−22.8, −15.9)[a]
GGT, U/L	308	95.6 (116.52)	49.3 (82.54)[b]	−43.4 (−52.6, −34.2)[b]
Total bilirubin, mg/dL	308	0.69 (0.34)	0.69 (0.34)[a]	0.01 (−0.02, 0.04)[a]
INR	308	1.06 (0.08)	1.05 (0.10)[a]	−0.01 (−0.03, −0.001)[a]
Platelets, 10^9/L	308	237.2 (68.97)	245.9 (78.89)[a]	9.0 (4.3, 13.7)[a]
Albumin, g/dL	308	4.46 (0.25)	4.33 (0.30)[b]	−0.14 (−0.16, −0.11)[b]
Composite fibrosis scores based on clinical parameters				
FIB-4	308	1.63 (0.85)	1.46 (0.95)[a]	−0.11 (−0.20, −0.02)[a]
APRI	308	0.79 (0.62)	0.51 (0.43)[a]	−0.25 (−0.31, −0.19)[a]
NFS	304	−0.91 (1.40)	−0.81 (1.50)[c]	0.13 (0.03, 0.22)[d]
Proprietary serum fibrosis markers				
FibroTest™ score	295	0.43 (0.22)	0.36 (0.21)[e]	−0.06 (−0.07, −0.04)[f]
ELF™ score	296	9.72 (0.94)	9.61 (1.01)[g]	−0.04 (−0.14, 0.06)[d]
Imaging-based markers				
FibroScan® VCTE, kPa	228	12.36 (7.28)	10.06 (5.67)[h]	−1.32 (−2.42, −0.22)[i]
Emerging markers of fibrosis and NASH				
FAST score	103	0.60 (0.21)	0.41 (0.25)[j]	−0.18 (−0.24, −0.12)[k]
FibroMeter™	133	0.55 (0.24)	0.41 (0.23)[l]	−0.10 (−0.14, −0.07)[m]

FibroMeter™ VCTE	131	0.60 (0.27)	0.46 (0.30)[l]	−0.11 (−0.16, −0.06)[n]
CK-18 (M30), U/L	303	733.5 (745.76)	429.0 (346.30)[g]	−295.2 (−358.3, −232.1)[o]
Pro-C3, µg/L	216	16.66 (9.50)	16.60 (12.27)[p]	−0.50 (−1.99, 0.98)[q]

[a]n = 253; [b]n = 254; [c]n = 249; [d]n = 245; [e]n = 252; [f]n = 241; [g]n = 255; [h]n = 206; [i]n = 171; [j]n = 126; [k]n = 61; [l]n = 173; [m]n = 86; [n]n = 85; [o]n = 250; [p]n = 143; [q]n = 139.

All parameter values are mean (SD) unless otherwise indicated.

APRI, AST-to-platelet ratio index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; FAST, FibroScan®-AST; FIB-4, fibrosis-4; GGT, gamma-glutamyl transferase; INR, international normalized ratio; LS, least squares; MRI, magnetic resonance imaging; NA, not applicable; NASH, nonalcoholic steatohepatitis; NFS, nonalcoholic fatty liver disease fibrosis score; OCA, obeticholic acid; SD, standard deviation; VCTE, vibration-controlled transient elastography.

FIGURE LEGENDS

Fig. 1. LS mean percentage change from baseline in liver biochemistry and FIB-4 tests over time by treatment group. LS mean (SEM) percentage change from baseline (intention-to-treat population) in ALT (panel A), AST (panel B), GGT (panel C) and FIB-4 (panel D). ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; GGT; gamma-glutamyl transferase; LS, least squares; OCA, obeticholic acid; SEM, standard error of the mean.

Fig. 2. LS mean percentage change from baseline in proprietary markers of fibrosis over time by treatment group. LS mean (SEM) percentage change from baseline (intention-to-treat population) in FibroTest™ (panel A) and ELF™ (panel B). ELF™, enhanced liver fibrosis; LS, least squares; OCA, obeticholic acid; SEM, standard error of the mean.

Fig. 3. LS mean change from baseline in liver stiffness measured by VCTE over time by treatment group. LS mean (SE) change from baseline (intention-to-treat population) in VCTE. LS, least squares; OCA, obeticholic acid; SE, standard error; VCTE, vibration-controlled transient elastography.

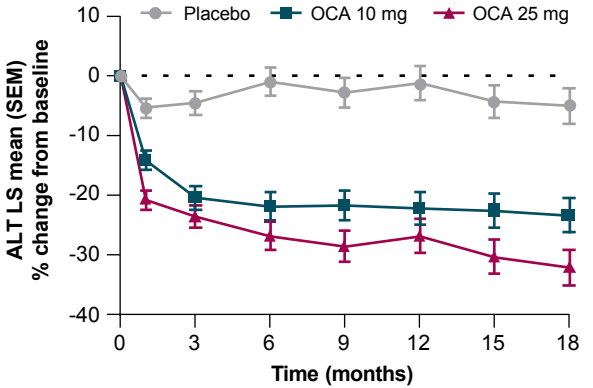
Fig. 4. LS mean change from baseline in emerging markers over time by treatment group. LS Mean (SE) change in from baseline over time (intention-to-treat population) in FibroMeter™, FibroMeter™ VCTE, and FAST. FAST, FibroScan®-AST; LS, least squares; OCA, obeticholic acid; SE, standard error; VCTE, vibration-controlled transient elastography.

Fig. 5. Mean percentage change from baseline in aminotransferases and FIB-4 over time by treatment group and fibrosis improvement status. Mean (SE)

percentage change over time by treatment group and histologic fibrosis status at Month 18 (intention-to-treat population). ALT (panel A), AST (panel B), FIB-4 (panel C). Axes on each panel are matched to facilitate comparison of performance across the treatment groups. ALT, alanine aminotransferase; AST, aspartate aminotransferase; OCA, obeticholic acid; SE, standard error.

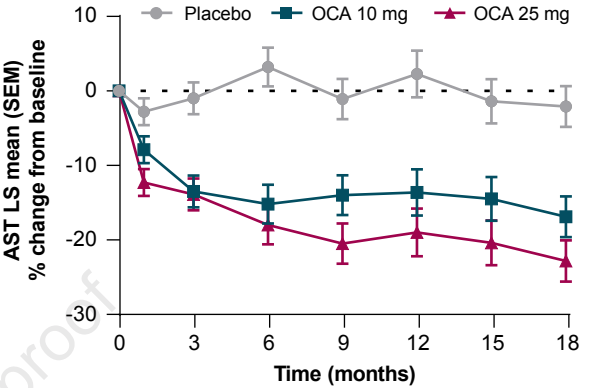
Fig. 6. Mean percentage change from baseline in liver stiffness and proprietary markers of fibrosis over time by treatment group and fibrosis improvement status. Mean (SE) percentage change in NITs over time by treatment group and histologic fibrosis status at Month 18 (intention-to-treat population). FibroTest™ (panel A), ELF™ (panel B), VCTE (panel C). Axes on each panel are matched to facilitate comparison of performance across the treatment groups. ELF, enhanced liver fibrosis; OCA, obeticholic acid; SE, standard error; VCTE, vibration-controlled transient elastography.

A



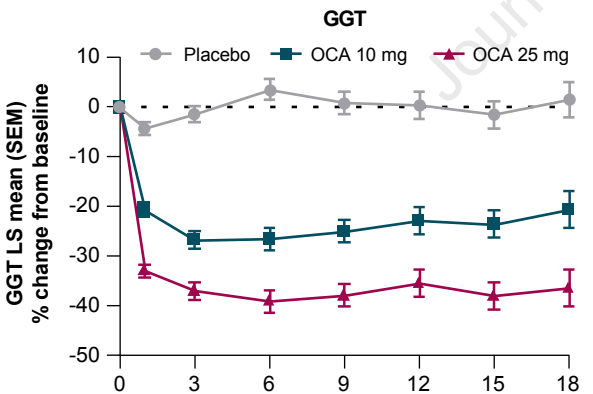
Placebo	311	298	294	286	279	275	257
OCA 10 mg	312	303	297	292	286	275	255
OCA 25 mg	308	297	290	276	269	267	253

B



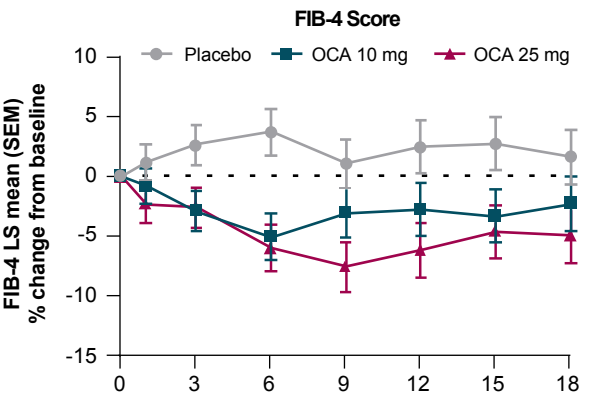
Placebo	311	297	295	285	280	275	257
OCA 10 mg	312	303	295	292	285	275	253
OCA 25 mg	308	297	291	276	268	267	253

C



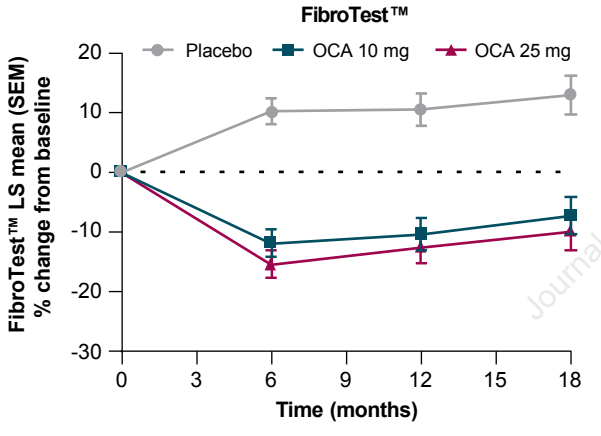
Placebo	311	298	296	288	281	276	257
OCA 10 mg	312	304	297	294	286	275	255
OCA 25 mg	308	297	291	276	269	268	254

D



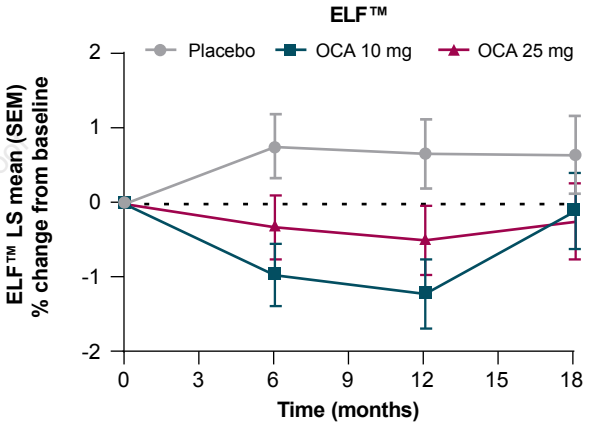
Placebo	311	294	293	282	273	274	253
OCA 10 mg	310	295	288	286	280	272	249
OCA 25 mg	308	293	287	275	267	262	253

A

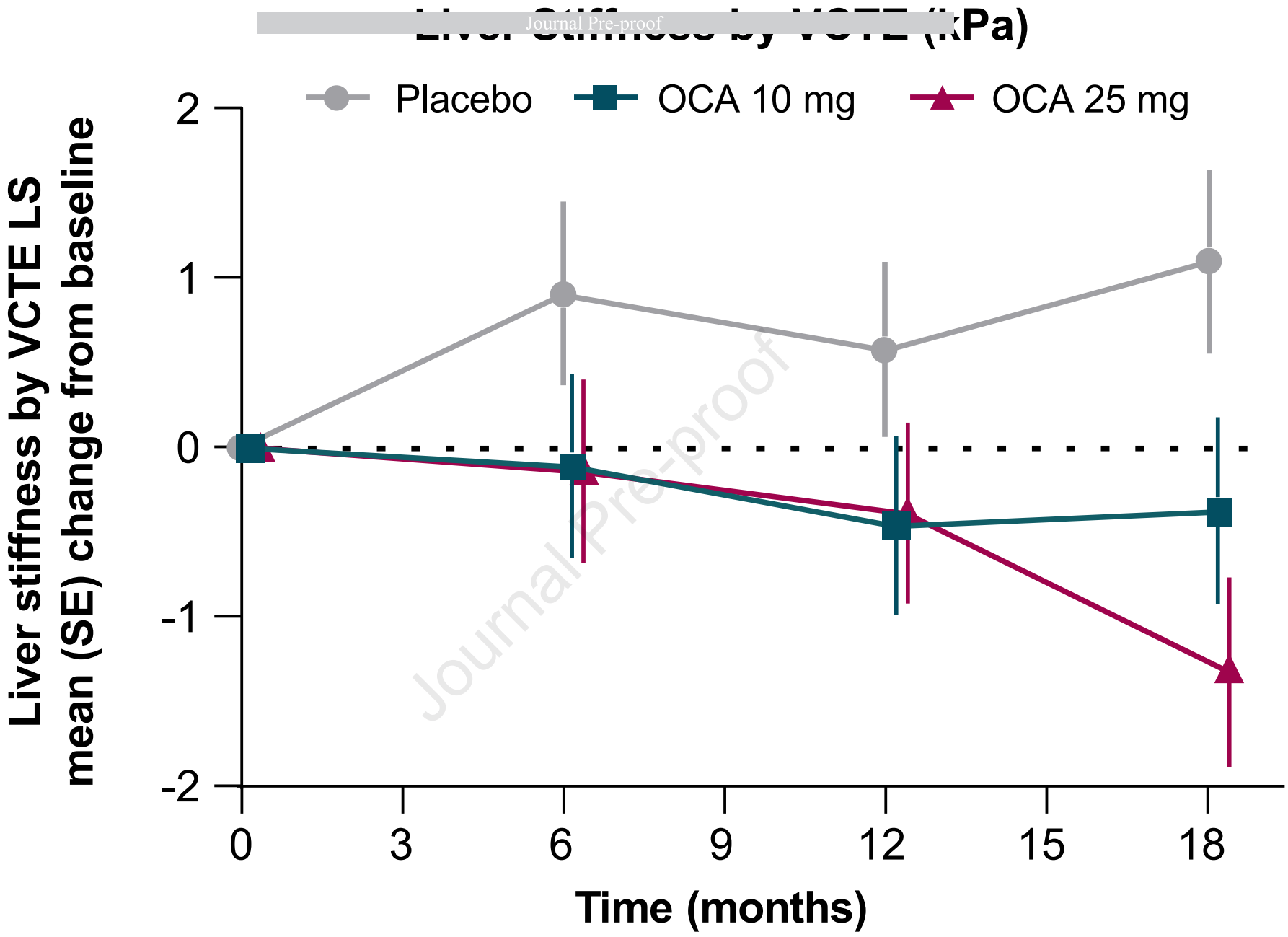


Placebo	302	286	267	246
OCA 10 mg	305	285	281	250
OCA 25 mg	295	281	258	241

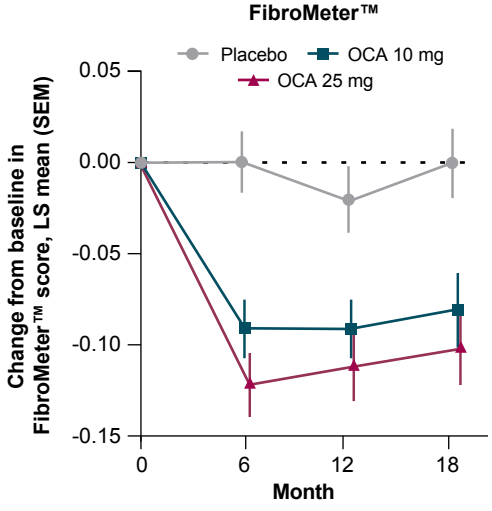
B



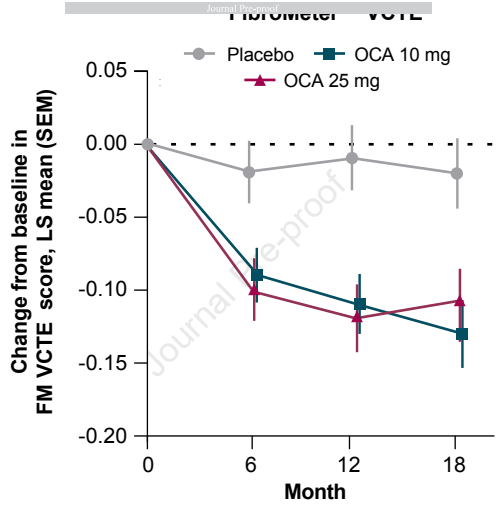
Placebo	295	281	266	245
OCA 10 mg	303	285	279	252
OCA 25 mg	296	284	262	245



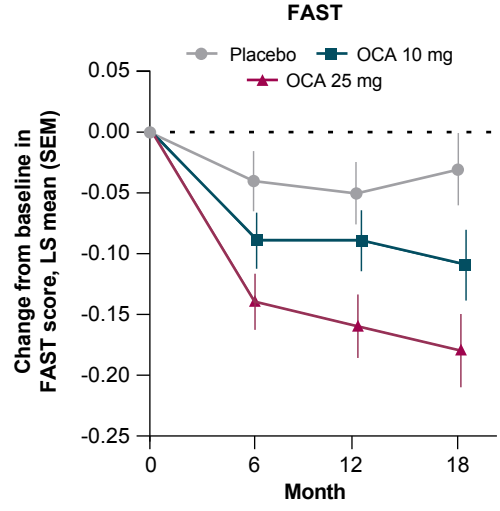
Placebo	225	203	199	183
OCA 10 mg	225	208	200	182
OCA 25 mg	228	206	184	171



Placebo	131	106	103	91
OCA 10 mg	166	134	136	111
OCA 25 mg	133	110	95	86



Placebo	129	104	102	89
OCA 10 mg	155	134	134	111
OCA 25 mg	131	109	93	85

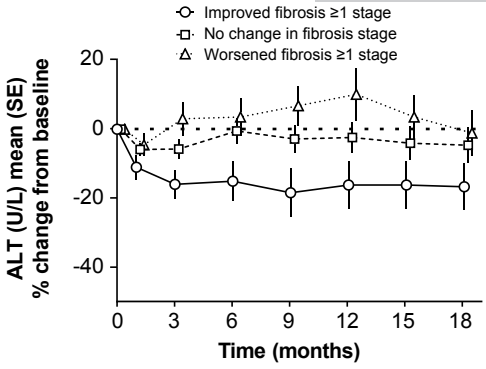


Placebo	100	83	80	68
OCA 10 mg	107	92	86	73
OCA 25 mg	103	90	76	61

A

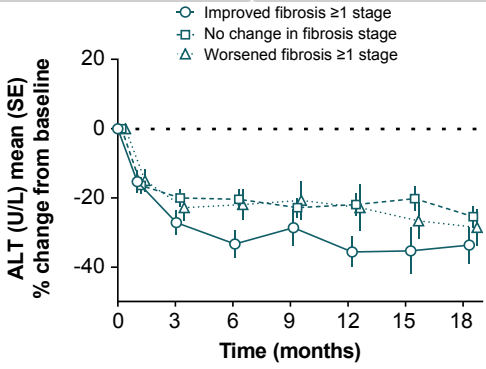
ALT

Placebo



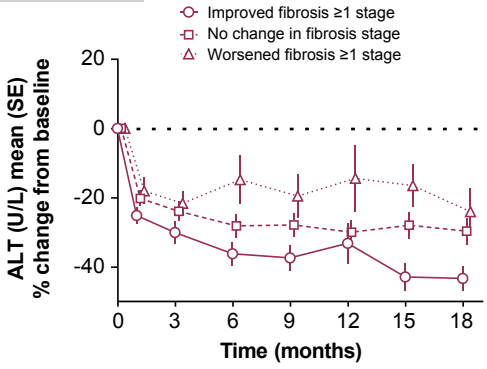
Improved, n =	60	58	60	59	58	59	57
No change, n =	146	148	147	146	144	143	139
Worsened, n =	55	55	53	54	54	55	52

OCA 10 mg



Improved, n =	73	70	73	72	72	72	67
No change, n =	146	143	144	144	144	143	135
Worsened, n =	43	44	44	44	42	43	43

OCA 25 mg

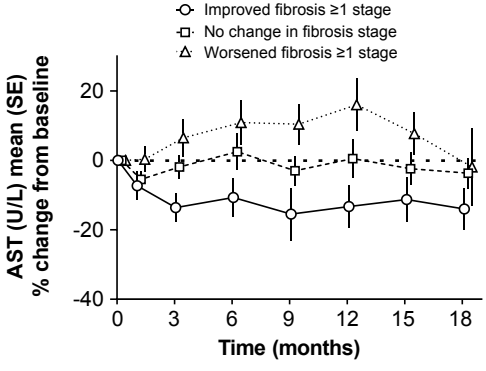


Improved, n =	92	92	92	92	91	92	90
No change, n =	124	124	124	123	123	121	119
Worsened, n =	34	34	34	34	34	33	31

B

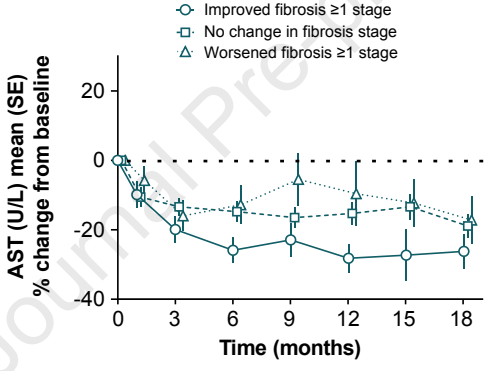
AST

Placebo



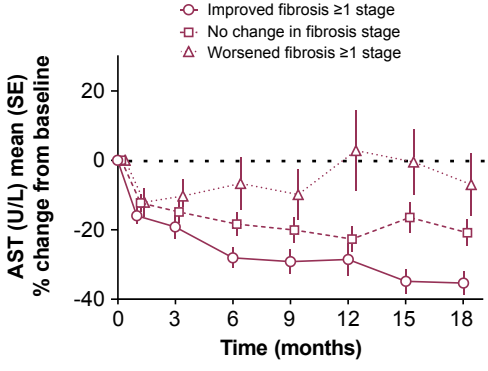
Improved, n =	59	58	60	59	59	59	57
No change, n =	145	148	147	144	143	143	139
Worsened, n =	55	54	53	55	55	54	52

OCA 10 mg



Improved, n =	70	72	71	73	72	72	67
No change, n =	143	144	144	143	143	143	134
Worsened, n =	43	44	44	44	42	43	42

OCA 25 mg

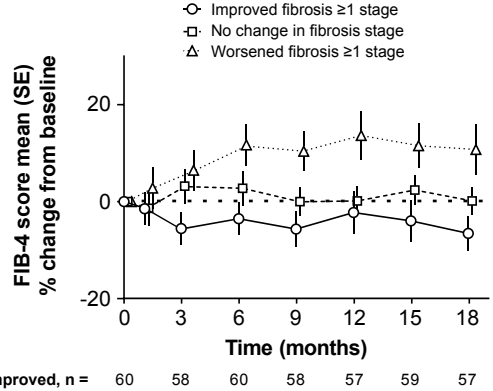


Improved, n =	92	92	93	92	91	92	90
No change, n =	123	124	124	123	122	122	119
Worsened, n =	33	34	34	34	34	33	31

C

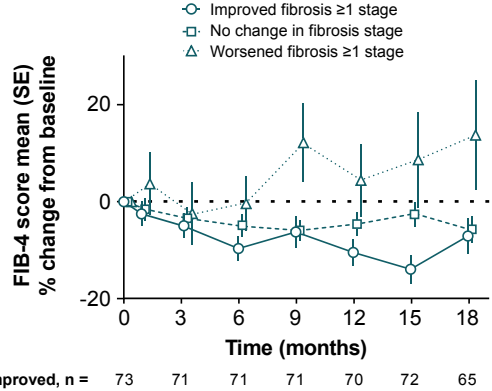
FIB-4

Placebo



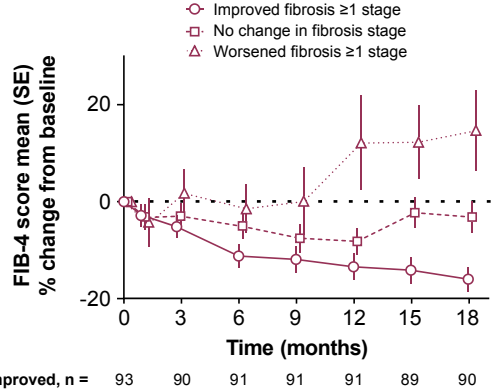
Improved, n =	60	58	60	58	57	59	57
No change, n =	148	146	146	143	141	143	136
Worsened, n =	55	53	53	54	52	54	51

OCA 10 mg



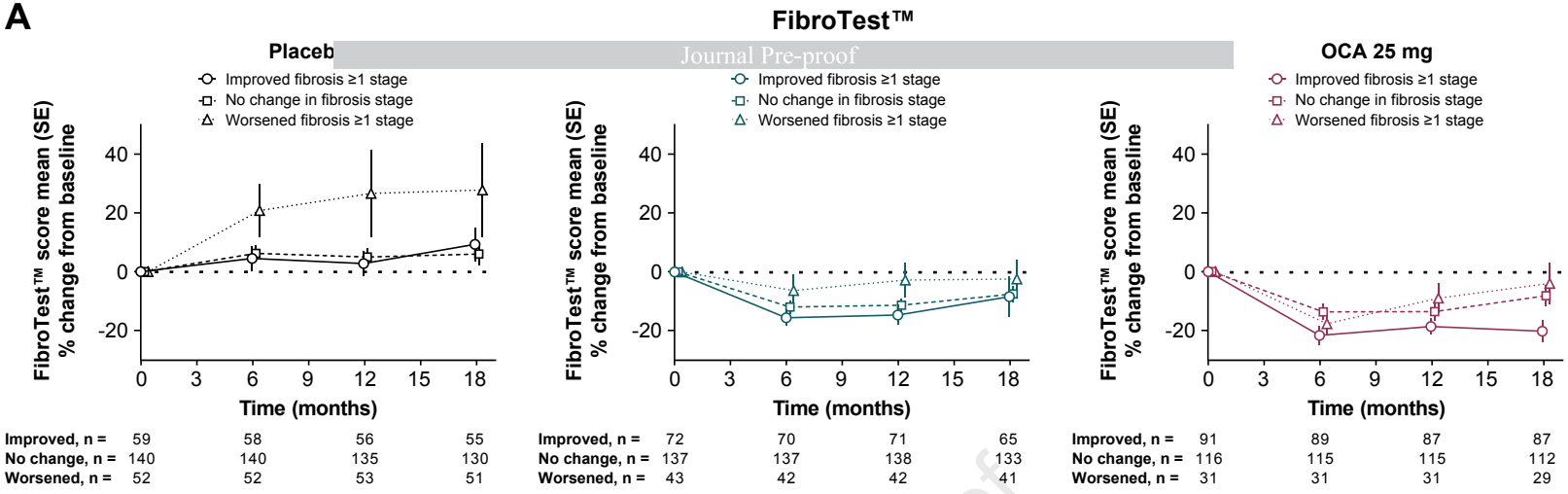
Improved, n =	73	71	71	71	70	72	65
No change, n =	146	141	141	142	143	142	134
Worsened, n =	44	42	42	42	42	43	41

OCA 25 mg

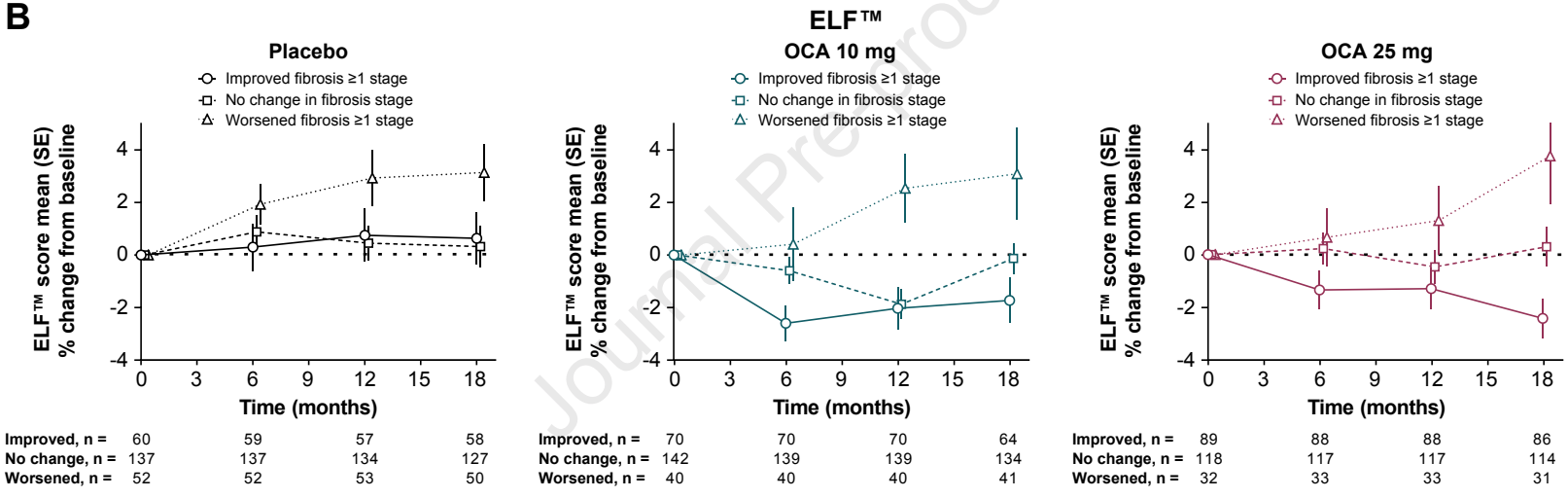


Improved, n =	93	90	91	91	91	89	90
No change, n =	124	123	123	123	121	120	119
Worsened, n =	34	34	34	34	34	33	31

A



B



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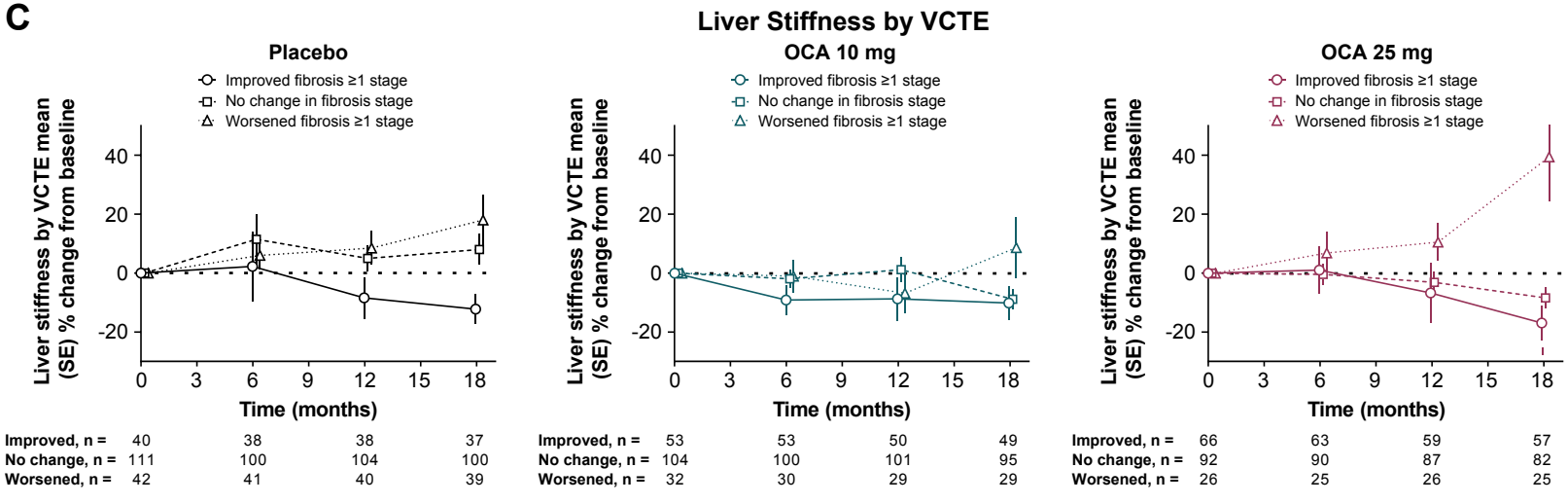

Highlights

- Reduced ALT, AST, GGT, FIB-4, and FibroTest™ scores were seen with OCA vs placebo
- Reduced liver stiffness by VCTE was observed in OCA vs placebo arms at Month 18
- NIT changes in OCA treatment arms were associated with shifts in fibrosis stage
- The antifibrotic effect of OCA might be measurable with commonly used NITs