Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial

Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis—Interim Analysis From a Randomised Phase 3 Study

Zobair M. Younossi*, Vlad Ratziu*, Rohit Loomba, Mary Rinella, Quentin M. Anstee, Zachary Goodman, Pierre Bedossa, Andreas Geier, Susanne Beckebaum, Philip Newsome, David Sheridan, Muhammad Y. Sheikh, James Trotter, Whitfield Knapple, Eric Lawitz, Manal F. Abdelmalek, Kris V. Kowdley, Aldo J. Montano-Loza, Jerome Boursier, Philippe Mathurin, Elisabetta Bugianesi, Giuseppe Mazzella, Antonio Olveira, Helena Cortez-Pinto, Isabel Graupera, David Orr, Lise Lotte Gluud, Jean-Francois Dufour, David Shapiro, Jason Campagna, Luna Zaru, Leigh MacConell, Reshma Shringarpure, Stephen Harrison†, Arun J. Sanyal†, on behalf of the REGENERATE Study Investigators

Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, USA (Z M Younossi MD, Z Goodman MD); **Sorbonne Université, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié – Salpêtrière, Institute for Cardiometabolism and Nutrition, Paris, France** (V Ratziu MD); **University of California San Diego, San Diego, CA, USA** (R Loomba MD); **Feinberg School of Medicine, Northwestern University, Chicago, IL, USA** (M Rinella MD); **The Newcastle Liver Research Group, Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom & Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom** (Q M Anstee MD); **Service d'Anatomie Pathologique, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Paris, France** (P Bedossa MD); **University of Wuerzburg, Wuerzburg, Germany** (A Geier MD); **St. Josef-Krankenhaus Kupferdreh, Essen, Germany** (S Beckebaum MD); **University of Birmingham, Birmingham, United Kingdom** (P Newsome MD); **Institute of Translational & Stratified Medicine, University of Plymouth & University Hospitals Plymouth NHS Trust, Plymouth, United Kingdom (**D Sheridan MD**); Fresno Clinical Research Center, Fresno, CA, USA** (M Y Sheikh MD); **Baylor Health, Liver Consultants of Texas, Dallas, TX, USA** (J Trotter MD); **Arkansas Gastroenterology, North Little Rock, AR, USA** (W Knapple MD); **Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, USA** (E Lawitz MD); **Duke University Medical Center Division of Gastroenterology and Hepatology, Durham, NC, USA** (M F Abdelmalek MD); **Swedish Liver Center, Seattle, WA, USA** (Prof K Kowdley MD); **Division of Gastroenterology and Liver Unit, University of Alberta, Edmonton, Canada** (A J Montano-Loza MD); **Angers University Hospital, Angers, France** (J Boursier MD); **Hepato-gastroenterology, CHU Lille, Lille, France** (P Mathurin MD); **Department of Medical Sciences, University of Turin, Turin, Italy** (E Bugianesi MD); **University of Bologna, Bologna, Italy** (G Mazzella MD); **Hospital Universitario La Paz, Madrid, Spain** (A Oliveira MD); **Clínica Universitária de Gastrenterologia, Faculdade de Medicina, Universidade de Lisboa, Portugal** (H Cortez-Pinto MD); **Hospital Clinic de Barcelona, Barcelona, Spain** (I Graupera MD); **Auckland City Hospital, Auckland, New Zealand** (D Orr MD); **Copenhagen University Hospital Hvidovre, Hvidovre, Denmark** (L Gluud MD); **University Clinic for Visceral Surgery and Medicine, Inselspital, University of Bern, Bern, Switzerland** (J F Dufour MD); **Intercept Pharmaceuticals, San Diego, CA, USA** (D Shapiro MD, J Campagna MD, L Zaru PhD, L MacConell PhD, R Shringarpure MD); **Pinnacle Clinical Research Center, San Antonio, TX, USA** (S Harrison MD); **Virginia Commonwealth University, Richmond, VA, USA** (Prof A J Sanyal MD)

*Equal contribution as first author.
†Equal contribution as senior author.

Correspondence to:
Prof Arun J Sanyal, MD
Department of Internal Medicine
Division of Gastroenterology, Hepatology and Nutrition
Virginia Commonwealth University
1250 E. Marshall St, Richmond, VA 23298, USA
Phone: 804-828-4060, E-mail: arun.sanyal@vcuhealth.org

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SUMMARY

Background: Nonalcoholic steatohepatitis (NASH) is a common type of chronic liver disease that can lead to cirrhosis. Obeticholic acid (OCA), a farnesoid X receptor agonist, has been previously shown to improve the histologic features of NASH. Results of a planned interim analysis of an ongoing, randomised, double-blind, multicentre, placebo-controlled phase 3 global study of OCA for NASH are reported.

Methods: Patients with NASH, non-alcoholic fatty liver disease (NAFLD) activity score ≥4 and fibrosis stages F2–F3, and an exploratory cohort with fibrosis stage F1, were randomised to receive placebo, OCA 10-mg, or OCA 25-mg daily in a 1:1:1 ratio. The primary endpoints for the month 18 interim analysis were fibrosis improvement (≥1 stage) with no worsening of NASH, or NASH resolution with no worsening of fibrosis, with the study considered successful if either primary endpoint was met. The study also evaluated histologic and biochemical markers of NASH and fibrosis, and safety (NCT02548351; EudraCT 2015-002560-16).

Findings: The intent-to-treat population included 931 patients with stage F2–F3 fibrosis (placebo, n=311; OCA 10-mg, n=312; OCA 25-mg, n=308). Fibrosis improvement by ≥1 stage was met by 12% of placebo patients, 18% of OCA 10-mg patients, and 23% of OCA 25-mg patients (p=0·0002). Although NASH resolution was not met (placebo, 8%; OCA 10-mg, 11%; OCA 25-mg, 12%), more OCA-treated patients had absence of definite NASH at month 18 based on pathologist's assessment. Improvements, including normalization, were noted in liver biochemistry. In the safety population (F1–F3, N=1968), the most common adverse event was pruritus (placebo, 19%; OCA 10-mg, 28%; OCA 25-mg, 51%). The overall safety profile was similar to that in previous studies, and incidence of serious adverse events was similar across treatment groups (11–14%).

Interpretation: Obeticholic acid 25-mg significantly improved fibrosis and NASH disease activity among NASH patients with fibrosis.

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INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is an increasingly common cause of chronic liver disease characterized by hepatocellular injury, inflammation, and progressive fibrosis. Models of disease progression project that the overall burden of end-stage liver disease due to NASH is likely to increase two- to three-fold over the next two decades.[1] Currently, there are no approved therapies for NASH.

The farnesoid X receptor (FXR) is a nuclear receptor that plays a central role in regulation of bile acids and also regulation of metabolism.[2] Recent data indicate that activation of FXR can decrease hepatic fibrosis and also reduce inflammation.[2-5] Prior studies demonstrated that obeticholic acid (OCA), an FXR agonist, improved glucose disposal after short-term administration[6] and the individual histologic features of NASH including fibrosis.[7] Based upon a prior phase 3 study, OCA was approved for the treatment of primary biliary cholangitis (PBC), a progressive autoimmune liver disease, in patients with an inadequate response to, or who were unable to tolerate, ursodeoxycholic acid.[8] These results provided a strong rationale to assess the efficacy and safety of OCA in patients with NASH and fibrosis in this pivotal phase 3 study.

Liver-related outcomes occur in patients with NASH principally after the development of cirrhosis. Decreased progression to cirrhosis is therefore the goal of treatment in patients with pre-cirrhotic NASH. Given the length of time to progress to cirrhosis and clinical outcomes, a conditional approval pathway based on demonstration of histological improvement following 12-24 months of treatment is being pursued by both the US Food and Drug Administration (FDA) and the European Medicines Agency.[9,10]

The RandomizEd Global phase 3 Study to Evaluate the impact on NASH with fibRosis of obeticholic Acid TreatmEnt (REGENERATE) study is an international, prospective, randomised, double-blind, placebo-controlled phase 3 study of OCA in patients with NASH and fibrosis (NCT02548351).[11] Here we report the final results of the prespecified month-18 interim analysis on the safety and efficacy of OCA in improving fibrosis and underlying disease activity.

METHODS

Study design and participants

This study is being conducted in 332 centres across 20 countries. Eligible patients were adults (aged ≥18 years) with histologic evidence (per central reading of a liver biopsy obtained within 6 months of randomisation) of steatohepatitis; a non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4; and fibrosis stage per the NASH CRN scoring criteria of F2 or F3, or F1 with ≥1 accompanying comorbidity (obesity, type 2 diabetes, or alanine amino transferase [ALT] >1·5 times the upper limit of normal [ULN]). Patients were excluded if cirrhosis, other chronic liver disease, significant alcohol consumption (>2 units/day for women or >4 units/day for men for >3 months within 1 year before screening), or confounding conditions were present. All patients provided written informed consent. Complete study design including inclusion and exclusion criteria were previously reported.[11]

A planned interim analysis was to be performed after a minimum of 750 randomised patients with fibrosis stages F2 or F3 reached their actual/planned month-18 visit. The end-of-study analysis will evaluate the effect of OCA on liver-related clinical outcomes including progression to cirrhosis, all-cause mortality, and the long-term safety of OCA, and will be completed once approximately 291 adjudicated clinical outcome events occur in the OCA 25-mg and placebo groups combined in patients with fibrosis stage F2 or F3. Patients are expected to have a minimum follow-up time of approximately 4 years.

Randomisation and blinding

Eligible patients were randomised in a 1:1:1 ratio to receive daily placebo, OCA 10-mg, or OCA 25-mg orally. To determine eligibility at enrollment, two central pathologists were required to confirm histological presence of NASH and fibrosis, and a NAS ≥4 with a score of at least 1 in each component of NAS. Randomisation was performed using an Interactive Web Response System (IWRS); for patients with fibrosis stage F2 or F3, randomization was stratified by both the presence of type 2 diabetes at enrollment and the use of thiazolidinediones (TZD) or vitamin E at baseline. Placebo and OCA were supplied as identical tablets in coded containers. All patients, study investigators, and other site research staff were blinded to treatment assignment.

Procedures and assessments

Biopsies were obtained at screening, and month 18/end-of-treatment. Histologic assessments followed standardised criteria to ensure consistency, and all biopsies were read centrally. The month 18 or early termination biopsy slides were read with the screening biopsy slides by one of the two pathologists who were blinded to the slide sequence and the patient's treatment. Assessments of liver biochemistry were performed at each study visit. Safety and tolerability of OCA were assessed by analysis of adverse events (AEs), vital signs, electrocardiograms, and clinical laboratory assessments (including lipid profile changes). An independent data and safety monitoring committee reviewed, and continues to review, safety and efficacy during the study.

Endpoints

REGENERATE was designed to assess liver histology at month 18 as a surrogate endpoint for clinical outcomes.[11] The primary endpoints were defined as improvement in fibrosis (reduction

of ≥1 stage) with no worsening of NASH (defined as no increase of hepatocellular ballooning, lobular inflammation, or steatosis), or NASH resolution (defined as the overall histopathologic interpretation of "no fatty liver disease" or "fatty liver disease without steatohepatitis" and a NAS of grade 0 for ballooning and 0–1 for inflammation) with no worsening of fibrosis. The key secondary endpoint was improvement of fibrosis by ≥1 stage without worsening of NASH and/or resolution of NASH, without worsening of fibrosis. Secondary endpoints also included evaluation of the effect of OCA versus placebo on histologic improvement of features of NASH as well as NAS, liver biochemistry, and markers of liver function.[11] A post hoc analysis evaluated NASH resolution based on the pathologist diagnostic assessment of presence/absence of definite steatohepatitis as determined by the overall pattern of injury rather than scoring of individual NAS parameters.

Statistical analyses

For the month 18 primary efficacy endpoint of improvement in fibrosis with no worsening of NASH, a sample size of 250 per group with an assumed 15% discontinuation rate will provide 98% power to demonstrate a statistically significant treatment difference between the OCA (10-mg and 25-mg) and placebo groups based on the Cochran-Mantel-Haenszel test with a two-sided type I error at the 0·01 level, assuming an adjusted response rate of 36·7% and 17·6% in the OCA (10-mg and 25-mg) and placebo groups, respectively. Inferential testing was performed sequentially in the dose level, adjusting for multiplicity using truncated Hochberg procedure, to test the two primary endpoints within each dose level, starting by comparing the OCA 25-mg group with placebo for the two primary endpoints, then comparing the OCA 10-mg group with placebo in the intent-to-treat (ITT) population. All other testing and the associated p values

presented in this article are not controlled for type II error. Success of the study was defined as meeting one of the two primary endpoints at the predetermined significance level. The analyses of histologic endpoints at the month-18 interim analysis were performed with an alpha level of 0·02. The statistical analysis plan and primary endpoints were agreed with the FDA prior to study initiation.

As shown in figure 1, all patients (fibrosis stages F1-F3) who received ≥1 dose of study treatment by the pre-specified month-18 interim analysis cutoff date were included in the safety population, which was used for all safety and tolerability analyses. The primary analysis population for efficacy endpoints was the ITT population, comprised of patients with more advanced disease (fibrosis stage F2-F3) who had received ≥1 dose of treatment and reached or would have reached the month-18 visit by the pre-specified interim analysis cutoff date. Efficacy endpoints were also analysed in the per-protocol population, defined as the ITT population who completed ≥15 months of treatment, had a month-18/end of treatment biopsy, were on treatment ≥30 days immediately preceding biopsy, and did not have any major protocol deviation

Role of the funding source

The REGENERATE study was designed by VR, AJS, and ZMY in collaboration with Intercept Pharmaceuticals; operational and protocol-specific aspects of the study were supervised by a steering committee comprising AJS, MR, PB, QMA, RL, SH, VR, ZG, and ZMY (chair). All authors vouch for the fidelity of the study to the protocol, the accuracy and completeness of the data, and approved publication of the manuscript. The first and corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for

publication. Funding for the study was provided by Intercept Pharmaceuticals. No funding was provided to any author for writing and editing of the manuscript.

RESULTS

Between November 2015 and October 2018, a total of 1968 patients were enrolled and randomly assigned to one of the three treatment groups (figure 1). The ITT population included 931 patients randomised to receive placebo (n=311), OCA 10-mg (n=312), or OCA 25-mg (n=308). At the time of the interim analysis, 23% of placebo patients, 23% of OCA 10-mg patients, and 25% of OCA 25-mg patients had discontinued treatment (figure 1); 81% of patients receiving placebo or OCA 10-mg and 79% receiving OCA 25-mg completed the month 18 biopsy. An additional 3% of patients in each treatment group completed any postbaseline biopsy (patients who discontinued the treatment before month 18 and underwent an end-of-treatment biopsy). The per-protocol population included 668 patients (placebo, n=224; OCA 10-mg, n=226; OCA 25-mg, n=218) and the safety population included 1968 patients (placebo, n=657; OCA 10-mg, n=653; OCA 25-mg, n=658).

In the ITT population, baseline characteristics were balanced across treatment groups and reflective of a noncirrhotic NASH population (table 1). A majority of patients had stage F3 fibrosis (54–58%) and NAS ≥6 (68–70%) indicative of advanced fibrosis and high disease activity. Consistent with NASH epidemiology, more than half of the patients had type 2 diabetes (55–56%), and 52-54% overall were receiving antidiabetic medication at baseline. Additionally, 41–46% of patients were receiving statin therapy and a minority were receiving NASH-modifying agents, TZD (1-3%) and Vitamin E (10-14%). A similar pattern of baseline characteristics was observed in the per-protocol population (table S1).

The primary endpoint of fibrosis improvement by ≥1 stage with no worsening of NASH was met by 12% of placebo patients, 18% of OCA 10-mg patients (p=0·04 vs placebo) and 23% of OCA 25-mg patients (p=0·0002 vs placebo) with an OCA:placebo response ratio (95% confidence

interval [CI]) of 1·48(1·01, 2·18) and 1·94(1·35, 2·78) for OCA 10-mg and OCA 25-mg, respectively (figure 2, table 2). OCA 25-mg was statistically significant per the inferential testing method pre-specified in the statistical analysis plan. Similar results were observed in the per-protocol population (placebo 13%, OCA 10-mg 21% [p=0·02], OCA 25-mg 28% [p<0·0001]) (figure 2, table 2). Across subgroups of interest in the ITT population, a ≥1 stage improvement in fibrosis was consistently observed in the OCA 25-mg group (fibrosis stage F2 or F3 [p=0·006 and p=0·02]; NAS ≥6 [p=0·0003]; presence or absence of type 2 diabetes [p=0·02 and p=0·005]). The NAS <6 subgroup did not include enough patients for a meaningful comparison (figure S1).

In the per-protocol population, which includes patients with ≥15 months of treatment, three times as many patients in the OCA 25-mg group achieved ≥1 stage improvement in fibrosis (38%) as opposed to progression of fibrosis (13%) compared to the placebo group, which showed a similar number of patients that improved (23%) or worsened (21%) (figure 3).

The primary endpoint of NASH resolution based on no hepatocellular ballooning and no or residual lobular inflammation with no worsening of fibrosis did not meet statistical significance in the ITT population (placebo 8%, OCA 10-mg 11% [p=0·18], OCA 25-mg 12% [p=0·13]) with an OCA:placebo response ratio (95% CI) of 1·39(0·86, 2·25) and 1·45(0·90, 2·35) for OCA 10-mg and OCA 25-mg, respectively (figure 2, table 2). Similar results were observed in the per-protocol population (figure 2, table 2). Despite not meeting NASH resolution, a dose-dependent response was observed in the ITT population with more OCA 25-mg patients compared to placebo achieving ≥1-point improvement in scores of lobular inflammation (44% vs 36%, p=0·03) and hepatocellular ballooning (35% vs 23%, p=0·001), key features of NASH (figure S2).

In a post hoc analysis, NASH resolution was evaluated by assessing a change in diagnosis from presence of definite steatohepatitis at baseline to absence of definite steatohepatitis (without worsening of fibrosis) at month 18. This pathologist diagnostic assessment of NASH, based on the overall pattern of liver injury, showed that in the ITT population approximately twice as many patients in the OCA 25-mg group achieved NASH resolution compared with the placebo group (23% vs 12%, p=0·0004) (figure S3). A similar dose-dependent response was observed in the per-protocol population (29% vs 16%, p=0·0005 (figure S3).

The key secondary endpoint of improvement of fibrosis by ≥1 stage and/or resolution of NASH, without worsening of either fibrosis or NASH was achieved by 16% of placebo, 22% of OCA 10-mg (p=0·07) and 27% of OCA 25-mg patients (p=0·0005) (ITT population) (table 2, figure S4). A significantly higher proportion of patients receiving OCA 25-mg compared to placebo achieved improvement in NAS by ≥2-points with no worsening of fibrosis (36% vs 24%, p=0·001), had no disease progression as assessed by no worsening of fibrosis and no worsening of NASH (48% vs 38%, p=0·011), and had improvement in fibrosis by ≥2 stages (10% vs 5%, p=0·018) (table 2). Results of additional secondary NASH and fibrosis endpoints are provided in table 2.

Favourable changes in key liver enzyme levels were observed in patients who received OCA. Early dose-dependent decreases in ALT and aspartate aminotransferase (AST) were observed by month 3 and continued through month 18 (mean [standard error (SE)] change at month-18 ALT: placebo –15·6 [3·3] U/L, OCA 10-mg –23·8 [2·6] U/L, OCA 25-mg –36·0 [3·6] U/L; AST: placebo –9·8 [2·4] U/L, OCA 10-mg –14·1 [2·1] U/L, OCA 25-mg –20·4 [2·3] U/L) (figure 4). These changes correspond to a decrease in ALT of 6% for placebo, 26% for OCA 10-mg, and 33% for OCA 25-mg and in AST of 4%, 19%, and 24%, for placebo, OCA 10-mg, and OCA 25-

mg, respectively (figure 4). A post hoc analysis demonstrated that a higher proportion of patients receiving OCA with elevated ALT and AST at baseline achieved levels below the ULN at month 18 compared with placebo (figure S5). Gamma-glutamyl transferase (GGT) levels dropped rapidly and were generally stable after month 3 (change at month 18: placebo 1%, OCA 10-mg –24%, OCA 25-mg –38%) (figure 4). Slight increases in alkaline phosphatase (ALP) were observed with OCA treatment, but levels remained below ULN through month 18 (change at month 18: placebo –1%, OCA 10-mg 9%, OCA 25-mg 20%) (figure 4).

Additionally, patients receiving OCA versus placebo had a higher, dose-dependent decrease in body weight throughout the 18-month observation period (mean [SE] change: placebo, –0·7 [0·4] kg; OCA 10-mg, –1·8 [0·4] kg; OCA 25-mg –2·2 [0·3] kg).

A total of 1968 patients were included in the safety analysis, comprised of 15% with fibrosis stage F1 (15%), stage F2 (35%), and stage F3 (50%). The duration of exposure was generally similar across treatment groups. Overall, treatment-emergent AEs occurred in 83% of placebo, 89% of OCA 10-mg, and 91% of OCA 25-mg patients; most (69–74%) were mild to moderate in severity (table S2). The frequency of serious AEs (SAEs) was similar across treatment groups (11–14%) and no single SAE occurred in >1% of patients in any treatment group (table S2). The most frequent AE was pruritus (placebo, 19%; OCA 10-mg, 28%; OCA 25-mg, 51%) (table 3). The incidence of pruritus was highest during the first 3 months of treatment with OCA, and generally mild to moderate in severity. Treatment discontinuation due to pruritus occurred in five placebo patients (<1%), five OCA 10-mg patients (<1%), and 57 OCA 25-mg patients (9%). Of those 57 patients in the OCA 25-mg group who discontinued due to pruritus, 36 discontinuations were protocol-mandated based on the investigator-assessed grade of the event.

In patients receiving OCA, LDLc increased through month 1 (mean [SE]: placebo –3·0 [0·9] mg/dL, OCA 10-mg, 17·8 [1·0] mg/dL, OCA 25-mg 23·8 [1·1] mg/dL) and decreased thereafter, approaching baseline by month 18 (mean [SE]: placebo –7·1[1·7] mg/dL, OCA 10-mg, 1·4 [2·0] mg/dL, OCA 25-mg 2·7 [2·1] mg/dL) (figure 5). A total of 380 patients started statin therapy during the study (placebo, n=66; OCA 10-mg, n=155; OCA 25-mg, n=159). Among OCA-treated patients who initiated statins, increases from baseline in LDLc diminished with statin treatment, and levels of LDLc were below baseline levels from month 6 through month 18 (figure S6). Levels of HDLc showed dose-dependent decreases through month 1 (mean [SE]: placebo –0·7 [0·2] mg/dL, OCA 10-mg, –1·8 [0·2] mg/dL, OCA 25-mg –4·6 [0·3] mg/dL) and were sustained through month 18; mean HDLc remained within the normal limit (<46 mg/dL) at all timepoints. Changes in total cholesterol over time were similar to LDLc. A dose-dependent decrease in triglycerides was observed by month 1 in the OCA groups and continued to gradually decline over the study period with a maximum mean change from baseline of –37·4 mg/dL in the OCA 25-mg group at month 18 (figure 5).

The incidence of cardiovascular AEs and SAEs was similar across the treatment groups (AEs: 5% placebo, 7% OCA 10-mg, and 6% OCA 25-mg; SAEs 2% placebo, 1% OCA 10-mg, 2% OCA 25-mg). Treatment with OCA was associated with a generally modest and transient rise in glycemic parameters (glucose, insulin, HOMA-IR, and HbA1c) that occurred early and returned to levels similar to placebo after approximately 6 months of OCA treatment. In a subgroup analysis of patients with type 2 diabetes, OCA treatment was associated with a transient increase in glucose (month 1) and HbA1C (month 3) with return to levels similar to placebo by month 6. In nondiabetic patients, small, sustained increases in glucose were seen with OCA 25-mg by month 1 (mean [SE]: 8·2 [1·0] mg/dL); there were no changes in HbA1C in this group (figure

S7). Blood pressure was generally stable, but variable, with no significant difference between treatment groups. Other vital signs were not affected by study treatments.

Gallstone-related AEs occurred at a rate of <1%, 1% and 3% in placebo, OCA 10-mg and OCA 25-mg patients respectively. Pancreatitis, a more serious and potentially cholelithiasis-related event, was rare and evenly distributed across treatment groups (incidence <1%). Hepatic SAEs were uncommon, and each case was reviewed by independent expert hepatologists. While more events occurred in the OCA 25-mg group (6 [< 1%]) than the OCA 10-mg group (2 [<1%]) or placebo group (2 [<1%]), expert reviewers did not identify any consistent pattern of liver injury and all cases were associated with confounding severe intercurrent illness and/or concomitant medications.

A total of three deaths occurred on study (two placebo [bone cancer and cardiac arrest], and one OCA 25-mg [glioblastoma]); none were considered related to study treatment.

DISCUSSION

The REGENERATE study is the first positive phase 3 trial in NASH and represents a landmark in the development of new therapies for an increasingly common chronic liver disease.[12-15] Treatment with OCA 25-mg met the primary endpoint of improvement in fibrosis with no worsening of NASH in patients with stage F2 or F3 fibrosis, at the month-18 interim analysis. The robust antifibrotic effect of OCA was dose-dependent and consistent across different patient populations, subgroups, and was further supported by fibrosis-related secondary endpoints including a ≥2-stage improvement in fibrosis. Per the draft guidance from the FDA on efficacy endpoints for clinical trials in NASH, improvement in fibrosis by ≥1 stage with no worsening of

NASH is likely to predict clinical benefit.[10] Patients with NASH have an almost 65 times greater risk of liver-specific mortality and almost 3 times greater risk/rate of overall mortality compared to healthy subjects[14]. Fibrosis has been shown to be the strongest histological predictor of liver-related adverse outcomes, including liver-related death.[16-19] Treatment with OCA 25-mg both improved fibrosis and prevented progression of fibrotic disease, demonstrating a halting of disease progression. To slow or reverse the progression of fibrosis is the ultimate goal of NASH treatment as fibrosis is the most reliable predictor of liver-related mortality and once patients progress to cirrhosis, preventing complications of cirrhosis may become even more difficult.[16,18] More OCA-treated patients relative to placebo achieved NASH resolution with no worsening of fibrosis, the second primary endpoint; however, neither OCA dose achieved statistical significance. More patients receiving OCA 25-mg showed improvements in hepatocellular ballooning and lobular inflammation, the two key individual histologic features of the pre-specified NASH resolution endpoint. These data are relevant given that features of steatohepatitis, such as hepatocellular ballooning, are predictive of increased liver-related events and reduced liver transplant-free survival.[19] In addition, more patients receiving OCA 25-mg had no worsening of fibrosis and ≥2-point improvement in NAS, the primary endpoint traditionally used in phase 2 studies such as FLINT[7] and PIVENS,[20] indicating that OCA reduces NASH disease activity.

A greater proportion of OCA 25-mg patients compared to placebo achieved NASH resolution as defined in the pathologist diagnostic assessment of the absence of definite steatohepatitis at month 18. This evaluation was based on an assessment of the overall pattern of histologic lesions or injury, as opposed to the more rigid categorical scoring system of the pre-specified methodology described above. This finding has clinical relevance given that this definition is

commonly used to diagnose NASH in clinical practice, as well as in natural history studies evaluating any correlation between presence of NASH and mortality[16]. The apparent dichotomy of substantial improvements in key individual components of NASH, while failing to meet the pre-specified primary endpoint of NASH resolution demonstrates the challenges associated with assessing histological response in complex, composite pathological patterns such as steatohepatitis. The NAS, a tool designed to measure disease activity and severity in NASH, is distinct from a clinical diagnosis of definite steatohepatitis. In an investigation into the relationship between NAS and the diagnosis of steatohepatitis, threshold values of NAS did not always correlate with pathologist overall assessment of presence of NASH.[21] Therefore, as the field continues to evolve it may be more appropriate to establish the presence/absence of NASH using diagnostic criteria as an endpoint.

In addition to consistent improvements in multiple histologic parameters, improvement in liver health was also evident based on clinically relevant, dose-dependent, improvements in markers of liver injury (ALT and AST) and oxidative stress (GGT). The modest increases in ALP are consistent with earlier observations and are associated with an on-target effect of FXR activation.

Lifestyle modifications including weight loss have been shown to be an effective nonpharmacologic therapy for NAFLD. Weight loss >7% has been associated with improvement in NAS, and weight loss ≥10% has been associated with improvement in fibrosis.[22] OCA-treated patients in REGENERATE experienced weight loss of approximately 2%, an amount lower than that expected to have an effect on histologic parameters of NASH. Although modest, the effect of OCA on weight is important to note given the prevalence of obesity and metabolic abnormalities in this population.

Based on a substantial database including almost 2000 patients, of whom approximately 900 were exposed for ≥18 months, OCA was generally well tolerated. The majority of AEs were mild to moderate in severity and were generally consistent with the known safety profile of OCA.[7] As previously seen, mild to moderate pruritus was the most commonly reported AE, the incidence of which was dose dependent. More subjects in the OCA 25-mg group experienced pruritus that led to treatment discontinuation; however, the vast majority of randomizsed patients were ongoing in the study through at least month 18. The impact of pruritus in this study on patient-reported outcomes and its relationship to OCA is being investigated.[23] The incidence of hepatic-related AEs was balanced across treatment groups, and serious hepatic complications were rare; although numerically more occurred in the OCA 25-mg treated group, there was no clear pathologic pattern seen consistently among these SAEs and all cases were confounded by severe intercurrent illness. Treatment with OCA was associated with serum lipid changes that were consistent with a class effect of FXR activation, as well as limited increases in glycemic parameters. However, these increases were manageable by clinical practice measures. The impact of lipid and glycemic laboratory changes on cardiovascular risk should be assessed in the context of other OCA-related reductions in risk factors, including a decrease in weight, serum triglyceride levels, and GGT, a promising marker for assessing cardiovascular risk.[24,25] The incidence of cardiovascular AEs and SAEs was low and similar across treatment groups.

The results of the interim analysis of REGENERATE reported here are clinically relevant in the context of fibrosis due to NASH but may underestimate the long-term benefit of OCA on the target illness. Improvement in fibrosis, a generally slow-changing feature, was observed at the month-18 interim analysis of the ongoing study, and the effect size may increase with prolonged therapy. This has been shown with other interventions that reported improvement in fibrosis at

early time points with a greater effect over the longer term. For example, tenofovir treatment resulted in 10% fewer patients with hepatitis B virus-associated advanced fibrosis or cirrhosis after the first year of treatment (28% vs 38% at baseline).[26] In the tenofovir study, patients continued to improve on treatment, and the proportion of patients with advanced fibrosis or cirrhosis declined to 12% at year 5.[26] In REGENERATE, the continuing improvement in liver enzyme markers of fibrosis such as ALT and AST suggest the potential for further antifibrotic response. Data from the ongoing long-term outcome portion of the study will inform whether prolonged therapy will result in a higher rate of antifibrotic response.

In conclusion, the totality of data from the month 18 interim analysis of this pivotal, phase 3 study provides strong evidence of an improvement in clinically significant histologic endpoints deemed reasonably likely to predict clinical benefit with OCA treatment and affirms the positive benefit-risk of OCA for the treatment of NASH with fibrosis. Beneficial effects of OCA on fibrosis and components of NASH disease activity were robust, based on the observed consistency of results across multiple histologic endpoints with reproducible response ratios, as well as the evident dose-response and markedly consistent benefit across analysis populations. Treatment with OCA had a beneficial effect on other markers of chronic liver disease (hepatocellular ballooning and lobular inflammation), hepatocellular injury (ALT and AST), and oxidative stress (GGT). OCA was generally well tolerated, with a profile that is generally consistent with prior studies. Following the month-18 interim analysis, REGENERATE continues in a blinded fashion, and patients will be followed over an extended period for clinical outcomes, such as all-cause mortality, liver-related clinical outcomes, and long-term safety, to confirm clinical benefit. In a chronic disease with no approved therapies and potential for serious

sequelae, these findings provide compelling evidence that patients with non-cirrhotic advanced fibrosis due to NASH may benefit from OCA treatment.

CONTRIBUTORS

VR, AJS, and ZMY participated in initial study design in collaboration with the sponsor (DS, LMcC, RS). AJS, MR, PB, QMA, RL, SH, VR, ZG, and ZMY (chair) make up the steering committee which is responsible for ongoing conduct of the study. ZMY, VR, RL, MR, QMA, AG, SB, PN, DS, JT, WK, EL, MFA, KK, MYS, AJM-L, JB, PM, EB, GM, AO, HC-P, IG, DO, LLG, and J-FD participated in data collection. AJS, MR, PB, QMA, RL, SH, VR, MFA, DS, JC, LZ, LMcC, RS, ZG and ZMY participated in data analysis and interpretation. All authors participated in manuscript development.

DECLARATION OF INTERESTS

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DATA SHARING STATEMENT

The authors declare that all data supporting the findings of this interim analysis are available within the article and its supplementary information files. The study is ongoing at the time of publication and blinded at the individual level; patient-level data therefore are not available.

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TABLES

[[SUPPLEMENTARY TABLES ARE INCLUDED IN THIS SECTION FOR REVIEW, AND WILL BE MOVED TO A SUPPLEMENTARY APPENDIX PRIOR TO SUBMISSION; ADDITIONALLY, TABLES 1-3 WILL BE SUBMITTED AS A SEPARATE WORD DOCUMENT.]]

Table 1 Demographic and baseline clinical characteristics (ITT population, N=931)

	Placebo (n=311)	OCA 10 mg (n=312)	OCA 25 mg (n=308)
Age, years	55 (12)	55 (11)	55 (11)
Female, n (%)	187 (60)	177 (57)	175 (57)
White, n (%)*	264 (94)	263 (92)	249 (87)
Hispanic ethnicity, n (%)†	52 (18)	42 (15)	47 (17)
Fibrosis stage F3, n (%)	169 (54)	182 (58)	169 (55)
NAS ≥6, n (%)	215 (70)	211 (68)	208 (68)
Type 2 diabetes,‡ n (%)	175 (56)	171 (55)	171 (56)
Dyslipidaemia, n (%)	211 (68)	217 (70)	205 (67)
Hypertension, n (%)	215 (69)	215 (69)	196 (64)
Lipids			
Total cholesterol, mg/dL	184·5 (42·7)	185·2 (53·0)	183·5 (44·7)
HDLc, mg/dL	45·6 (11·1)	44·9 (12·1)	44·3 (11·0)
LDLc, mg/dL	114·8 (38·2)	113·8 (38·4)	113·3 (38·8)
Triglycerides, mg/dL	178·7 (154·5)	184·6 (195·0)	181·7 (131·6)
Metabolic factors			
Fasting glucose, mg/dL	119·1 (38·3)	120·8 (43·6)	119·5 (40·3)
Body weight, kg	95 (19)	95 (19)	95·40 (19)
HOMA-IR	9·6 (11·8)	9·9 (16·9)	8·3 (10·2)
HbA1c, %	6·6 (1·22)	6·5 (1·2)	6·5 (1·3)
Laboratory parameters			
ALT, U/L	80 (57)	76 (47)	80 (56)
AST, U/L	59 (41)	57 (34)	57 (34)
Platelet count, $x10^9$/L	241·9 (67·0)	238·5 (68·0)	237·2 (69·0)
Total bilirubin, mg/dL	0·64 (0·3)	0·65 (0·3)	0·69 (0·3)
Concomitant medication use			
Lipid lowering, n (%)§	175 (56)	170 (54)	160 (52)
Statins, n (%)	144 (46)	142 (46)	127 (41)
Antidiabetic medication, n (%)	167 (54)	171 (55)	159 (52)

Thiazolidinediones,‡ n (%)	5 (2)	9 (3)	4 (1)
Vitamin E,* n (%)	42 (14)	34 (11)	32 (10)

Data are mean (SD) unless otherwise noted.
*Percentages calculated based on patients for whom race information was not missing.
†Percentages calculated based on patients for whom ethnicity information was not missing.
§In addition to statins, lipid lowering drugs included fibrates, cholesterol-absorbing resins, PCSK9 inhibitors, and omega-3 fatty acids
‡Randomisation was stratified based on presence of type 2 diabetes and treatment with thiazolidinediones or vitamin E.
ALT=alanine aminotransferase. AST=aspartate aminotransferase. NAS=NAFLD activity score. PCSK9=proprotein convertase subtilisin-kexin type 9. SD=standard deviation.

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Table 2 Efficacy outcome measures

	ITT population (N=931)			Per-protocol population (N=668)		
Primary Endpoint, RR (95% CI)	**Placebo (n=311)**	**OCA 10 mg (n=312)**	**OCA 25 mg (n=308)**	**Placebo (n=224)**	**OCA 10 mg (n=226)**	**OCA 25 mg (n=218)**
Improvement of fibrosis with no worsening of NASH	-	1·48 (1·01, 2·18) p=0·04	1·94 (1·35-2·78) p=0·0002	-	1·62 (1·06, 2·48) p=0·02	2·15 (1.44, 3.21) p<0·0001
Resolution of NASH with no worsening of fibrosis	-	1·39 (0·86, 2·25) p=0·18	1·45 (0·90, 2·35) p=0·13	-	1·49 (0·86, 2·33) p=0·11	1·41 (0·86, 2·33) p=0·18
Secondary Endpoint, n (%)	**Placebo (n=311)**	**OCA 10 mg (n=312)**	**OCA 25 mg (n=308)**	**Placebo (n=224)**	**OCA 10 mg (n=226)**	**OCA 25 mg (n=218)**
Improvement of fibrosis by ≥1 stage and/or resolution of NASH without worsening of either	49 (15·8)	67 (21·5) p=0·07	84 (27·3) p=0·0005	41 (18·3)	59 (26·1) p=0·04	71 (32·6) p=0.0004
No worsening of fibrosis and no worsening of NASH	117 (37·6)	127 (40·7) p=0·43	147 (47·7) p=0·011	100 (44·6)	109 (48·2) p=0·43	125 (57·3) p=0·006
Improvement of NAS by ≥2 with no worsening of fibrosis	76 (24·4)	94 (30·1) p=0·11	112 (36·4) p=0·001	69 (30·8)	82 (36·3) p=0·19	96 (44·0) p=0·004
Improvement of fibrosis and resolution of NASH as a composite endpoint	13 (4·2)	23 (7·4) p=0·090	23 (7·5) p=0·080	11 (4·9)	22 (9·7) p=0·045	20 (9·2) p=0·064
Improvement in fibrosis by ≥2 stages	15 (4·8)	19 (6·1) p=0·49	30 (9·7) p=0·018	10 (4·5)	16 (7·1) p=0·22	29 (13·3) p=0·0008
Resolution of fibrosis	4 (1·3)	8 (2·6) p=0·25	10 (3·2) p=0·10	4 (1·8)	8 (3·5) p=0·21	9 (4·1) p=0·14

CI=confidence interval, NAS=NAFLD activity score, NASH=nonalcoholic steatohepatitis, RR=response ratio.
P values compare OCA treatment with placebo.

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Table 3 Adverse events occurring in ≥5% of patients in either OCA group (safety population, N=1968)

System Organ Class Preferred Term, n (%)	Placebo (n=657)	OCA 10 mg (n=653)	OCA 25 mg (n=658)
Skin and Subcutaneous Tissue Disorders			
Pruritus	123 (19)	183 (28)	336 (51)
Grade 1 (mild or localised)	90 (14)	113 (17)	148 (22)
Grade 2 (intense or wide spread)	30 (5)	67 (10)	152 (23)
Grade 3 (intense or widespread and limit activities of daily living)	3 (<1)	3 (<1)	36 (5)
Gastrointestinal Disorders			
Nausea	77 (12)	72 (11)	83 (13)
Constipation	36 (5)	65 (10)	70 (11)
Abdominal pain	62 (9)	66 (10)	67 (10)
Diarrhoea	79 (12)	44 (7)	49 (7)
Abdominal pain upper	35 (5)	46 (7)	45 (7)
Vomiting	33 (5)	34 (5)	44 (7)
Abdominal distension	23 (4)	31 (5)	31 (5)
Infections and Infestations			
Urinary tract infection	49 (7)	54 (8)	62 (9)
Upper respiratory tract infection	44 (7)	47 (7)	54 (8)
Nasopharyngitis	41 (6)	34 (5)	45 (7)
Bronchitis	28 (4)	34 (5)	35 (5)
Sinusitis	35 (5)	36 (6)	30 (5)
Investigations			
Low density lipoprotein increased	47 (7)	109 (17)	115 (17)
Blood cholesterol increased	12 (2)	30 (5)	38 (6)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	55 (8)	50 (8)	50 (8)
Back pain	50 (8)	56 (9)	40 (6)
Metabolism and Nutrition Disorders			
Hyperlipidaemia	18 (3)	42 (6)	55 (8)
Diabetes mellitus	36 (5)	46 (7)	45 (7)
Hypercholesterolaemia	14 (2)	35 (5)	29 (4)
General Disorders and Administration Site Conditions			
Fatigue	88 (13)	78 (12)	71 (11)
Nervous System Disorders			
Headache	51 (8)	42 (6)	34 (5)
Dizziness	28 (4)	32 (5)	25 (4)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	27 (4)	29 (4)	38 (6)
Vascular Disorders			
Hypertension	28 (4)	36 (6)	39 (6)

LDLc=low density lipoprotein cholesterol.
Note: Arranged by descending order of incidence (system organ class and preferred term within system organ class) in the OCA 25-mg group, followed by descending order of incidence in the OCA 10-mg group.

3

Supplementary Table S1 Demographic and baseline clinical characteristics (PP population, N=668)

Characteristics	Placebo (n=224)	OCA 10 mg (n=226)	OCA 25 mg (n=218)
Age, years, mean (SD)	55 (12)	55 (11)	54 (12)
Female, n (%)	133 (59)	126 (56)	122 (56)
White, n (%)*	189 (94)	192 (94)	185 (89)
Hispanic ethnicity, n (%)†	29 (14)	29 (14)	33 (16)
Fibrosis stage F3, n (%)	122 (54)	135 (60)	117 (54)
NAS ≥6, n (%)	159 (72)	152 (67)	144 (66)
Type 2 diabetes,‡ n (%)	120 (54)	121 (54)	119 (55)
Weight, mean kg (SD)	96 (19)	94 (19)	97 (20)
Laboratory parameters, mean (SD)			
ALT, U/L	77 (53)	73 (44)	82 (61)
AST, U/L	57 (38)	55 (31)	56 (34)
Concomitant medication use			
Lipid lowering, n (%)§	131 (58)	128 (57)	113 (52)
Statins, n (%)	108 (48)	108 (48)	86 (39)
Antidiabetic medication, n (%)	117 (52)	120 (53)	111 (51)
Thiazolidinedones,‡ n (%)	3 (1)	8 (4)	2 (<1)
Vitamin E,* n (%)	29 (13)	25 (11)	23 (11)

*Percentages calculated based on patients for whom race information was not missing
†Percentages calculated based on patients for whom ethnicity information was not missing
§In addition to statins, lipid lowering drugs included fibrates, cholesterol-absorbing resins, PCSK9 inhibitors, and omaga-3 fatty acids
‡Randomisation was stratified based on presence of type 2 diabetes and treatment with thiazolidinediones or vitamin E.
ALT=alanine aminotransferase. AST=aspartate aminotransferase. NAS=NAFLD activity score. PCSK9=proprotein convertase subtilisin-kexin type 9. SD=standard deviation.

1

Supplementary Table S2 Summary of treatment-emergent adverse events (safety population, N=1968)

n (%)	Placebo (n=657)	OCA 10 mg (n=653)	OCA 25 mg (n=658)
≥1 Treatment-emergent adverse event (TEAE)	548 (83)	579 (89)	601 (91)
TEAEs by severity[a]			
Mild	160 (24)	163 (25)	130 (20)
Moderate	294 (45)	323 (49)	338 (51)
Severe	87 (13)	89 (14)	130 (20)
Life-threatening	5 (<1)	4 (<1)	2 (<1)
Death	2 (<1)	0	1 (<1)
TEAEs leading to treatment discontinuation	41 (6)	39 (6)	83 (13)
Serious adverse events (SAEs)	75 (11)	72 (11)	93 (14)

[a] Subjects reporting more than one adverse event are counted only once using the highest severity. Adverse events are graded for severity using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

FIGURE LEGENDS

Figure 1. Patient flow diagram.

Figure 2. Primary endpoints. The proportion of patients with improvement in fibrosis ≥1 stage and no worsening of NASH in the ITT (Panel A) and per protocol (Panel B) populations, and the proportion of patients with resolution of NASH and no worsening of fibrosis in the ITT (Panel C) and per protocol (Panel D) populations. Fibrosis improvement was evaluated per NASH CRN criteria; no worsening of NASH defined as defined as no worsening of hepatocellular ballooning, lobular inflammation or steatosis. NASH resolution defined as: (i) overall pathologist assessment of "no steatohepatitis," and (ii) hepatocellular ballooning = 0 and lobular inflammation = 0 or 1. *Statistically significant in accordance with the statistical analysis plan as agreed with the FDA.

Figure 3. Regression or progression of fibrosis by ≥1 stage. The proportion of patients with improved or worsened fibrosis by ≥1 stage is shown for patients in the per-protocol population with available fibrosis stage data at month-18/end of treatment (n=656).

Figure 4. Changes in liver biochemistry over time. Mean (SE) values of change from baseline up to month 18 are shown for patients from each treatment group in the ITT population (○ placebo, ▲ OCA 10-mg, ▼ OCA 25-mg).

Figure 5. Changes in serum lipids over time. Mean (SE) values of change from baseline up to month 18 are shown for patients from each treatment group in the safety population (○ placebo, ▲ OCA 10-mg, ▼ OCA 25-mg).

Supplementary Figure S1. Subgroup analysis of fibrosis improvement by ≥1 stage with no worsening of NASH. Odds ratios and 95% confidence intervals of obeticholic acid versus placebo for patients in the ITT population grouped by fibrosis stage, NAFLD Activity Score (NAS), and type 2 diabetes. An odds ratio greater than 1 favours obeticholic acid.

Supplementary Figure S2. The proportion of patients with improvements in histologic features of NASH (steatosis, lobular inflammation, and hepatocellular ballooning) in the ITT population.

Supplementary Figure S3. The proportion of patients with resolution of NASH with no worsening of fibrosis, based on the pathologist diagnostic assessment of the absence of definite steatohepatitis in the ITT (Panel A) and per protocol (Panel B) populations.

Supplementary Figure S4. The proportion of patients with improvement of fibrosis and/or resolution of NASH with no worsening of either in the ITT population. NASH resolution defined as hepatocellular ballooning = 0 and lobular inflammation = 0 or 1.

Supplementary Figure S5. The proportion of patients in the ITT population with elevated ALT (n=546) (Panel A) or AST (n=665) (Panel B) at baseline who achieved transaminase levels ≤ULN. For ALT, ULN = 55U/L; for AST, ULN = 34 U/L.

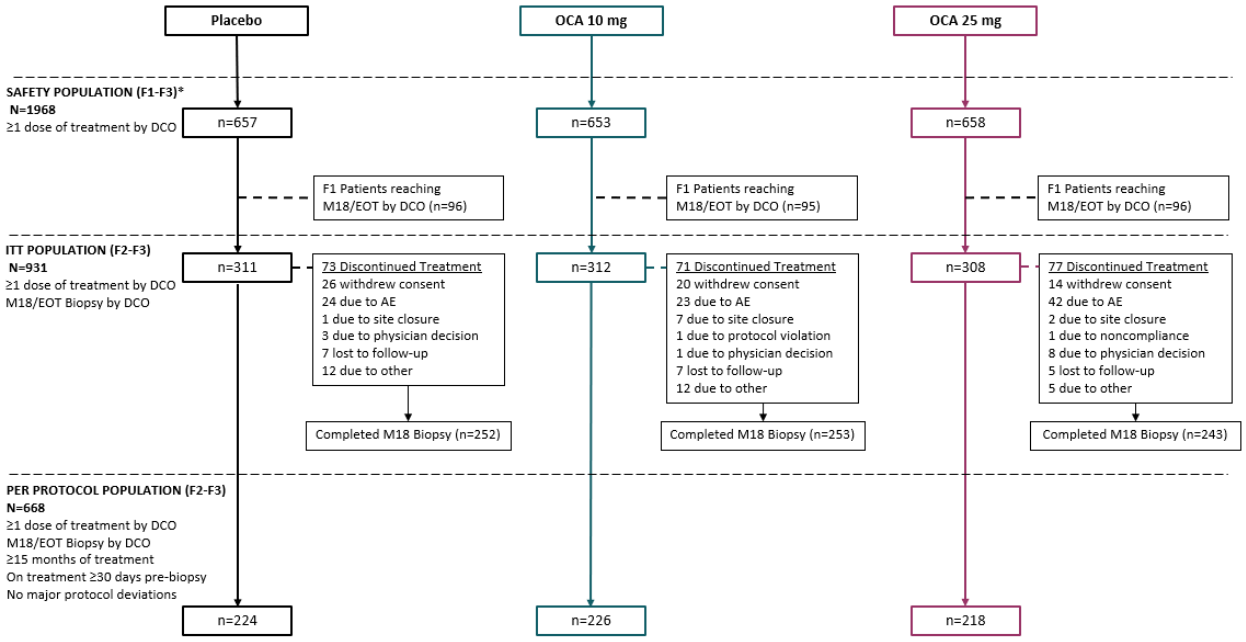
Supplementary Figure S6. Changes in LDLc over time by statin use. Mean (SE) values of change in LDLc from baseline up to month 18 are shown patients who never used statins, patients who were using statins at baseline, and patients who started using statins during the study for each treatment group in the safety population (○ placebo, ▲ OCA 10-mg, ▼ OCA 25-mg).

Supplementary Figure S7. Changes in glucose and HbA1c over time. Mean (SE) values of change in glucose (Panels A and C) and HbA1c (Panels B and D) from baseline up to month 18 are shown based on diabetes status for patients from each treatment group in the safety population (○ placebo, ▲ OCA 10-mg, ▼ OCA 25-mg).

FIGURES

[[SUPPLEMENTARY FIGURES ARE INCLUDED IN THIS SECTION FOR REVIEW, AND WILL BE MOVED TO A SUPPLEMENTARY APPENDIX PRIOR TO SUBMISSION]]

Figure 1 Patient flow diagram



*750 patients included in the safety population had not reached their M18/EOT visit by DCO and were therefore not included in the ITT or per protocol populations.
AE: Adverse Event, DCO: Data Cutoff, ITT: intent-to-treat, OCA: Obeticholic Acid

Figure 2 Primary endpoint

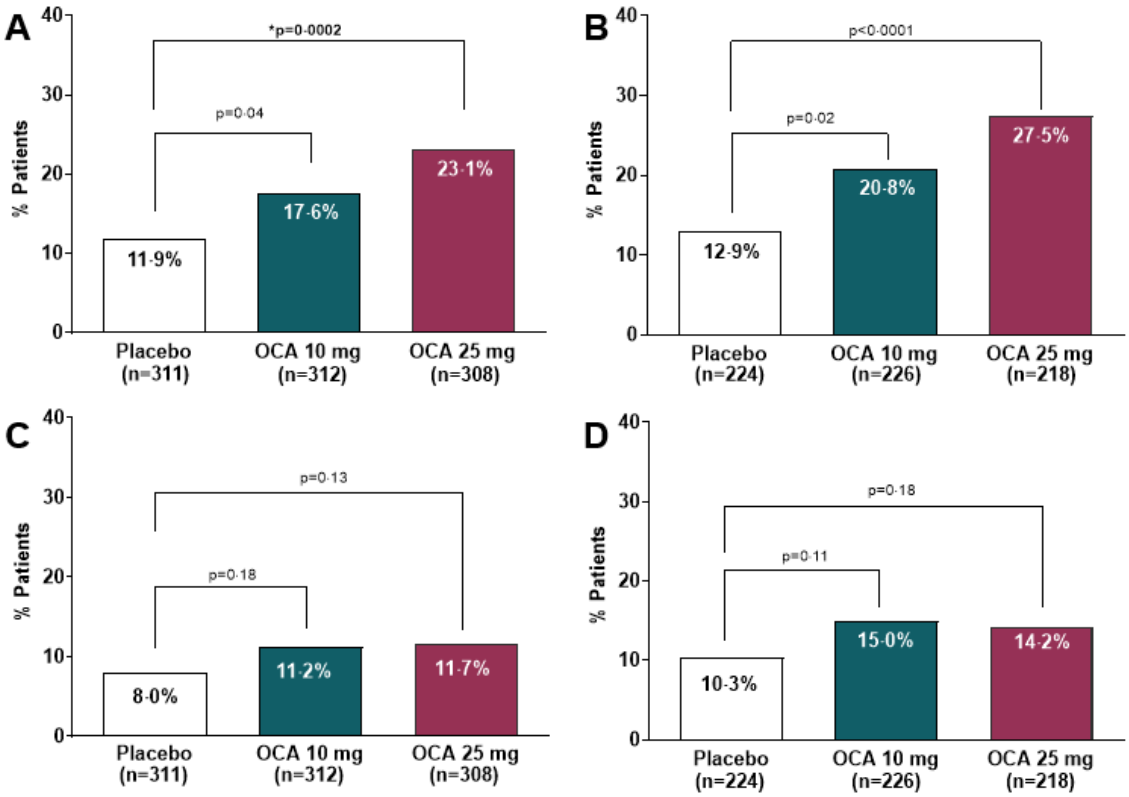


Figure 3. Improvement versus progression of fibrosis by ≥1 stage

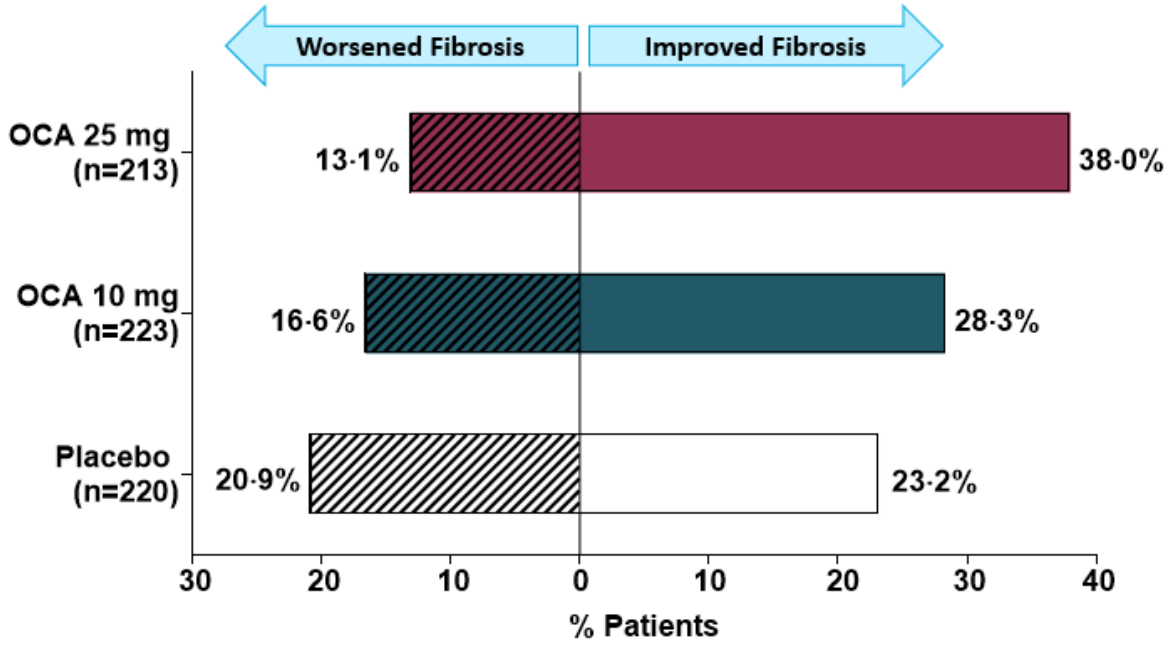


Figure 4 Changes in liver biochemistry over time

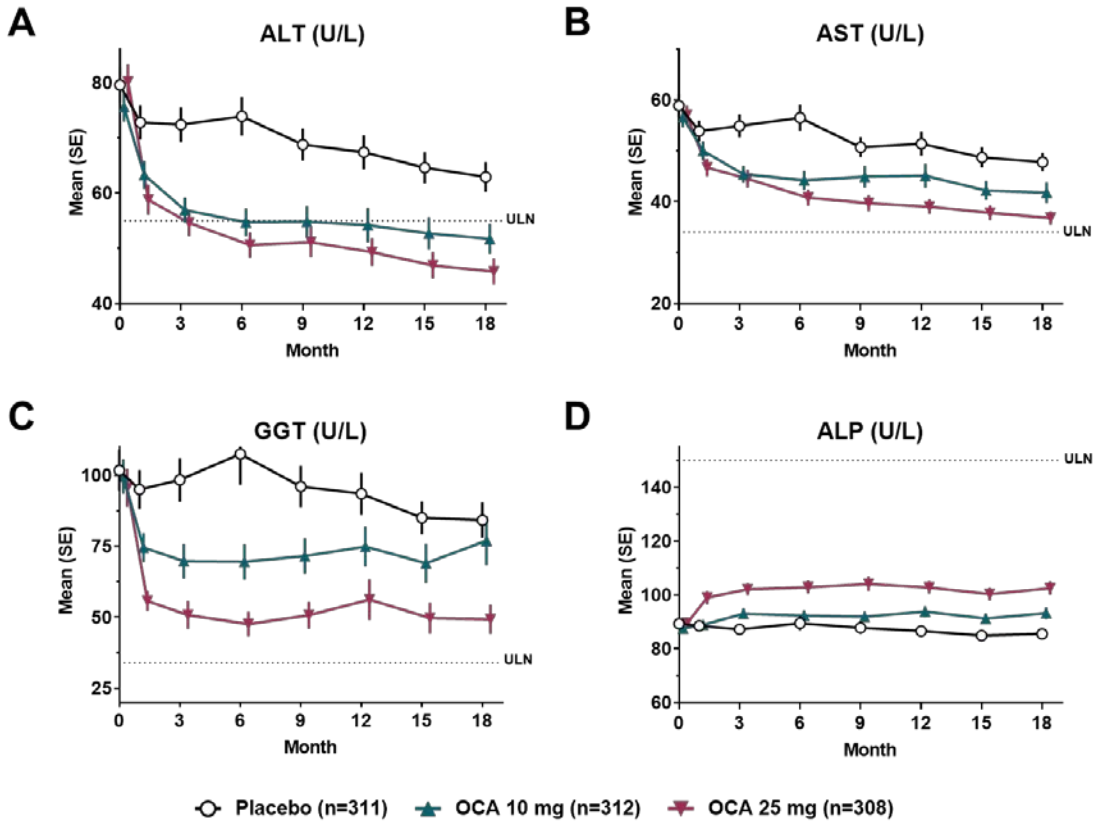
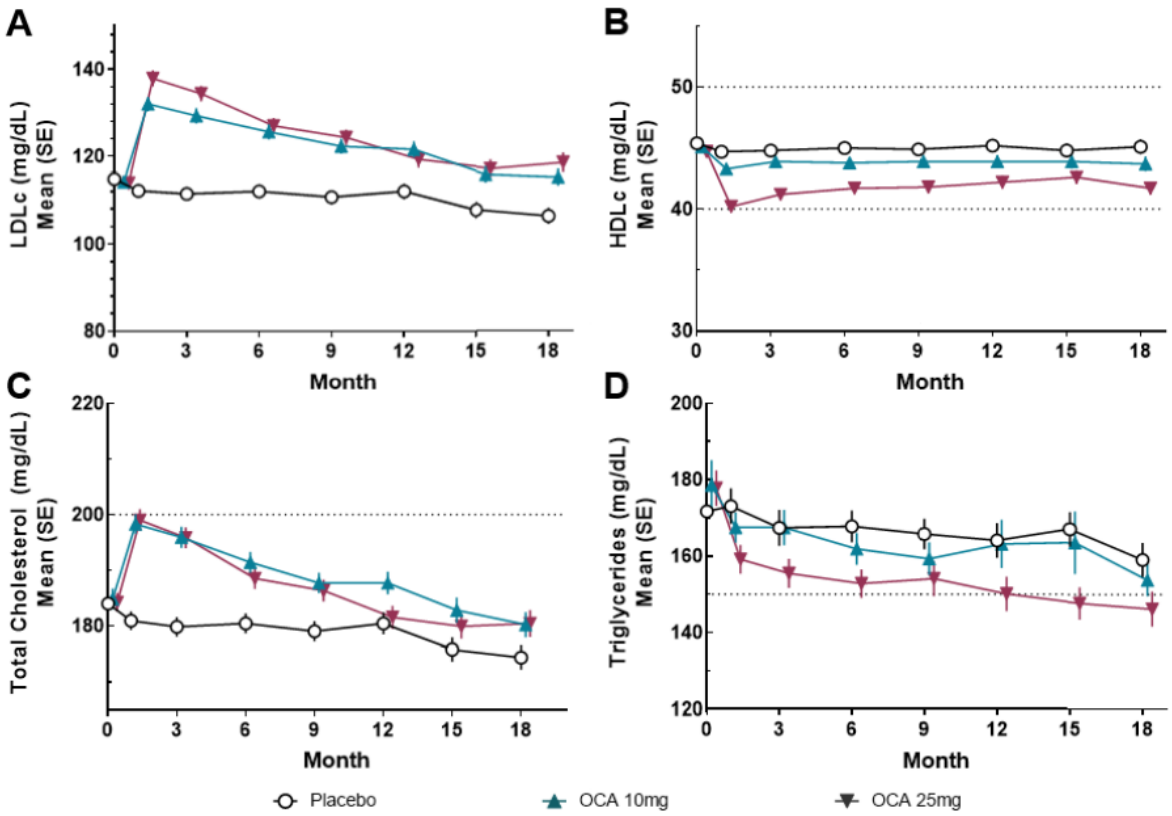
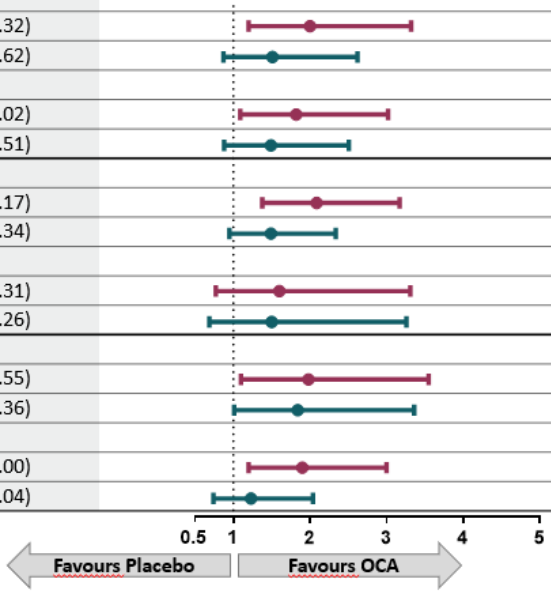


Figure 5 Changes in serum lipids over time

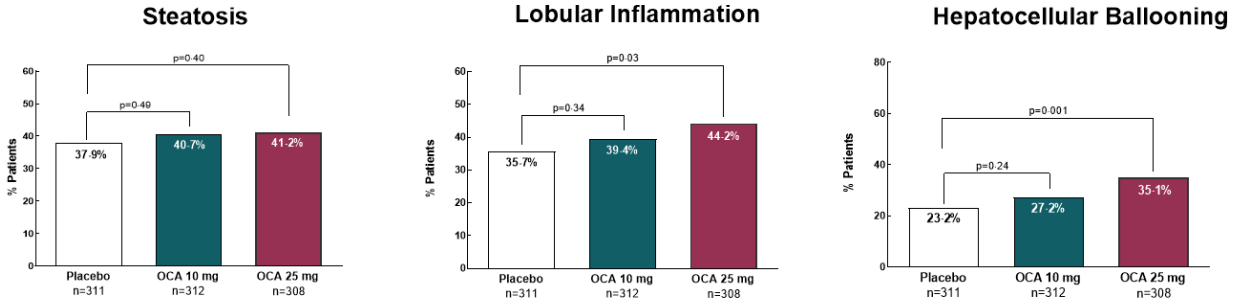


Supplementary Figure S1 Subgroup analysis of fibrosis improvement by ≥1 stage with no worsening of NASH

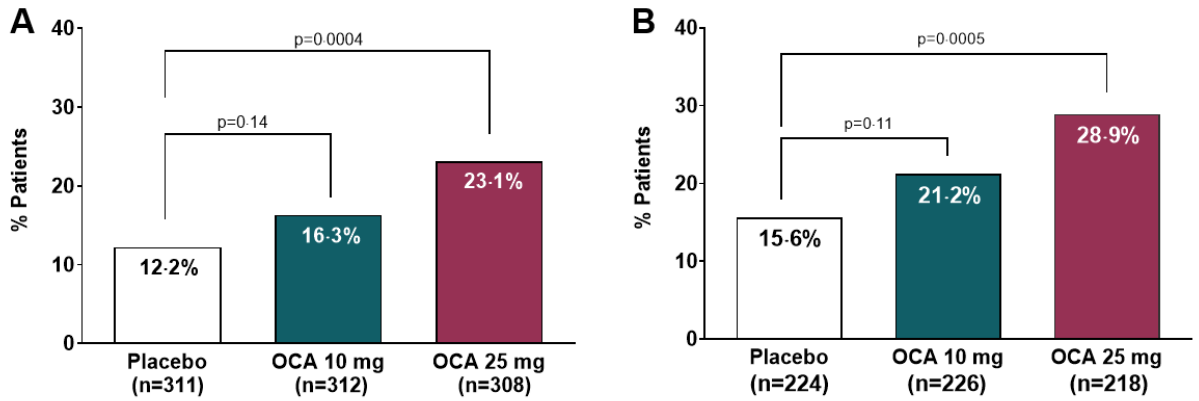
Subgroups	OCA : Placebo Response Ratio (95% CI)	P Value
Fibrosis Stage 2		
25 mg (n=139)	2.00 (1.20, 3.32)	0.006
10 mg (n=130)	1.51 (0.87, 2.62)	0.14
Fibrosis Stage 3		
25 mg (n=169)	1.82 (1.09, 3.02)	0.02
10 mg (n=182)	1.49 (0.88, 2.51)	0.13
NAS ≥6		
25 mg (n=208)	2.09 (1.38, 3.17)	0.0003
10 mg (n=211)	1.49 (0.95, 2.34)	0.08
NAS <6		
25 mg (n=100)	1.60 (0.77, 3.31)	0.20
10 mg (n=101)	1.50 (0.69, 3.26)	0.30
Type 2 Diabetes		
25 mg (n=171)	1.98 (1.10, 3.55)	0.02
10 mg (n=171)	1.84 (1.01, 3.36)	0.04
No Type 2 Diabetes		
25 mg (n=137)	1.90 (1.20, 3.00)	0.005
10 mg (n=141)	1.23 (0.74, 2.04)	0.42



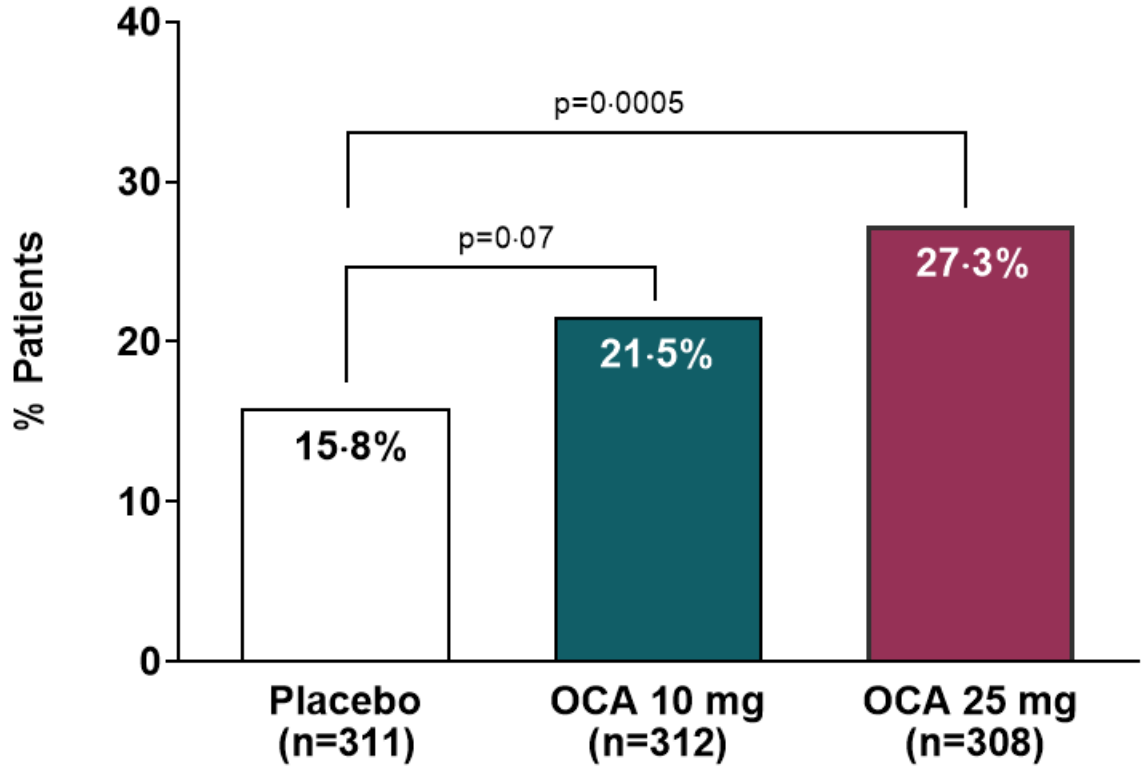
Supplementary Figure S2 Improvements in histologic features of NASH (steatosis, lobular inflammation, and hepatocellular ballooning)



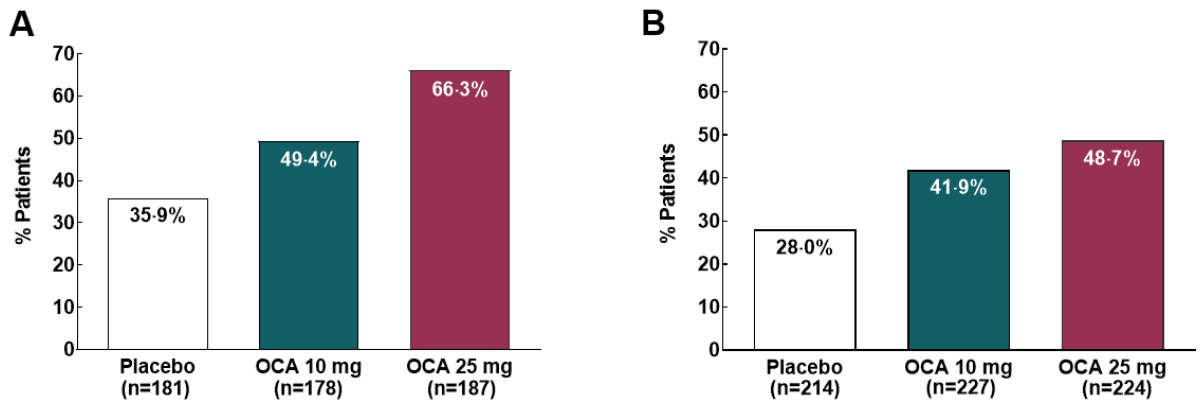
Supplementary Figure S3 Pathologist diagnostic assessment of NASH: Resolution of NASH with no worsening of fibrosis based on the absence of definite steatohepatitis



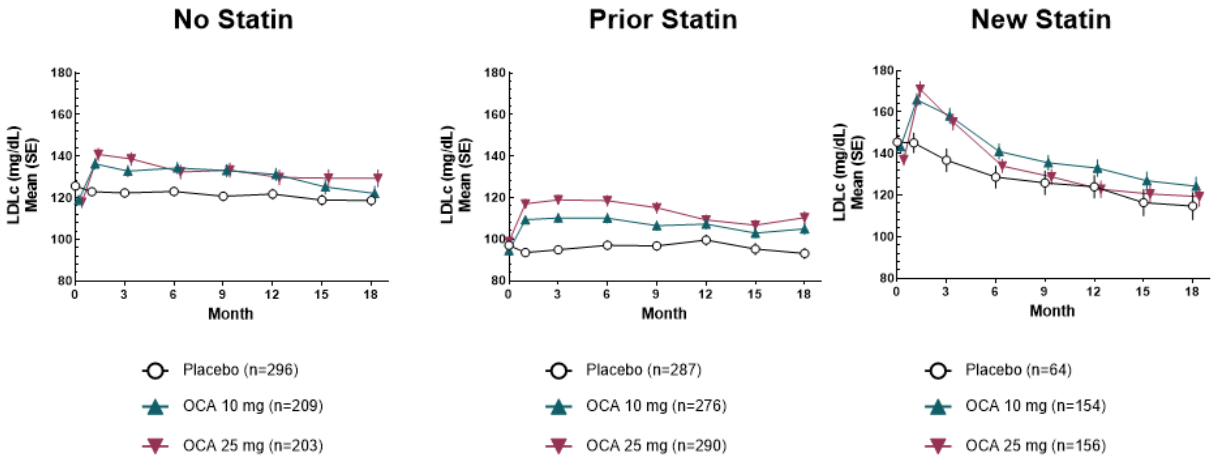
Supplementary Figure S4 Improvement of fibrosis and/or resolution of NASH with no worsening of either



Supplementary Figure S5 Normalisation of elevated transaminase levels



Supplementary Figure S6 Changes in LDLc over time by statin use



Supplementary Figure S7 Changes in glucose and HbA1C over time by diabetes status.