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Research Article
NAFLD and Alcohol-Related Liver Diseases

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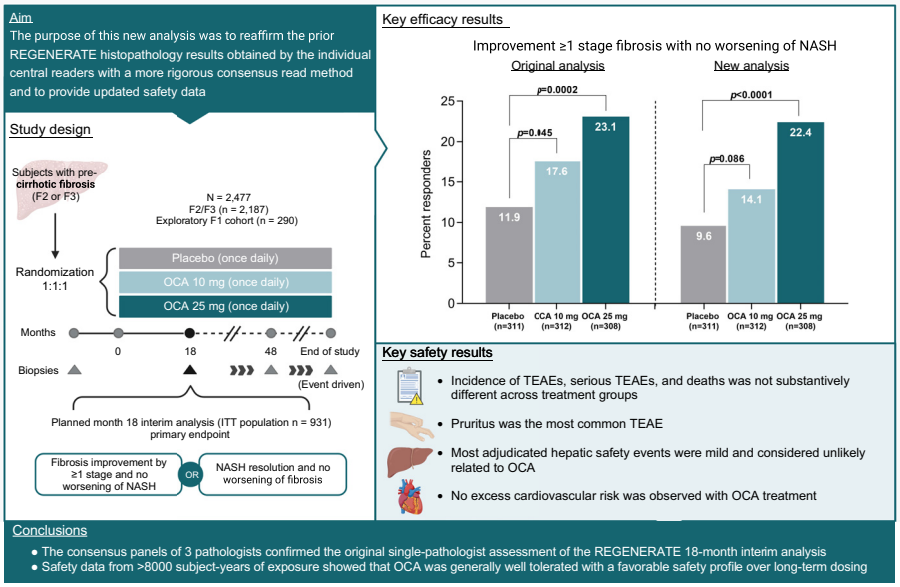
Graphical abstract



Highlights

- OCA was superior to placebo in improving fibrosis by ≥1 stage with no worsening of NASH.
- OCA treatment resulted in dose-dependent reductions of serum ALT levels.
- OCA reduced liver stiffness compared to placebo regardless of histologic response.
- OCA was generally well tolerated and demonstrated a favorable safety profile.

Impact and implications

Patients with non-alcoholic steatohepatitis (NASH) often have liver scarring (fibrosis), which causes an increased risk of liver-related illness and death. Preventing progression of fibrosis to cirrhosis or reversing fibrosis are the main goals of drug development for NASH. In this clinical trial of obeticholic acid (OCA) in patients with NASH (REGENERATE), we reaffirmed our previous results demonstrating that OCA was superior to placebo in improving fibrosis using a more rigorous consensus panel analysis of liver biopsies taken at month 18. We also showed that OCA treatment resulted in dose-dependent reductions of serum liver biochemistries and liver stiffness measurements compared with placebo, even in participants in whom histologic fibrosis did not change at 18 months, providing evidence that the benefit of OCA extends beyond what is captured by the ordinal NASH CRN scoring system. OCA was well tolerated with a favorable safety profile supporting a positive benefit: risk profile in patients with pre-cirrhotic liver fibrosis due to NASH.

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Results from a new efficacy and safety analysis of the REGENERATE trial of obeticholic acid for treatment of pre-cirrhotic fibrosis due to non-alcoholic steatohepatitis

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Background & Aims: Obeticholic acid (OCA) is a first-in-class farnesoid X receptor agonist and antifibrotic agent in development for the treatment of pre-cirrhotic liver fibrosis due to non-alcoholic steatohepatitis (NASH). We aimed to validate the original 18-month liver biopsy analysis from the phase III REGENERATE trial of OCA for the treatment of NASH with a consensus panel analysis, provide additional histology data in a larger population, and evaluate safety from >8,000 total patient-years' exposure with nearly 1,000 participants receiving study drug for >4 years.
Methods: Digitized whole-slide images were evaluated independently by panels of three pathologists using the NASH Clinical Research Network scoring system. Primary endpoints were (1) ≥1 stage improvement in fibrosis with no worsening of NASH or (2) NASH resolution with no worsening of fibrosis. Safety was assessed by laboratory values and adverse events.
Results: Prespecified efficacy analyses included 931 participants. The proportion of participants achieving a ≥1 stage improvement in fibrosis with no worsening of NASH was 22.4% for OCA 25 mg *vs*. 9.6% for placebo (p <0.0001). More participants receiving OCA 25 mg *vs.* placebo achieved NASH resolution with no worsening of fibrosis (6.5% *vs*. 3.5%, respectively; p = 0.093). Histology data in a larger population of 1,607 participants supported these results. Safety data included 2,477 participants. The incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, and deaths was not substantively different across treatment groups. Pruritus was the most common TEAE. Rates of adjudicated hepatic, renal, and cardiovascular events were low and similar across treatment groups.
Conclusions: These results confirm the antifibrotic effect of OCA 25 mg. OCA was generally well tolerated over long-term dosing. These data support a positive benefit:risk profile in patients with pre-cirrhotic liver fibrosis due to NASH.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis in the absence of significant alcohol consumption or other causes of fatty liver disease.[1] Non-alcoholic steatohepatitis (NASH) is a chronic and progressive form of NAFLD affecting 3% to 5% of the US adult population,[2] with a global prevalence of 1.5% to 6.5%.[3] NASH is characterized by lipid accumulation in hepatocytes (steatosis), which is accompanied by inflammation and hepatocyte damage. Steatohepatitis leads to fibrosis, which may progress to cirrhosis.[1,4]

Hepatic fibrosis is the most robust predictor of negative clinical outcomes in NASH.[5–9] The risk of liver-related morbidity and mortality, as well as all-cause mortality, increases as fibrosis progresses. Patients with advanced fibrosis (stage 3/F3 = bridging fibrosis and stage 4/F4 = cirrhosis) are at the greatest risk[6–13]; thus, halting progression or reversing fibrosis at any stage is the primary goal of pharmacotherapy. Approximately one in five patients with evidence of stage 3 liver fibrosis due to NASH experience progression to cirrhosis within ~2.5 years.[5] These data highlight the urgent need to treat patients with pre-cirrhotic fibrosis due to NASH to prevent progression to cirrhosis.

Although NASH is the fastest-growing indication for liver transplantation in the US[14] and Europe[15] and is the leading cause of liver transplantation in women,[14,16,17] there are currently no approved pharmacotherapeutic options for the

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disease.[18] Lifestyle modifications such as dietary restrictions and increased physical activity are first-line treatments for patients with NASH.[1,19,20] Unfortunately, the ~10% weight loss necessary to improve fibrosis is not sustainable for most individuals.[21] Once a pharmacotherapy is approved, it is expected to be the standard of care for patients at risk of progressing to cirrhosis.[19,20]

Obeticholic acid (OCA) is a first-in-class farnesoid X receptor (FXR) agonist and antifibrotic agent in development for the treatment of pre-cirrhotic liver fibrosis due to NASH.[10,22] OCA is an analogue of the bile acid chenodeoxycholic acid (CDCA), the natural FXR ligand, but it is ~100x more potent than CDCA.[10] Because of its bile acid–like properties, OCA circulates enterohepatically and engages FXR in the liver and gut.[23–25] OCA reduced the progression of liver fibrosis in animal models of NASH[26–29] and demonstrated improved fibrosis in 35% of participants on OCA 25 mg in the phase II FLINT study of participants with non-cirrhotic NASH after 72 weeks of therapy.[30]

For the previously reported planned 18-month interim analysis of REGENERATE (NCT02548351) in the prespecified intent-to-treat (ITT) population, fibrosis improved ≥1 stage with no worsening of NASH in 23.1% of participants receiving OCA 25 mg *vs.* 11.9% of those receiving placebo (p = 0.0002).[22] Histologic assessments of biopsies were performed by one of two central expert liver pathologists.[22] Recently, the US FDA recommended a consensus approach to reduce variability and increase concordance for histopathology analyses of liver biopsies in NASH trials.[31,32] Following this guidance, a consensus read method was developed using panels of three board-certified pathologists who underwent additional training and proficiency testing specific to reading NASH Clinical Research Network (CRN) fibrosis stage and NAFLD activity score (NAS) parameters.

The purpose of this new analysis was to reaffirm the prior histopathology results obtained by the individual central readers with a rigorous consensus read method in the same 931 participants included in the original interim analysis. Biopsies from additional participants who reached month 18 and who elected to undergo liver biopsy since the original interim analysis have also been evaluated by this method. In addition, updated safety and tolerability data from the ongoing REGENERATE trial are presented here, representing >8,000 total patient-years (PYs) of study drug exposure and nearly 1,000 participants who received study drug for >4 years.

Patients and methods

Study design and participants

The study design for this multicenter, randomized, double-blind, placebo-controlled phase III trial has previously been reported.[22] Eligible participants were aged ≥18 years with biopsy-confirmed NASH and a NAS score ≥4, with fibrosis stage 1 (an exploratory group of <12% of the total population), 2, or 3, per NASH CRN criteria. The main exclusion criteria included evidence of other chronic liver disease; histologic or laboratory values consistent with cirrhosis; hemoglobin A1c >9.5%; major cardiovascular (CV) event in the preceding 12 months; or significant alcohol consumption.

Randomization and masking

Participants were randomized 1:1:1 to receive once-daily oral placebo, OCA 10 mg, or OCA 25 mg with local standard of care and minimum follow-up time expected to be approximately 4 years. Randomization of participants with fibrosis stage 2 or stage 3 was stratified by the presence of type 2 diabetes and the use of thiazolidinediones/glitazones or vitamin E.

Histology

In the original analysis, two expert central pathologists were each randomly assigned to evaluate approximately one-half of the glass slides from baseline and month 18 liver biopsies as paired reads following the NASH CRN scoring system.[22,33]

The consensus approach was conducted on the same 931 participants from the original analysis. Digitized whole-slide images were evaluated by panels of three pathologists (different from the pathologists in the original analysis) using the NASH CRN scoring system. Each slide image was read independently by each of the three pathologists, who were blinded to each other's read. Consensus was defined as agreement by two of the three pathologists for each of the histologic features of NASH (steatosis, hepatocellular ballooning, lobular inflammation, and fibrosis stage)[31] to agree on a final score. If agreement was not achieved on a parameter, slide images were jointly read by the entire panel in an effort to reach consensus for that parameter; if consensus could not be achieved, the slide was considered non-evaluable and thus treated as a non-responder. Unlike in the original analysis, slides were not read as "pairs" (baseline + month 18) and the consensus panel pathologists were not blinded to whether the biopsy was taken at baseline or month 18.

Efficacy endpoints

The REGENERATE study was designed to assess the effect of OCA treatment on liver histology at month 18 as a surrogate endpoint for clinical outcomes.[22] The two primary endpoints for the interim analysis were (1) improvement in fibrosis (reduction of ≥1 stage) with no worsening of NASH (defined as no worsening in any of the three NAS components [hepatocellular ballooning, lobular inflammation, or steatosis]) or (2) NASH resolution (defined as "no fatty liver disease" or "fatty liver disease [simple or isolated steatosis] without steatohepatitis" and hepatocellular ballooning of 0 and lobular inflammation of 0 or 1) with no worsening of fibrosis. At least one endpoint needed to be met at month 18 to achieve the primary objective for accelerated FDA approval.

Key secondary endpoints included (1) change from baseline to month 18 in liver stiffness measurement, Fibrosis-4 (FIB-4) index and enhanced liver fibrosis (ELF) score; (2) percentage of participants with improvement in fibrosis by ≥2 stages; (3) percentage of participants with no worsening of fibrosis and no worsening of NASH; and (4) percentage of participants with improvement of fibrosis and resolution of NASH as a composite endpoint. The ITT population for non-histology analyses included all participants who were randomized, received at least one dose of investigational product, had original eligibility baseline fibrosis stage 2 or 3, and had any post-baseline measurement. All efficacy results presented herein are

considered supportive of the original month 18 interim analysis and, therefore, all *p* values comparing OCA arms *vs.* placebo are nominal.

Safety endpoints

Safety and tolerability of OCA were assessed by analysis of adverse events (AEs); AEs of special interest (AESIs); adjudicated hepatic safety, CV, and renal events; vital signs; electrocardiograms; and clinical laboratory assessments. Specific safety events were analyzed as AESIs based on OCA's mechanism of action as an FXR agonist, underlying comorbidities in this patient population, and OCA's known safety profile in patients with primary biliary cholangitis.[34,35] AESIs included pruritus, hepatic disorders, CV AEs, dyslipidemia, gallstone-related events, pancreatitis, renal disorders, urolithiases, and hyperglycemia/new-onset diabetes (additional information on AESIs may be found in the supplementary appendix). Adverse events were graded for severity using Common Terminology Criteria for Adverse Events version 4.03.

An independent data-monitoring committee was tasked with reviewing unblinded safety data on an ongoing basis. Four blinded independent committees comprising experts were assembled to review and adjudicate all potential cases of (1) hepatic outcome events, (2) hepatic safety events, (3) acute kidney injury, and (4) major adverse cardiovascular events (MACEs) that occurred after administration of the first dose of investigational product. Improvement in adjudicated clinical outcomes, such as death, liver transplant, and progression to cirrhosis, will serve as the final primary endpoint of the REGENERATE study. As the study is ongoing, they are not included in this planned 18-month interim analysis. In 2017, a major safety amendment was implemented for the study with the goal of improving participant safety. The amendment provided focused education and training for participants and investigators for the prompt recognition and reporting of signs and symptoms indicative of liver injury. In addition, specific liver biochemical monitoring based on standard liver function tests (*e.g.*, alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, alkaline phosphatase) and management criteria, including prompt interruption of study drug and close follow-up in situations indicative of liver injury, were provided. The amendment did not change the frequency of study visits which were scheduled at month 1, every 3 months through month 18, and then every 6 months thereafter.

Results

The safety population included participants who received ≥1 dose of study drug (N = 2,477). The ITT population for the planned interim analysis comprised the same 931 participants included in the original 18-month reported results.[22] Baseline demographics, clinical characteristics, and disease characteristics (Table 1) were balanced across treatment groups and were generally reflective of a population with significant fibrosis due to NASH. The majority of participants in the total OCA and placebo groups were female (58.7% and 57.9%, respectively), White (89.9% and 92.4%, respectively), and not Hispanic or Latino (81.4% and 80.1%, respectively).

Efficacy

The interim analysis primary endpoint of improvement in fibrosis by ≥1 stage with no worsening of NASH was achieved for the ITT population, with the response rate of OCA 25 mg at least double that for placebo. For the consensus panel assessments of the month 18 results, 22.4% of participants receiving once-daily oral OCA 25 mg achieved a ≥1 stage improvement of fibrosis with no worsening of NASH compared with 9.6% of participants receiving placebo (p <0.0001); results were highly consistent with the original analysis (Fig. 1A).[22] Similarly, a subgroup analysis of participants with type 2 diabetes at baseline was consistent with the results observed in the overall population (Fig. S1).

A greater percentage of participants with fibrosis stage 3 experienced improvement of fibrosis by ≥1 stage without worsening of NASH in the OCA 25 mg treatment group compared to participants with fibrosis stage 2 (25.4% *vs.*18.7%; Fig. 1B). Considering fibrosis stage only (*i.e.*, independent of NAS component assessments), 15.8% of participants receiving placebo experienced improved fibrosis by ≥1 stage compared with 22.1% of participants receiving OCA 10 mg and 29.5% of participants receiving OCA 25 mg (Fig. 1C).

Following the same ITT approach as the interim analysis population, an exploratory analysis including all participants who had or were expected to have a month 18 biopsy (n = 1,607) provides supportive evidence, with 21.0% of participants receiving once-daily oral OCA 25 mg achieving a ≥1 stage improvement of fibrosis with no worsening of NASH compared with 12.3% of participants receiving placebo (p = 0.0001) (Fig. 1D).

Further, in a subset of the interim analysis population with available baseline and month 18 biopsies, a greater proportion of participants in the OCA 25 mg group experienced improved fibrosis by ≥1 stage, and more participants in the placebo group had worsening of fibrosis by ≥1 full stage. Improvement in fibrosis by ≥1 stage was achieved in 19.8% of those receiving placebo, 27.1% of those receiving OCA 10 mg, and 37.3% of participants receiving OCA 25 mg (Fig. 2A).

A similar exploratory analysis was performed including participants after the data cut-off for the month 18 interim analysis. There were an additional 405 participants who reached the month 18 visit, underwent a biopsy, and have available baseline biopsy for comparison. The exploratory analysis including these participants further supported the antifibrotic effect of OCA 25 mg. In this analysis, 40.4% of participants receiving OCA 25 mg, 33.1% receiving OCA 10 mg, and 25.4% receiving placebo showed improved fibrosis by ≥1 stage (Fig. 2B).

The NASH resolution interim analysis primary endpoint required hepatocellular ballooning of 0 and lobular inflammation of 0 or 1; a higher percentage of participants in the OCA 25 mg group (6.5%) and OCA 10 mg group (6.1%) were considered responders compared with the placebo group (3.5%).

The mean baseline values for markers of hepatocellular injury and oxidative stress (ALT, AST, and gamma-glutamyltransferase [GGT]) were elevated in all treatment groups. At month 18, OCA treatment produced dose-

Table 1. Baseline demographics, clinical characteristics, and disease characteristics.

Safety population (N = 2,477)	Placebo (n = 825)	OCA 10 mg (n = 825)	OCA 25 mg (n = 827)
Age, mean (SD), yr	54.4 (11.2)	55.3 (10.8)	55.3 (11.7)
Female, n (%)	478 (57.9)	475 (57.6)	494 (59.7)
Race, n (%)			
American Indian or Alaska Native	6 (0.8)	5 (0.7)	8 (1.1)
Asian	29 (3.9)	47 (6.2)	43 (5.7)
Black or African American	12 (1.6)	14 (1.9)	20 (2.7)
Native Hawaiian or Other Pacific Islander	2 (0.3)	4 (0.5)	4 (0.5)
White	685 (92.4)	679 (90.2)	674 (89.6)
Other	7 (0.9)	4 (0.5)	3 (0.4)
Ethnicity, n (%)			
Hispanic or Latino	147 (19.9)	129 (17.2)	149 (20.1)
Not Hispanic or Latino	592 (80.1)	620 (82.8)	594 (79.9)
Geographic region, n (%)			
North America	582 (70.5)	572 (69.3)	581 (70.3)
BMI, mean (SD), kg/m^2	34.1 (5.5)	33.7 (5.6)	33.7 (5.5)
ALT, mean (SD), U/L	77.1 (51.7)	71.4 (46.3)	72.6 (52.7)
LDL, n (%), ≥100 mg/dl	496 (61.0)	489 (60.2)	511 (62.5)
Concomitant medication use, n (%)			
Bile acid sequestrants	18 (2.2)	14 (1.7)	22 (2.7)
Statins	377 (45.7)	359 (43.5)	377 (45.6)
Antidiabetic medications	465 (56.4)	472 (57.2)	467 (56.5)
GLP-1 agonists	73 (8.8)	83 (10.1)	76 (9.2)
Thiazolidinedione only	14 (1.7)	13 (1.6)	15 (1.8)
Vitamin E	85 (10.3)	71 (8.6)	82 (9.9)
Medical history, n (%)			
Cholelithiasis	159 (19.3)	149 (18.1)	160 (19.3)
Diabetes status, yes*	470 (57.0)	476 (57.7)	479 (57.9)
Hypertension	554 (67.2)	549 (66.5)	537 (64.9)
Cardiac disorders	103 (12.5)	107 (13.0)	108 (13.1)
Renal and urinary disorders	186 (22.5)	210 (25.5)	186 (22.5)
ITT population (n = 931)	**Placebo (n = 311)**	**OCA 10 mg (n = 312)**	**OCA 25 mg (n = 308)**
Fibrosis stage F2, n (%)	142 (45.7)	130 (41.7)	139 (43.4)
Fibrosis stage F3, n (%)	169 (54.3)	182 (58.3)	169 (54.9)
Liver stiffness, mean (SD), kPa	12.50 (7.59)	11.98 (5.59)	12.38 (7.28)
FIB-4, mean (SD)	1.62 (0.89)	1.63 (0.88)	1.63 (0.85)
ELF, mean (SD)	9.71 (0.94)	9.73 (0.92)	9.73 (0.95)

ALT, alanine aminotransferase; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; GLP-1, glucagon-like peptide 1; OCA, obeticholic acid.
*Medical history of diabetes, baseline use of antidiabetic medication with a diabetes indication, or hemoglobin A1c ≥6.5%.

dependent reductions in mean serum ALT, AST, and GGT levels to a greater extent than placebo, a pattern that was consistent through month 48 (Fig. S2). Of the participants with elevated ALT levels (>1.5x the upper limit of normal) at baseline, 7.9%, 20.7%, and 23.9% of participants receiving placebo, OCA 10 mg, and OCA 25 mg, respectively, had normal ALT levels (<30 U/L) at month 18. Of those with normal or near-normal ALT levels (≤1.5x the upper limit of normal) at baseline, 33.2%, 55.8%, and 52.3% normalized or remained normal with placebo, OCA 10 mg, and OCA 25 mg, respectively (Fig. S3). In a responder analysis that evaluated subgroups of improvement in fibrosis by ≥1 stage at month 18, OCA treatment resulted in dose-dependent reductions of ALT even in participants who did not show fibrosis improvement on histologic assessment; the magnitude of effect for OCA 25 mg compared with placebo was greater in participants with improvement or no change in histologic fibrosis compared to those with worsening fibrosis (Fig. 3A). As expected, liver stiffness increased at month 18 in participants with worsening fibrosis on histology; the increase in liver stiffness was smaller in those treated with OCA (Fig. 3B). The change from baseline in additional non-invasive tests (FIB-4 and ELF) by responder status are shown in Fig. S4.

Safety

The original interim analysis included safety data from the first 1,968 participants enrolled with a median of 15 months of exposure to the study drug.[22] Since that time, full enrollment was achieved, and additional safety data from a total of 2,477 participants has been incorporated. As of the data cut-off, 8,054 total PYs of exposure data were available, with a median exposure of 39 months. A total of 976 participants had received study drug for >4 years. Deaths were balanced across treatment groups. Treatment-emergent adverse events (TEAEs) and serious TEAEs were numerically higher for the combined OCA groups *vs.* placebo, with the difference primarily driven by pruritus (Table 2).

AESIs

Pruritus, dyslipidemia, and gallstone-related events occurred at a higher incidence with OCA 25 mg compared with placebo. No difference between treatment groups was observed for the incidence of hyperglycemia, pancreatitis, or urolithiasis events (Table 2). Pruritus was the most common AE leading to investigational product discontinuation in 1.0% (placebo), 1.7% (OCA 10 mg), and 11.2% (OCA 25 mg). Approximately half of

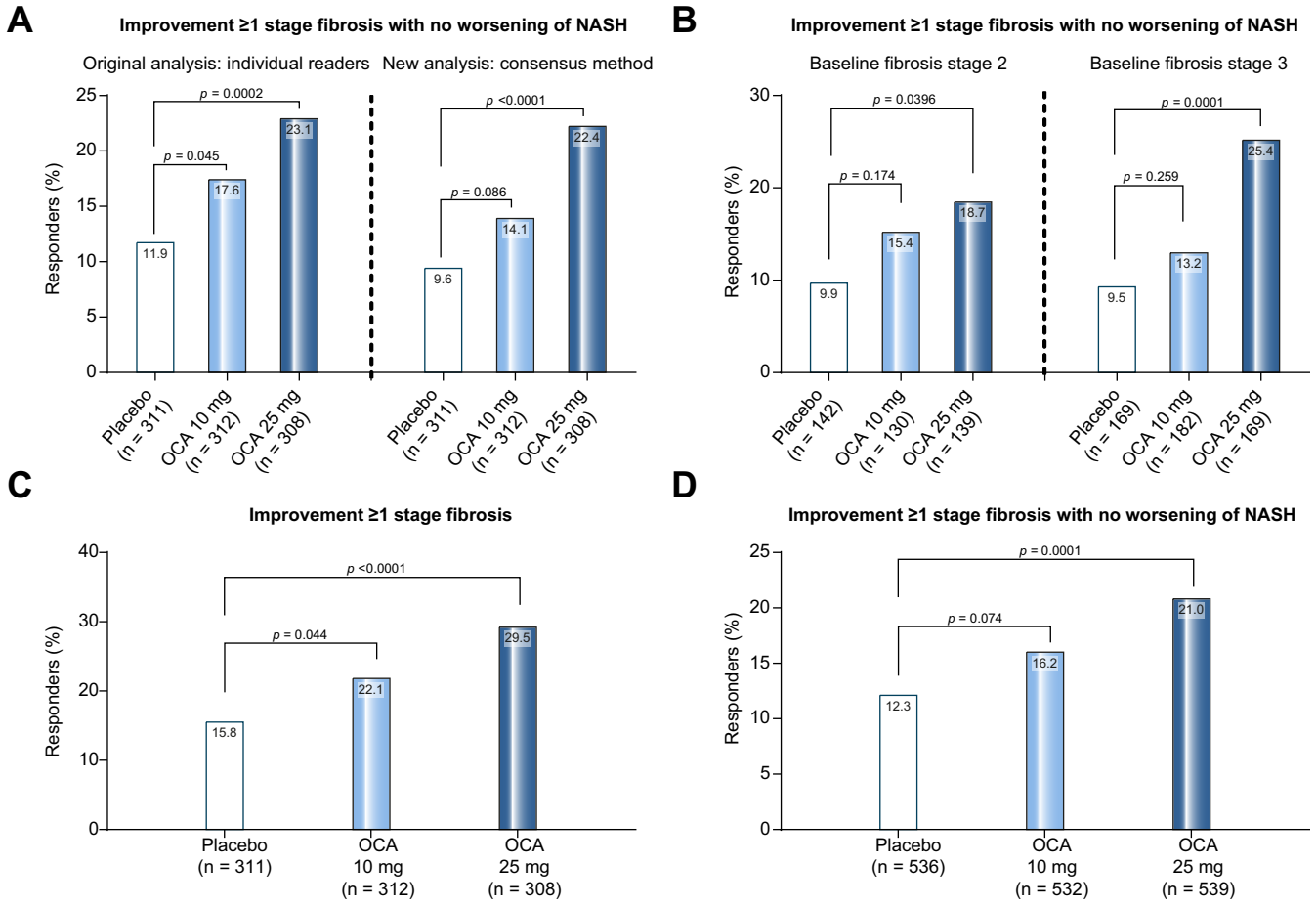

Fig. 1. Histologic endpoints. Results represent the new consensus scoring by three pathologists. (A) Improvement of fibrosis by ≥1 stage without worsening of NASH for the original and new analyses, (B) improvement of fibrosis by ≥1 stage without worsening of NASH by baseline fibrosis stage, (C) improvement of fibrosis by ≥1 stage, and (D) improvement of fibrosis by ≥1 stage without worsening of NASH in the exploratory ITT population. Data in Panels A-C are for the original ITT population (n = 931). Data in Panel D are for the exploratory ITT population (n = 1,607). Fibrosis stage was defined using NASH CRN criteria. "No worsening of NASH" was defined as no worsening of hepatocellular ballooning grade, no worsening of lobular inflammation grade, and no worsening of steatosis grade. *p* values are nominal and supportive of the original results (Cochran-Mantel-Haenszel test). ITT intent-to-treat; NAS; non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; NASH CRN, NASH Clinical Research Network; OCA, obeticholic acid.

the discontinuations due to pruritus in the OCA 25 mg treatment group were protocol-mandated, requiring participants with grade 3 or greater pruritus to permanently discontinue treatment. The relative risk for pruritus, dyslipidemia, and gallstone-related events was greater for OCA 25 mg compared with placebo (Fig. S5). Consistent with known FXR agonism, a transient increase in LDL cholesterol was observed, which returned to near baseline levels by month 18 regardless of initiating a statin; the addition of a statin led to a faster decrease in LDL levels (Fig. S6).

Serious gallstone-related AESIs occurred infrequently (<2.5%), although they were numerically higher in the OCA 25 mg group compared with placebo. The incidence of participants undergoing a cholecystectomy after study entry was 2.1%, 1.8%, and 4.6% in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively. Notably, 87% of participants in the OCA 25 mg group resumed the investigational product after cholecystectomy, with no subsequent TEAEs related to gallstone/pancreatitis reported after restarting OCA 25 mg. The relative risk for gallstone-related TEAEs was similar in participants receiving OCA 25 mg with known gallstones at baseline and participants with no gallstones/unknown gallstone status at baseline: 1.10 (95% CI 0.95–1.29) and 1.05 (95% CI 1.01–1.08), respectively.

A comprehensive list of search criteria based on predefined liver lab tests and adverse events was used to capture events to be reviewed by an independent committee with expertise in drug-induced liver injury. An equal number of participants with at least one event meeting trigger criteria were submitted for review by the committee (254 [31%], 260 [32%], 251 [31%] in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively). Of these events, 111 (14%), 110 (13%), and 130 (16%) participants had at least one adjudicated event of potential liver injury as determined by the expert committee. The majority of adjudicated hepatic safety events were mild and considered unlikely to be related to study drug treatment by the blinded independent adjudication committee. Events considered probably or highly likely to be related to the investigational product occurred in 1 (0.1%), 1 (0.1%), and 7 (0.8%) participants in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively (Fig. S7).

Prior to the safety amendment in 2017, the exposure-adjusted incidence rate of cases of adjudicated hepatic events at least moderate in severity, regardless of causality,

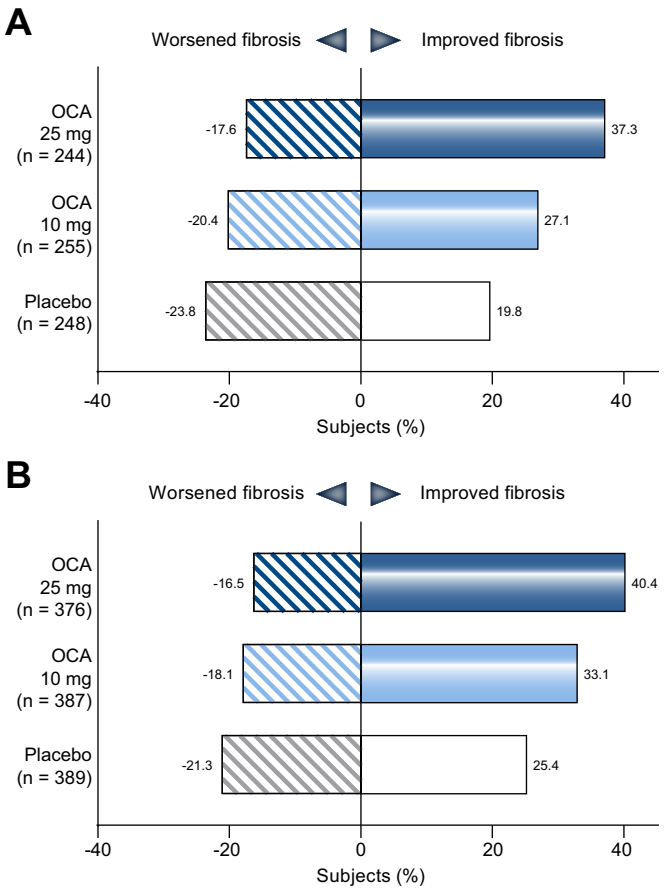

Fig. 2. Shift in fibrosis from baseline to month 18 for subjects with both baseline and post-baseline biopsies. (A) Original interim analysis and (B) exploratory analysis that included additional participants after the interim analysis data cut-off. Shift in fibrosis is defined as worsened by ≥1 stage or improved by ≥1 stage. OCA, obeticholic acid.

was 0.25 (95% CI 0.00–1.52) per 100 PYs in participants receiving placebo, 0 per 100 PYs in participants receiving OCA 10 mg, and 1.75 (95% CI 0.77–3.63) per 100 PYs in participants receiving OCA 25 mg. After implementation of the safety amendment, there was a marked reduction in the exposure-adjusted incidence rate of adjudicated potential liver injury events, and especially severe events; 0.12 (95% CI 0.02–0.36) per 100 PYs, 0.24 (95% CI 0.09–0.53) per 100 PYs, and 0.38 (95% CI 0.19–0.73) per 100 PYs in participants receiving placebo, OCA 10 mg, and OCA 25 mg, respectively (Fig. 4). Importantly, there were no liver-related deaths or liver transplants due to an OCA-induced liver injury reported after implementation of the 2017 safety amendment. Furthermore, a review of the clinically important events adjudicated as at least moderate in severity and assessed as at least possibly related to OCA by the committee indicated that these events occurred within the first 12 to 18 months of initiating OCA and were reversible after stopping treatment with OCA.

Hepatic safety was further assessed by evaluating biochemical lab excursions via eDISH (evaluation of drug-induced serious hepatotoxicity). Based on the analysis of maximum ALT and total bilirubin levels, biochemical Hy's law range (upper right quadrant) and cholestasis range (upper left quadrant) excursions were similar across the three treatment groups, whereas more participants receiving placebo experienced excursions into the Temple's corollary range (lower right quadrant) (Fig. 5A). Similar patterns were observed for eDISH analyses using serum alkaline phosphatase and total bilirubin (Fig. 5B).

No clear signal for an increased risk of renal disorder events was observed for OCA compared with placebo (Fig. S5). The number of participants with renal safety events referred for adjudication was 45, 57, and 59 for placebo, OCA 10 mg, and OCA 25 mg, respectively. Of those, the incidence of adjudicated events with evidence of acute kidney injury (AKI) was 1.5%, 2.5%, and 2.9% for participants in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively. Most of the adjudicated AKI events were assessed as stage 1 (serum creatinine 1.5–2x baseline or ≥0.3 mg/dl). No events were assessed as highly likely to be related to study drug; events assessed as probably related to study drug occurred in 0.2%, 1.0%, and 0.4% of the adjudicated AKI events in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively. No difference was observed in mean serum creatinine or estimated glomerular filtration rate over 48 months across treatment groups.

Adjudicated on-study (time to the earliest of the first event, death, date of end of study, or date of data cut-off) CV events are shown in Table 3. No difference among placebo or OCA groups was observed for 3-point, 4-point, or 5-point MACE in participants with low baseline risk of atherosclerotic cardiovascular disease (10-year risk <20%) or high baseline risk (10-year risk ≥20%). The incidence of adjudicated on-treatment (time to the earliest of the first event, death, date of end of study, date of last dose + 30 days, or date of data cut-off) CV events was less than 2% and balanced between the placebo and OCA treatment groups (Table S1).

Discussion

A significant unmet need exists in patients with NASH to prevent the progression of pre-cirrhotic liver fibrosis to cirrhosis. Our consensus analysis by panels of three pathologists independently confirms the original, single-pathologist assessment of the REGENERATE 18-month interim analysis, reinforces the antifibrotic benefit of OCA, and further contributes to the positive benefit:risk profile for OCA in participants with pre-cirrhotic fibrosis due to NASH. The prespecified interim analysis was designed to assess efficacy based on a surrogate endpoint reasonably likely to predict a clinical benefit. After 18 months of therapy, the interim analysis primary endpoint of fibrosis improvement by ≥1 stage without worsening of NASH using the consensus reading method was achieved and was consistent with the results from the original interim analysis performed by individual central readers.[22] The proportion of participants with a ≥1 stage improvement in fibrosis without worsening of NASH for OCA 25 mg was at least double that of placebo. It is important to note that this response rate is likely conservative and may underestimate OCA's antifibrotic effect, as achieving this interim analysis endpoint required both (1) improvement in fibrosis by ≥1 full ordinal CRN stage and (2) no worsening of any of the three NAS components. The antifibrotic effects of OCA were substantiated despite the potential variability in assessing liver biopsies,[36] persistent comorbidities, and the short period of intervention prior to the month 18 biopsy. Since the original analysis in 2019, the importance of fibrosis stage as a predictor of all-cause and liver-specific mortality has become

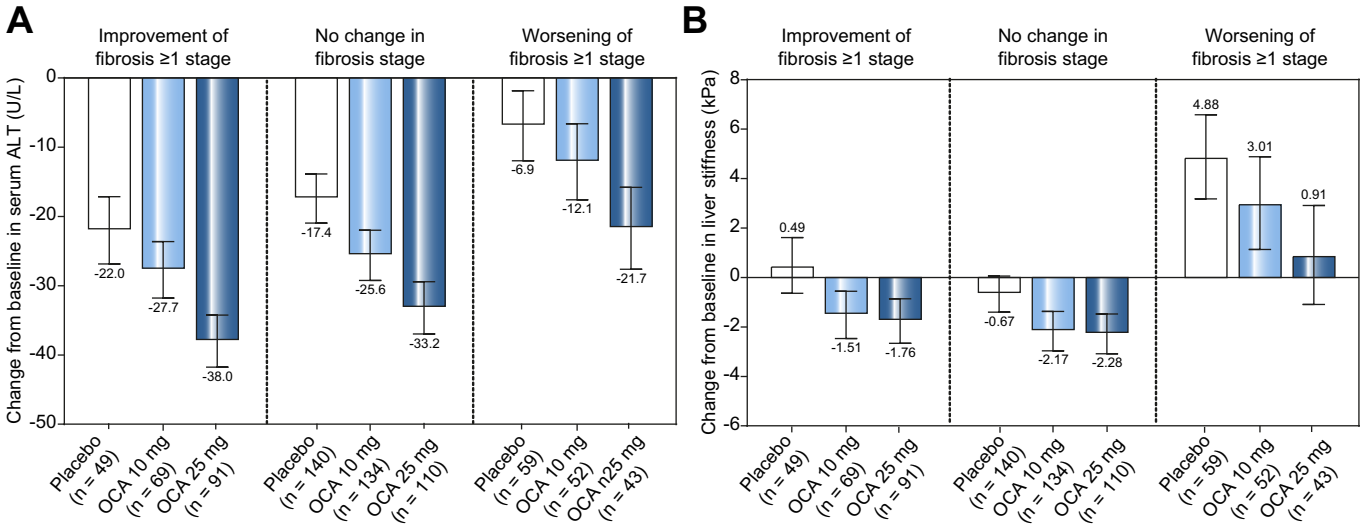

Fig. 3. Non-invasive measures of OCA efficacy. (A) Change from baseline in serum ALT by fibrosis responder status and (B) change from baseline in liver stiffness (transient elastography) by fibrosis responder status. Data are LSM ± SE for the original ITT population (n = 931). Baseline was defined as the mean of all measurements prior to first dose of investigational product. (A) LSM was calculated using a mixed-effect repeated-measures model with an unstructured covariance structure and treatment group, visit, visit by treatment interaction, and stratification factors as fixed effects and baseline as a covariate. (B) LSM was calculated using mixed-effect repeated-measures model with treatment group and stratification factors as fixed effects and baseline as a covariate. ALT, alanine aminotransferase; LSM, least squares mean; OCA, obeticholic acid.

Table 2. Treatment-emergent adverse events and key adverse events of special interest.

	Placebo (n = 825)	OCA 10 mg (n = 825)	OCA 25 mg (n = 827)
Deaths	8 (1.0)	9 (1.1)	10 (1.2)
TEAEs	766 (92.8)	795 (96.4)	807 (97.6)
Serious TEAEs	181 (21.9)	204 (24.7)	216 (26.1)
TEAEs leading to IP withdrawal	93 (11.3)	102 (12.4)	179 (21.6)
Most frequent TEAE: pruritus	200 (24.2)	274 (33.2)	453 (54.8)
Most frequent TEAE leading to IP discontinuation: pruritus	8 (1.0)	14 (1.7)	93 (11.2)*
Neoplasms: benign, malignant, and unspecified	84 (10.2)	91 (11.0)	76 (9.2)
AESIs			
Gallstone-related events	33 (4.0)	44 (5.3)	63 (7.6)
Pancreatitis	7 (0.8)	5 (0.6)	8 (1.0)
Hyperglycemia	190 (23.0)	223 (27.0)	201 (24.3)
Urolithiases	32 (3.9)	31 (3.8)	28 (3.4)
Dyslipidemia	193 (23.4)	354 (42.9)	390 (47.2)
Serious AESIs			
Gallstone-related events	6 (0.7)	8 (1.0)	21 (2.5)
Pancreatitis	4 (0.5)	5 (0.6)	6 (0.7)
Hyperglycemia	2 (0.2)	5 (0.6)	11 (1.3)
Urolithiasis	5 (0.6)	7 (0.8)	6 (0.7)
Dyslipidemia	0	0	0

Data presented for the safety population (N = 2,477). All values are n (%).
AESIs, adverse events of special interest; IP, investigational product; OCA, obeticholic acid; TEAE, treatment-emergent adverse event.
*>50% of discontinuations due to pruritis were protocol-mandated.

more definitive.[12] Currently, NAS components such as hepatocyte ballooning are believed to be less predictive of liver-related morbidity and mortality and are subject to substantial inter-observer variation.[37,38]

Secondary analyses also support the antifibrotic and anti-inflammatory effects of OCA *vs.* placebo. OCA demonstrated improvements in non-invasive measures of liver stiffness, including in participants who were assessed to have had no change in fibrosis based on histology. This observation might indicate improvements in NASH pathophysiology and/or liver fibrosis with OCA that are not fully captured by the ordinal NASH CRN histologic fibrosis scale. Dose-dependent reductions in markers of liver cell injury (ALT and AST) and oxidative stress (GGT) were observed in OCA-treated participants, suggesting a potential impact on underlying hepatocellular injury and NASH pathophysiology.[39,40] Notably, in participants with elevated ALT at baseline, serum ALT completely normalized (<30 U/L) in nearly 3x as many receiving OCA 25 mg compared to placebo at 18 months. Considerable reductions in mean serum ALT were also seen in participants with no change in fibrosis stage, implying a potential benefit in some participants considered non-responders by the interim analysis primary endpoints.

While histology data at month 48 remain blinded as the study is ongoing, sustained improvements in the non-invasive markers observed in OCA-treated participants through month

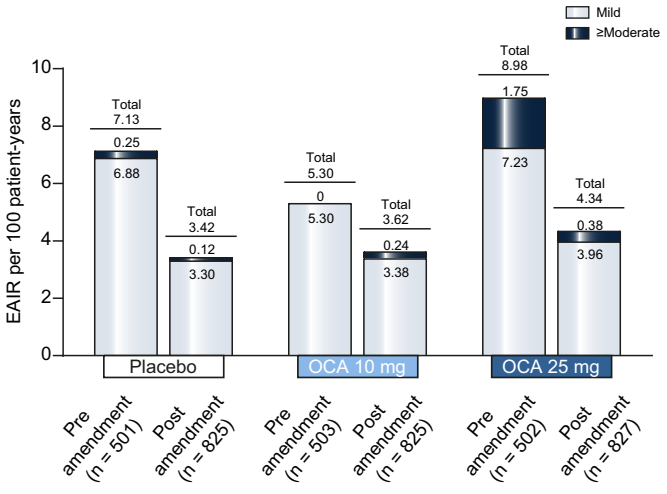

Fig. 4. Impact of the REGENERATE safety amendment: adjudicated hepatic safety events. Data are presented for the safety population (N = 2,477). EAIR, exposure-adjusted incidence rate; OCA, obeticholic acid; PYs, patient-year.

48 demonstrate ongoing therapeutic benefit and the likelihood of continued histologic improvement with longer durations of therapy. Our results indicate that even in participants who do not experience a full stage of fibrosis improvement, OCA reduced the proportion with worsening fibrosis.

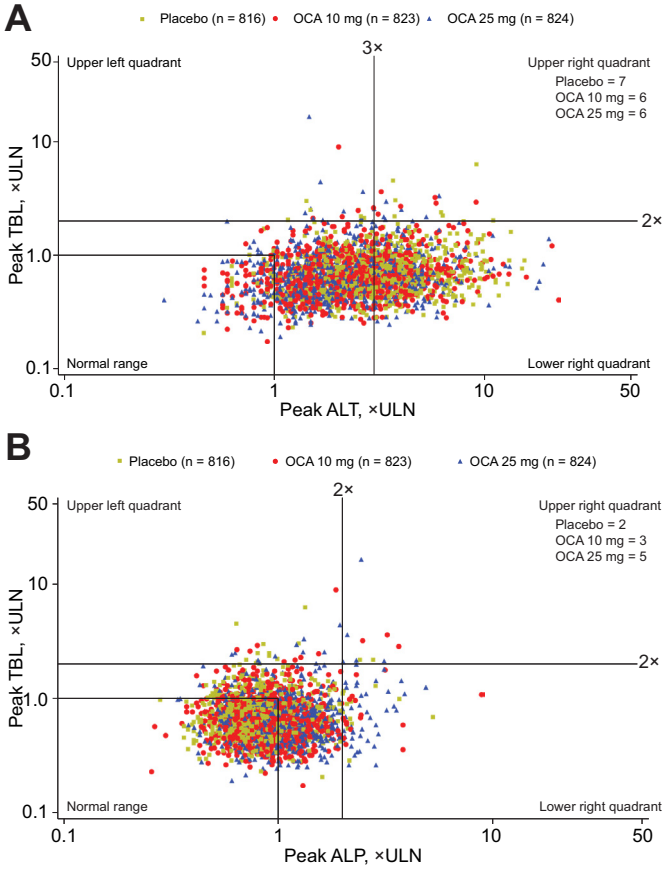

Fig. 5. Evaluation of drug-induced serious hepatotoxicity. (A) Total bilirubin *vs.* ALT and (B) total bilirubin *vs.* ALP. Data are presented for the safety population with both baseline and post-baseline laboratory values (n = 2,463). The following ULN thresholds were used, ALP 120 U/L, ALT 30 U/L, TBL 1.25 mg/dl. ALP, alkaline phosphatase; ALT, alanine aminotransferase; eDISH, evaluation of drug-induced serious hepatotoxicity; OCA, obeticholic acid; TBL, total bilirubin; ULN, upper limit of normal.

REGENERATE represents the largest and longest-duration trial in pre-cirrhotic fibrosis due to NASH and provides the most extensive safety database in NASH to date. The length of study, including many participants receiving OCA for >4 years, allowed for examination of the long-term tolerability of the drug. This large and long-term safety exposure enables appropriate characterization of a favorable safety profile in this population and supports chronic dosing. Treatment groups did not show substantial differences in TEAEs, serious TEAEs, or deaths. Although there was an increase in cholelithiasis and cholecystitis events with OCA treatment, the data from the study confirm that these events are not uncommon in this patient population and were appropriately managed by study investigators in gastrointestinal or hepatology clinical practices. Moreover, the majority (>80%) of participants who reported a gallstone-related event and underwent cholecystectomy were able to resume therapy after the resolution of the event without further gallstone-related AEs.

Following implementation of the safety amendment in 2017, which incorporated specific thresholds for monitoring standard-of-care liver tests and prompt interruption of OCA when a threshold was met, a marked decrease in the incidence of adjudicated hepatic safety events was observed, including in the placebo group. The greatest impact of these safety measures appears to have been in the OCA 25 mg group, with an approximate 3- to 4-fold reduction in the incidence of hepatic events by both causality and severity. These results highlight that the risk of hepatic safety events with OCA in patients with pre-cirrhotic fibrosis due to NASH can be managed with standard-of-care clinical monitoring and with interruption of OCA when hepatic injury is suspected. Furthermore, interruption of OCA led to the reversal of excursions in liver lab tests in the majority of cases, an observation which is consistent with an exposure-related liver injury rather than an immune-mediated, idiosyncratic hepatotoxicity which can continue to progress despite removal of the precipitating etiology. No difference was observed for adjudicated core MACEs across treatment groups. Given the risk of CV disease in this patient population independent of OCA treatment, LDL should be managed per clinical guidelines.[41] While no clear signal for an impact on renal function was observed with OCA, monitoring renal function is recommended.

A recent study demonstrated that FXR antagonism may be a novel target for preventing SARS-CoV-2 (COVID-19) infection[42]; however, in the REGENERATE study coronavirus infection rates were higher in the placebo group than in the OCA groups (8.7% in the placebo group *vs.* 7.2% and 6.4% in the OCA 10 mg and OCA 25 mg groups) with no difference in serious COVID-19 events.

REGENERATE remains ongoing, and the final end-of-study analysis will evaluate the effect of OCA on clinical outcomes, as well as long-term safety; the end-of-study analysis will be complete after 291 adjudicated clinical outcome events are accrued in the placebo and OCA 25 mg groups combined.

Limitations

Assessing histologic change in fibrosis currently relies on the NASH CRN staging system, which may not completely capture

Table 3. Adjudicated on-study* CV events.

10-year ASCVD risk <20%			
No. of participants with ≥1 event (%)	**Placebo (n = 572)**	**OCA 10 mg (n = 541)**	**OCA 25 mg (n = 522)**
Core MACE†	4 (0.7)	1 (0.2)	5 (1.0)
4-point MACE‡	6 (1.0)	1 (0.2)	8 (1.5)
5-point MACE§	8 (1.4)	1 (0.2)	8 (1.5)
10-year ASCVD risk ≥20%			
No. of participants with ≥1 event (%)	**Placebo (n = 90)**	**OCA 10 mg (n = 105)**	**OCA 25 mg (n = 121)**
Core MACE†	6 (6.7)	2 (1.9)	8 (6.6)
4-point MACE‡	6 (6.7)	4 (3.8)	8 (6.6)
5-point MACE§	6 (6.7)	4 (3.8)	8 (6.6)

Data presented for the safety population (N = 2,477).
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; MACE, major adverse cardiac event; MI, myocardial infarction; OCA, obeticholic acid.
*Defined as the time to the earliest of the first event, death, date of end of study, or date of data cut-off.
†Core MACE: CV death + nonfatal MI + nonfatal stroke.
‡4-point MACE: Core MACE + hospitalization for unstable angina.
§5-point MACE: Core MACE + hospitalization for unstable angina + hospitalization/urgent visit for heart failure.

changes reflective of disease improvements, such as liver stiffness and other parameters measured by non-invasive techniques. Clinically meaningful incremental improvements in liver fibrosis that reflect positive outcomes in disease progression may not be captured by this scoring system with sufficient sensitivity. Although the baseline demographic and clinical characteristics were well balanced across the treatment groups, participants were predominantly White and not Hispanic or Latino, which may affect the generalizability of findings.

Conclusions

This re-analysis of the planned month 18 liver biopsies, utilizing a consensus panel of three board-certified pathologists, confirms the statistically significant original interim analysis.[22] The antifibrotic effect of OCA 25 mg was demonstrated through an incremental improvement by ≥1 full stage of fibrosis in nearly 30% of participants with pre-cirrhotic fibrosis due to NASH after 18 months of therapy, a histologic change highly predictive of a more favorable clinical outcome. Additional benefits beyond fibrosis regression in the OCA 25 mg group were demonstrated by its ability to halt fibrosis progression, an equally important treatment goal, and sustain improvements in biochemical markers of liver injury and oxidative stress, and measures of liver stiffness.

Our additional safety data demonstrate that OCA was generally well tolerated over long-term dosing. The confirmed antifibrotic effect, together with extended exposure within the largest safety database in NASH to date, supports a positive benefit:risk profile in patients with pre-cirrhotic liver fibrosis due to NASH. The REGENERATE study remains ongoing, with clinical outcome events being collected for the final end-of-study analysis.

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Abbreviations

AE, adverse event; AESI, adverse event of special interest; AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDCA, chenodeoxycholic acid; CRN, clinical research network; CV, cardiovascular; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; FXR, farnesoid x receptor; GGT, gamma-glutamyltransferase; ITT, intent-to-treat; MACE, major adverse cardiovascular events; NAFLD, non-alcoholic fatty liver disease; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; OCA, obeticholic acid; PYs, patient-years; TEAE, treatment-emergent adverse event.

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Conflicts of interest

AJS has stock options from Genfit, Exhalenz, Tiziana, Indalo, NorthSea, Durect, HemoShear, and Rivus. He has been a consultant for Intercept Pharmaceuticals, Inc., AstraZeneca, Amgen, Salix, Janssen, Gilead, Mallinckrodt, Terns, Merck, Siemens, 89bio, NGM Bio, Poxel, Boehringer Ingelheim, Eli Lilly, HemoShear, Bristol Myers Squibb, Novartis, Novo Nordisk, Pfizer, Albireo, Regeneron, Genentech, Alnylam, Roche, Madrigal, Inventiva, Covance, ProSciento, HistoIndex, PathAI, and Genfit. He has received research grant support to Virginia Commonwealth University from Intercept Pharmaceuticals, Inc., Gilead, Bristol Myers Squibb, Eli Lilly, Merck, Boehringer Ingelheim, Novo Nordisk, Fractyl, Mallinckrodt, Madrigal, Inventiva, Novartis, and Pfizer. He has received royalties from Elsevier and UpToDate. RL has served as a consultant for Aardvark, Altimmune, Anylam/Regeneron, Amgen, Arrowhead, AstraZeneca, Bristol Myers Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse, HighTide, Inipharm, Intercept Pharmaceuticals, Inc., Inventiva, Ionis, Janssen, Madrigal, Metacrine, NGM Bio, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89bio, Terns, and Viking; has received research grants from Arrowhead, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galectin, Galmed, Gilead, Hanmi, Intercept Pharmaceuticals, Inc., Inventiva, Ionis, Janssen, Madrigal, Merck, NGM Bio, Novo Nordisk, Pfizer, Sonic Incytes, and Terns; and is co-founder of LipoNexus. QMA is coordinator of the EU IMI-2 LITMUS consortium, which is funded by the EU Horizon 2020 program and EFPIA. This multistakeholder consortium includes industry partners. QMA has

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EJL has served as a researcher for 89bio, AbbVie, Akero, Allergan, Alnylam, Amgen, Ascelia, Assembly Bio, AstraZeneca, Axcella, BioCryst, Bird Rock Bio, Boehringer Ingelheim, Bristol Myers Squibb, Conatus, CymaBay, CytoDyn, DSM, Durect, Lilly, Enanta, Enyo, Exalenz Bioscience, Galectin Therapeutics, Galmed, Genfit, Genentech, Gilead, GSK, Hanmi, HighTide, Intercept, Inventiva, Janssen, Laboratory for Advanced Medicine, Loxo Oncology, Madrigal, Merck, Metacrine, NGM Bio, NorthSea, Novartis, Novo Nordisk, Pfizer, Poxel, Roche, Sagimet, Synlogic, Terns, Viking, and Zydus; has served as an advisor for Akero, Boehringer Ingelheim, Bristol Myers Squibb, Intercept, Novo Nordisk, Metacrine, Sagimet, and Terns; and has served as a speaker for AbbVie, Gilead, and Intercept. 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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

The study was designed in conjunction with the authors. Intercept Pharmaceuticals, Inc. was involved in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study, participated in drafting and editing the manuscript and were responsible for the decision to submit for publication.

Data availability statement

Questions regarding data availability should be directed to the study Sponsor (Intercept Pharmaceuticals, Inc.) at sangeeta.sawhney@interceptpharma.com.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.07.014.

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Author names in bold designate shared co-first authorship

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