Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis— Interim Analysis From a Multicentre, Randomised, Placebo-Controlled Phase 3 Study

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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 shown to improve the histologic features of NASH. Results of a planned interim analysis of an ongoing, multicentre, randomised, double-blind, placebo-controlled phase 3 study of OCA for NASH are reported.

Methods: Patients with definite NASH, nonalcoholic fatty liver disease (NAFLD) activity score ≥4 and fibrosis stages F2–F3, and an exploratory cohort (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 other 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). The fibrosis improvement endpoint was achieved by 12% of placebo patients, 18% of OCA 10-mg patients, and 23% of OCA 25-mg patients (p=0·0002). Although the NASH resolution endpoint was not met (placebo, 8%; OCA 10-mg, 11%; OCA 25-mg, 12%), more OCA 25-mg patients achieved resolution of definite NASH based on pathologist's assessment (p=0.0004). 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%); incidence was generally mild to moderate in severity. 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: OCA 25-mg significantly improved fibrosis and key components of NASH disease activity among patients with NASH.

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INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is an increasingly common cause of chronic liver disease characterised 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 the regulation of bile acids and metabolism.[2] Recent data indicate that activation of FXR can also reduce hepatic fibrosis and inflammation.[2–5] Prior placebo-controlled clinical studies demonstrated that obeticholic acid (OCA), a potent and selective FXR agonist, improved glucose disposal after short-term administration[6] and key histologic features of NASH, including fibrosis.[7] Based upon a prior phase 3 study, OCA was approved for the treatment of primary biliary cholangitis, a progressive autoimmune liver disease, in patients with an inadequate response to, or unable to tolerate, ursodeoxycholic acid.[8] Collectively, this provided a strong rationale for assessing the efficacy and safety of OCA in patients with NASH and fibrosis in this pivotal phase 3 study.

Liver-related outcomes in patients with NASH principally occur after the development of cirrhosis; halting progression to cirrhosis is therefore a key treatment goal. Given the length of time to progress to cirrhosis and clinical outcomes, a conditional approval pathway based on demonstration of histologic improvement following at least 12 months of treatment is supported by 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 a multi-centre, randomised, double-blind,

placebo-controlled phase 3 study of OCA in patients with NASH and fibrosis (NCT02548351).[11] Here, we report the 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 at 332 centres in 20 countries. Eligible patients were adults (aged ≥18 years) with histologic evidence (per central expert pathologist reading of a liver biopsy obtained ≤6 months from randomisation) of definite steatohepatitis; a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 points, including ≥1 point for each of steatosis, lobular inflammation, and hepatocellular ballooning; 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] >1·5x 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 ≤1 year before screening), or confounding conditions were present. All patients provided written informed consent. The detailed study design, including inclusion and exclusion criteria, was previously reported[11] and a summary of protocol changes can be reviewed on clinicaltrials.gov.

A planned interim analysis was 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 clinical outcomes (including progression to cirrhosis and all-cause mortality) and the long-term safety of OCA, and will be completed once approximately 291 adjudicated clinical outcome events occur in the combined OCA 25-mg and placebo groups 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. Randomisation was performed using an Interactive Web Response System; for patients with fibrosis stage F2 or F3, randomisation was stratified by both the presence of type 2 diabetes 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 paired together with the screening biopsy slides and randomly assigned for reading by one of two central expert liver pathologists who was blinded to both 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 monitoring committee reviewed, and continues to review, safety during the study.

Endpoints

This study 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 0 for ballooning and 0–1 for inflammation) with no worsening of fibrosis. The key secondary endpoint was improvement of fibrosis by ≥1 stage and/or resolution of NASH without worsening of either. Secondary endpoints also included histologic improvement of features of NASH as well as NAS, and liver biochemistry.[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 (CMH) 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. The 2-sided Type I error (alpha) allocated to testing both histologic endpoints at the month 18 interim analysis is 0.02. Inferential testing was performed sequentially in the dose level, adjusting for multiplicity using a 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 (see supplemental methods). All other testing and the associated p values reported here are not controlled for Type I error and are considered nominal and descriptive. Success of the study was

defined as meeting one of the two primary endpoints at the predetermined significance level. For histologic endpoints, the comparison between treatment groups was performed using the CMH test stratified by the randomisation strata (type 2 diabetes and use of TZDs/glitazones or vitamin E at baseline [yes/no]). Continuous endpoints, change from baseline and percentage change from baseline over time were analysed using a mixed-effect repeated measure (MMRM) model with treatment, baseline, visit, visit by treatment interaction and stratification factors included in the model. The statistical analysis plan, primary endpoints, and requirement for study success were agreed with the FDA prior to database lock. More information can be found in the supplemental methods.

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 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 the data in the study and had final responsibility for the decision to submit for publication.

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RESULTS

Between December 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, 23% of OCA 10-mg, 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 post-baseline biopsy (patients who discontinued 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, 18% of OCA 10-mg (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, ≥1 stage improvement in fibrosis was observed in the OCA 25-mg group. Several of the subgroups analyses were limited by imbalances in sample sizes within a given subgroup to an extent that precluded 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 who improved (23%) or worsened (21%) (figure 3). Based on this analysis, after 18 months of treatment, on a placebo-subtracted basis 4 to 5 patients with NASH and fibrosis F2/F3 would need to be treated with OCA 25-mg for one such patient to achieve either improvement (≥1 stage) or no worsening of fibrosis.

The primary endpoint of NASH resolution (based on no hepatocellular ballooning and no/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 the NASH resolution endpoint, 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 histologic features of NASH (figure S2).

In a post-hoc analysis, NASH resolution was evaluated by assessing a change 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 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). Additional secondary NASH and fibrosis endpoints are provided in table 2.

Favourable changes in key liver enzymes were observed in OCA-treated patients. 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 declined rapidly and were generally stable after month 3 (change at month 18: placebo 1%, OCA 10-mg –24%, OCA 25-mg –38%) (figure 4). 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, treatment with OCA versus placebo resulted in a dose-dependent decrease in body weight at month 18 (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 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 3). 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 3). 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 (<1%), five OCA 10-mg (<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, low-density lipoprotein cholesterol (LDLc) increased by 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, the initial LDLc increases reversed to below baseline levels as of month 6 and were sustained through month 18 (figure S6). There was no clear pattern of fibrosis improvement by statin use. Levels of high-density lipoprotein cholesterol (HDLc) showed dose-dependent decreases by 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 (>40 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, with levels continuing to decline 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 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). Effects on glycemic parameters were evaluated by baseline diabetes status (figure S7). In patients with type 2 diabetes, OCA treatment was associated with an early transient increase in glucose and HbA1C with return to levels similar to placebo by month 6. No clinically meaningful changes were noted in nondiabetic patients. 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 gallstone-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 (0·9%) than the OCA 10-mg group (0·3%) or placebo group (0·3%), expert reviewers did not identify any consistent pattern of liver injury and all cases were associated with confounding concomitant medications and/or severe intercurrent illness.
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

This 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 reasonably 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 histologic

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]

Although the percentage of patients achieving NASH resolution was not statistically significant between OCA and placebo, 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 a ≥2-point improvement in NAS with no worsening of fibrosis, the primary endpoint traditionally used in phase 2 studies such as FLINT[7] and PIVENS,[20] indicating that OCA reduces NASH disease activity.

Twice as many OCA 25-mg patients compared to placebo achieved NASH resolution as determined by 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 the correlation of definite NASH and mortality[16]. T The assessment of NASH resolution based on NAS parameters appears to be more rigid and may be associated with greater

intra- and inter-rater variability compared to the diagnostic classification of NASH.[21] 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.[22] Therefore, as the field continues to evolve it may be more appropriate to establish the presence/absence of NASH using histologic diagnostic criteria as an endpoint as has been done by NIDDK's NASH CRN in the past.

In addition to consistent improvements in multiple histologic parameters, improvement in liver health was also evident based on clinically meaningful, 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.[23] OCA-treated patients 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 safety population 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, with

dose-dependent incidence. More patients in the OCA 25-mg group experienced pruritus that led to treatment discontinuation; however, the majority of randomised patients were ongoing in the study through at least month 18 and the overall treatment discontinuation rate was similar to placebo. The impact of pruritus in this study on patient-reported outcomes and its relationship to OCA is being investigated.[24] The incidence of hepatic AEs was balanced across treatment groups, and serious hepatic events 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 concomitant medications and/or 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 and generally transient increases in glycemic parameters. Such increases were manageable by clinical practice measures. The impact of lipid 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, as well as improvements in liver fibrosis, which may have a downstream effect on cardiovascular risk.[19,25-27] The incidence of cardiovascular AEs and SAEs was low and similar across treatment groups and continues to be monitored in the outcomes portion of the study.

The results of the interim analysis 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 process, 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).[28] 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.[27] In REGENERATE, the continuing improvement in liver enzyme markers of fibrosis such as ALT and AST suggest the potential for further increase in antifibrotic response. Data from the ongoing long-term outcomes portion of the study will inform whether prolonged therapy will result in a greater antifibrotic benefit.

In conclusion, the totality of data from the month 18 interim analysis of this pivotal, phase 3 study provides strong evidence that OCA treatment improves clinically significant histologic endpoints deemed reasonably likely to predict clinical benefit and affirms the positive benefit-risk of OCA for the treatment of NASH with fibrosis. Beneficial effects of OCA on fibrosis and key 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 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, this study continues in a blinded fashion, and patients will be followed over an extended period through clinical outcomes (including all-cause mortality and liver-related clinical outcomes) and long-term safety, to confirm clinical benefit. In a chronic liver 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, PNN, 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, PNN, 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

Authors of research articles should disclose any financial arrangement they may have with a company whose product is pertinent to the submitted manuscript or with a company making a competing product.

ZMY has research funds and/or consultation fees from Gilead Sciences, NovoNordisk, Intercept, Novartis, Terns, Viking, Siemens and Echosens. **QMA** is coordinator of the EU IMI2 funded LITMUS consortium. His institution has received research grants from AbbVie, Allergan/Tobira, AstraZeneca, GlaxoSmithKline, Glympse Bio, Novartis Pharma AG, Pfizer Ltd., Vertex. He has performed consultancy on behalf of Newcastle University for Abbott Laboratories, Acuitas Medical, Allergan/Tobira, Blade, BNN Cardio, Cirius, CymaBay, EcoR1, E3Bio, Eli Lilly & Company Ltd., Galmed, Genfit SA, Gilead, Grunthal, HistoIndex, Indalo, Imperial Innovations, Intercept Pharma Europe Ltd., Inventiva, IQVIA, Janssen, Kenes, Madrigal, MedImmune,

Metacrine, NewGene, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk A/S, Pfizer Ltd., Poxel, ProSciento, Raptor Pharma, Servier, Viking Therapeutics. He has received speaker fees from Abbott Laboratories, Allergan/Tobira, BMS, Clinical Care Options, Falk, Fishawack, Genfit SA, Gilead, Integritas Communications, MedScape and royalties from Elsevier Ltd. **AJS** is President of Sanyal Bio. He has stock options in Indalo, Durect, Tiziana, Exhalenz, Northsea. He is a consultant to Gilead, Allergan, Bristol Myers Squibb, Pfizer, Merck, Galmed, Novartis, Novo Nordisk, Lilly, Siemens, Genentech, Boehringer Ingelhiem, Glympse Bio, Genfit, Coherus, Surrozen, Poxel, 89 Bio, Perspectum, Astra Zeneca, Medimmune, Lipocine. He is an unpaid consultant to Intercept, Zydus, Echosense, Immuron, Madrigal, Galectin, Blade, Pliant, Albireo. AMRA. **RL** serves as a consultant or advisory board member for Arrowhead Pharmaceuticals, AstraZeneca, Bird Rock Bio, Boehringer Ingelheim, Bristol-Myer Squibb, Celgene, Cirius, CohBar, Conatus, Eli Lilly, Galmed, Gemphire, Gilead, Glympse bio, GNI, GRI Bio, Intercept, Ionis, Janssen Inc., Merck, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Prometheus, Sanofi, Siemens, and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Boehringer-Ingelheim, Bristol-Myers Squibb, Cirius, Eli Lilly and Company, Galectin Therapeutics, Galmed Pharmaceuticals, GE, Genfit, Gilead, Intercept, Grail, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, NuSirt, Pfizer, pH Pharma, Prometheus, and Siemens; he is also co-founder of Liponexus, Inc. **PNN** reports consultancy/speaker fees on behalf of the University of Birmingham from Boehringer Ingelheim, Gilead, Pfizer, Affimmune, Intercept, Johnson and Johnson, Novo Nordisk, Shire and Poxel Pharmaceuticals. His institution receives grant funding from Pharmaxis, Boehringer Ingelheim and Novo Nordisk.

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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 will not be available until the end-of-study analysis.

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FIGURE LEGENDS

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, EOT=end-of-treatment; ITT=intent-to-treat, M18=month 18, OCA=obeticholic acid.

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 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. FDA=US Food and Drug Administration; ITT=intent to treat; NASH=nonalcoholic steatohepatitis; OCA=obeticholic acid.

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). OCA=obeticholic acid.

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). ALP=alkaline phosphatase; ALT=alanine aminotransferase;

AST, aspartate aminotransferase; GGT=gamma-glutamyl transferase; ITT=intent to treat; OCA=obeticholic acid; SE=standard error.

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). HDLc=high-density lipoprotein cholesterol; LDLc=low-density lipoprotein cholesterol; OCA=obeticholic acid; SE=standard error.