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

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Summary

Background Non-alcoholic steatohepatitis (NASH) is a common type of chronic liver disease that can lead to cirrhosis. Obeticholic acid, a farnesoid X receptor agonist, has been shown to improve the histological features of NASH. Here we report results from a planned interim analysis of an ongoing, phase 3 study of obeticholic acid for NASH.

Methods In this multicentre, randomised, double-blind, placebo-controlled study, adult patients with definite NASH, non-alcoholic fatty liver disease (NAFLD) activity score of at least 4, and fibrosis stages F2–F3, or F1 with at least one accompanying comorbidity, were randomly assigned using an interactive web response system in a 1:1:1 ratio to receive oral placebo, obeticholic acid 10 mg, or obeticholic acid 25 mg daily. Patients were excluded if cirrhosis, other chronic liver disease, elevated alcohol consumption, or confounding conditions were present. 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. Primary analyses were done by intention to treat, in patients with fibrosis stage F2–F3 who received at least one dose of treatment and reached, or would have reached, the month 18 visit by the prespecified interim analysis cutoff date. The study also evaluated other histological and biochemical markers of NASH and fibrosis, and safety. This study is ongoing, and registered with ClinicalTrials.gov, NCT02548351, and EudraCT, 20150-025601-6.

Findings Between Dec 9, 2015, and Oct 26, 2018, 1968 patients with stage F1–F3 fibrosis were enrolled and received at least one dose of study treatment; 931 patients with stage F2–F3 fibrosis were included in the primary analysis (311 in the placebo group, 312 in the obeticholic acid 10 mg group, and 308 in the obeticholic acid 25 mg group). The fibrosis improvement endpoint was achieved by 37 (12%) patients in the placebo group, 55 (18%) in the obeticholic acid 10 mg group (p=0·045), and 71 (23%) in the obeticholic acid 25 mg group (p=0·0002). The NASH resolution endpoint was not met (25 [8%] patients in the placebo group, 35 [11%] in the obeticholic acid 10 mg group [p=0·18], and 36 [12%] in the obeticholic acid 25 mg group [p=0·13]). In the safety population (1968 patients with fibrosis stages F1–F3), the most common adverse event was pruritus (123 [19%] in the placebo group, 183 [28%] in the obeticholic acid 10 mg group, and 336 [51%] in the obeticholic acid 25 mg group); 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 (75 [11%] patients in the placebo group, 72 [11%] in the obeticholic acid 10 mg group, and 93 [14%] in the obeticholic acid 25 mg group).

Interpretation Obeticholic acid 25 mg significantly improved fibrosis and key components of NASH disease activity among patients with NASH. The results from this planned interim analysis show clinically significant histological improvement that is reasonably likely to predict clinical benefit. This study is ongoing to assess clinical outcomes.

Funding Intercept Pharmaceuticals.

Introduction

Non-alcoholic 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 times over the next two decades.[1] Currently, there are no approved therapies for NASH.

The farnesoid X receptor is a nuclear receptor that plays a central role in the regulation of bile acids and metabolism.[2] Recent data indicate that activation of the farnesoid X receptor can also reduce hepatic fibrosis and inflammation.[2–5] Previous placebo-controlled clinical

Research in context

Evidence before this study

Non-alcoholic steatohepatitis (NASH) is a chronic progressive liver disease, which can progress to cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related death. Currently, there are no approved therapeutic options for NASH and treatment is largely limited to lifestyle modifications. We searched PubMed for clinical trials treating NASH published up to Sept 30, 2019, using the terms "nonalcoholic fatty liver disease", "nonalcoholic steatohepatitis", "NAFLD", and "NASH". Early clinical study results for several compounds with various mechanisms of action have shown evidence of improvement in steatohepatitis or fibrosis, but several such studies lacked placebo controls and none of these results have been confirmed in a pivotal phase 3 study setting. The farnesoid X receptor is a nuclear receptor expressed at high levels in the liver. In animal models of liver disease, activation of farnesoid X receptor has been associated with both anti-inflammatory and antifibrotic effects. The placebo-controlled phase 2b FLINT study showed that obeticholic acid, a potent selective farnesoid X receptor agonist, improved key histological features of NASH, including fibrosis. These promising results led to this randomised, placebo-controlled global phase 3 study of obeticholic acid in patients with fibrosis due to NASH (REGENERATE).

Added value of this study

To our knowledge, REGENERATE is the first positive phase 3 study in patients with NASH. In this interim analysis, a significantly higher proportion of patients treated with obeticholic acid 25 mg had an improvement of fibrosis by at least one stage with no worsening of NASH. Additionally, a post-hoc analysis showed that obeticholic acid treatment resulted in NASH resolution with no worsening of fibrosis based on pathologist diagnostic assessment. Obeticholic acid treatment also improved underlying disease activity, as shown by decreased lobular inflammation and hepatocellular ballooning. In addition to improvement in these key histological features, meaningful reduction in laboratory parameters, including robust normalisation of alanine aminotransferase and aspartate aminotransferase, was observed with obeticholic acid treatment. Consistent with previous obeticholic acid clinical studies, pruritus and increased LDL cholesterol were the most commonly reported adverse events. Pruritus incidence was generally mild to moderate in severity and dose dependent. Greater treatment discontinuation was seen in the obeticholic acid 25 mg group, mainly due to protocol requirements. Early increases in LDL cholesterol were observed with obeticholic acid treatment; however, levels approached baseline by month 18.

Implications of all the available evidence

Halting progression to cirrhosis, and therefore preventing serious liver-related outcomes, is a key treatment goal in patients with NASH with fibrosis. Advanced liver fibrosis is strongly associated with risk of liver-related adverse outcomes and all-cause mortality, so therapies with proven antifibrotic benefit are highly desirable. Because NASH disease progression occurs over a number of years, assessing clinical outcomes requires long-term evaluation. The positive results of the prespecified REGENERATE month-18 interim analysis are based on surrogate endpoints considered to be reasonably likely to predict clinical benefit, and the study is ongoing through clinical outcomes to confirm long-term benefit.

studies have shown that obeticholic acid, a potent and selective farnesoid X receptor agonist, improves glucose disposal after short-term administration[6] and key histological features of NASH, including fibrosis.[7] Based on a previous phase 3 study, obeticholic acid 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 obeticholic acid 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 histological 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 Randomised Global Phase 3 Study to Evaluate the Impact on NASH with Fibrosis of Obeticholic Acid Treatment (REGENERATE) study is a randomised, controlled, phase 3 study of obeticholic acid in patients with NASH and fibrosis.[11] Here, we report the results of the prespecified month 18 interim analysis on the safety and efficacy of obeticholic acid in improving fibrosis and underlying disease activity.

Methods

Study design and participants

This multicentre, randomised, double-blind, placebo-controlled, phase 3 study is being conducted at 332 centres in 20 countries across the world. Eligible patients were adults (aged ≥18 years) with histological evidence of (per central expert pathologist reading of a liver biopsy obtained ≤6 months from randomisation) definite steatohepatitis; a non-alcoholic fatty liver disease (NAFLD) activity score (NAS) of at least 4, including at least one point for each of steatosis, lobular inflammation, and hepatocellular ballooning; and fibrosis stage per the NASH Clinical Research Network scoring criteria of F2 or F3, or F1 with at least one accompanying comorbidity (obesity [body-mass index ≥30 kg/m²], type 2 diabetes, or

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alanine amino transferase [ALT] >1·5×upper limit of normal [ULN]). Patients were excluded if cirrhosis, other chronic liver disease, elevated alcohol consumption (>2 units/day for women or >4 units/day for men for more than 3 consecutive months in the year before screening), or confounding conditions were present; ALT greater than or equal to 10×ULN; or if they had HbA_{1c} greater than 9·5% or total bilirubin greater than 1·5 mg/dL.

A planned interim analysis was done after a minimum of 750 randomised patients with fibrosis stages F2 or F3 reached their actual or planned month-18 visit.

Patients were recruited primarily from hepatologists, and from gastroenterologists, academic centres, and community sites. All patients provided written informed consent. This study is being conducted in accordance with the European Union Clinical Trials Directive (2001/20/EC and subsequent amendments), 21 Code of Federal Regulations Part 312, Good Clinical Practice (CPMP/International Council on Harmonisation/135/95), and with the ethical principles laid down in the Declaration of Helsinki and applicable regulatory requirements. The detailed study design, including inclusion and exclusion criteria, has been previously reported[11] and a summary of protocol changes can be reviewed on ClinicalTrials.gov.

Randomisation and blinding

Eligible patients were randomly assigned in a 1:1:1 ratio to receive daily placebo, obeticholic acid 10 mg, or obeticholic acid 25 mg orally. Randomisation was based on a predefined randomisation code generated by electronic data capture and done 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 or vitamin E at baseline. Placebo and obeticholic acid were supplied as identical tablets in coded containers. All patients, study investigators, and other site research staff were blinded to treatment assignment.

Procedures

Patients received daily placebo, obeticholic acid 10 mg, or obeticholic acid 25 mg orally, in the form of one tablet. Biopsies were obtained at baseline screening and month 18 or end of treatment. Histological assessments followed standardised criteria to ensure consistency, and all biopsies were read centrally. The month-18 (or early termination) biopsy slides were paired with the screening biopsy slides and randomly assigned for reading by one of two central expert liver pathologists (PB and ZG), who was masked to both the slide sequence and the patient's treatment. Assessments of liver biochemistry including ALT, aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), and alkaline phosphatase (ALP) were done at each study visit, which took place every 3 months for the first 18 months. Additionally, glucose, glycated haemoglobin A_{1c}, lipids, and bodyweight were measured every 3 months.

Outcomes

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 at least one 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 an NAS of 0 for ballooning and 0–1 for inflammation) with no worsening of fibrosis. The key secondary endpoint was improvement of fibrosis by at least one stage or resolution of NASH, or both, without worsening of either. Secondary endpoints comprised histological improvement of features of NASH as well as NAS, and liver biochemistry.[11] A post-hoc analysis evaluated NASH resolution on the basis of the pathologist diagnostic assessment of presence or absence of definite steatohepatitis as determined by the overall pattern of injury rather than scoring of individual NAS parameters.

The end-of-study analysis will evaluate the effect of obeticholic acid on clinical outcomes (including progression to cirrhosis and all-cause mortality) and the long-term safety of obeticholic acid, and will be completed once approximately 291 adjudicated clinical outcome events occur. Patients are expected to have a minimum follow-up time of approximately 4 years.

Safety and tolerability of obeticholic acid were assessed by analysis of adverse events, vital signs, electrocardiograms (ECGs), and clinical laboratory assessments (including lipid profile changes); these were all assessed once every 3 months, except for ECGs, which were done on day 1 and at the month-18 visit. Adverse events were graded for severity using Common Terminology Criteria for Adverse Events version 4.03. An independent data monitoring committee reviewed, and continues to review, safety during the study.

Statistical analysis

For the month-18 interim analysis primary efficacy endpoint of improvement in fibrosis with no worsening of NASH, a sample size of 250 patients per group with an assumed 15% discontinuation rate was anticipated to provide 98% power to show a significant treatment difference between the obeticholic acid (10 mg and 25 mg) and placebo groups based on the Cochran-Mantel-Haenszel test with a two-sided type I error (α) at the 0·01 level, assuming an adjusted response rate of 36·7% in each of the obeticholic acid groups and 17·6% in the placebo group. The two-sided type I error allocated to testing both histological endpoints at the month-18 interim analysis is 0·02. Inferential testing was done sequentially in the dose level, adjusting for multiplicity

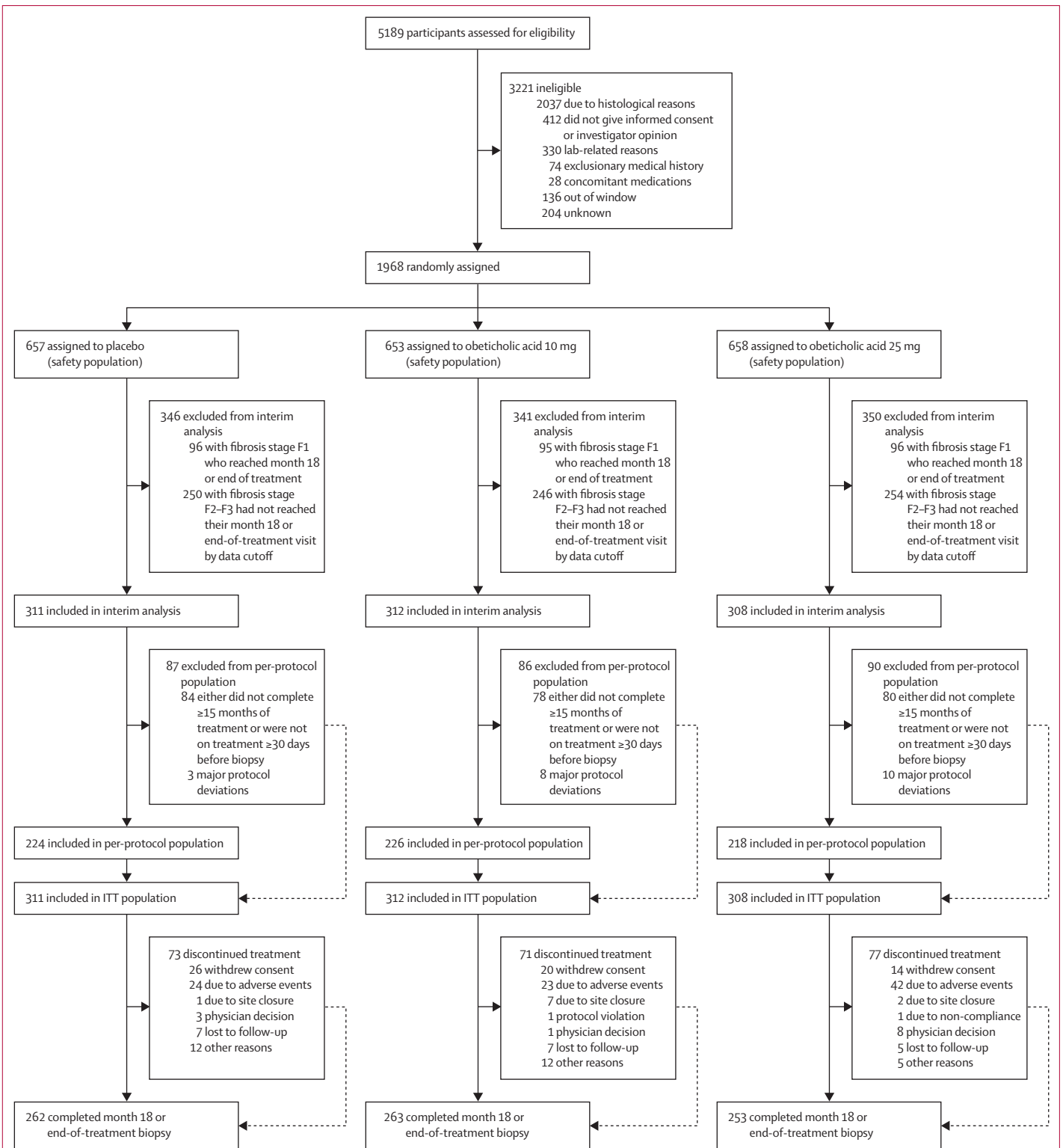

Figure 1: **Patient flow diagram**
Figure shows patient inclusion in per-protocol and ITT populations, as well as details on discontinuation of treatment and month 18 or end-of-treatment biopsies. Some patients who discontinued treatment had an end-of-treatment biopsy. ITT=intention to treat.

using a truncated Hochberg procedure, to test the two primary endpoints within each dose level, starting by comparing the obeticholic acid 25 mg group with placebo for the two primary endpoints, then comparing the obeticholic acid 10 mg group with placebo in the intention-to-treat (ITT) population (appendix pp 2–3).

See Online for appendix

	Placebo (n=311)	Obeticholic acid 10 mg (n=312)	Obeticholic acid 25 mg (n=308)
Age, years	55 (12)	55 (11)	55 (11)
Sex			
Female	187 (60%)	177 (57%)	175 (57%)
Male	124 (40%)	135 (43%)	133 (43%)
Race*			
Asian	10/280 (4%)	17/287 (6%)	20/286 (7%)
White	264/280 (94%)	263/287 (92%)	249/286 (87%)
Other	6/280 (2%)	7/287 (2%)	17/286 (6%)
Ethnicity*			
Hispanic	52/282 (18%)	42/286 (15%)	47/282 (17%)
Other	230/282 (82%)	244/286 (85%)	235/282 (83%)
Fibrosis stage			
F2	142 (46%)	130 (42%)	139 (45%)
F3	169 (54%)	182 (58%)	169 (55%)
NAS ≥6	215/309 (70%)	211 (68%)	208 (68%)
Type 2 diabetes†	175 (56%)	171 (55%)	171 (56%)
Dyslipidaemia	211 (68%)	217 (70%)	205 (67%)
Hypertension	215 (69%)	215 (69%)	196 (64%)
Lipids			
Total cholesterol, mg/dL	184·5 (42·7)	185·2 (53·0)	183·5 (44·7)
HDL cholesterol, mg/dL	45·6 (11·1)	44·9 (12·1)	44·3 (11·0)
LDL cholesterol, 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)
Bodyweight, kg	95·3 (19·0)	95·2 (19·1)	95·4 (19·5)
HOMA-IR	9·6 (11·8)	9·9 (16·9)	8·3 (10·2)
HbA_{1c}	6·6% (1·2)	6·5% (1·2)	6·5% (1·3)
Laboratory parameters			
ALT, U/L	79·6 (56·6)	75·6 (47·0)	80·2 (56·4)
AST, U/L	58·9 (40·5)	56·6 (34·0)	57·0 (34·1)
Platelet count, $\times 10^9$/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‡	175 (56%)	170 (54%)	160 (52%)
Statins	144 (46%)	142 (46%)	127 (41%)
Antidiabetic medication	167 (54%)	171 (55%)	159 (52%)
Thiazolidinediones†	5 (2%)	9 (3%)	4 (1%)
Vitamin E†	42 (14%)	34 (11%)	32 (10%)

Data are n (%) or mean (SD). ITT=intention-to-treat. NAS=non-alcoholic fatty liver disease activity score. HOMA-IR=Homeostatic Model Assessment of Insulin Resistance. ALT=alanine aminotransferase. AST=aspartate aminotransferase. PCSK9=proprotein convertase subtilisin-kexin type 9. *Percentages are calculated on patients for whom race or ethnicity information was available. †Randomisation was stratified by presence of type 2 diabetes and treatment with thiazolidinediones or vitamin E. ‡Lipid-lowering drugs included statins, fibrates, cholesterol-absorbing resins, PCSK9 inhibitors, and omega-3 fatty acids.

Table 1: **Demographic and baseline clinical characteristics in the ITT population**

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 histological endpoints, the comparison between treatment groups was done using the Cochran-Mantel-Haenszel test stratified by the randomisation strata (type 2 diabetes and use of thiazolidinediones or vitamin E at baseline [yes *vs* no]). Continuous endpoints, change from baseline, and percentage change from baseline over time were analysed using a mixed-effect repeated measure model with treatment, baseline, visit, visit by treatment interaction, and stratification factors included in the model. SEs and 95% CIs were presented by treatment group. The statistical analysis plan, primary endpoints, and requirement for study success were agreed with the FDA before database lock. More information can be found in the appendix (pp 2–3).

All patients (fibrosis stages F1–F3) who received at least one dose of study treatment by the prespecified 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 received at least one dose of treatment and reached, or would have reached, the month-18 visit by the prespecified interim analysis cutoff date. Efficacy endpoints were also analysed in the per-protocol population, defined as the ITT population who completed at least 15 months of treatment, had a biopsy at month 18 or at the end of treatment, were on treatment for at least 30 days immediately preceding biopsy, and did not have any major protocol deviations.

This trial was registered with ClinicalTrials.gov, NCT02548351, and EudraCT, 20150-025601-6.

Role of the funding source

The REGENERATE study was designed by VR, AJS, and ZMY in collaboration with the funder, Intercept Pharmaceuticals, which was involved in data collection, analysis, and interpretation. 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.

Results

Between Dec 9, 2015, and Oct 26, 2018, 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), obeticholic acid 10 mg (n=312), or obeticholic acid 25 mg (n=308). At the time of the interim analysis, 73 (23%) patients in the placebo group, 71 (23%) in the obeticholic acid 10 mg group, and 77 (25%) in the obeticholic acid 25 mg group had discontinued treatment (figure 1); 252 (81%) patients receiving placebo, 253 (81%) receiving obeticholic acid 10 mg, and 243 (79%) receiving obeticholic acid 25 mg completed the month 18 biopsy. An additional 3% of patients in each treatment group (ten patients in each group) completed any post-baseline biopsy (ie, patients who discontinued treatment before month 18 and underwent an end-of-treatment biopsy). The per-protocol population included 668 patients and the safety population included 1968 patients.

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

The primary endpoint of fibrosis improvement by at least one stage with no worsening of NASH was met by 37 (12%) patients in the placebo group, 55 (18%) patients in the obeticholic acid 10 mg group (p=0·045 *vs* placebo), and 71 (23%) patients in the obeticholic acid 25 mg group (p=0·0002 *vs* placebo) with an obeticholic acid-to-placebo response ratio of 1·5 (95% CI 1·0–2·2) for the obeticholic 10 mg group and 1·9 (1·4–2·8) for the obeticholic acid 25 mg group (figure 2; table 2). Obeticholic acid 25 mg was significant per the prespecified inferential testing method. Similar results were observed in the per-protocol population (figure 2; table 2). Across subgroups of interest in the ITT population, an improvement of at least one stage in fibrosis with no worsening of NASH was observed in the obeticholic acid 25 mg group (appendix p 7). Several of the subgroup analyses (ie, use of thiazolidinediones or vitamin E, race, and age) were limited by imbalances in sample sizes within a given subgroup to an extent that precluded meaningful comparison (appendix p 7).

In the per-protocol population, which includes patients with at least 15 months of treatment, three times as many patients achieved an improvement in fibrosis of at least one stage compared with progression of fibrosis in the obeticholic acid 25 mg group (81 [38%] *vs* 23 [13%]); in the placebo group, a similar number of patients improved (51 [23%]) or worsened (46 [21%]; figure 3). This analysis suggests that on a placebo-adjusted basis, after 18 months

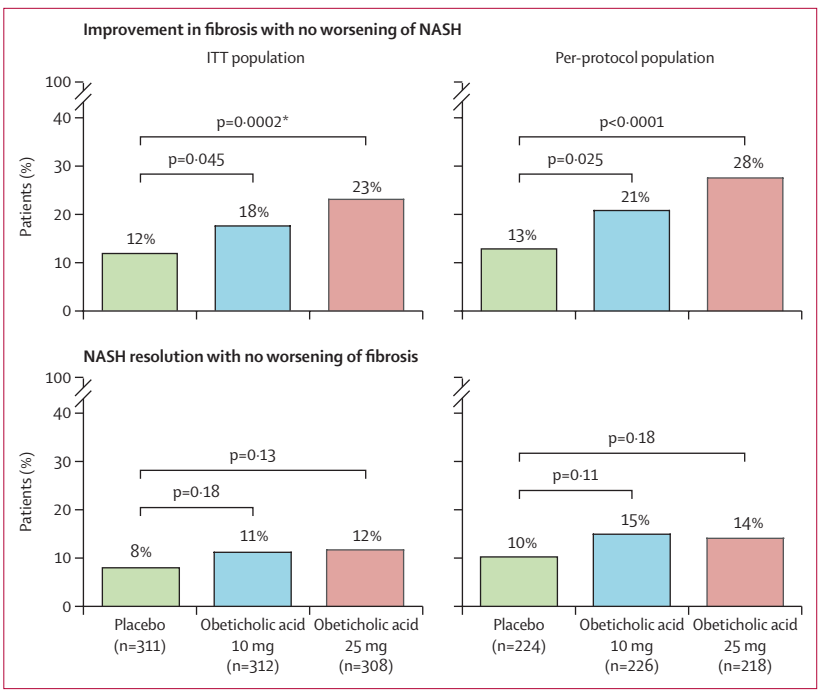

Figure 2: **Primary endpoints in the ITT population**
The proportion of patients with improvement in fibrosis of at least one stage and no worsening of NASH and the proportion of patients with resolution of NASH and no worsening of fibrosis are shown in the ITT and per-protocol populations. Fibrosis improvement was evaluated per NASH Clinical Research Network criteria; no worsening of NASH defined as no worsening of hepatocellular ballooning, lobular inflammation, or steatosis. NASH resolution defined as overall pathologist assessment of no steatohepatitis, and hepatocellular ballooning=0 and lobular inflammation=0 or 1. ITT=intention to treat. NASH=non-alcoholic steatohepatitis. *Significant in accordance with the statistical analysis plan as agreed with the US Food and Drug Administration.

of treatment, four to five patients with NASH and fibrosis stage F2–F3 would need to be treated with obeticholic acid 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 (25 [8%] patients in the placebo group *vs* 35 [11%] in the obeticholic acid 10 mg group [p=0·18] or 36 [12%] in the obeticholic acid 25 mg group [p=0·13]), with a response ratio of 1·4 (95% CI 0·9–2·3) for obeticholic acid 10 mg and 1·5 (0·9–2·4) for obeticholic acid 25 mg (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 patients in the obeticholic acid 25 mg group showing at least a 1-point improvement in scores in key histological features of NASH compared with the placebo group (136 [44%] patients *vs* 111 [36%] for lobular inflammation [p=0·032] and 108 [35%] *vs* 72 [23%] for hepatocellular ballooning [p=0·0011]; table 2; appendix p 8).

In a post-hoc analysis, NASH resolution was evaluated by assessing a change from presence of definite

	ITT population (N=931)					Per-protocol population (N=668)				
	Placebo (n=311)	Obeticholic acid 10 mg (n=312)		Obeticholic acid 25 mg (n=308)		Placebo (n=224)	Obeticholic acid 10 mg (n=226)		Obeticholic acid 25 mg (n=218)	
		Patients	RR (95% CI); p value	Patients	RR (95% CI); p value		Patients	RR (95% CI); p value	Patients	RR (95% CI); p value
Primary endpoints										
Improvement of fibrosis with no worsening of NASH	37 (12%)	55 (18%)	1·5 (1·0–2·2); p=0·045	71 (23%)	1·9 (1·4–2·8); p=0·0002	29 (13%)	47 (21%)	1·6 (1·1–2·5); p=0·025	60 (28%)	2·2 (1·4–3·2); p<0·0001
Resolution of NASH with no worsening of fibrosis	25 (8%)	35 (11%)	1·4 (0·9–2·3); p=0·18	36 (12%)	1·5 (0·9–2·4); p=0·13	23 (10%)	34 (15%)	1·5 (0·9–2·4); p=0·11	31 (14%)	1·4 (0·9–2·3); p=0·18
Secondary endpoints*										
Improvement of fibrosis by ≥1 stage or resolution of NASH without worsening of either	49 (16%)	67 (21%)	1·4 (1·0–1·9); p=0·068	84 (27%)	1·7 (1·3–2·4); p=0·0005	41 (18%)	59 (26%)	1·4 (1·0–2·1); p=0·041	71 (33%)	1·8 (1·3–2·5); p=0·0004
No worsening of fibrosis and no worsening of NASH	117 (38%)	127 (41%)	1·1 (0·9–1·3); p=0·43	147 (48%)	1·3 (1·1–1·5); p=0·011	100 (45%)	109 (48%)	1·1 (0·9–1·3); p=0·43	125 (57%)	1·3 (1·1–1·6); p=0·0062
Improvement of NAS by ≥2 with no worsening of fibrosis	76 (24%)	94 (30%)	1·2 (1·0–1·6); p=0·11	112 (36%)	1·5 (1·2–1·9); p=0·0012	69 (31%)	82 (36%)	1·2 (0·9–1·5); p=0·19	96 (44%)	1·4 (1·1–1·8); p=0·0035
Improvement of fibrosis and resolution of NASH as a composite endpoint†	13 (4%)	23 (7%)	1·8 (0·9–3·4); p=0·090	23 (7%)	1·8 (0·9–3·4); p=0·080	11 (5%)	22 (10%)	2·0 (1·0–4·1); p=0·045	20 (9%)	1·9 (1·0–3·9); p=0·064
Improvement in fibrosis by ≥2 stages	15 (5%)	19 (6%)	1·3 (0·7–2·4); p=0·49	30 (10%)	2·0 (1·1–3·7); p=0·018	10 (4%)	16 (7%)	1·6 (0·8–3·5); p=0·22	29 (13%)	3·1 (1·5–6·1); p=0·0008
Resolution of fibrosis	4 (1%)	8 (3%)	2·0 (0·6–6·4); p=0·25	10 (3%)	2·5 (0·8–7·9); p=0·10	4 (2%)	8 (4%)	2·1 (0·6–6·7); p=0·21	9 (4%)	2·4 (0·7–7·6); p=0·14
≥1-point improvement in steatosis	118 (38%)	127 (41%)	1·1 (0·9–1·3); p=0·49	127 (41%)	1·1 (0·9–1·3); p=0·40	97 (43%)	108 (48%)	1·1 (0·9–1·4); p=0·33	113 (52%)	1·2 (1·0–1·5); p=0·072
≥1-point improvement in lobular inflammation	111 (36%)	123 (39%)	1·1 (0·9–1·4); p=0·34	136 (44%)	1·2 (1·0–1·5); p=0·032	94 (42%)	104 (46%)	1·1 (0·9–1·4); p=0·38	114 (52%)	1·3 (1·0–1·5); p=0·031
≥1-point improvement in hepatocellular ballooning	72 (23%)	85 (27%)	1·2 (0·9–1·5); p=0·24	108 (35%)	1·5 (1·2–2·0); p=0·0011	64 (29%)	77 (34%)	1·2 (0·9–1·6); p=0·19	95 (44%)	1·5 (1·2–2·0); p=0·0008
Pathologist assessment of NASH resolution with no worsening of fibrosis‡	38 (12%)	51 (16%)	1·3 (0·9–2·0); p=0·14	71 (23%)	1·9 (1·3–2·7); p=0·0004	35 (16%)	48 (21%)	1·4 (0·9–2·0); p=0·11	63 (29%)	1·9 (1·3–2·7); p=0·0005

ITT=intention-to-treat. RR=response ratio. NASH=non-alcoholic steatohepatitis. NAS=non-alcoholic fatty liver disease activity score. *p values compare obeticholic acid treatment with placebo, using the Cochran-Mantel-Haenszel test, stratified by baseline diabetes status (yes *vs* no) and use of thiazolidinediones or vitamin E at baseline (yes *vs* no). †Improvement of fibrosis and resolution of NASH is defined as a composite endpoint where both of the primary endpoints are met in the same patient. ‡Post-hoc analysis of NASH resolution as defined by the pathologist's overall assessment of a change from presence of definite steatohepatitis at baseline to absence of definite steatohepatitis (without worsening of fibrosis) at month 18.

Table 2: **Efficacy endpoints**

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 obeticholic acid 25 mg group achieved NASH resolution compared with the placebo group (71 [23%] *vs* 38 [12%], p=0·0004; appendix p 9). A similar dose-dependent response was observed in the per-protocol population (63 [29%] *vs* 35 [16%], p=0·0005; appendix p 9).

The key secondary endpoint of improvement of fibrosis of at least one stage or resolution of NASH, without worsening of either, was observed in 49 (16%) patients in the placebo group, 67 (21%) in the obeticholic acid 10 mg group, and 84 (27%) in the obeticholic acid 25 mg patients in the ITT population (table 2; appendix p 10). A significantly higher proportion of patients receiving obeticholic acid 25 mg compared with placebo showed improvement in NAS by at least two points with no worsening of fibrosis, had no disease progression as assessed by no worsening of fibrosis and no worsening of NASH, and had improvement in fibrosis of at least two stages (table 2). Additional secondary NASH and fibrosis endpoints are provided in table 2.

Favourable changes in key liver enzymes were observed in patients treated with obeticholic acid. Early dose-dependent decreases in ALT and AST were observed by month 3 and continued through month 18 (mean change from baseline at month 18 in ALT: –15·6 U/L [SE 3·3] for the placebo group, –23·8 U/L [2·6] for the obeticholic acid 10 mg group, and –36·0 U/L [3·6] for the obeticholic acid 25 mg group; mean change in AST of –9·8 U/L [2·4] for the placebo group, –14·1 U/L [2·1] for the obeticholic acid 10 mg group, and –20·4 U/L [2·3] for the obeticholic acid 25 mg group; figure 4). These changes correspond to a decrease in ALT of 6% for placebo, 26% for obeticholic acid 10 mg, and 33% for obeticholic acid 25 mg and in AST of 4%, 19%, and 24% (figure 4). A post-hoc analysis showed that a higher proportion of patients receiving

obeticholic acid with elevated ALT and AST at baseline achieved levels below the ULN at month 18 compared with placebo (appendix p 11). GGT levels declined rapidly and were generally stable after month 3 (change at month 18: 1% increase for the placebo group, 24% decrease for the obeticholic acid 10 mg group, and 38% decrease for the obeticholic acid 25 mg group; figure 4). Increases in ALP were observed with obeticholic acid treatment, but levels remained below the ULN throughout the study period (change at month 18: 1% decrease for the placebo group, 9% increase for the obeticholic acid 10 mg group, and 20% increase for the obeticholic acid 25 mg group; figure 4).

Additionally, treatment with obeticholic acid resulted in a dose-dependent decrease in bodyweight at month 18 (mean change from baseline –0·7 kg [SE 0·4] for the placebo group, –1·8 kg [0·4] for the obeticholic acid 10 mg group, and –2·2 kg [0·3] for the obeticholic acid 25 mg group).

1968 patients were included in the safety population, comprised of fibrosis stage F1 (290 [15%] patients), stage F2 (698 [35%]), and stage F3 (980 [50%]; figure 1). The duration of exposure was generally similar across treatment groups. Overall, treatment-emergent adverse events occurred in 548 (83%) patients in the placebo group, 579 (89%) in the obeticholic acid 10 mg group, and 601 (91%) in the obeticholic acid 25 mg group (table 3). Most treatment-related adverse events were of mild or moderate severity (table 3). The frequency of serious adverse events was similar across treatment groups (11–14%) and no single serious adverse event occurred in more than 1% of patients in any treatment group (table 3). The most frequent adverse event was pruritus (table 3). The incidence of pruritus was highest during the first 3 months of treatment with obeticholic acid, and generally mild to moderate in severity. Treatment discontinuation due to pruritus occurred in five (<1%) patients in the placebo group, five (<1%) in the obeticholic acid 10 mg group, and 57 (9%) in the obeticholic acid 25 mg group. Of the 57 patients in the obeticholic acid 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 obeticholic acid, LDL cholesterol increased by month 1 (mean change from baseline –3·0 mg/dL [SE 0·9] in the placebo group, 17·8 mg/dL [1·0] in the obeticholic acid 10 mg group, and 23·8 mg/dL [1·1] in the obeticholic acid 25 mg group) and decreased thereafter, approaching baseline by month 18 (mean change from baseline –7·1 mg/dL [1·7] for the placebo group, 1·4 mg/dL [2·0] for the obeticholic acid 10 mg group, and 2·7 mg/dL [2·1] for the obeticholic acid 25 mg group; appendix p 12). 380 patients started statin therapy during the study (66 in the placebo group, 155 in the obeticholic acid 10 mg group, and 159 in the obeticholic acid 25 mg group). Among obeticholic acid-treated patients who initiated statins, the initial LDL cholesterol increases reversed to below baseline levels as of month 6 and were sustained through month 18 (appendix p 13). There was no clear pattern of fibrosis improvement by statin use. Levels of HDL cholesterol showed dose-dependent decreases by month 1 (mean change from baseline –0·7 mg/dL [0·2] in the placebo group, –1·8 mg/dL [0·2] in the obeticholic acid 10 mg group, and –4·6 mg/dL [0·3] in the obeticholic acid 25 mg group) and were sustained through month 18; mean HDL cholesterol remained within the normal limit (>40 mg/dL) at all timepoints (appendix p 12). Changes in total cholesterol over time were similar to

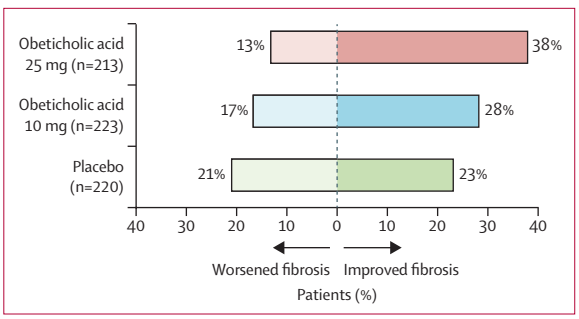

Figure 3: **Regression or progression of fibrosis by at least one stage in the per-protocol population**
The proportion of patients with improved or worsened fibrosis by at least one stage is shown for the 656 patients in the per-protocol population with available fibrosis stage data at month 18 or end of treatment.

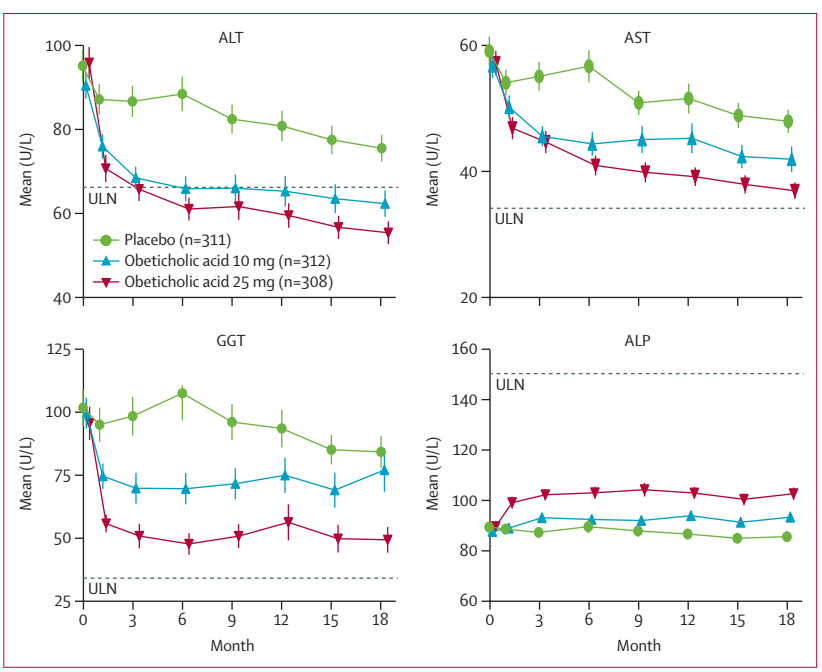

Figure 4: **Changes in liver biochemistry over time in the ITT population**
Mean values of change from baseline up to month 18 are shown for patients from each treatment group in the ITT population, with vertical bars indicating SEs. ALP=alkaline phosphatase; ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=γ-glutamyl transferase. ITT=intention to treat. ULN=upper limit of normal.

	Placebo (n=657)	Obeticholic acid 10 mg (n=653)	Obeticholic acid 25 mg (n=658)
Treatment-emergent and serious adverse events			
At least one treatment-emergent adverse event	548 (83%)	579 (89%)	601 (91%)
Severity*			
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%)
Leading to treatment discontinuation	41 (6%)	39 (6%)	83 (13%)
Serious adverse events	75 (11%)	72 (11%)	93 (14%)
Adverse events occurring in ≥5% of patients in either obeticholic acid group			
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			
LDL cholesterol 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	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%)

(Table 3 continues on next page)

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Table is arranged by descending order of incidence (system organ class and preferred term within system organ class) in the obeticholic acid 25 mg group, followed by descending order of incidence in the obeticholic acid 10 mg group.
*Patients reporting more than one adverse event are counted only once using the highest severity.

***Table 3*: Summary of treatment-emergent adverse events in the safety population**

those for LDL cholesterol (appendix p 12). A dose-dependent decrease in triglycerides was observed by month 1 in the obeticholic acid groups, with levels continuing to decline with a maximum mean change from baseline of –37·4 mg/dL in the obeticholic acid 25 mg group at month 18 (appendix p 12).

The incidence of cardiovascular adverse events and serious adverse events was similar across treatment groups (adverse events: 30 [5%] in the placebo group, 43 [7%] in the obeticholic acid 10 mg group, and 42 [6%] in the obeticholic acid 25 mg group; serious adverse events: ten [2%] placebo, nine [1%] obeticholic acid 10 mg, and 13 [2%] obeticholic acid 25 mg). Effects on glycaemic parameters were evaluated by baseline diabetes status (appendix p 14). In patients with type 2 diabetes, obeticholic acid treatment was associated with an early transient increase in glucose and HbA_{1c} with return to levels similar to placebo by month 6. No clinically meaningful changes were noted in patients without diabetes. Blood pressure was generally stable, but variable, with no significant difference between treatment groups. Other vital signs were not affected by study treatments (data not shown).

Gallstone-related adverse events occurred in two (<1%) patients in the placebo group, seven (1%) in the obeticholic acid 10 mg group, and 19 (3%) in the obeticholic acid 25 mg group. Pancreatitis, a more serious and potentially gallstone-related event, was rare and evenly distributed across treatment groups (one [<1%] patient in each of the placebo and obeticholic acid 10 mg groups and three [<1%] patients in the obeticholic acid 25 mg group). Hepatic serious adverse events were uncommon, and each case was reviewed by independent expert hepatologists. Although more events occurred in the obeticholic acid 25 mg group (six [1%] patients) than the obeticholic acid 10 mg group (two [<1%] patients) or placebo group

(two [<1%] patients), expert reviewers did not identify any consistent pattern of liver injury and all cases were associated with confounding concomitant medications or severe intercurrent illness.

Three deaths occurred on study: two in the placebo group (bone cancer and cardiac arrest) and one in the obeticholic acid 25 mg group (glioblastoma). None were considered related to study treatment.

Discussion

To our knowledge, 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 obeticholic acid 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 obeticholic acid was dose dependent and consistent across different patient populations and subgroups, and was further supported by fibrosis-related secondary endpoints, including an improvement in fibrosis of at least two stages. Per the draft guidance from the FDA on efficacy endpoints for clinical trials in NASH, improvement in fibrosis by at least one 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 three times greater risk of overall mortality compared with healthy individuals.[14] Fibrosis has been shown to be the strongest histological predictor of liver-related adverse outcomes, including liver-related death.[16–19] Treatment with obeticholic acid 25 mg both improved fibrosis and prevented progression of fibrotic disease. 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 can become even more difficult.[16,18]

Although the percentage of patients achieving NASH resolution was not significant between obeticholic acid and placebo, more patients receiving obeticholic acid 25 mg showed improvements in hepatocellular ballooning and lobular inflammation, the two key histological features of the prespecified 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] Additionally, more patients receiving obeticholic acid 25 mg had an improvement of at least two points 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 obeticholic acid reduces NASH disease activity.

Twice as many obeticholic acid 25 mg patients compared with placebo achieved NASH resolution as determined by the post-hoc pathologist diagnostic assessment of the absence of definite steatohepatitis at month 18. This evaluation was based on an assessment of the overall pattern of histological lesions or injury, as opposed to the more rigid categorical scoring system of the prespecified 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] The assessment of NASH resolution based on NAS parameters appears to be more rigid and might be associated with greater intra-rater and inter-rater variability compared with 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 might be more appropriate to establish the presence or absence of NASH using histological diagnostic criteria as an endpoint, as has been done by the National Institute of Diabetes and Digestive and Kidney Diseases' NASH Clinical Research Network in the past.

In addition to consistent improvements in multiple histological 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 farnesoid X receptor activation.

Lifestyle modifications including weight loss have been shown to be an effective non-pharmacological therapy for NAFLD. Weight loss greater than 7% has been associated with improvement in NAS and weight loss of at least 10% with improvement in fibrosis.[23] Obeticholic acid-treated patients experienced weight loss of approximately 2%, an amount lower than that expected to have an effect on histological parameters of NASH. Although modest, the effect of obeticholic acid 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 at least 18 months, obeticholic acid was generally well tolerated. Most adverse events were mild to moderate in severity and were generally consistent with the known safety profile of obeticholic acid.[7] As previously seen, mild-to-moderate pruritus was the most commonly reported adverse event, with a dose-dependent incidence. More patients in the obeticholic acid 25 mg group experienced pruritus that led to treatment discontinuation; however, most 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 obeticholic acid is being investigated.[24] The incidence of hepatic adverse events was balanced across treatment groups, and serious hepatic events were rare; although numerically more occurred in the obeticholic acid 25 mg treated group, there was no clear pathological pattern seen consistently among these serious adverse events and all cases were confounded by concomitant medications or severe intercurrent illness. Treatment with obeticholic acid was associated with serum lipid changes that were consistent with a class effect of farnesoid X receptor activation, as well as small and generally transient increases in glycaemic parameters. Such increases were manageable by clinical practice measures. The effect of lipid changes on cardiovascular risk should be assessed in the context of other obeticholic acid-related reductions in risk factors, including a decrease in bodyweight, serum triglyceride levels, and GGT, a promising marker for assessing cardiovascular risk, as well as improvements in liver fibrosis, which might have a downstream effect on cardiovascular risk.[19,25–27] The incidence of cardiovascular adverse events and serious adverse events 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 might underestimate the long-term benefit of obeticholic acid 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 might increase with prolonged therapy. This has been shown with other interventions that reported improvement in fibrosis at early timepoints 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.

This is a prespecified interim analysis of an ongoing study and the histological outcomes, in particular fibrosis stage, have been shown to be reasonably likely to predict clinical outcomes and therefore supports regulatory submission based upon the conditional approval pathway. However, a limitation of this analysis is that clinical outcomes data are not yet available. Additionally, the study population consists of patients selected on the basis of biopsy evidence of NASH and fibrosis; however, physicians increasingly rely on non-invasive means to diagnose and stage patients with NASH with fibrosis, which might have an implication for the real world relevance of the results. Non-invasive assessments of liver fibrosis such as the Fibrosis-4 Index and transient elastography are potentially more sensitive continuous parameters than categorical assessment of change in histological fibrosis stage; these were assessed throughout the study and will be reported at a later date. Finally, this interim analysis was completed with evolving regulatory authority guidances in which, for example, the definition of histological NASH resolution has changed, with the implication that future pivotal study designs could continue to be modified.

In conclusion, the totality of data from the month-18 interim analysis of this phase 3 study provides strong evidence that obeticholic acid treatment improves clinically significant histological endpoints deemed reasonably likely to predict clinical benefit, and affirms the positive benefit–risk ratio of obeticholic acid for the treatment of NASH with fibrosis. Beneficial effects of obeticholic acid on fibrosis and key components of NASH disease activity were robust, based on the observed consistency of results across multiple histological endpoints with reproducible response ratios, as well as the evident dose-response and markedly consistent benefit across analysis populations. Treatment with obeticholic acid had a beneficial effect on other markers of hepatocellular injury (ALT and AST) and oxidative stress (GGT). Obeticholic acid 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 up 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 might benefit from obeticholic acid treatment.

Contributors

VR, AJS, and ZMY participated in initial study design in collaboration with the sponsor (DSha, LM, 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, DShe, JT, WK, EL, MFA, KVK, 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, DSha, JC, LZ, LM, RS, ZG, and ZMY participated in data analysis and interpretation. All authors participated in manuscript development.

Declaration of interests

All declarations are outside of the submitted work. ZMY has received research funds 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, Pfizer, and 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, Galmed, Genfit, Gilead, Grunthal, HistoIndex, Indalo, Imperial Innovations, Intercept Pharma Europe, Inventiva, IQVIA, Janssen, Kenes, Madrigal, MedImmune, Metacrine, NewGene, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk, Pfizer, Poxel, ProSciento, Raptor Pharma, Servier, and Viking Therapeutics. He has received speaker fees from Abbott Laboratories, Allergan/Tobira, Bristol-Myers Squibb, Clinical Care Options, Falk, Fishawack, Genfit, Gilead, Integritas Communications, and MedScape, and royalties from Elsevier. AJS is president of Sanyal Bio. He has stock options in Indalo, Durect, Tiziana, Exhalenz, and 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, AstraZeneca, Medimmune, and Lipocine. He is an unpaid consultant to Intercept, Zydus, Echosense, Immuron, Madrigal, Galectin, Blade, Pliant, Albireo, and AMRA. RL serves as a consultant or advisory board member for Arrowhead Pharmaceuticals, AstraZeneca, Bird Rock Bio, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cirius, CohBar, Conatus, Eli Lilly, Galmed, Gemphire, Gilead, Glympse bio, GNI, GRI Bio, Intercept, Ionis, Janssen, Merck, Metacrine, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Prometheus, Sanofi, Siemens, and Viking Therapeutics. 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. PNN reports consultancy or speaker fees on behalf of the University of Birmingham from Boehringer Ingelheim, Gilead, Pfizer, Affimmune, Intercept, Johnson & Johnson, Novo Nordisk, Shire, and Poxel Pharmaceuticals. His institution receives grant funding from Pharmaxis, Boehringer Ingelheim, and Novo Nordisk. All remaining authors declare no competing interests.

Data sharing

The authors declare that all data supporting the findings of this interim analysis are available within the Article and its appendix. 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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