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REGENERATE: Design of a pivotal, randomised, phase 3 study evaluating the safety and efficacy of obeticholic acid in patients with fibrosis due to nonalcoholic steatohepatitis

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ABSTRACT

Background: Nonalcoholic steatohepatitis (NASH) is a chronic, progressive, and severe form of nonalcoholic fatty liver disease. In FLINT, obeticholic acid (OCA) treatment improved multiple histological NASH features. The design and endpoints of REGENERATE, an ongoing phase 3 study, further evaluate OCA treatment in patients with fibrosis due to NASH.

Aims: The Month 18 interim analysis assesses the effect of OCA on liver histology, defined as improvement of fibrosis by ≥1 stage with no worsening of NASH or resolution of NASH with no worsening of fibrosis. The end-of-study analyses evaluate the effect of OCA on mortality, liver-related clinical outcomes, and long-term safety.

Methods: REGENERATE is a pivotal, long-term study of ~2400 patients with NASH, including ~2100 patients with stage 2 or 3 liver fibrosis. Additionally, ~300 patients with stage 1 fibrosis and ≥1 accompanying comorbidity are included to gather information on the safety of OCA and liver disease progression. Patients are randomised 1:1:1 to receive placebo or OCA (10 or 25 mg). A liver biopsy evaluation occurs at screening, Months 18 and 48, and end of study. The duration of the study is dependent upon accrual of a predetermined number of clinical outcome events.

Conclusions: REGENERATE is designed in conjunction with regulatory authorities to support regulatory approvals in NASH. This robust phase 3 study assesses the effect of OCA on liver histology as a surrogate for transplant-free survival and liver-related outcomes, including progression to cirrhosis and mortality, and will ultimately assess clinical benefit through specific evaluation of these outcomes.

Clinical trial registration: ClinicalTrials.gov with the identifier NCT02548351.

Abbreviations: NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; FXR, farnesoid X receptor; OCA, obeticholic acid; TEAE, treatment-emergent adverse event; FDA, food and drug administration; MELD, model for end-stage liver disease; LDLc, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events

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1. Introduction

1.1. Nonalcoholic steatohepatitis (NASH)

Nonalcoholic fatty liver disease (NAFLD) covers a wide spectrum of diseases, including NASH, that can progress to advanced fibrosis, cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related death [1]. NASH is a chronic, progressive, and severe form of NAFLD with non-specific symptomatology [2]. The overall global prevalence of NAFLD, as diagnosed by imaging, is 25.2%, and the prevalence of NASH ranges between 1.5% and 6.5% [3,4]. It is currently estimated that NASH will become the leading cause of liver transplantation in the next decade [5]. Of the histological features of NASH, the strongest predictor of adverse clinical outcomes and liver-related death is fibrosis [6,7]. Liver-related mortality is driven principally by the development of cirrhosis, which can lead to clinical decompensation events, sepsis, and hepatocellular carcinoma [3,4,8]. Prevention of cirrhosis is therefore a major therapeutic objective in patients with advanced fibrosis due to NASH. Given the high prevalence and progressive nature of NASH and the fact that radical lifestyle and dietary changes are difficult to implement, the development of effective pharmacological therapies is a top priority.

In conjunction with thought leaders, regulatory authorities are outlining approvable pathways for NASH treatments, including the identification of endpoints and patient populations that can be prioritised for therapy. The Subpart H pathway in the United States and conditional approval in Europe describe accelerated drug approval guidelines based on achieving a histological surrogate endpoint followed by confirmation of clinical benefit via the evaluation of rigourously quantitative outcomes [9,10].

The farnesoid X receptor (FXR) is a ligand-activated nuclear receptor expressed predominantly in the liver and small intestine [11]. In the liver, FXR is expressed primarily in hepatocytes, Kupffer cells, and endothelial cells [11,12]. FXR activation has pleiotropic effects on NASH including increased glucose disposal, even in type 2 diabetic patients, and decreased lipogenesis along with decreased inflammation [13]. Together, these reduce fibrosis and complement direct antifibrotic effects on hepatic stellate cells [11]. Through these effects, FXR hits key elements of the NASH cascade and has a strong biological rationale for use.

Obeticholic acid (OCA) is a potent, selective FXR agonist derived from the primary bile acid chenodeoxycholic acid [14]. The efficacy and safety of OCA in NASH was studied in FLINT, a phase 2b, 18-month, placebo-controlled study [15]. Daily OCA 25 mg improved fibrosis as well as other histological features of the disease, such as hepatocellular ballooning, steatosis, and lobular inflammation, at a significantly higher proportion than placebo [15]. This histological response was correlated with a greater reduction in serum aminotransferases [15]. OCA treatment in the FLINT study was generally safe and well tolerated. Pruritus was the most common treatment-emergent adverse event (TEAE) and was generally mild to moderate in severity [15].

These promising results and close collaboration with regulatory authorities led to the design of REGENERATE, the first phase 3 pivotal study to evaluate the long-term clinical benefit of OCA treatment for patients with NASH.

2. Materials and methods

2.1. Study design

REGENERATE (ClinicalTrials.gov, NCT02548351) is a pivotal phase 3, prospective, randomised, double-blind, placebo-controlled, multicentre study comparing the clinical benefits of once-daily OCA 10 or 25 mg with those of placebo. This study includes approximately 2400 adult patients with non-cirrhotic NASH and evidence of stage 1, 2, or 3 liver fibrosis in up to 400 clinical sites worldwide; the majority of patients (approximately 2100) are either fibrosis stage 2 or stage 3. This study is designed to assess liver histology as a surrogate endpoint for clinical outcomes at Month 18 (interim analysis). Patients are followed long term for clinical outcomes (as a composite of endpoints reflective of liver failure). According to accelerated approval guidelines, the planned histological interim analysis is designed to provide a marketing application to regulatory authorities. The study remains blinded and ongoing until a sufficient number of clinical outcomes are achieved (Fig. 1).

2.2. Endpoint rationale

Because of the slow rate of progression in NASH, assessing hard clinical endpoints is a long-term endeavor. For this reason and because of the significant healthcare burden, the Food and Drug Administration (FDA) and European Medicines Agency have described an expedited approval pathway using a surrogate endpoint to predict clinical benefit [9,10,16]. For a surrogate endpoint to be clinically meaningful, it must measure how a patient feels, functions, or survives [17]. Previous analyses have shown that fibrosis and definite NASH are strongly correlated with liver-related mortality and transplant-free survival and could therefore be used as a histology-based surrogate endpoint [6,7]. Under Subpart H, accelerated pathway for the conditional approval of non-cirrhotic NASH in phase 3 clinical trials, these surrogate endpoints are defined as a complete resolution of NASH with no worsening of fibrosis and/or ≥ 1-point improvement in fibrosis with no worsening of NASH [16,18].

Conditional approval of the previously mentioned endpoints must be followed by an outcomes study to confirm clinical benefit [10]. *Clinical benefit* is defined as showing superiority over placebo in delaying disease progression as evaluated by progression to cirrhosis,

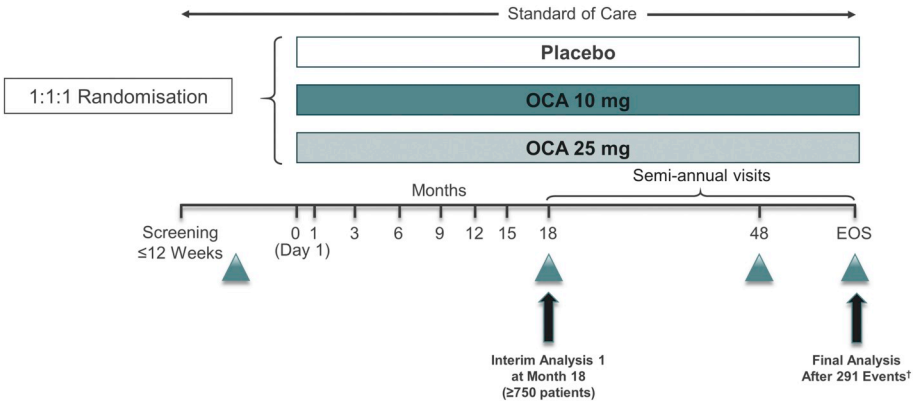

Fig. 1. REGENERATE study design.
Abbreviations: EOS, end of study; OCA, obeticholic acid
▲ Biopsy (patients without a liver biopsy performed within 6 months before Day 1 will have a biopsy at the second Screening Visit).
† Number of adjudicated events accrued in placebo and OCA 25 mg groups combined.

reduction in hepatic decompensation events, change in model for end-stage liver disease (MELD) score from ≤12 to > 15, liver transplantation, or all-cause mortality [9,10].

The design of the REGENERATE phase 3 study originated from the FDA–American Association for the Study of Liver Diseases workshop report in 2015; with close collaboration with regulatory authorities, it has helped define these approval pathways. Both the histology-based surrogate endpoints being evaluated with the Month 18 interim analysis and the end-of-study clinical outcomes align with these recommendations.

2.3. Dosing rationale

Dosing was selected on the basis of results from the preceding FLINT trial, which demonstrated the efficacy of OCA 25 mg over placebo in improving measures of steatosis and fibrosis [15]. Although the 25-mg dose of OCA was generally safe and well tolerated, a higher incidence of mild to moderate pruritus and an increase in low-density lipoprotein cholesterol (LDLc) was observed in OCA-treated patients compared with placebo-treated patients [15]. In a phase 1 trial, OCA 10 mg showed robust FXR activation that was similar to that of OCA 25 mg in patients with NASH Child-Pugh A [19]. Therefore, to mitigate the incidence of pruritus, but maintain similar efficacy, once-daily OCA 10 mg is also included in this study.

2.4. Study objectives

The primary objective of the Month 18 interim analysis is improvement in fibrosis (reduction of ≥1 stage) with no worsening of NASH (no worsening of hepatocellular ballooning, lobular inflammation, or steatosis) or resolution of NASH defined as “no fatty liver disease” or “fatty liver disease without steatohepatitis” and a histological score of 0 for ballooning and 0–1 for inflammation with no worsening of fibrosis as determined by liver biopsy with OCA treatment compared with placebo. For the end-of-study assessments, clinical benefit is confirmed by evaluating a composite endpoint defined as the time to first occurrence of any of the following adjudicated events: death (all-cause); liver transplantation; a MELD score ≥ 15; hospitalisation for variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis; ascites secondary to cirrhosis; or histological progression to cirrhosis (Table 1) [20]. Secondary objectives, including additional histology assessments and liver biochemistry for both the Month 18 interim (histology) and end-of-study (clinical outcomes) analyses, are also included in Table 1. Exploratory objectives, including patient-reported outcomes, noninvasive measures of liver fibrosis, markers of inflammation, glucose metabolism, apoptosis, and cardiovascular safety (including core major adverse cardiovascular events [MACE] and expanded MACE), for both the Month 18 interim and end-of-study analyses are outlined in **Tables A.1 and A.2**.

2.5. Study duration

A planned interim analysis occurs after a minimum of 750 patients complete 18 months of treatment. This duration is based on the histology-related changes observed in FLINT, which demonstrated that OCA improved the histological features of NASH as well as fibrosis after 72 weeks of treatment [15].

The overall study duration is event driven and is determined by the time required to achieve a sufficient number of adjudicated events in the OCA 25 mg and placebo groups in patients with fibrosis stage 2 or 3. Although disease progression can be highly variable, this is projected to be approximately 7 years, with a minimum follow-up of approximately 4 years.

2.6. Sample size justification and statistical considerations

The estimated overall study sample size is based on the clinical outcomes endpoint analysis at the end of the study. According to the limited literature available on the natural history of NASH, a placebo event rate of 20% over 4 years is assumed [21–24]. With this assumption, approximately 2100 patients with fibrosis stage 2 or 3 are randomised in a 1:1:1 ratio to placebo, OCA 10 mg, or OCA 25 mg to accrue the required 291 clinical outcomes (OCA 25 mg + placebo groups) for 80% power. The assumption is that at least that number of events will also occur in the OCA 10 mg + placebo groups. Randomisation is stratified by type 2 diabetes at enrolment and use of thiazolidinediones (TZDs)/glitazones or vitamin E at baseline. An exploratory cohort of fibrosis stage 1 patients is also enroled, leading to an overall study size of approximately 2400 patients. These patients do not contribute to the Subpart H approval endpoint.

Each OCA treatment group is tested against placebo using a log-rank test stratified by presence of type 2 diabetes at enrolment and use of TZDs/glitazones or vitamin E at baseline. The alpha will be split between the Month 18 interim analysis and the end-of-study analysis for a total overall study alpha of 0.05.

The planned Month 18 interim analysis is performed when a minimum of 750 randomised patients (the first sequential) with fibrosis stage 2 or 3 have/should have reached their actual/planned Month 18 visit. This ensures a minimum power of 90% for both primary endpoints.

The primary endpoints are tested using Cochran–Mantel–Haenszel tests stratified by (I) presence of type 2 diabetes at enrolment (yes/no) and (II) use of TZDs/glitazones or vitamin E at baseline (yes/no). To adjust for multiplicity due to two doses as well as two endpoints, a truncated Hochberg procedure was used.

For all analyses (Month 18 interim and clinical outcomes at the end of the study), the two doses are tested in a sequential manner with the OCA 25 mg dose tested first. For the Month 18 interim analysis, if both primary efficacy endpoints are rejected at 25 mg, the primary endpoints will be tested in a similar manner for the 10 mg dose. The primary efficacy population for analysis is the intent-to-treat population with fibrosis stage 2 or 3 patients.

3. Study procedures

3.1. Eligibility

Patients aged 18 years or older with definite steatohepatitis, a nonalcoholic fatty liver disease activity score (NAS) ≥ 4, and fibrosis stage 2 (approximately 40%) or stage 3 (approximately 60%) confirmed by central reading of a liver biopsy obtained within 6 months of randomisation are eligible for the study. To gain further insight into the population at an earlier stage of NASH, a subgroup of patients with steatohepatitis and mild fibrosis (stage 1) who are also considered at high risk of disease progression because of ≥1 accompanying comorbidity (obesity, type 2 diabetes, or alanine aminotransferase > 1.5 times the upper limit of normal) is included for an expanded safety database analysis. Patients were not included if they currently or have a history of significant alcohol consumption (> 2 units per day for females and 4 units per day for males for ≥3 months) or any other documented causes of chronic liver disease. If providing a historical biopsy, they also need to be in a stable metabolic condition, defined as having a stable body weight (no weight change > 10% for ≥3 months) and not taking or on stable doses of TZDs/glitazones or vitamin E for 6 months. Additional key inclusion and exclusion criteria are listed in Table 2.

3.2. Study blinding

During the entire conduct of the study, patients, investigators, and

Table 1
Primary and secondary objectives with corresponding assessments.

Month 18 interim analyses (All patients)	
Primary objectives	**Assessment (Based on liver biopsy using NASH CRN criteria)**
Improvement in fibrosis with no worsening of NASH	A ≥ 1-stage reduction in fibrosis and no increase in hepatocellular ballooning, lobular inflammation, or steatosis from baseline
Resolution of NASH with no worsening of fibrosis	NASH resolution defined as the overall histopathologic interpretation of I) "no fatty liver disease" or II) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a NAS of 0 for ballooning and 0–1 for inflammation with no increase in fibrosis stage from baseline
End-of-Study analyses (All patients)	
Primary objective	**Assessment**
Clinical outcomes composite endpoint	Time to first occurrence of any of the following adjudicated events: 1. Death (all cause); 2. MELD score ≥ 15; 3. Liver transplantation; 4. Hospitalisation[a] for onset of variceal bleed, hepatic encephalopathy,[b] spontaneous bacterial peritonitis[c]; 5. Ascites secondary to cirrhosis and requiring medical intervention (e.g. diuretics or paracentesis); 6. Histological progression to cirrhosis
Month 18 interim analyses and End-of-Study analyses (All patients)	
Secondary objectives	**Assessment (Based on liver biopsy using NASH CRN criteria)**
≥1-stage reduction in fibrosis AND/OR resolution of NASH, without worsening of either	Please see definitions above
No worsening of fibrosis AND no worsening of NASH	No increase from baseline in fibrosis stage AND no increase in hepatocellular ballooning, lobular inflammation, or steatosis
Improvement in each key histological feature of NASH	A ≥ 1-score reduction from baseline for steatosis, lobular inflammation, or hepatocellular ballooning
≥2-stage improvement in fibrosis	A ≥ 2-stage reduction in fibrosis from baseline at Month 18
≥2-point improvement in NAS with no worsening of fibrosis	A ≥ 2-point reduction in NAS with no increase in fibrosis stage from baseline
Improvement of fibrosis and resolution of NASH as a composite endpoint (both endpoints being met in the same patient)	A reduction in fibrosis stage ≥1 and a reduction in NAS ≥2 points with ≥1-point improvement each for hepatocellular ballooning and lobular inflammation from baseline
Resolution of fibrosis (fibrosis stage 0)	A fibrosis stage of 0
Liver biochemistry and markers of liver function	ALT, AST, GGT, ALP, total and direct bilirubin, albumin, INR, and platelets
Secondary objective: month 18 interim analysis only	
Histological progression to cirrhosis	A fibrosis stage of 4
Secondary objective: End-of-Study analysis only	
Improvement in fibrosis with no worsening of NASH	A ≥ 1-stage reduction in fibrosis and no increase in hepatocellular ballooning, lobular inflammation, or steatosis from baseline
Resolution of NASH with no worsening of fibrosis	NASH resolution defined as the overall histopathologic interpretation of I) "no fatty liver disease" or II) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a NAS of 0 for ballooning and 0–1 for inflammation with no increase in fibrosis stage from baseline

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRN, clinical research network; GGT, gamma-glutamyl transferase; INR, international normalised ratio; MELD, model for end-stage liver disease scoring system; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

[a] As defined by a stay of ≥24 h.

[b] As defined by a West Haven score of ≥2.

[c] Confirmed diagnostic paracentesis.

the sponsor are blinded to individual treatment assignments. If necessary to ensure safety throughout the study, the data monitoring committee will have access to unblinded individual patient data. To maintain the integrity of the final post–Month 18 analysis, only a minimal number of personnel are unblinded to the patient-level data, primarily to facilitate regulatory filings and required public disclosures.

3.3. Histological grading

The pathologists are highly qualified and follow a standardised criterion to ensure consistency between histology readings. All biopsy specimens are read centrally, including biopsies to determine study eligibility (collected within 6 months of screening), scheduled biopsies (Month 18, Month 48, and end of study), unscheduled biopsies, and biopsies performed to confirm suspected cirrhosis. At Month 18 or early termination, biopsy slides are pair-read with the screening biopsy in a blinded fashion, ensuring that pathologists are blinded to biopsy sequence. Fibrosis staging and the key features of NASH, including steatosis, lobular inflammation, and hepatocellular ballooning, are graded according to the NASH Clinical Research Network criteria for scoring [15,26].

3.4. Safety monitoring and assessments

Because of the progressive nature of NASH, the MELD scores are reviewed by the clinician at each visit to ensure early identification of disease progression to cirrhosis or decompensation (Fig. A.1). To determine the tolerability of a long-term OCA treatment regimen, TEAEs, vital signs, electrocardiograms, adjudicated cardiovascular events (MACE and expanded MACE), and clinical laboratory assessments (including lipid profile changes) are evaluated at Month 18 and at the end of the study [20].

Table 2
REGENERATE Key inclusion and exclusion criteria [25].

Key inclusion criteria	Key exclusion criteria
Histological evidence of NASH[a]	Histological presence of cirrhosis
Age ≥18 years	HbA1c > 9.5% ≤60 days before Day 1
Stable body weight (≤10% variation for ≥3 months before Day 1)	Prior exposure to OCA
Stable dose of vitamin E or TZD	History of biliary diversion
Histological evidence of fibrosis assessed by NASH CRN scoring system:	Significant alcohol consumption[b]
1. Stages 2–3 (primary efficacy analysis)	Prior or planned ileal resection
2. Stages 1a-1b if accompanied by ≥1 of the following:	Bariatric surgery within 5 years
1. Obesity (BMI ≥30 kg/m^2)	MELD score > 12
2. Type 2 diabetes[c]	Other causes of concomitant liver disease and history of liver transplantation
3. Elevated ALT (> 1.5xULN)	Total bilirubin > 1.5 mg/dL
	Conjugated bilirubin ≥1.5xULN
	AST or ALT ≥10xULN; INR ≥1.4; serum creatinine ≥1.5 mg/dL; creatine phosphokinase > 5xULN
	Platelet count < 100,000/mm^3
	LDL ≥190 mg/dL with stable statin use or PCSK9 inhibitor ≥30 days prior to screening
	Acute cholecystitis or biliary obstruction

Abbreviations: ADA, American Diabetes Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRN, clinical research network; HbA1c, hemoglobin A1c; INR, international normalised ratio; LDL, low-density lipoprotein; MELD, model for end-stage liver disease scoring system; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PCSK9, proprotein convertase subtilisin/kexin type 9; TZD, thiazolidinedione; ULN, upper limit of normal.

[a] Biopsy obtained ≤6 months before Day 1 defined by the presence of all 3 key histological features of NASH (steatosis, ballooning degeneration, and lobular inflammation) with a score of ≥1 for each histological feature and a combined score ≥ 4 according to the NASH CRN criteria [26].

[b] Defined as > 2 units per day for females and > 4 units per day for males, on average.

[c] Diagnosed per 2013 ADA criteria (HbA1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, 2-h plasma glucose ≥200 mg/dL during oral glucose tolerance test, or random plasma glucose ≥ 200 mg/dL).

All suspected liver-related clinical outcomes are adjudicated by a blinded hepatic outcomes committee composed of experts who are not involved in the study as investigators, data monitoring committee members, or consultants. Similarly, cardiovascular events are adjudicated by an independent committee in accordance with the standardised definitions for cardiovascular endpoints in clinical trials [27]. Adjudicated events are analysed for core MACE (comprising cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) as well as expanded MACE (transient ischaemic attack, coronary or peripheral revascularisation procedures, and hospitalisation for congestive heart failure or unstable angina). MACE are assessed as an exploratory objective at the Month 18 interim analysis and the end of the study. Hepatic events are assessed at the end of the study only.

Given the prevalence of dyslipidaemia in patients with NASH and the potential increase in LDLc with OCA treatment, investigators are closely monitoring and managing lipid levels. Following a ≥ 15% increase in LDLc from baseline, investigators further assess other cardiovascular risk factors, the risk-benefit of statins or other appropriate therapy, and other factors relevant for dyslipidaemia management. As the investigator deems appropriate, statins are initiated or up-titrated, a regimen that mitigated OCA-induced increases in LDLc in a phase 2 clinical study [28] (Fig. A.2).

3.5. Human studies and patients

This study is in full compliance with the International Council for Harmonisation Guidance on General Considerations for Clinical Trials and has been approved by the institutional review board and independent ethics committee at all study sites. Prior to participation, all patients provided written informed consent in accordance with the Declaration of Helsinki, the United States Code of Federal Regulations, and Good Clinical Practice guidelines.

4. Discussion

REGENERATE initiated patient enrolment in September 2015 to evaluate histological outcomes and hepatic and metabolic parameters in patients with advanced fibrosis due to NASH treated with placebo, OCA 10 mg, or OCA 25 mg. Upon completion, approximately 2400 patients with liver fibrosis will have been enroled across approximately 400 clinical sites worldwide; however, given the limited information on the natural history of NASH during the design of the study and the difficulties in characterising targets for an evolving therapeutic area, the sample size may be too conservative.

The primary objectives of this study focus on the most recent recommended guidelines for phase 3 endpoints for biopsy-based non-cirrhotic NASH (Table 1) and ≥ 1-point improvement in fibrosis with no worsening of NASH or the resolution of NASH on overall histopathologic interpretation by an experienced pathologist with no worsening of fibrosis followed by a long-term assessment of clinical benefit [9,10,16]. Liver-related outcomes are driven by worsening of fibrosis and development of cirrhosis. As one of the leading drivers of fibrosis, NASH contributes to these outcomes. Therefore, resolution of NASH as the primary disease, in theory, should prevent progression to cirrhosis. Current phase 3 trials are testing the hypothesis that short-term improvements in either of these parameters will translate into a reduced rate of liver-related outcomes. This will help support the transition towards general acceptance of NASH resolution and fibrosis improvement as surrogate endpoints.

The study design of REGENERATE will provide scientific and medical insights into the histopathology of long-term effects of OCA treatment on NASH. Patients in REGENERATE will receive 18 months of OCA prior to interim analyses and subsequent long-term assessments. Based on results from the FLINT study, a histology assessment following 18 months of OCA treatment should be sufficient to observe effects on features of NASH as well as fibrosis. Although lengthy treatments in clinical trials can be logistically challenging, the approximately 7-year treatment period in REGENERATE will allow for robust investigation into the safety and therapeutic potential of OCA and also provide insight into the natural history of advanced disease in NASH.

The results from REGENERATE may also confirm additional clinical benefits by accelerating innovations in the use of bile acid modulators for various liver-related conditions. REGENERATE will provide additional, clinically meaningful outcomes by evaluating OCA treatment in patients with varying disease states, including those with advanced disease who are at a high risk of disease progression. This will help to capture the effects of OCA in patients with NASH who have the greatest unmet clinical needs. The enrolment criteria implemented in this trial (Table 2) maximise the likelihood of assessing outcomes that confirm the clinical benefits of OCA.

The optimal trial duration for assessing benefits on steatohepatitis and fibrosis stage is currently unsettled but most likely depends on the study drug's mechanism of action and study endpoint(s). A previous study demonstrated effects of pioglitazone on inflammation and liver cell injury in steatohepatitis in as little as 6 months; another study confirmed fibrosis reduction after only 6 months of treatment [29,30]. However, the small sample size of these studies may correspond to a high risk of alpha-type error. Other studies have shown the antifibrotic effects of cenicriviroc and elafibranor after 12 months of treatment, but the antifibrotic effects of elafibranor were apparent only in patients who cleared NASH (i.e. responders for NASH resolution, defined as the disappearance of ballooning together with either disappearance of lobular inflammation or persistence of mild lobular inflammation only) [31,32]. Therefore, depending on the mechanism of action, the time necessary to capture the full antifibrotic effect may be variable, and

longer treatment durations may allow both direct and indirect (subsequent to the clearance of steatohepatitis) antifibrotic effects to become visible. The FLINT trial, which was conducted over 18 months, demonstrated an improvement in all histological parameters including fibrosis; therefore, an 18-month period was chosen as a conservative assumption in REGENERATE.

Although liver biopsies remain the gold reference standard in NASH trials, there is a need for a reliable NASH biomarker that accurately identifies NASH features and correlates with steatohepatitis over time. The study design of REGENERATE includes exploratory endpoints such as non-invasive assessments, which have the potential for use as NASH biomarkers in future trials (Tables A.1 and A.2).

As the clinical landscape continues to evolve and regulatory pathways are put into place, the robustness of the REGENERATE study provides critical insights on how to study NASH and the disease state.

5. Conclusions

REGENERATE is a pivotal phase 3 study designed in close collaboration with regulatory authorities to evaluate short-term and long-term effects of OCA on liver histology and on progression to cirrhosis, liver-related clinical outcomes, and mortality. It assesses predictors of histological response as well as the interaction between histological improvement and liver biochemical and metabolic effects. In addition, this study provides key data on the natural history of NASH owing to the systematic, protocol-based assessment of histological progression over several years in the placebo group, as well as the role of the FXR pathway in the treatment of NASH. Therefore, REGENERATE should provide valuable information for the development of future NASH trials and for scientific justification of the regulatory approval process (ClinicalTrials.gov, NCT02548351).

Conflicts of interests

This study was funded in full by Intercept Pharmaceuticals.

VR has served as a consultant for Intercept Pharmaceuticals.

AJS's institution was a clinical site for the REGENERATE trial and has received research funding from Intercept Pharmaceuticals, Merck, Bristol Myers, Novartis, Boehringer Ingelheim, Gilead, Conatus, Immuron, Echosens, Mallinckrodt, Cumberland, and Sequana; has served as a consultant for Novartis, Pfizer, Eli Lilly, Novo Nordisk, Sanofi, Gilead, Conatus, Tern, Hemoshear, Glympse, Birdrock, Blade, Teva, Echosens, Prosciento, Artham, Medimmune, Astra Zeneca, Salix, and NASH Pharmaceuticals; has served as a scientific advisor for Albireo, Astra Zeneca, and Medimmune; has ownership of Sanyal Bio; owns stocks and shares in Genfit, Indalo, Tiziana, Durect, Exhalenz, and Galmed; and has had research collaborations with Second Genome, CymaBay, and LabCorp.

RL and SH have received research funding from and have served on the REGENERATE trial Steering Committee for Intercept Pharmaceuticals.

MR has served on an advisory committee or review panel for Intercept Pharmaceuticals, Enanta, and Gilead; has served as a speaker and teacher for Echosense; and has served as a consultant for BMS, NGM Bio, Enanta, Genfit, Immuron, and Novartis.

QMA has served as a consultant for Acuitas Medical, Allergan/Tobira, E3Bio, Eli Lilly, Galmed, Genfit, Gilead, Grunthal, Imperial Innovations, Intercept Pharmaceuticals, Inventiva, Janssen, MedImmune, NewGene, Pfizer, Raptor Pharmaceuticals, Novartis, BMS, NGM Bio, Madrigal, Servier, EcoR1, Novo Nordisk, Pozel Pharmaceuticals, Metacrine, Viking Therapeutics, IQVIA, and Histoindex; has received research funding from Allergan/Tobira, Genfit, Intercept Pharmaceuticals, Pfizer, GlaxoSmithKline, Novartis, AbbVie, GSK, and NovoNordisk; has served as a speaker for Kenes, Abbott Laboratories, Clinical Care Options, Fishawack, and Integritas Communications; and has served on the REGENERATE trial Steering Committee for Intercept Pharmaceuticals.

ZG has received research finding from Intercept Pharmaceuticals, Gilead, Galectin, Conatus, Novartis, Bristol-Myers Squibb, Allergan, and Alexion.

PB has received personal fees from Intercept Pharmaceuticals.

LM and RS are employees of and own stocks and shares in Intercept Pharmaceuticals.

AS has served as a consultant for and owns stocks and shares in Intercept Pharmaceuticals.

ZY has served as a consultant for Gilead, Intercept Pharmaceuticals, BMS, Novo Nordisk, Shinogi, and Novartis.

Authorship statement

VR, AJS, RL, MR, SH, QMA, ZG, PB, LM, RS, AS, and ZY contributed to the acquisition, analysis, or interpretation of data for this article, revised the manuscript critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the article. All authors had full access to all data and had sole discretion in data interpretation, writing of the manuscript, review and approval prior to submission, and the decision to submit for publication.

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Appendix A. Supplementary data

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