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


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, 2015O-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.

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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 to 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 fibrosis. 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.

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.

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 prespecified 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 advanced age). 

This information is from the abstract and may not be comprehensive. For more detailed information, please refer to the full text of the article.
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 HbA1c 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 reported11 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 A1c, 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.31 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.
5189 participants assessed for eligibility

3221 ineligible
- 2037 due to histological reasons
- 412 did not give informed consent or investigator opinion
- 330 lab-related reasons
- 74 exclusionary medical history
- 28 concomitant medications
- 136 out of window
- 204 unknown

1968 randomly assigned

657 assigned to placebo (safety population)

653 assigned to obeticholic acid 10 mg (safety population)

658 assigned to obeticholic acid 25 mg (safety population)

346 excluded from interim analysis
- 96 with fibrosis stage F1 who reached month 18 or end of treatment
- 250 with fibrosis stage F2–F3 had not reached their month 18 or end of treatment by data cutoff

341 excluded from interim analysis
- 95 with fibrosis stage F1 who reached month 18 or end of treatment
- 246 with fibrosis stage F2–F3 had not reached their month 18 or end of treatment by data cutoff

350 excluded from interim analysis
- 96 with fibrosis stage F1 who reached month 18 or end of treatment
- 254 with fibrosis stage F2–F3 had not reached their month 18 or end of treatment by data cutoff

311 included in interim analysis

312 included in interim analysis

308 included in interim analysis

87 excluded from per-protocol population
- 84 either did not complete ≥15 months of treatment or were not on treatment ≥30 days before biopsy
- 3 major protocol deviations

86 excluded from per-protocol population
- 78 either did not complete ≥15 months of treatment or were not on treatment ≥30 days before biopsy
- 8 major protocol deviations

90 excluded from per-protocol population
- 80 either did not complete ≥15 months of treatment or were not on treatment ≥30 days before biopsy
- 10 major protocol deviations

224 included in per-protocol population

226 included in per-protocol population

218 included in per-protocol population

262 completed month 18 or end-of-treatment biopsy

263 completed month 18 or end-of-treatment biopsy

253 completed month 18 or end-of-treatment biopsy

311 included in ITT population

312 included in ITT population

308 included in ITT population

73 discontinued treatment
- 26 due to adverse events
- 24 due to site closure
- 3 physician decision
- 7 lost to follow-up
- 12 other reasons

71 discontinued treatment
- 20 due to adverse events
- 23 due to site closure
- 1 protocol violation
- 1 physician decision
- 7 lost to follow-up
- 12 other reasons

77 discontinued treatment
- 42 due to adverse events
- 2 due to site closure
- 1 due to non-compliance
- 8 physician decision
- 5 lost to follow-up
- 5 other reasons

262 completed month 18 or end-of-treatment biopsy

263 completed month 18 or end-of-treatment biopsy

253 completed month 18 or end-of-treatment biopsy

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). 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.

The statistical analysis plan, prior to the first interim analysis, was described in the protocol, with minor changes 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).

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=311)</th>
<th>Obeticholic acid 10 mg (n=312)</th>
<th>Obeticholic acid 25 mg (n=308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55 (12)</td>
<td>55 (11)</td>
<td>55 (11)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>187 (60%)</td>
<td>177 (57%)</td>
<td>175 (57%)</td>
</tr>
<tr>
<td>Male</td>
<td>124 (40%)</td>
<td>135 (43%)</td>
<td>133 (43%)</td>
</tr>
<tr>
<td>Race*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>10/280 (4%)</td>
<td>17/287 (6%)</td>
<td>20/286 (7%)</td>
</tr>
<tr>
<td>White</td>
<td>264/280 (94%)</td>
<td>263/287 (92%)</td>
<td>249/286 (82%)</td>
</tr>
<tr>
<td>Other</td>
<td>6/280 (2%)</td>
<td>7/287 (2%)</td>
<td>17/286 (6%)</td>
</tr>
<tr>
<td>Ethnicity*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>52/282 (18%)</td>
<td>42/286 (15%)</td>
<td>47/282 (17%)</td>
</tr>
<tr>
<td>Other</td>
<td>230/282 (82%)</td>
<td>244/286 (85%)</td>
<td>235/282 (83%)</td>
</tr>
<tr>
<td>Fibrosis stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>142 (46%)</td>
<td>130 (42%)</td>
<td>139 (45%)</td>
</tr>
<tr>
<td>F3</td>
<td>169 (54%)</td>
<td>182 (58%)</td>
<td>169 (55%)</td>
</tr>
<tr>
<td>NAS ≥6</td>
<td>215/209 (70%)</td>
<td>211 (68%)</td>
<td>208 (68%)</td>
</tr>
<tr>
<td>Type 2 diabetes†</td>
<td>175 (56%)</td>
<td>171 (55%)</td>
<td>171 (55%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>211 (68%)</td>
<td>217 (70%)</td>
<td>205 (67%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>215 (69%)</td>
<td>215 (69%)</td>
<td>196 (64%)</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>184.5 (42.7)</td>
<td>185.2 (53.3)</td>
<td>183.5 (44.7)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>45.6 (11.1)</td>
<td>44.9 (12.1)</td>
<td>44.3 (11.0)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>114.8 (38.2)</td>
<td>113.8 (38.4)</td>
<td>113.3 (38.8)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>178.7 (154.5)</td>
<td>184.6 (195.0)</td>
<td>181.7 (131.6)</td>
</tr>
<tr>
<td>Metabolic factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>119.1 (38.3)</td>
<td>120.8 (43.6)</td>
<td>119.5 (40.3)</td>
</tr>
<tr>
<td>Bodyweight, kg</td>
<td>95.3 (19.0)</td>
<td>95.2 (19.1)</td>
<td>95.4 (19.5)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>9.6 (11.8)</td>
<td>9.9 (16.9)</td>
<td>8.3 (10.2)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.6% (1.2)</td>
<td>6.5% (1.2)</td>
<td>6.5% (1.3)</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>79.6 (56.6)</td>
<td>75.6 (47.0)</td>
<td>80.2 (56.4)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>58.9 (40.5)</td>
<td>56.6 (34.0)</td>
<td>57.0 (34.1)</td>
</tr>
<tr>
<td>Platelet count, ×10⁹/L</td>
<td>241.9 (67.0)</td>
<td>238.5 (66.0)</td>
<td>237.2 (69.0)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.64 (0.3)</td>
<td>0.65 (0.3)</td>
<td>0.69 (0.3)</td>
</tr>
<tr>
<td>Concomitant medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid lowering†</td>
<td>175 (56%)</td>
<td>170 (54%)</td>
<td>160 (52%)</td>
</tr>
<tr>
<td>Statins</td>
<td>144 (46%)</td>
<td>142 (46%)</td>
<td>127 (41%)</td>
</tr>
<tr>
<td>Antidiabetic medication</td>
<td>167 (54%)</td>
<td>171 (55%)</td>
<td>159 (52%)</td>
</tr>
<tr>
<td>Thiazolidinediones†</td>
<td>5 (2%)</td>
<td>9 (3%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Vitamin E†</td>
<td>42 (14%)</td>
<td>34 (11%)</td>
<td>32 (10%)</td>
</tr>
</tbody>
</table>

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.

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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 acid 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 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 steatohepatitis at baseline to absence of definite steatohepatitis characteristics was observed in the per-protocol population (appendix p 6).
(without worsening of fibrosis) at month 18. This pathologist diagnostic assessment of NAS, 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 NAS 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 NAS, 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 NAS, and had improvement in fibrosis of at least two stages (table 2). Additional secondary NAS 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 placebo, –14·1 U/L [2·1] for the obeticholic acid 10 mg group; figure 4). These changes correspond to additional secondary NASH and fibrosis endpoints as a composite endpoint†.

<table>
<thead>
<tr>
<th>ITT population (N=931)</th>
<th>Per-protocol population (N=668)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=313)</td>
</tr>
<tr>
<td><strong>Primary endpoints</strong></td>
<td>Patients</td>
</tr>
<tr>
<td>Improvement of fibrosis with no worsening of NASH</td>
<td>37 (12%)</td>
</tr>
<tr>
<td>Resolution of NAS with no worsening of fibrosis</td>
<td>25 (8%)</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td>Patients</td>
</tr>
<tr>
<td>Improvement of fibrosis by ≥1 stage or resolution of NASH without worsening of either</td>
<td>49 (16%)</td>
</tr>
<tr>
<td>No worsening of fibrosis and no worsening of NAS</td>
<td>117 (38%)</td>
</tr>
<tr>
<td>Improvement of NAS by ≥2 with no worsening of fibrosis</td>
<td>76 (24%)</td>
</tr>
<tr>
<td>Improvement of fibrosis and resolution of NAS as a composite endpoint†</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Resolution of fibrosis</td>
<td>15 (5%)</td>
</tr>
<tr>
<td>≥1-point improvement in steatosis</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>≥1-point improvement in lobular inflammation</td>
<td>111 (36%)</td>
</tr>
<tr>
<td>≥1-point improvement in hepatocellular ballooning</td>
<td>72 (23%)</td>
</tr>
<tr>
<td>Pathologist assessment of NAS resolution with no worsening of fibrosis†</td>
<td>38 (12%)</td>
</tr>
</tbody>
</table>

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 NAS is defined as a composite endpoint where both of the primary endpoints are met in the same patient. ‡Post-hoc analysis of NAS 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.
Changes in liver biochemistry over time in the ITT population

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.

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 –7·1 mg/dL [1·7] for 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 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 HbA1c, 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.8–11 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.12 Fibrosis has been shown to be the strongest histological predictor of liver-related adverse outcomes, including liver-related death.14–19 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.14,19

### Adverse events occurring in ≥5% of patients in either obeticholic acid group

#### Skin and subcutaneous tissue disorders

- **Pruritus**:
  - Placebo 123 (19%) 183 (28%) 336 (51%)
  - Obeticholic acid 10 mg 90 (14%) 113 (17%) 148 (22%)
  - Obeticholic acid 25 mg 30 (5%) 67 (10%) 152 (23%)

#### Gastrointestinal disorders

- **Nausea**:
  - Placebo 77 (12%) 72 (11%) 83 (13%)
  - Obeticholic acid 10 mg 62 (9%) 66 (10%) 67 (10%)
  - Obeticholic acid 25 mg 35 (5%) 46 (7%) 45 (7%)

#### Infectious and infestations

- **Urinary tract infection**:
  - Placebo 49 (7%) 54 (8%) 62 (9%)
  - Obeticholic acid 10 mg 44 (7%) 47 (7%) 54 (8%)
  - Obeticholic acid 25 mg 34 (5%) 35 (5%) 35 (5%)

#### Musculoskeletal and connective tissue disorders

- **Arthralgia**:
  - Placebo 55 (8%) 50 (8%) 50 (8%)
  - Obeticholic acid 10 mg 50 (8%) 56 (9%) 40 (6%)

#### Table 3 continues on next page
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. 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 and PIVENS, 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. 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. 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. 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. 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. 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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Placebo (n=657)</th>
<th>Obeticholic acid 10 mg (n=653)</th>
<th>Obeticholic acid 25 mg (n=658)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>88 (13%)</td>
<td>78 (12%)</td>
<td>71 (11%)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>51 (8%)</td>
<td>42 (6%)</td>
<td>34 (5%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>28 (4%)</td>
<td>32 (5%)</td>
<td>25 (4%)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>27 (4%)</td>
<td>29 (4%)</td>
<td>38 (6%)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (4%)</td>
<td>36 (6%)</td>
<td>39 (6%)</td>
</tr>
</tbody>
</table>

| (Continued from previous page)                                          |                 |                               |                               |
| **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%)                       |

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.
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.\textsuperscript{19,20–27} 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).\textsuperscript{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.\textsuperscript{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 guidelines 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, AJ, and ZMY participated in initial study design in collaboration with the sponsor (DSHi, LM, RS). AJ, 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, DShi, JT, WR, EL, MFA, KVK, MY, AJM-L, JB, PM, EB, GM, AO, HC-P, IG, DO, LLG, and JFD participated in data collection. AJ, MR, PB, QMA, PNN, RL, SH, VR, MFA, DShi, 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, Glysoph Bio, Novartis Pharma, Pfizer, and Vertex.
He has performed consultancy on behalf of Newcastle University for Abbott Laboratories, Acutus Medical, Allergan/Tobira, Blade, BNN Cardio, Cirius, CymaBay, Ecori, EBiO, Eli Lilly & Company, Galmed, Genfit, Gilead, Grunthal, Histolindex, Indalo, Imperial Innovations, Intercept Pharma Europe, Invenitiva, IQVIA, Janssen, Kenes, Madrigal, MedImmune, Metacrine, NewGene, NGMbio, North Sea Therapeutics, Novartis, Novo Nordisk, Pfizer, Posei, Procienco, 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, Integrata Communications, and MedScape, and royalties from Elsevier. AJ is president of Sanay Bio. He has stock options in Indalo, Durect, Tiziana, Ehalaene, and Northsea. He is a consultant to Gilead, Allergan, Bristol-Myers Squibb, Pfizer, Merck, Galmed, Novartis, Novo Nordisk, Lilly, Siemens, Genentech, Boehringer Ingelheim, Glysoph Bio, Genfit, Coherus, Surrozen, Posei, 89 Bio, Perspectum, AstraZeneca, MedImmune, and Lipocine. He is an unpaid consultant to Intercept, Zydus, EchoSensone, Immunon, Madrigal, Galectin, Blade, Plantnt, 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, Genphire, Gilead, Glysoph lso, 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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