# Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial

*Elisa Pose, Laura Napoleone, Ahmed Amin, Daniela Campion, César Jimenez, Salvatore Piano, Olivier Roux, Frank Erhard Uschner, Koos de Wit, Giacomo Zaccherini, Carlo Alessandria, Paolo Angeli, Mauro Bernardi, Ulrich Beuers, Paolo Caraceni, François Durand, Rajeshwar P Mookerjee, Jonel Trebicka, Victor Vargas, Raúl J Andrade, Marta Carol, Judit Pich, Juan Ferrero, Gema Domenech, Marta Llopis, Ferran Torres, Patrick S Kamath, Juan G Abraldes, Elsa Solà, Pere Ginès*

## Summary

**Background** Statins have beneficial effects on intrahepatic circulation and decrease portal hypertension and rifaximin modulates the gut microbiome and might prevent bacterial translocation in patients with cirrhosis. Therefore, this drug combination might be of therapeutic benefit in patients with decompensated cirrhosis. However, there is concern regarding the safety of statins in patients with decompensated cirrhosis. We assessed the safety of two different doses of simvastatin, in combination with rifaximin, in patients with decompensated cirrhosis.

**Methods** We did a double-blind, randomised, placebo-controlled, phase 2 trial in patients with decompensated cirrhosis and moderate-to-severe liver failure from nine university hospitals in six European countries (Italy, France, Holland, Germany, the UK, and Spain). Patients older than 18 years with Child-Pugh class B or C disease were eligible. We randomly assigned patients (1:1:1) to receive either simvastatin 40 mg/day plus rifaximin 1200 mg/day, simvastatin 20 mg/day plus rifaximin 1200 mg/day, or placebo of both medications for 12 weeks. Randomisation was stratified according to Child-Pugh class (B *vs* C) and restricted using blocks of multiples of three. The primary endpoint was development of liver or muscle toxicity, as defined by changes in liver aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), alkaline phosphastase, and creatine kinase. The study is registered with the European Union Clinical Trials Register, 2016-004499-23, and with ClinicalTrials.gov, NCT03150459.

**Findings** The study recruitment period was between July 28, 2017, and Jan 2, 2018. Follow-up finished on March 12, 2018. 50 patients were randomly assigned to simvastatin 40 mg/day plus rifaximin 1200 mg/day (n=18), simvastatin 20 mg/day plus rifaximin 1200 mg/day (n=16), or placebo of both medications (n=16). Six patients (two from each group) were excluded. Therefore, the full analysis set included 44 patients (16 in the simvastatin 40 mg/day plus rifaximin 1200 mg/day group, 14 in the simvastatin 20 mg/day plus rifaximin mg/day group, and 14 in the placebo group). After a safety analyses when the first ten patients completed treatment, treatment was stopped prematurely in the simvastatin 40 mg/day plus rifaximin group due to recommendations by the data safety monitoring board. Patients in the simvastatin 40 mg/day plus rifaximin group showed a significant increase in AST and ALT compared with the placebo group (mean differences between the groups at the end of treatment for AST 130 IU/L [95% CI 54 to 205; p=0·0009] and for ALT 61 IU/L [22 to 100; p=0·0025]. We observed no significant differences at 12 weeks in AST and ALT between the simvastatin 20 mg/day plus rifaximin and placebo group (for AST –14 IU/L [–91 to 64; p=0·728] and for ALT –8 IU/L [–49 to 33; p=0·698]). We observed no significant differences in alkaline phosphatase between the the simvastatin 40 mg/day plus rifaximin or the simvastatin 20 mg/day plus rifaximin groups compared with placebo. Patients in the simvastatin 40 mg/day plus rifaximin group showed an increase in creatine kinase at the end of treatment compared with patients in the placebo group (1009 IU/L [208 to 1809]; p=0·014). We observed no significant changes in creatine kinase in the simvastatin 20 mg/day plus rifaximin group (4·2 IU/L [–804 to 813]; p=0·992). Three (19%) patients in the simvastatin 40 mg/day group developed liver and muscle toxicity consistent with rhabdomyolysis. The number of patients who stopped treatment because of adverse events was significantly higher in the simvastatin 40 mg/day plus rifaximin group (nine [56%] of 16 patients) compared with the other two groups (two [14%] of 14 for both groups; p=0·017). There were no serious unexpected adverse reactions reported during the study.

**Interpretation** Treatment with simvastatin 40 mg/day plus rifaximin in patients with decompensated cirrhosis was associated with a significant increase in adverse events requiring treatment withdrawal, particularly rhabdomyolysis, compared with simvastatin 20 mg/day plus rifaximin. We recommend simvastatin 20 mg/day as the dose to be used in studies investigating the role of statins in patients with decompensated cirrhosis.

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**Institut D'investigacions Biomèdiques August Pi I Sunyer (IDIBAPS)** (E Pose MD, L Napoleone MD, M Carol RN, M Llopis PhD, E Solà PhD, Prof P Ginès PhD) **and Liver Unit, Hospital Vall d'Hebron and Vall d'Hebron Research Unit (VHIR), Universitat Autònoma de Barcelona** (C Jimenez MD, Prof V Vargas MD), **Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEReHD), Barcelona, Spain; Liver Unit, Hospital Clínic De Barcelona, School of Medicine and Health Sciences University of Barcelona, Barcelona, Spain** (E Pose, L Napoleone, E Solà, Prof P Ginès, M Coral RN); **Institute of Liver and Digestive Health, University College London, London, UK** (A Amin MD, R P Mookerjee PhD); **Division of Gastroenterology and Hepatology, Città della Salute e della Scienza Hospital, University of Turin, Turin, Italy** (D Campion MD, C Alessandria PhD); **Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine—DIMED, University of Padova, Padova, Italy** (S Piano PhD, Prof P Angeli PhD); **Hepatology and Liver Intensive Care Unit, Hospital Beaujon, APHP, Clichy, France** (O Roux MD, F Durand PhD); **Department of Internal Medicine I, University of Bonn, Bonn, Germany** (F E Uschner MD, Prof J Trebicka PhD); **Department of Internal**

**Medicine I, Goethe University Frankfurt, Frankfurt, Germany** (F E Uschner, Prof J Trebicka)**; Department of Gastroenterology and Hepatology, University of Amsterdam, Academic Medical Center, University of Amsterdam, Netherlands** (K de Wit MD, Prof U Beuers PhD)**; Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy** (G Zaccherini MD, Prof M Bernardi PhD, P Caraceni PhD)**; European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain** (Prof J Trebicka)**; Institute for Bioengineering of Catalonia, Barcelona, Spain** (Prof J Trebicka)**; Unidad de Gestión Clínica de Enfermedades Digestivas, Instituto de Investigación Biomédica de Málaga—IBIMA, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, CIBERehd, Málaga, Spain** (Prof R J Andrade PhD)**; Clinical Trials Unit, Clinical Pharmacology Department, Hospital Clínic de Barcelona, Barcelona, Spain** (J Pich MD)**; European Clinical Research Infrastructure Network, Paris, France** (J Ferrero MD)**; Biostatistics and Data Management Core Facility, Institut D'Investigacions Biomédiques August Pi i Sunyer, Hospital Clinic Barcelona, Spain** (G Domenech PhD, F Torres PhD)**; Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA** (Prof P S Kamath PhD)**; and Cirrhosis Care Clinic, Division of Gastroenterology (Liver Unit), University of Alberta, CEGIIR, Edmonton, AB, Canada** (Prof J G Abraldes PhD)

Correspondence to:
Prof Pere Ginès, Liver Unit, Hospital Clínic Barcelona, 08036 Barcelona, Spain
**pgines@clinic.cat**

## Research in context

### Evidence before this study

We systematically searched PubMed from inception to Jan 1, 2019, for articles on the effects and safety of statins in patients with cirrhosis with the search terms "cirrhosis" and "statins", "simvastatin" and "muscle toxicity", "liver toxicity", "DILI", and "safety". Of 180 search results, we identified nine studies, including four randomised controlled trials and five cohort studies. In three of the randomised trials, statin therapy was associated with a decrease in portal pressure and no serious adverse events were observed. In, to our knowledge, the largest randomised trial reported to date, treatment with simvastatin 40 mg/day was associated with a significant reduction in mortality compared with placebo, but with an unexpectedly high occurrence of rhabdomyolysis.

We did a search of PubMed focused on rifaximin safety in liver cirrhosis for the same time period as above with the search terms "cirrhosis", "rifaximin", and "safety". Only articles in English were considered. Of 23 search results, we identified four placebo-controlled clinical trials specifically designed to investigate rifaximin safety in patients with cirrhosis. No increased frequency of serious adverse events associated with rifaximin therapy was reported compared with placebo or control groups.

### Added value of this study

To our knowledge, this is the first study to investigate the safety of different doses of simvastatin in combination with rifaximin in a randomised, placebo-controlled trial in patients with advanced decompensated cirrhosis. Treatment with simvastatin at a dose of 40 mg/day in combination with rifaximin resulted in an unexpectedly high proportion of adverse events, particularly liver and muscle toxicity. By contrast, simvastatin 20 mg/day plus rifaximin was safe and not associated with an increased risk of adverse events compared with placebo.

### Implications of all the available evidence

This trial provides evidence from a specifically designed study that simvastatin at 40 mg/day in combination with rifaximin in patients with advanced decompensated cirrhosis is associated with a high proportion of adverse events. This information is of value for the design of future studies investigating the effects of simvastatin on disease progression and survival in patients with decompensated cirrhosis. From a clinical perspective, this trial provides evidence in favour of using low doses of statins in patients with decompensated cirrhosis for safety reasons. In the current setting of increasing prevalence of cirrhosis due to non-alcoholic fatty liver disease, which is frequently associated with dyslipidaemia, this information could be of clinical value.

## Introduction

There is accumulating evidence that statins have beneficial effects in cirrhosis.[1,2] This evidence is mainly derived from retrospective cohort studies, some of which included large numbers of patients, and a small number of randomised clinical trials.[3–6] Results of cohort studies have consistently shown that patients with cirrhosis who received treatment with statins to reduce cholesterol had a lower risk of decompensation and death compared with patients who did not receive statins. The risk of development of hepatocellular carcinoma was also lower in patients who received statins in one study.[2] The favourable effects of statins were shown with propensity score analyses and persisted after adjustment for the most important predictive variables.[2] To date, few randomised trials have been designed to assess the beneficial effects of statins in cirrhosis. These studies have shown beneficial effects in portal hypertension[3,4,6] and survival.[5] Treatment with statins (simvastatin 40 mg/day, in addition to standard treatment for cirrhosis), was associated with a significant reduction in portal pressure gradient compared with placebo.[3,4] Moreover, a 2016 randomised, double-blind study showed that simvastatin 40 mg/day improved survival in patients with cirrhosis who recovered from variceal bleeding.[5] The mechanism(s) by which statins exert their potential beneficial effects in patients with cirrhosis is not known, but is thought to be related to an improvement in intrahepatic circulation through an increase in nitric oxide synthesis[7] or due to anti-inflammatory effects.[8] In cirrhosis, there is enhanced systemic inflammation, which increases as the disease progresses and is associated with poor prognosis.[9] Nonetheless, despite positive findings, the 2018 clinical guidelines do not recommend the use of statins in clinical practice because there is only one positive randomised trial with survival endpoints; therefore, results of further trials are awaited before statins can be advocated for use in clinical practice.[10]

Rifaximin is a broad-spectrum, poorly-absorbed antibiotic that is effective in patients with cirrhosis to prevent recurrent hepatic encephalopathy.[11] A 2019 retrospective cohort study suggested that rifaximin could also be effective in preventing other portal hypertension-related complications, yet conclusive evidence is lacking.[12] The mechanisms by which rifaximin exerts its beneficial effects in patients with cirrhosis have not been completely elucidated, but might be related, at least in part, to modulation of the gut microbiome and reduction in bacterial translocation;[13] however, these effects have not been confirmed in all studies.[14] Therefore, considering the different mechanisms of action of statins and

rifaximin, it would be of interest to explore the potential beneficial effects of this combined therapy in the prevention of progression of decompensated cirrhosis. However, the safety of this combination in patients with decompensated cirrhosis is important and has so far not been assessed. Rifaximin has been evaluated in many studies, from phase 2 to phase 4, including in large numbers of patients with decompensated cirrhosis and no clinically significant safety issues have been observed.[15] Rifaximin does not seem to increase the risk of infections by multidrug-resistant bacteria or have clinically significant interactions with other drugs, despite its potential effect on CYP3A4. Only drugs that inhibit p-glycoprotein and organic anion-transporting polypeptides (OATPs), such as ciclosporin, have been shown to increase systemic exposure to rifaximin. Statins are thought to be safe in patients with chronic liver disease without cirrhosis and in patients with compensated cirrhosis, but there is a paucity of information about the safety of statins in patients with decompensated cirrhosis due to possibly impaired metabolism of these drugs in the setting of liver failure.[3–6] In four prospective studies,[2] most included patients had either compensated or mild decompensated cirrhosis. In, to our knowledge, the largest randomised trial to date of statins in patients with decompensated cirrhosis, two (3%) of 69 patients treated with simvastatin 40 mg/day developed severe rhabdomyolysis, an incidence that was considered higher than expected.[5]

This study was designed to investigate the safety of two different doses of simvastatin in combination with rifaximin compared with placebo in patients with decompensated cirrhosis. This study is part of the LIVERHOPE project, which aims to assess the efficacy of simvastatin in combination with rifaximin to prevent progression of cirrhosis and development of acute-on-chronic liver failure.

## Methods

### Study design and participants

The LIVERHOPE-SAFETY study was a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial, which included patients with decompensated cirrhosis and moderate-to-severe liver failure from nine university hospitals in six European countries (Italy, France, Holland, Germany, the UK, and Spain).

Patients with decompensated cirrhosis were considered eligible for the study if they met the following inclusion criteria: older than 18 years, cirrhosis defined by standard clinical or histological criteria, Child-Pugh class B or C up to 12 points, and negative pregnancy test and agreement to use highly effective contraceptive methods for women of child-bearing potential. Exclusion criteria were: patients on the waiting list for liver transplantation, patients with acute-on-chronic liver failure (defined by the CANONIC study[16]), serum creatinine 2 mg/dL or greater, serum bilirubin greater than 5 mg/dL, international normalised ratio (INR) greater than 2·5, creatine kinase at inclusion of at least 50% above the upper limit of the normal (ULN), gastrointestinal bleeding or active bacterial infection within 15 days before study inclusion, current overt hepatic encephalopathy, HIV infection, hepatocellular carcinoma outside Milan criteria, antiviral treatment for hepatitis C virus in the previous 6 months, history of myopathy, treatment with potent inhibitors of CYP3A4 enzyme, treatment with drugs with potential interactions with simvastatin, history of extrahepatic disease with impaired short-term prognosis, extrahepatic tumours or haematological disorders, history or increased risk of intestinal obstruction, pregnancy or breastfeeding, inclusion in other clinical trials in the previous month, current alcohol consumption of more than three units per day, psychiatric or social conditions precluding adequate understanding or compliance with the study, severe alcoholic hepatitis requiring corticosteroid therapy, refusal to give informed consent, current use or contraindications to simvastatin or rifaximin or conditions that could increase the risk of adverse events related to these drugs, and known hypersensitivity to rifaximin or simvastatin. Patients gave written informed consent for inclusion in the study.

The study was approved by the regulatory agencies of the six countries involved and by the institutional review board of each participating centre.

### Randomisation and masking

We randomly assigned patients (1:1:1) to receive one of two different doses of simvastatin with rifaximin, or identical placebo of both medications. Centralised computer-generated randomisation was used through an electronic case report form. Randomisation was stratified according to Child-Pugh class (B *vs* C) using the PROC PLAN of the SAS system and restricted using blocks of multiples of three. Masking was achieved by administration of pills to the three groups that were identical in number and appearance. Neither the investigators, nor the monitors had access to the unblinding list, which was used only for unmasking by the data safety monitoring board (DSMB). Otherwise, the unblinding list was unavailable to invstigators, monitors, or statistitians at any other point in the study. Unblinding was not expected until all subjects had completed the study and the database had been locked after data completion and verification. However, it was foreseen that a specific patient could be unblinded, if needed, as judged by the investigator in emergent cases with side-effects possibly related to study medication.

### Procedures

Patients were randomly assigned to receive oral simvastatin 40 mg/day (Alfasigma; Bologna, Italy) plus rifaximin 1200 mg/day (Alfasigma), simvastatin 20 mg/day plus rifaximin 1200 mg/day, or identical placebo of both medications for 12 weeks.

Patients received simvastatin 40 mg (two 20 mg tablets) per day plus rifaximin 400 mg every 8 h, or simvastatin 20 mg (one 20 mg tablet and one placebo tablet) per day plus rifaximin 400 mg every 8 h; patients from the placebo group received placebo of simvastatin (two tablets per day) plus placebo of rifaximin (one tablet every 8 h). The pharmaceutical formulation of rifaximin (rifaximin-extended intestinal release 400 mg) used in this study was slightly different from the commercially available product, in that rifaximin was coated with a gastro-resistant polymer that allows a higher bioavailability of the drug in the intestine compared with the commercial formulation. A group of patients treated only with rifaximin was not considered necessary given the extensive evidence base for rifaximin use in patients with decompensated cirrhosis and the few drug-related adverse events observed.

Treatment was started after the baseline visit and was given for 12 weeks. Study visits were every 2 weeks; standard clinical and analytical data were collected and complications of cirrhosis and treatment-related adverse events, if any, were assessed and registered. Compliance with study medication was assessed at each visit by self-reporting and confirmed by counting the pills returned by patients at the end of the treatment period. Individuals with a compliance of less than 70% of the total supplied study medication were excluded from the per-protocol analysis. Study medication was permanently withdrawn if patients developed liver or muscle toxicity. Treatment was also permanently withdrawn in patients who developed hepatic encephalopathy and met the criteria for treatment with rifaximin according to the European Association for the Study of the Liver guidelines,[17] and in those patients with severe treatment-related side-effects, according to the judgment of the investigator. Complications of cirrhosis occurring during the study period were treated according to international guidelines.[10]

The main safety outcome measures in patients included in the study were monitored by an independent DSMB, comprising a group of experts. The study followed regulatory recommendations regarding the functions and procedures of this committee.[18] The DSMB held a meeting after completion of the study by the first ten patients. As a conclusion of this meeting, the DSMB provided a written report in which they recommended stopping the study medication in the simvastatin 40 mg/day plus rifaximin 1200 mg/day group, without breaking the blinding procedure. The investigators decided to fully implement the advice of the DSMB and study treatment was discontinued in all patients allocated to the simvastatin 40 mg/day plus rifaximin 1200 mg/day group, but continued in the other two groups.

### Outcomes

As this was a safety study, the primary endpoints were based on the most common side-effects related to statin therapy. No efficacy endpoints were assessed. The primary endpoint was the development of liver or muscle toxicity. Liver toxicity was evaluated by comparing increases from baseline in aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and alkaline phosphatase between the three groups during treatment; additionally, we assessed the proportion of patients who developed a three-times increase in aminotransferase levels or a two-times increase in alkaline phosphatase levels from baseline, as a modification for patients with decompensated cirrhosis according to the internationally accepted criteria for drug-induced liver injury case definition.[19] We evaluated muscle toxicity by comparing changes from baseline in creatine kinase during treatment and also by the proportion of patients who developed an increase in creatine kinase during treatment to a final value at least five-times the ULN. If patients reached the primary endpoint of muscle toxicity, study medication was withdrawn. In cases where patients reached the primary endpoint of liver toxicity, blood tests were repeated after 2 days, and if the increase in aminotransferases or alkaline phosphatase persisted, study medication was also withdrawn.

Secondary endpoints were the development of muscle toxicity at weeks 2, 4, 6, 8, 10, and 12, changes from baseline in plasma renin concentration, serum aldosterone, plasma norepinephrine, and plasma copeptin at weeks 4, 8, and 12, changes from baseline in a large array of plasma cytokines including, but not limited to, VCAM-1, VEGF-A, fractalkine, MIP-1α, eotaxin, IP-10, RANTES, GM-CSF, IL-1β, IL-2, ICAM-1, MCP-1, L-6, and IL-8, as well as an oxidised form of albumin, human nonmercaptalbumin-2 at weeks 4, 8, and 12, changes from baseline in plasma biomarkers FABP4 and CD-163 and urine biomarkers NGAL, IL-18, MCP-1, osteopontin, and albumin at weeks 4, 8, and 12, changes in blood levels of bacterial DNA or bacterial products at weeks 4, 8, and 12, the proportion of patients developing treatment-related adverse events in each study group, and assessment of the relationship between muscle toxicity symptoms and rs4149056 polymorphism of *SLCO1B1* (the existence of this polymorphism has been reported to be associated with an increased risk of muscle toxicity in patients treated with simvastatin[20]). The results of the following secondary endpoints are not presented in this Article and will be presented elsewhere: changes from baseline in plasma renin concentration, serum aldosterone, plasma norepinephrine, and plasma copeptin at weeks 4, 8, and 12, changes from baseline in plasma cytokines at weeks 4, 8, and 12, changes from baseline in plasma biomarkers FABP4 and CD-163 and urine biomarkers NGAL, IL-18, MCP-1, osteopontin, and albumin at weeks 4, 8, and 12, and changes in bacterial DNA or bacterial products at weeks 4, 8, and 12.

Adverse events related or unrelated to study medication were closely recorded. Severe adverse events were reported to a specific system (Drug Safety Office, Clinical Research and Clinical Trials Unit, Hospital Universitario

Virgen del Rocío, Seville, Spain), which informed the principal investigators of all severe adverse events that occurred during the treatment period.

### Statistical analysis

We considered 15 patients per study group to be sufficient for this phase 2 exploratory trial. According to the binomial distribution, the study would have 80% power to detect at least one muscle toxicity adverse event if the actual incidence in the population was more than 10%. However, for the sake of sensitivity in dose selection, the primary outcome was focused on the detection of baseline changes versus placebo of aminotransferases, alkaline phosphatase, and creatine kinase, which were expected to be more sensitive than the incidence of limiting adverse events. Because of the high uncertainty due to the paucity of existing data in this population and the exploratory nature of this trial, no further statistical analyses for calculation of sample size were done.

We summarised categorical variables by counts and proportions and continuous variables by mean (SD), as appropriate. We analysed longitudinal continuous variables by assessing the individual laboratory parameters measured to evaluate toxicity (AST, ALT, alkaline phosphatase, and creatine kinase) with mixed models for repeated measurements (MMRM), including the Child-Pugh stratum and the baseline measurement. We used Fischer's exact test to compare categorical variables.

We handled missing data for longitudinal variables through the MMRM strategy, which relies on the missing at random assumption. We handled categorical variables with a worst-case imputation strategy and any treatment discontinuation due to relevant safety issues was considered a failure. Since the objective of this exploratory trial was to assess and discard safety signals, no multiplicity adjusting strategy was planned. The level of significance was established at the two-sided 5% level.

We did intention-to-treat and per-protocol analyses for the primary endpoint. Results are presented for the intention-to-treat population. The study was monitored by the clinical trials units of the European Clinical Research Infrastructure Network (Paris, France) and the statistical analysis was done by the Medical Statistics Core Facility of the Institut d'Investigacions Biomèdiques August Pi-Sunyer (Barcelona, Spain).

All analyses were done using SAS version 9.4 software. The study was registered with the European Union Clinical Trials Register, 2016-004499-23, and with ClinicalTrials.gov, NCT03150459.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

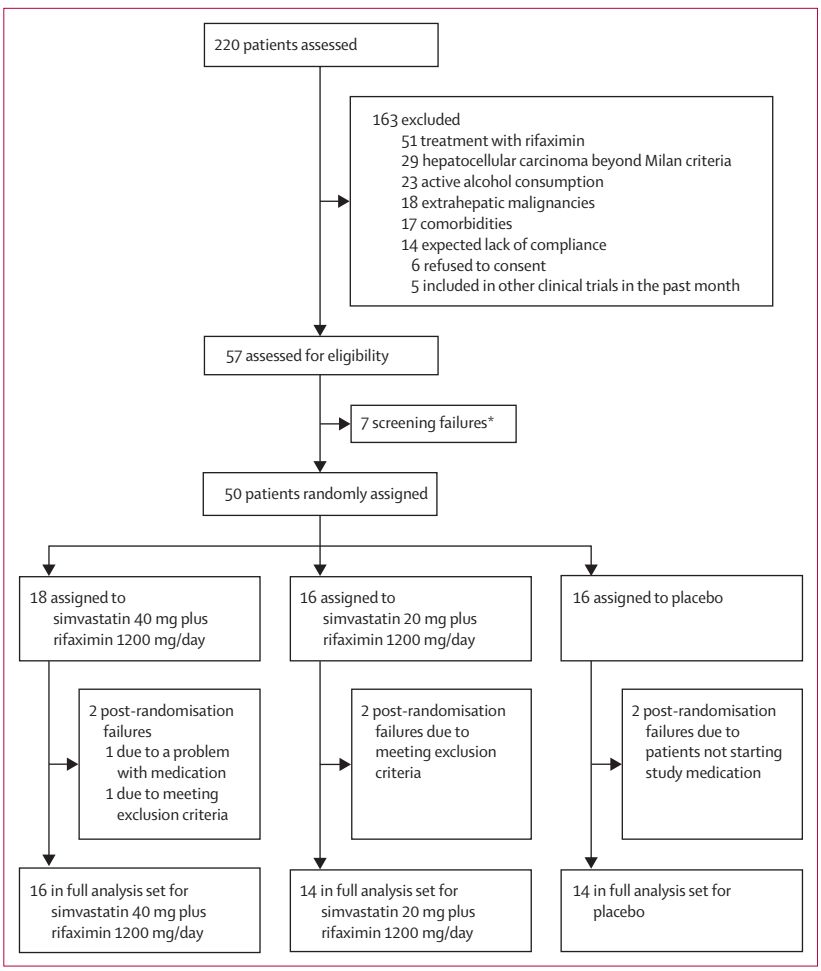


***Figure 1:*** **Trial profile**
*Screening failures were due to patients meeting exclusion criteria after assessment for eligibility.

## Results

The study recruitment period started on July 28, 2017, and finished on Jan 2, 2018. Follow-up finished on March 12, 2018. 220 patients were assessed and 163 were excluded because they met exclusion criteria or denied consent (figure 1). The most common reasons for exclusion were current treatment with rifaximin or hepatocellular carcinoma. Seven (12%) of the remaining 57 patients were excluded because of screening failure. Therefore, 50 patients were randomly assigned to receive treatment with simvastatin 40 mg/day plus rifaximin 1200 mg/day (n=18), simvastatin 20 mg/day plus rifaximin 1200 mg/day (n=16) or placebo (n=16). Six patients (two from each study group) were excluded, three because they did not meet the inclusion criteria, two because they did not initiate the study medication, and one because of a problem with supply of the study medication. Therefore, the full analysis set (ie, intention-to-treat population) included 44 patients (16 patients in the simvastatin 40 mg/day plus rifaximin 1200 mg/day group, 14 patients in the simvastatin 20 mg/day plus rifaximin mg/day

| | Simvastatin 40 mg/day plus rifaximin 1200 mg/day (n=16) | Simvastatin 20 mg/day plus rifaximin 1200 mg/day (n=14) | Placebo (n=14) |
|---|---|---|---|
| Age, years | 60 (12) | 49 (11) | 59 (12) |
| Sex | | | |
| Female | 4 (25%) | 3 (21%) | 5 (36%) |
| Male | 12 (75%) | 11 (79%) | 9 (64%) |
| Cause of cirrhosis | | | |
| Alcohol | 9 (56%) | 9 (64%) | 9 (64%) |
| Other* | 7 (44%) | 5 (36%) | 5 (36%) |
| Previous complications of cirrhosis | | | |
| Ascites | 12 (75%) | 11 (79%) | 13 (93%) |
| Variceal bleeding | 4 (25%) | 4 (29%) | 6 (43%) |
| Hepatic encephalopathy | 3 (19%) | 4 (29%) | 6 (43%) |
| Spontaneous bacterial peritonitis | 0 | 2 (14%) | 2 (14%) |
| Laboratory data | | | |
| Bilirubin (mg/dL) | 2·5 (1·5) | 2·7 (1·3) | 2·1 (1·1) |
| Albumin (g/L) | 32 (5) | 33 (6) | 34 (8) |
| Serum creatinine (mg/dL) | 1·0 (0·5) | 0·8 (0·2) | 1·1 (0·3) |
| Serum sodium (mEq/L) | 134 (5) | 136 (4) | 137 (5) |
| Leukocytes (×10$^9$ per L) | 3·7 (0·7) | 3·6 (0·6) | 3·7 (0·6) |
| Platelets (×10$^9$ per L) | 113 (54) | 104 (66) | 119 (50) |
| Child-Pugh score | | | |
| B | 12 (75%) | 10 (71%) | 10 (71%) |
| C | 4 (25%) | 4 (29%) | 4 (29%) |
| Model for end-stage liver disease score | 14 (3) | 14 (3) | 13 (3) |

Data are mean (SD) or n (%). *Simvastatin 40 mg/day plus rifaximin 1200 mg/day group: two cryptogenic, two non-alcoholic steatohepatitis, two hepatitis C, and one autoimmune hepatitis; simvastatin 20 mg/day plus rifaximin 1200 mg/day group: one hepatitis C, one hepatitis B, one non-alcoholic steatohepatitis, one autoimmune hepatitis, and one cryptogenic; and placebo group: three non-alcoholic steatohepatitis, one cryptogenic, and one hepatitis C.

***Table 1:*** **Baseline characteristics**

See Online for appendix

group, and 14 patients in the placebo group). The median follow-up period was 84 days (IQR 36–84). Most patients were compliant with the study medication (mean compliance 91% for simvastatin, SD 19; and 90% for rifaximin, SD 15). Only four patients (three in the simvastatin 40 mg/day plus rifaximin group and one in the simvastatin 20 mg/day plus rifaximin group) were excluded from the per-protocol analysis because of lack of compliance with the study medication. Three patients were excluded due to follow-up of less than 2 weeks (two in the simvastatin 40 mg/day group and one in the simvastatin 20 mg/day group). The per protocol population thus consisted of 37 patients. Baseline demographic, clinical, and analytical data were similar in the three groups, except for a younger mean age in the simvastatin 20 mg/day plus rifaximin group and a slightly higher frequency of hepatic encephalopathy and variceal bleeding in the placebo group compared with the other two groups (table 1). Treatment was stopped prematurely in the simvastatin 40 mg/day plus rifaximin group because of the recommendation of the DSMB on the basis of safety issues. At the time of this decision (meeting held on Jan 1, 2018, and treatment stopped 5 days later), all patients except one in this group had stopped treatment because of severe adverse events (grade 3) or had already completed the treatment period (seven patients completed the study period and nine stopped treatment because of adverse events after a mean of 8 weeks from starting treatment), therefore treatment only had to be stopped in one patient.

Patients in the simvastatin 40 mg/day plus rifaximin group showed a significant increase in AST and ALT compared with placebo (mean differences between the groups at the end of treatment [week 12 for patients that completed the study period and the last visit for patients who prematurely stopped study medication] for AST 130 IU/L [95% CI 54 to 205; p=0·0009] and for ALT 61 IU/L [22 to 100; p=0·0025]; table 2).

By contrast, we observed no significant differences at the end of treatment visit in AST and ALT between the simvastatin 20 mg/day plus rifaximin and placebo groups (mean differences between the groups for AST –14 IU/L [95% CI –91 to 64; p=0·728] and for ALT –8 IU/L [–49 to 33; p=0·698]; table 2).

Patients in the simvastatin 40 mg/day plus rifaximin group had significantly higher mean AST and ALT at the end of the treatment visit compared with patients from the simvastatin 20 mg/day plus rifaximin group (mean differences between the groups for AST 143 IU/L [66 to 220; p=0·0003] and for ALT 69 IU/L [29 to 109; p=0·0009]; table 2; figure 2; appendix p 1). We observed no significant changes in alkaline phosphatase between the simvastatin 40 mg/day plus rifaximin group or the simvastatin 20 mg/day plus rifaximin group, versus the placebo group. Three (19%) of 16 patients in the simvastatin 40 mg/day plus rifaximin group had an increase in AST or ALT of more than three times the ULN. One patient had a marked increase in aminotransferases (peak values for ALT 696 IU/L and AST 1350 IU/L) consistent with drug-induced liver injury related to simvastatin, which was associated with an increase in INR from 1·4 to 1·9. We found no other abnormalities and the patient did not develop complications of cirrhosis. Abnormal liver tests returned to baseline values 2 months after the patient stopped the study medication. The other two patients had moderate increases in ALT and AST (peak ALT 141 IU/L and 147 IU/L; peak AST 426 IU/L and 251 IU/L), without changes in other liver tests. Aminotransferase levels returned to baseline values 8 weeks and 2 weeks after stopping the study medication, respectively. All three patients who developed increases in aminotransferases also had increases in creatine kinase indicative of muscle toxicity. Only one (7%) of 14 patients in the simvastatin 20 mg/day plus rifaximin group had an increase in serum ALT and AST of more than three times the ULN at week 6 (peak ALT 206 IU/L, peak AST 143 IU/L), with no changes in other liver tests; ALT and AST returned to normal values after 48 h without stopping the study medication.

| | Simvastatin 40 mg/day plus rifaximin 1200 mg/day (n=16) | Simvastatin 20 mg/day plus rifaximin 1200 mg/day (n=14) | Placebo (n=14) |
|---|---|---|---|
| **Aspartate aminotransferase (IU/L)** | | | |
| Baseline | 52 (22) | 60 (30) | 43 (15) |
| End of treatment* | 191 (138 to 245) | 48 (–9 to 105) | 62 (7 to 116) |
| End of treatment* change from baseline [relative change] | 139 (86 to 193) [270%] | –4 (–61 to 53) [–6%] | 10 (–45 to 64) [23%] |
| Difference *vs* placebo at the end of treatment | 130 (54 to 205); p=0·0009 | –14 (–91 to 64); p=0·728 | .. |
| Simvastatin 40 mg/day plus rifaximin 1200 mg/day *vs* simvastatin 20 mg/day plus rifaximin 1200 mg/day at the end of treatment | 143 (66 to 220); p=0·0003 | .. | .. |
| **Alanine aminotransferase (IU/L)** | | | |
| Baseline | 32 (16) | 40 (33) | 26 (16) |
| End of treatment* | 96 (68 to 123) | 27 (–3 to 59) | 35 (6 to 64) |
| End of treatment* change from baseline [relative change] | 64 (36 to 91) [201%] | –5 (–35 to 25) [–13%] | 3 (–26 to 32) [10%] |
| Difference *vs* placebo at the end of treatment | 61 (22 to 100); p=0·0025 | –8 (–49 to 33); p=0·698 | .. |
| Simvastatin 40 mg/day plus rifaximin 1200 mg/day *vs* simvastatin 20 mg/day plus rifaximin 1200 mg/day at the end of treatment | 69 (29 to 109); p=0·0009 | .. | .. |
| **Alkaline phosphatase (IU/L)** | | | |
| Baseline | 148 (70) | 146 (57) | 151 (45) |
| End of treatment* | 145 (133 to 158) | 145 (131 to 158) | 141 (129 to 154) |
| End of treatment* change from baseline [relative change] | 3 (–9 to 15) [2%] | 2 (–11 to 16) [2%] | –1 (–14 to 12) [–1%] |
| Difference *vs* placebo at the end of treatment | 4 (–14 to 22); p=0·655 | 3 (–15 to 22); p=0·714 | .. |
| Simvastatin 40 mg/day plus rifaximin 1200 mg/day *vs* simvastatin 20 mg/day plus rifaximin 1200 mg/day at the end of treatment | 1 (–17 to 18); p=0·948 | .. | .. |
| **Creatine kinase (IU/L)** | | | |
| Baseline | 122 (96) | 106 (74) | 67 (37) |
| End of treatment* | 1160 (596 to 1725) | 156 (–443 to 755) | 152 (–426 to 729) |
| End of treatment* change from baseline [relative change] | 1060 (496 to 1624) [870%] | 56 (–543 to 654) [147%] | 51 (–526 to 629) [228%] |
| Difference *vs* placebo at the end of treatment | 1009 (208 to 1809); p=0·014 | 4·2 (–804 to 813); p=0·992 | .. |
| Simvastatin 40 mg/day plus rifaximin 1200 mg/day *vs* simvastatin 20 mg/day plus rifaximin 1200 mg/day at the end of treatment | 1004 (192 to 1817); p=0·016 | .. | .. |

Data are mean (SD) or mean (95% CI), unless otherwise indicated. *End of treatment values represent values at week 12 or last laboratory values available before study withdrawal due to side-effects.

***Table 2:*** **Aminotransferases and alkaline phosphatase levels at baseline and at the end of treatment**

No further changes in AST or ALT were observed in this patient during the remaining treatment period. No patients in the placebo group had an increase in AST or ALT of more than three times the ULN during treatment.

Patients in the simvastatin 40 mg/day plus rifaximin group showed a significant increase in creatine kinase during treatment compared with patients in the placebo group (mean 1009 IU/L [95% CI 208 to 1809]; p=0·014). By contrast, we observed no significant changes in creatine kinase in the simvastatin 20 mg/day plus rifaximin group compared with the placebo group (4·2 IU/L [–804 to 813]; p=0·992; table 2; figure 3). Creatine kinase levels at the end of treatment were higher in the simvastatin 40 mg/day plus rifaximin group compared with the simvastatin 20 mg/day plus rifaximin group (1004 IU/L [192 to 1817]; p=0·016).

Three (19%) of 16 patients in the simvastatin 40 mg/day plus rifaximin group had an increase in creatine kinase to a final value more than five times the ULN, compared with no patients in the simvastatin 20 mg/day plus rifaximin or placebo groups (table 3). No patients in the study developed renal failure associated with muscle toxicity. Of the 16 patients in the simvastatin 40 mg/day plus rifaximin group, one (8%) of 12 patients with Child-Pugh B disease and two (50%) of four patients with Child-Pugh C disease developed muscle toxicity.

The number of patients developing de-novo muscle symptoms (eg, cramps, aches, and weakness) without meeting the criteria of muscle toxicity was not significantly different among groups (five patients in the simvastatin 40 mg/day plus rifaximin group, six patients in the simvastatin 20 mg/day plus rifaximin group, and three patients in the placebo group; p=0·424).

In the whole study population, 13 (30%) of 44 patients had CT heterozygosis for the rs4149056 polymorphism of *SLCO1B1*. No patient was a homozygote for the

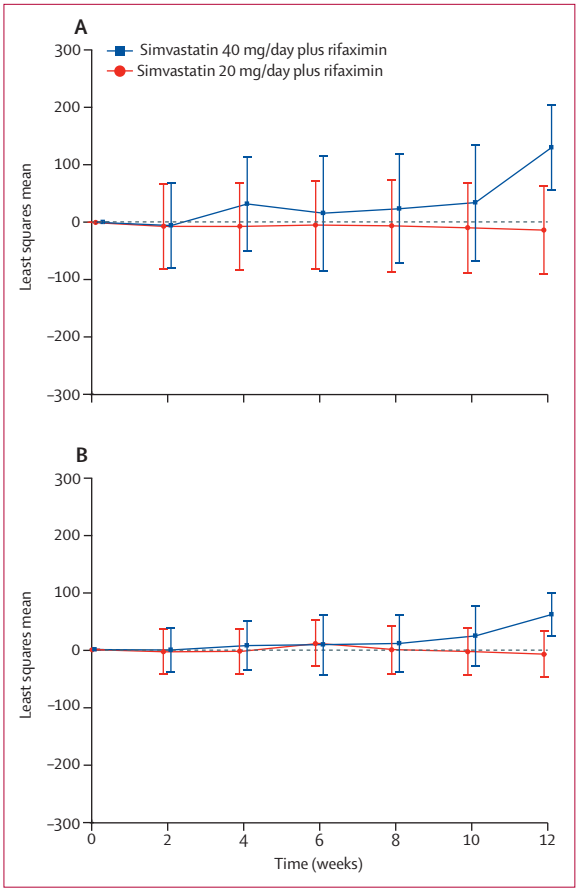


***Figure 2:*** **Changes in aspartate aminotransferase (A) and alanine aminotransferase (B) in the simvastatin 40 mg/day plus rifaximin 1200 mg/day group and simvastatin 20 mg/day plus rifaximin 1200 mg/day group compared with placebo**
Units are IU/L. 0 represents no change compared with placebo. Error bars represent 95% CIs.

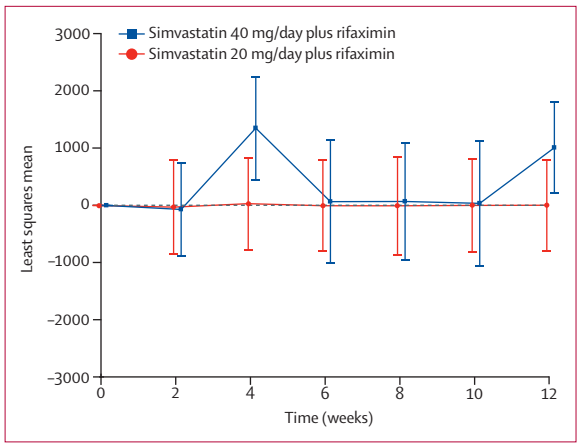


***Figure 3:*** **Changes in creatine kinase in the simvastatin 40 mg/day plus rifaximin 1200 mg/day group and simvastatin 20 mg/day plus rifaximin 1200 mg/day group compared with placebo**
Units are IU/L. 0 represents no change compared with placebo. Error bars represent 95% CIs.

CC polymorphism. The distribution of the CT variant among the three treatment groups was similar (four [25%] of 16 patients in the simvastatin 40 mg/day plus rifaximin group, five [36%] of 14 patients in the simvastatin 20 mg/day plus rifaximin group, and four [29%] of 14 patients in the placebo group). We observed no relationship between both muscle toxicity or muscle symptoms and the CT variant of rs4149056 polymorphism of *SLCO1B1*; four (29%) of 14 patients with muscle symptoms reported as adverse events during the study period had the *SLCO1B1* rs4149056 polymorphism versus nine (30%) of 30 patients who did not have muscle symptoms (p=0·244). Two (67%) of three patients in the simvastatin 40 mg/day group who had muscle toxicity that presented as rhabdomyolysis during the study had the *SLCO1B1* rs4149056 polymorphism versus 11 (27%) of 41 patients who did not develop muscle toxicity (p=0·082).

As expected for a study in patients with advanced cirrhosis, the number of patients with adverse events during follow-up was high (appendix p 3). Overall, 36 (82%) of 44 patients reported a total of 107 adverse events. Patients in the simvastatin 40 mg/day plus rifaximin group had more adverse events and serious adverse events, and more treatment-related serious adverse events, than did patients in the simvastatin 20 mg/day plus rifaximin group and placebo group. The number of patients who stopped treatment because of adverse events was significantly higher in the simvastatin 40 mg/day plus rifaximin group (nine [56%] of 16 patients) compared with the other two groups (two [14%] of 14 for both groups; p=0·017). There were no serious unexpected adverse reactions reported during the study.

## Discussion

In the LIVERHOPE-SAFETY trial, treatment with simvastatin 40 mg/day plus rifaximin for 12 weeks in patients with decompensated cirrhosis was associated with a significant increase in AST, ALT, and creatine kinase, whereas no changes in these parameters were observed in the simvastatin 20 mg/day plus rifaximin or placebo groups. Moreover, patients treated with simvastatin 40 mg/day plus rifaximin had a high incidence of liver and muscle toxicity.

To our knowledge, the safety of statins in patients with cirrhosis has been assessed in four randomised controlled trials, which aimed to investigate the efficacy of statins in reducing portal hypertension (three trials)[3,4,6] or a combined endpoint of reducing variceal bleeding and mortality (one trial).[5] No liver or muscle toxicity was observed in three of these studies. However, the sample sizes in these studies were very small or treatment was given for only 1 month, which could have accounted for the absence of side-effects.[3,4,6] The other study was a multicentre, double-blind, placebo-controlled, randomised

| | Age (years) | Sex | Child-Pugh class | Baseline serum bilirubin (mg/dL) | Weeks from start | Muscle symptoms | Peak creatinine kinase values (IU/L) | Hospitalisation (days) | Peak ALT and AST values (IU/L) | Time to resolution |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 60 | Male | C10 | 4·7 | 12 | Moderate muscle pain in upper and lower limbs | 7432 | 4 | AST 696; ALT 1350 | 2 weeks to normalisation of creatinine kinase; 8 weeks to normalisation of AST and ALT |
| 2 | 64 | Female | B7 | 3·1 | 4 | Moderate muscle pain and weakness in lower limbs | 11 921 | .. | AST 426; ALT 141 | 9 weeks to normalisation of creatinine kinase; 8 weeks to normalisation of AST and ALT |
| 3 | 52 | Male | C11 | 4·5 | 3 | Severe muscle pain in lower limbs | 2888 | 14 days* | AST 251; ALT 147 | 2 weeks to normalisation of creatinine kinase and AST and ALT |

ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Part of the duration of hospitalisation was due to concomitant spontaneous bacterial peritonitis.

***Table 3:*** **Characteristics of the three patients who developed muscle and liver toxicity in the group of patients treated with simvastatin 40 mg/day and rifaximin 1200 mg/day**

trial of 147 patients treated with simvastatin 40 mg/day or placebo and followed up for up to 2 years.[5] In this study, two (3%) of 69 patients treated with simvastatin developed clinically relevant muscle toxicity that required treatment withdrawal.[5] In the current study, three (19%) of 16 patients (two Child-Pugh class C and one Child-Pugh class B) treated with simvastatin 40 mg/day plus rifaximin developed muscle toxicity associated with liver toxicity, which required treatment discontinuation. Given that criteria for liver and muscle toxicity coincided in these three patients, we cannot rule out that the increase in AST and ALT could be related, at least in part, to muscle necrosis. Therefore, the liver origin of our observed increased AST and ALT cannot be established convincingly. Nevertheless, one of the patients in our study developed a concomitant increase in INR, which suggests that liver toxicity in addition to muscle toxicity was present in this case. By contrast, no cases of muscle toxicity and only one case of transient mild liver toxicity, not requiring discontinuation of treatment, was observed in patients treated with simvastatin 20 mg/day plus rifaximin. These findings suggest that side-effects related to simvastatin treatment in the setting of concurrent rifaximin therapy in patients with decompensated cirrhosis are dose-dependent and that 20 mg/day is safer than 40 mg/day. In this regard, it seems pertinent to mention that large studies in the general population without liver disease showed that simvastatin 80 mg/day was associated with a high frequency of muscle toxicity, which led to the concept that the safe dose in the general population is 40 mg/day.[21]

The reason for the higher frequency of side-effects in the current trial compared with previous studies is unclear. A possible explanation could be the greater severity of cirrhosis in the patients in the current study. All patients in our study had decompensated cirrhosis and were Child-Pugh class B or C, whereas a substantial proportion of the patients included in previous studies had compensated cirrhosis without previous complications of the disease, indicating lower disease severity. Compared with the study by Abraldes and colleagues,[5] patients included in the current study had a higher frequency of ascites (39% *vs* 82%) and hepatic encephalopathy (3% *vs* 30%), higher Model for End-stage Liver Disease score (median 10 *vs* 14), and higher frequency of Child-Pugh class C (14% *vs* 27%). As simvastatin undergoes extensive biotransformation in the liver and is eliminated through bile, severity of cirrhosis could affect exposure to the drug, which might be responsible, at least in part, for the higher frequency of adverse events observed in our study.[22] Several mechanisms could theoretically lead to impaired biotransformation of simvastatin in the presence of advanced cirrhosis, including a reduction in the metabolic activity of CYP3A4,[23] one of the key enzymes involved in simvastatin metabolism, and impaired transport of simvastatin to bile through MRP2, a canalicular membrane transporter that mediates transport of bilirubin conjugate to bile.[22] However, rifaximin treatment could theoretically induce CYP3A4 in in-vitro studies and thus compensate for the reduced activity of CYP3A4 in cirrhosis, but this possible effect on CYP3A4 was not confirmed in in-vivo studies.[24,25] In the current study, all three patients who had muscle and liver toxicity had increased baseline serum bilirubin. Side-effects were apparently not related to the presence or frequency of polymorphisms of the gene *SLCO1B1*, which encodes OATP1B1.

Another potential explanation for the high frequency of adverse events observed in our study could be a toxic effect of rifaximin, either by itself or by increasing the toxicity of simvastatin. The rifampin component of rifaximin could theoretically induce muscle toxicity through mitochondrial oxidative stress and perhaps act synergistically with statins. This potential mechanism was suggested based on a report of a chronological relationship between treatment with rifaximin and rhabomyolysis in a patient with cirrhosis.[26] However, the possibility of muscle toxicity due to rifaximin seems remote because of the following reasons: no cases of rhabomyolysis were reported in a pivotal trial of rifaximin for prevention of recurrent hepatic encephalopathy and its long-term follow-up;[15] as of July, 2019, only two cases of rhabdomyolysis possibly related to rifaximin have

been recorded in the post-marketing safety databases of AlfaSigma (Bologna, Italy) during more than 10 years; rhabdomyolysis has been reported in the setting of advanced cirrhosis and is idiopathic in 25–58% of cases,[27] therefore, a cause and effect relationship is difficult to establish; and no muscle toxicity was found in animal studies in rats and dogs treated with doses of rifaximin equivalent to those used in humans.[28] Nevertheless, since safety of the combination of simvastatin and rifaximin remains a relevant issue, the LIVERHOPE efficacy trial, a randomised, double-blind trial comparing simvastatin 20 mg/day plus rifaximin versus placebo in the prevention of acute-on-chronic liver failure in patients with decompensated cirrhosis, which is currently underway, includes an assessment of safety at the time when the first 40 patients randomly assigned to simvastatin plus rifaximin have reached at least 1 month of therapy (NCT03780673).

Liver safety monitoring and stopping rules for drug-induced liver injury in patients with decompensated cirrhosis enrolled in clinical trials remain a challenge because of potentially altered liver tests before initiation of treatment.[29] Therefore, we assessed potential liver toxicity by evaluating changes with respect to baseline. Furthermore, the role of simvastatin 40 mg/day in development of liver toxicity is supported by the fact that our causality assessment excluded other potential causes of liver damage and, upon discontinuation of the study drug, laboratory abnormalities returned to baseline values. Additionally, although the dose of simvastatin given in published randomised controlled studies of patients with cirrhosis was 40 mg/day,[3,4,5] a recent large cohort study including more than 70 000 patients—in which the effects of statins on survival of cirrhosis were evaluated—showed beneficial effects of simvastatin even at doses lower than 20 mg/day.[30]

A possible limitation of this study is the small sample size. The sample size was specifically calculated to investigate the safety of different doses of simvastatin in combination with rifaximin in patients with decompensated cirrhosis in the context of a phase 2 trial, and the design was correct for the primary endpoint of the study. However, possible signals of the efficacy of the combination of simvastatin plus rifaximin in patients with decompensated cirrhosis could have been identified with a larger sample size. Also, we cannot rule out that the slight imbalance in some of the baseline characteristics among groups could have affected the results of the study, probably because of the small sample size. Nevertheless, the group with the highest imbalance was the placebo group, whereas the two groups treated with simvastatin 40 mg/day or 20 mg/day plus rifaximin were more similar.

In conclusion, in this trial investigating the safety of two different doses of simvastatin—40 mg/day or 20 mg/day—combined with rifaximin 1200 mg/day for 12 weeks, we found that simvastatin 40 mg/day was associated with a high frequency of adverse events that required treatment discontinuation, specifically liver and muscle toxicity. By contrast, simvastatin 20 mg/day had a good safety profile, similar to that of placebo. In studies investigating the efficacy of simvastatin in patients with decompensated cirrhosis, 20 mg/day should be preferred to a 40 mg/day dose.

#### Contributors

PG, EP, ML, and ES conceived the study, designed the protocol, and supervised study execution. LN, AA, DC, CJ, SP, OR, FEU, KdW, GZ, CA, PA, MB, UB, PC, FD, RPM, JT, VV, and MC identified candidates for the study, enrolled and treated patients, acquired data, and collaborated in the design of the protocol. JP and JF provided administrative and monitoring support throughout the whole study period. GD and FT designed and performed the statistical analysis. EP drafted the manuscript. PG directly reviewed the manuscript. PSK, JGA, and RJA gave advice for the design and development of the study and contributed to interpretation of the results and intellectual content of the manuscript. All authors provided critical revision of the manuscript for important intellectual content and approved the final draft of the manuscript for submission.

#### Declaration of interests

PG reports grants from the Horizon 20/20 programme during the conduct of the study, has received research funding from Gilead, Mallinckrodt, Grifols, and Ferring Pharmaceuticals, and has consulted or attended advisory boards for Grifols, Ferring Pharmaceuticals, Gilead, Intercept, Martin Pharmaceuticals, Promethera, and Sequana, outside the submitted work. PG is a recipient of an Institut de Recerca i Estudis Avançats Acadèmia award. PC reports personal fees from Grifols, Octapharma, Baxalta, and Kedrion Biopharma, outside the submitted work. JGA has received consulting fees from Gilead, Theravance, and Pfizer, and lecture fees from Gilead, Lupin Pharma, and Ferring Pharmaceuticals, outside the submitted work. PA reports grants from the EU, during the conduct of the study and personal fees from Sequana Medical, Grifols, and Biovie, outside the submitted work. SP reports grants from the EU during the conduct of the study. VV reports personal fees from Promethera and Intercept, outside the submitted work. MB reports personal fees from Grifols, CSL Behring, Octapharma, Shire/Takeda, Martin Pharmaceuticals, and Plasma Protein Therapeutics Association, outside the submitted work. GZ reports personal fees from Octapharma outside the submitted work. UB reports grants from Intercept and Dr Falk, and personal fees from Abbvie, Falk Foundation, Gilead, and Intercept, outside the submitted work. All other authors declare no competing interests.

#### Data sharing

Data from this study will not be shared.

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