

Effect of rifaximin in patients with severe cirrhosis and ascites: A randomized double-blind placebo-controlled trial

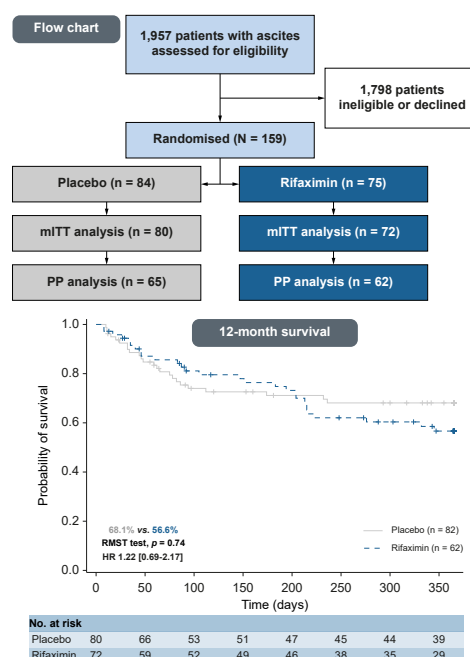
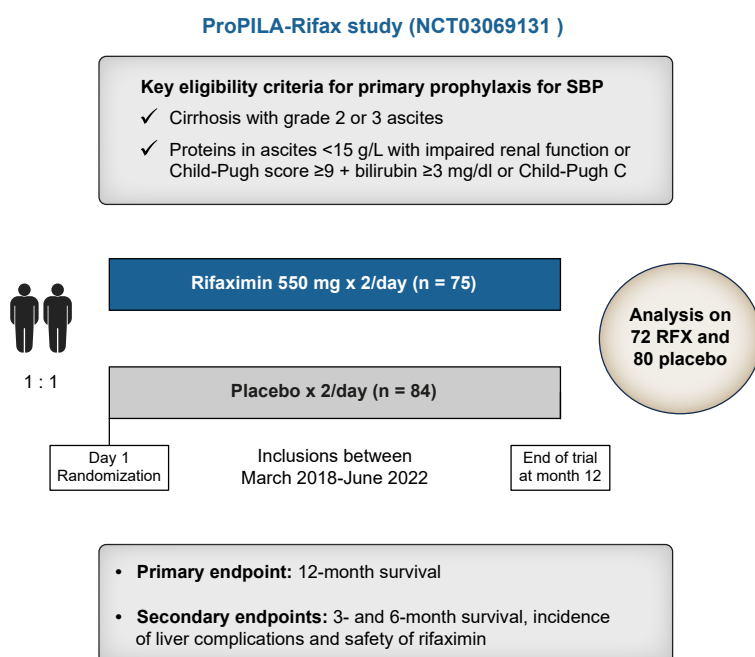
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Graphical abstract



Highlights

- Standard of care for primary prophylaxis of spontaneous bacterial peritonitis currently relies on norfloxacin.
- 159 patients with cirrhosis and ascites were enrolled in a double-blind, placebo-controlled, randomized trial.
- Rifaximin did not significantly improve 12-month survival or incidence of liver complications.
- In a *post hoc* per protocol analysis, the cumulative incidence of liver complications declined in patients adhering to rifaximin.

Impact and implications

Selective gut decontamination using norfloxacin is the standard of care for secondary prophylaxis of spontaneous bacterial peritonitis (SBP). Evidence for primary prophylaxis of SBP is weaker, and fluoroquinolones have been associated with an increased risk of antimicrobial resistance. Rifaximin, a well-tolerated broad-spectrum antibiotic associated with a lower risk of antimicrobial resistance emergence, may be an alternative to norfloxacin. Our trial did not demonstrate an improvement in survival or liver complications (SBP, gastrointestinal bleeding, hepatic encephalopathy or hepatorenal syndrome) at 12 months with rifaximin as primary prophylaxis for SBP vs. placebo. However, in the subgroup of patients who adhered to rifaximin, liver complications decreased. Our study underlines the importance of treatment adherence in clinical trials to ensure accurate assessment of outcomes.

Effect of rifaximin in patients with severe cirrhosis and ascites: A randomized double-blind placebo-controlled trial

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Background & Aims: Evidence supporting primary prophylaxis of spontaneous bacterial peritonitis (SBP) is weak and the selection of quinolone-resistant bacteria is a concern. Herein, we present results from a randomized, double-blind, placebo (PBO)-controlled trial to assess whether rifaximin (RFX) has a beneficial effect on 12-month survival in patients with severe cirrhosis and ascites.

Methods: In this trial conducted at 17 French centers, patients with severe cirrhosis and grade 2 or 3 ascites and ascites protein level <15 g/L were randomized 1:1 to receive RFX 550 mg or PBO twice daily for 12 months, as primary prophylaxis for SBP. The primary endpoint was 12-month survival. Secondary endpoints were 3- and 6-month survival, incidence of complications of cirrhosis, and safety of RFX.

Results: Between 2018 and 2022, 1,957 patients with cirrhosis and ascites were screened, 159 were randomized, and 152 (80/72 PBO/RFX) were analyzed in the modified intention-to-treat population. RFX did not improve 12-month (PBO vs. RFX: 68.1%, 95% CI 56.2–78.7 vs. 56.6%, 95% CI 43.5–67.8; $p = 0.74$), 6-month (71.1%, 95% CI 59.5–80.0 vs. 76.4%, 95% CI 64.3–84.8) or 3-month (75.4%, 95% CI 64.1–83.5 vs. 82.6%, 95% CI 71.4–89.7) survival, or the incidence of liver complications (SBP, encephalopathy, gastrointestinal bleeding or hepatorenal syndrome). In the per-protocol population (127 patients adherent to the study drug), a lower 12-month cumulative incidence of liver-related events was observed in the RFX group. RFX was well tolerated throughout the study.

Conclusions: RFX had no beneficial effect in terms of 12-month survival or incidence of complications of cirrhosis in patients with severe cirrhosis and low ascitic fluid protein levels. However, improved adherence may help reduce liver-related complications.

Clinical trial number: NCT03069131.

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Introduction

Bacterial infections in patients with cirrhosis represent the most important precipitating event for acute decompensation, and account for significant mortality.^{1,2} Infections, even when resolved, have been shown to increase mortality 4-fold in patients with cirrhosis.³ One of the most common infections observed worldwide is spontaneous bacterial peritonitis (SBP).⁴ SBP is a life-threatening condition associated with an in-hospital mortality rate of 15.5% and 12-month mortality rate of 56.6% in a contemporary national cohort study.⁵ Prevention of SBP using prophylactic antibiotics (usually norfloxacin) to

promote the growth of protective anaerobic bacteria and suppress potentially pathogenic Gram-negative bacteria is currently approved by international guidelines.^{6,7} However, the emergence of antimicrobial resistance (AMR), particularly quinolone-resistant bacteria, in patients with cirrhosis receiving long-term norfloxacin,⁸ prompted us to better refine selection of high-risk populations who will truly benefit from norfloxacin. The strongest evidence supporting the long-term use of norfloxacin is found in patients who recovered from a first SBP and acute gastrointestinal bleeding (GIB).^{7,9} Evidence for primary prophylaxis of SBP is weaker, and it may only be

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indicated in patients with very advanced cirrhosis.^{10–12} A randomized controlled trial (RCT) among Spanish patients assessed norfloxacin (vs. placebo, PBO) for primary prophylaxis of SBP in a highly selected population and showed a significant improvement in 3-month survival (94% vs. 62%; $p = 0.03$), but this beneficial effect disappeared at 1 year (primary endpoint: 60% vs. 48%; $p = 0.05$).¹³ It remains controversial whether norfloxacin plays a beneficial or detrimental role in the development of AMR. Some studies suggest a possible causal relationship between norfloxacin use and the rise of AMR^{8,14} while others find no such association.^{2,4,15} Rifaximin (RFX) is an oral, broad-spectrum, bactericidal antibiotic with low gastrointestinal absorption used to treat recurrent hepatic encephalopathy (HE). Research suggests that RFX induces minimal changes in stool microbiome composition and does not increase AMR rates.^{16,17} Furthermore, a mechanistic clinical trial showed that RFX promotes a TNF- α and IL-17E-enriched intestinal microenvironment conducive to improved antimicrobial function and gut barrier repair in patients with cirrhosis and HE.¹⁸ Given these properties, RFX may be an attractive alternative to norfloxacin to prevent intestinal bacterial translocation. To test this hypothesis, we conducted a multicenter RCT to determine whether RFX is associated with improved 12-month survival in patients with severe cirrhosis and ascites.

Patients and methods

Study design

The present “ProPILA-Rifax” study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03069131) NCT03069131) was a double-blind, PBO-controlled RCT conducted at 17 French centers treating patients with advanced liver diseases. Supplementary File 1 lists the study sites. This trial compared an RFX-based primary prophylaxis strategy in patients with severe cirrhosis and ascites against PBO. The trial was designed by a scientific committee and supervised by an independent Data Monitoring Committee (Supplementary File 2). Alfasigma laboratories (Bologna, Italy) provided RFX and PBO but had no other role in the study (Supplementary File 3). All authors critically reviewed the manuscript and approved the final draft for submission. The trial was conducted in accordance with the Declaration of Helsinki and with the approvals of the ethics committee “CPP Sud-Méditerranée IV” under the number #170709 PP, and the competent authorities (French National Agency for Medicines and Health Products Safety, #170392A-42). The study also adhered to the CONSORT reporting guidelines.¹⁹

Participants

All consecutive patients with cirrhosis and ascites who were admitted to any of the participating centers were screened for eligibility. Full eligibility criteria with detailed definitions are provided in Supplementary Files 4&5. Severe alcohol-associated hepatitis (SAH) was defined as a Maddrey discriminant function ≥ 32 in patients with excessive alcohol consumption.²⁰ Key inclusion criteria were age ≥ 18 and ≤ 80 years, patients with severe cirrhosis and grade 2 or 3 ascites, and protein levels in ascites lower than 15 g/L. Criteria for severity of cirrhosis were those reported by Fernandez *et al.*, *i.*

e. either impaired renal function (serum creatinine ≥ 1.2 mg/dl, blood urea nitrogen ≥ 25 mg/dl or natremia ≤ 130 mmol/L) or severe liver failure (Child-Pugh score ≥ 9 with a serum total bilirubin ≥ 3 mg/dl, or Child-Pugh C).¹³ Key exclusion criteria included: prior SBP; any present bacterial infection, or GIB within 7 days before randomization; a history of grade 3 HE within the past 6 months; and planned liver transplantation with an estimated waiting time of 3 months or less (for details, see Supplementary File 6).

Randomization and treatment allocation

Eligible patients who consented to participate were randomly assigned to receive either RFX or PBO, using a centralized interactive web response system. Randomization was done in blocks of four in a 1:1 ratio, based on a pre-specified randomization list stratified by center. After randomization, the first dose of the study drug was administered within 24 h. Patients were instructed to take 550 mg RFX (or PBO) twice daily for 12 months after randomization. Patients and investigators were blinded to the assignment and the active RFX was indistinguishable from the PBO (for details, see Supplementary File 7). After completion of the treatment period, patients were followed up for an additional 6 months for analysis of intestinal microbiota (day 1 and months 3, 6, 12 and 18).

Patient follow-up

Patients were followed up similarly in both arms; with eight scheduled follow-up visits (at 15 days and at 1, 2, 3, 6, 9, 12, and 18 months) to record biological and clinical data, and safety data. Self-reported or family member-reported alcohol consumption was recorded at each visit. Complications of cirrhosis were managed according to standard protocols.⁷ Adherence to the study drug at each visit was assessed by questioning the patient and consulting the paper diary given to all patients after enrolment, and by counting the number of returned tablets. We defined compliance with the study drug as the ingestion of at least 75% of the planned treatment within the study period, as suggested elsewhere.²¹ Criteria for stopping the study are reported in Supplementary File 8.

Endpoints

The primary endpoint was 12-month survival. Secondary endpoints were hospital mortality, 3- and 6-month survival, incidence of a composite event of cirrhosis complications (SBP, HE, hepatorenal syndrome [HRS], portal hypertension-related GIB), as well as each of its components, and length of hospital stay.

Safety

Safety was evaluated clinically and by patient interview at each visit and up to 8 weeks after the last study drug administration. Safety data concerned all randomized patients who received at least one dose of the study drug. Adverse drug reactions were identified through the System Organ Classes and Preferred Terms in MedDRA, version 26.1. An independent data monitoring committee reviewed unmasked safety data approximately every 4 months.

Statistical analysis

The sample size was estimated based on a projected 12-month survival rate of 40% in the PBO group and 60% in the RFX group.¹³ We calculated that 160 patients (80 per group) were required to provide 85% power to detect the survival difference between groups, at a two-sided significance level of $\alpha = 0.05$ and accounting for an expected attrition rate of 10%. One interim analysis was pre-specified after 112 participants had completed the treatment period, to detect any early survival benefit in the rifaximin arm. The significance boundaries of the interim and the final analyses were determined using an $\alpha \times \text{time}^2$ spending function. Consequently, the final significance boundary p value was 0.043. Sample size calculations were performed using PASS 14 software.

Patient characteristics are described as mean \pm SD or median (IQR) for quantitative variables, and as number and percentage for categorical variables. Analyses of the primary and secondary efficacy endpoints were performed on the modified intention-to-treat (mITT) population after exclusion of ineligible patients randomized in error. For the primary and secondary survival endpoints, survival curves were estimated using the Kaplan-Meier method. Cox proportional hazards models were built to estimate the treatment effect, expressed as hazard ratios (HRs) with 95% CIs. A violation of the proportional hazards assumption was detected for the primary endpoint using Schoenfeld residuals, suggesting that the HR may not be constant over time. Consequently, testing of the primary endpoint was based on restricted mean survival time (RMST) comparison, and the reported treatment effect should be interpreted as a time-averaged effect over the 12-month follow-up period. For the secondary composite cirrhosis complications endpoint, the cumulative incidence functions of the first event – considering death as a competing event – were computed. Fine-Gray models were built to estimate the treatment effect, expressed as subdistribution HRs. In all survival analyses, patients were censored at the time of liver transplantation, and tests and models were stratified on the center of enrolment to account for the randomization stratification factor. RMST analysis was adjusted on the center of enrolment. The treatment effect on hospital mortality was estimated based on the risk difference (with exact 95% CIs). The effect on days spent in hospital during follow-up was estimated using the Hodges-Lehmann estimator. Pre-specified subgroup analyses were performed according to age, Child-Pugh and MELD (model for end-stage liver disease) scores (dichotomized according to the median), and sex.

A per-protocol analysis of the primary endpoint was also conducted, excluding patients who did not adhere to the prescribed study drug regimen. Sensitivity analysis of the primary endpoint was also performed after exclusion of patients with SAH. A statistical analysis plan was posted to [ClinicalTrials.gov](https://www.clinicaltrials.gov) prior to unblinded analysis. *Post hoc* sensitivity analyses included analysis of liver complications (SBP, HE, HRS, and GIB) in the per-protocol population, and a power analysis based on observed effect.²² Confidence intervals were not adjusted for multiple testing. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and PASS v2024 (NCSS, Kaysville, UT).

Results

Study population

From March 2018 through June 2022, 1,957 patients were screened and 1,798 had exclusion criteria or declined to participate. A total of 159 patients were randomized (84 and 75 to the PBO and RFX groups, respectively). The 160th patient could not be enrolled because the time allotted by the ethics committee for patient inclusion had elapsed. Seven patients were ineligible (see flowchart, [Fig. 1](#)), leaving 152 patients in the mITT population (80 and 72 in the PBO and RFX groups, respectively). At baseline, demographic and laboratory parameters were similar between groups in the mITT population, except for SAH, which was twice as frequent in the RFX group (15% vs. 29.1%; [Table 1](#)). SAH was histologically proven for 20/33 cases (60.6%). Most patients were men (73.7%), alcohol was the most common cause of cirrhosis (90.8%), 16.4% had type 2 diabetes, and the mean (SD) age was 59.5 (10.5) years. Forty patients (20 in each group) reported drinking alcohol during the trial, with a mean alcohol consumption of 44.3 and 46.1 g per day in the RFX and PBO groups, respectively. The median [IQR] duration of treatment was similar between the RFX and PBO groups (184 [44-365] and 158 [65-365] days, respectively; $p = 0.70$). One hundred and twenty-seven patients (65 and 62 in the PBO and RFX groups, respectively) were adherent to the study drug and constituted the per-protocol population. These patients had similar baseline characteristics to those in the mITT population ([Table S1](#)).

Interim analyses

Interim analysis done at the end of the follow-up of the 112th patient revealed no significant difference in 12-month survival without liver transplantation between the two groups ($p = 0.65$). The study was allowed to continue.

Primary outcome

In the mITT population, the 12-month survival rates in the PBO and RFX groups were 68.1% (95% CI 56.2-78.7) and 56.6% (95% CI 43.5-67.8) ([Fig. 2](#)), respectively (RMST comparison $p = 0.74$). The associated treatment effect HR was 1.22 (95% CI 0.69-2.17). Fifty-two patients (34.2%) died during the 12-month study period and 36 of these deaths (69.2%) were due to liver-related complications. Causes of death (PBO/RFX: 24/28 deaths) in both groups are given in [Table S2](#). Seven and eight patients received a liver transplant in the PBO and RFX groups, respectively. Baseline characteristics of patients who died show that they were older (64 vs. 57 years, $p < 0.001$) and had lower natremia (131.4 vs. 134.3 mmol/L, $p = 0.001$) than patients who survived ([Table S3](#)).

Secondary outcomes

Very few patients died during hospitalization following randomization (PBO vs. RFX: 4 vs. 2; risk difference -2.4%, 95% CI -8.8% to 4.0%). Survival rates in the PBO and RFX groups were respectively 75.4% (95% CI 64.1-83.5) and 82.6% (95% CI 71.4-89.7) at 3 months, and 71.1% (95% CI 59.5-80.0) and 76.4% (95% CI 64.3-84.8) at 6 months. HRs for

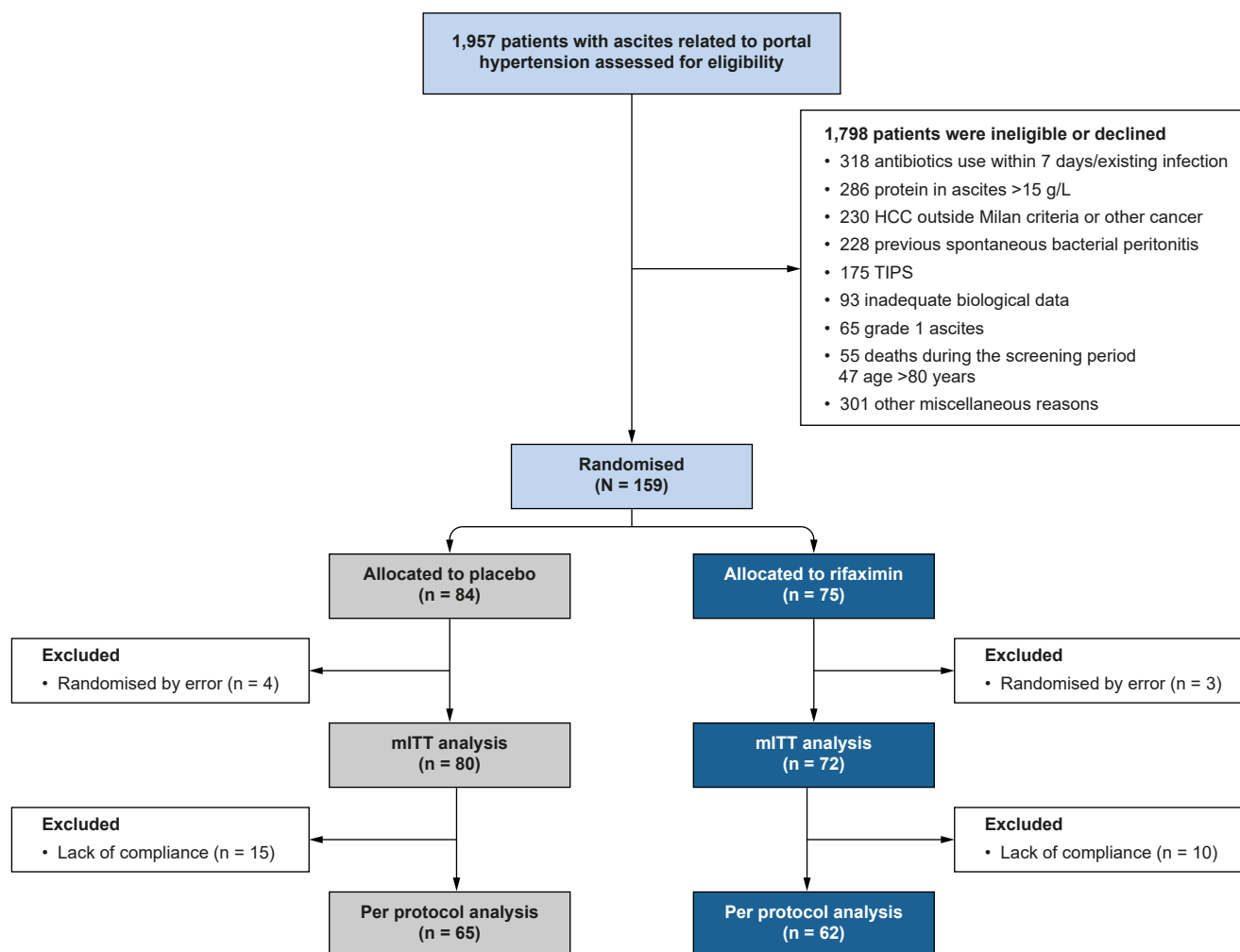


Fig. 1. Flowchart of the study population. Seven patients were randomized in error: 3 in the RFX group (2 history of SBP and 1 hepatocellular carcinoma beyond Milan criteria), 4 in the placebo group (1 history of SBP, 1 bacterial infection, 1 patient under RFX and inclusion criteria not validated for the last patient). Moreover, 9 patients withdrew their consent during follow-up (PBO vs. RFX: 6 vs. 3) and 5 were lost to follow-up (1 vs. 4). Finally, 15 patients received a liver transplantation during follow-up (7 vs. 8). HCC, hepatocellular carcinoma; PBO, placebo; RFX, rifaximin; SBP, spontaneous bacterial peritonitis.

3- and 6-month survival in the RFX group compared to the PBO group were 0.70 (95% CI 0.33-1.48) and 0.77 (95% CI 0.40-1.50).

The 12-month cumulative incidence of SBP was higher in the PBO group (PBO vs. RFX: 23.6% [n = 18] vs. 18.8% [n = 12]; HR 0.70, 95% CI 0.33-1.45). The cumulative incidences of the other secondary endpoints in the PBO vs. RFX groups respectively were 30.0% vs. 18.2% for GIB (22 vs. 12 cases; HR 0.68, 95% CI 0.34-1.34), 44.2% vs. 40.2% for HE (33 vs. 27 cases; HR 0.86, 95% CI 0.53-1.40), and 29.1% vs. 26.9% for HRS (22 vs. 18 cases; HR 0.81, 95% CI 0.44-1.50). The cumulative incidences of the composite endpoint of cirrhosis complications (SBP, GIB, HE or HRS) in the PBO and RFX groups were, respectively, 70.8% (54 events) and 56.2% (38 events, HR 0.68, 95% CI 0.46-1.02, Fig. S1).

Sensitivity and subgroup analyses of the primary endpoint

According to our definition of adherence to the study drug, 25 patients (16.4%) were considered non-adherent. Among the 127 adherent patients (per-protocol population), the survival

rates in the PBO/RFX (n = 65/62) groups were 71.0% (95% CI 57.9%-80.6%) and 81.4% (95% CI 68.9%-89.3%) (HR 0.74, 95% CI 0.34-1.61) at 3 months, 65.5% (95% CI 52.1%-76.0%) and 74.1% (95% CI 60.7%-83.5%) (HR 0.80, 95% CI 0.40-1.59) at 6 months, and 63.5% (95% CI 49.9%-74.4%) and 56.6% (95% CI 42.3%-68.6%) (HR 1.19, 95% CI 0.65-2.18) (Fig. S2) at 12 months, respectively. Subgroup analyses of 12-month survival according to age, sex and severity of cirrhosis are shown in Fig. S3 and did not reveal any significant difference in treatment effect.

Excluding the 33 patients with SAH (12 in the PBO group and 21 in the RFX group), the survival rates in the PBO/RFX groups were, respectively, 73% and 85.4% at 3 months (HR 0.50, 95% CI 0.21-1.20), 69.6% and 80.8% at 6 months (HR 0.58, 95% CI 0.26-1.26), and 67.8% and 56.9% at 12 months (HR 1.17, 95% CI 0.63-2.18) (Fig. S4).

Post hoc analyses

In the per-protocol population, SBP was more frequently observed in the PBO group at 12 months (cumulative

Table 1. Baseline characteristics of patients in the placebo and rifaximin groups.

	Total (n = 152)	Placebo (n = 80)	Rifaximin (n = 72)
Age, years	59.5 (10.5)	59.8 (10.0)	59.3 (10.1)
Male gender	112 (73.7)	62 (77.5)	50 (69.4)
Body mass index, kg/m ²	27.1 (5.7)	27.5 (5.8)	26.7 (5.7)
Mean arterial pressure, mmHg	82.8 (11.6)	83.2 (11.0)	82.3 (12.3)
Etiology of liver disease			
Alcohol	138 (90.8)	73 (91.2)	65 (90.3)
MASH	27 (17.8)	15 (18.8)	12 (16.7)
Viral hepatitis B or C	11 (7.2)	6 (7.5)	5 (6.9)
Severe alcohol-associated hepatitis suspected	33 (21.7)	12 (15)	21 (29.1)
Hepatocellular carcinoma [†]	8 (5.3)	3 (3.8)	5 (6.9)
Diabetes mellitus	25 (16.4)	14 (17.5)	11 (15.3)
Child-Pugh score	10.3 (1.8)	9.9 (1.9)	10.8 (1.6)
MELD score	17.8 (4.6)	16.9 (3.9)	18.9 (5.1)
Total bilirubin, μmol/L	82 (68)	67 (52)	99 (79)
Prothrombin index, %	50 (14)	52 (13)	48 (13)
Serum albumin, g/L	28 (6)	28 (5)	28 (6)
Serum creatinine, μmol/L	78 (39)	80 (44)	77 (32)
Serum sodium, mmol/L	133 (5)	133 (5)	133 (5)
Platelet count, G/L	131.8 (79.8)	132.8 (79.3)	128.6 (80.9)
C-reactive protein, mg/L	15.0 (7.7-26.0)	14.6 (7.0-27.0)	15.4 (8.0-23.9)
Total protein in ascites, g/L	10 (3)	10 (3)	10 (3)
Statins	22 (14.4)	15 (18.7)	7 (9.7)
Proton-pump inhibitors	78 (51.3)	44 (55)	34 (47.2)
Beta-blockers	76 (50)	38 (47.5)	38 (52.8)
Lactulose	75 (49.3)	42 (52.5)	33 (45.8)
Follow-up, days	320.5 [84-365]	340 [70-365]	282 [91-365]

MASH, metabolic dysfunction-associated steatohepatitis; MELD, model for end-stage liver disease.

Values are n (%), mean (SD) or median (IQR).

[†]Hepatocellular carcinoma within Milan criteria.

Severe alcohol-associated hepatitis was significantly higher in the rifaximin group (15% vs. 29.1%; *p* = 0.048, Fisher's exact test).

incidence 29.6% [n = 18] vs. 20.1% [n = 11] in the RFX group; HR 0.59, 95% CI 0.28-1.22). HE, HRS, and GIB were also more frequently observed in the PBO group (HE: 28% vs. 23%, HR 0.78, 95% CI 0.47-1.30; HRS: 19 vs. 14, HR 0.69, 95% CI 0.36-1.34; GIB: 19 vs. 10, HR 0.62, 95% CI 0.28-1.34).

The cumulative incidence of liver-related events (a composite event of SBP, GIB, HE or HRS) at 12 months was lower in adherent patients from the RFX group (54.0% vs. 76.9%, HR 0.55, 95% CI 0.36-0.84, Fig. 3).

A *post hoc* power analysis based on the observed 12-month survival and group sample sizes indicated an observed power of 53% for detecting this effect at a significance level of 0.05.

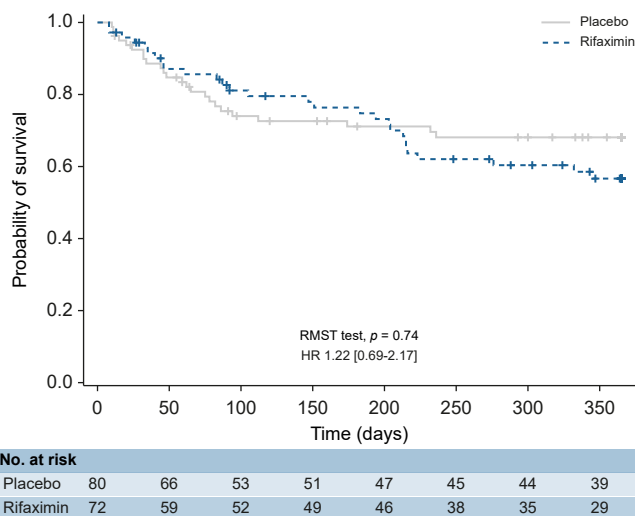


Fig. 2. Kaplan-Meier curves of the primary endpoint (12-month survival) in the mITT population. The Kaplan-Meier method was used to estimate survivals, and the 12-month restricted median survival time was compared. Level of significance: *p* = 0.74. Patients were censored at the time of liver transplantation. HR, hazard ratio; mITT, modified intention-to-treat.

Safety and length of hospital stay

There were no safety concerns regarding RFX throughout the study period (Fig. S5). Overall, 94.0% and 90.7% of patients in the PBO and RFX groups reported an adverse event, respectively. Four patients in the PBO group and six patients in the RFX group experienced adverse events that were considered related to the study drug. Only one suspected unexpected serious adverse reaction was reported in the RFX group (details are given in Fig. S5). The median [IQR] length of hospital stay was lower in the RFX group (27.5 days [15.0-42.0] vs. 40.0 days [21.0-60.0], difference -10.0, 95% CI -19.0 to -1.0).

Discussion

The main results of this interventional PBO-controlled trial of rifaximin for primary prophylaxis of SBP indicate that RFX failed to improve 12-month survival or to prevent liver complications in the mITT population. Alcohol was the primary disease etiology and SAH was more common in the RFX group. Since SAH is a life-threatening condition associated with high short-term mortality,²³ planned sensitivity analyses excluding SAH were performed but did not alter the results.

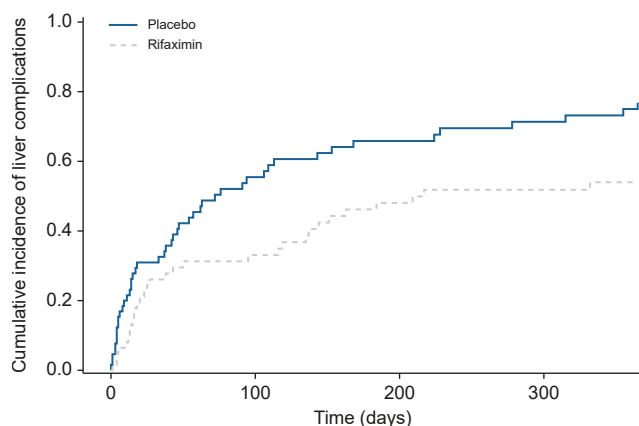


Fig. 3. Post hoc analysis of the 12-month cumulative incidence of liver complications in patients who were adherent to the study drug (per-protocol population). Liver complications include spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome and gastrointestinal bleeding. Comparisons of cumulative incidences were performed using Gray' test. Level of significance: $p = 0.01$.

Regardless of whether patients had SAH or not, RFX did not improve 3-, 6-, or 12-month survival or cirrhosis complications in the mITT population. Although the number of composite cirrhosis-related complications was higher in the PBO group, the cumulative incidence of each event at 3, 6, and 12 months did not differ significantly, regardless of the presence of SAH. RFX is currently approved to prevent the recurrence of HE, and we have gained significant insights into its mechanism of action since the landmark paper by Bass *et al.*^{16,18,24} Unlike the improvement of HE with RFX in the RIFSYS study,¹⁸ we failed to observe such a clinical benefit in our trial, probably because our patients taking RFX were more severely ill (median MELD 17 vs. 11 in the RIFSYS study).

Our study is the largest dedicated to primary antibiotic prophylaxis in highly selected patients with severe cirrhosis. The lack of evidence regarding the efficacy of RFX on survival and liver complications of cirrhosis in the mITT population could reinforce the skepticism of physicians vis-à-vis the use of this antibiotic for primary prophylaxis. This skepticism has previously been observed, notably when we evaluated the prescribing patterns of antibiotic prophylaxis among 389 French practitioners. Although 72% of practitioners prescribed primary antibiotic prophylaxis in highly selected patients with cirrhosis, they mostly chose norfloxacin, and only one-third of them prescribed it regularly.²⁵ A similar survey recently conducted in 23 UK hospitals found that only nine centers routinely used primary antibiotic prophylaxis.²⁶ The reluctance of practitioners to use primary antibiotic prophylaxis may be partly due to the acknowledged high risk of AMR emergence associated with the long-term use of antibiotics (up to 40%), including quinolones.²⁷ However, an increased risk of AMR with prophylactic quinolones has not been consistently reported,^{2,4} although recent reports suggest an increased risk of drug resistance and mortality with primary prophylaxis.^{28,29} Moreover, the FDA, EMA and MHRA issued a black box warning regarding the risk of disabling side effects (tendonitis, aortic aneurysm and neuropsychiatric disorders) of quinolones, leading to a restriction of their use.³⁰

Preventing bacterial infections, including SBP, remains crucial because they represent the main precipitating factor of

acute-on-chronic liver failure. More than 25% of acute-on-chronic liver failure cases associated with an identifiable infection are due to SBP, which carries a risk of death of approximately 50% at 1 month.^{31,32} Recognizing that nearly 90% of SBP cases are patients with no previous episode,³³ primary prophylaxis of SBP remains a growing area of research to better define the target population and the most appropriate treatment. At the time of writing our study protocol, we chose to adopt the inclusion criteria reported in the Spanish RCT using norfloxacin in patients with severe cirrhosis and low protein concentration (<15 g/L) in ascitic fluid.¹³ Studies published more than 30 years ago reported a clear-cut association between low ascitic fluid protein and an increased risk of SBP.^{33–36} However, *post hoc* analyses from two large prospective multicenter studies^{37,38} and a more recent study³⁹ failed to replicate this association in patients with decompensated cirrhosis. Among the patients screened for eligibility, patients with cirrhosis with a high protein level (≥ 15 g/L) in ascites represented the second most common exclusion criterion, partly explaining the long inclusion period (nearly 50 months) despite a high number of participating centers. Most scientific societies support primary antibiotic prophylaxis for SBP in patients with low protein in ascites,^{7,40} although the quality of evidence is considered low by the British Society of Gastroenterology.¹² A large UK RCT (NCT04395536) is currently underway to investigate the effect of primary prophylaxis for SBP using cotrimoxazole on survival in patients with cirrhosis and ascites, but without considering ascitic protein level.²⁶

The only positive result of our trial was observed in patients who were adherent to the study drug. Although the 3-, 6- and 12-month survival in adherent patients did not differ between the PBO and RFX groups, the cumulative incidence of complications of cirrhosis was significantly reduced in the RFX group. Because patients with decompensated cirrhosis may have low-grade encephalopathy affecting medication recall, we optimized the assessment of adherence to the study drug not only by questioning the patient at each visit, but also by consulting the paper diary and counting the pills returned to the pharmacy. Using this multimodal approach, 127 patients (83.5% of the mITT population) were considered as adherent to the study drug, and their characteristics did not differ noticeably from the mITT population. The reason the decline in complications in the per-protocol analysis did not translate into reduced 1-year mortality remains unclear. We hypothesize that, due to recent advances in management, most patients with severe cirrhosis now experience prolonged survival, but ultimately die after 12 months. Indeed, median survival in the decompensated stage is around 1.5 years.⁴¹ We also hypothesize that the significantly shorter hospital stay observed in the RFX group among adherent patients was the consequence of a significant decrease in the cumulative incidence of first-event liver complications. However, social factors, such as family support and living conditions, may have affected the length of hospitalization. The number of each complication (SBP, GI bleeding, HE and HRS) was not significantly reduced in the RFX group, most likely due to a lack of statistical power. Although per-protocol analysis cannot provide firm conclusions, we estimate that this reduced incidence of liver complications in adherent patients probably reflects the true effect of RFX over PBO. This result can provide useful information for

clinicians but needs to be externally validated in larger trials, using our highly selected inclusion criteria or not.

RFX was well tolerated throughout the study and safety results were consistent with prior studies in preventing recurrence of overt HE or in treating early decompensation of cirrhosis.^{16,42,43} No cases of *Clostridioides difficile*-associated diarrhoea were reported in the RFX arm. The good safety profile of RFX may rely on its low absorption, which limits non-GI side effects and systemic drug interactions. RFX offers an attractive opportunity to replace norfloxacin in France, since the French national health authority (HAS) decided in March 2018 to delist norfloxacin due to a lack of demonstrated medical benefit. Other formulations of RFX⁴⁴ and cotrimoxazole may also be promising.²⁶

The strengths of our randomized trial lie in its blinded, controlled, and prospective design, with inclusion of a well-described homogeneous cohort. Data on medication adherence in studies performed in patients with cirrhosis are scarce. In the GALA-RIF phase II trial on patients with alcohol-related liver disease who were adherent to RFX administered for 18 months, the progression of fibrosis was reduced compared to patients on PBO.²¹ We present here valuable insights into the outcomes of patients who are adherent to the study drug. However, the trial also has some limitations. Cost-effectiveness analysis was not part of our study. It is clear

that the cost per RFX 550 mg tablet (around 3.50 €) is currently higher than that of norfloxacin 400 mg (around 0.52 €) or cotrimoxazole 960 mg (around 0.18 €). The use of low protein levels in ascitic fluid to stratify the risk of SBP has become more controversial over time^{37–39} and probably overly restrictive when attempting to include a large sample size of highly selected patients with cirrhosis. The relatively small number of enrolled patients prevented separate analysis of the different types of liver complications. Likewise, the results of our study cannot be generalized to all patients with cirrhosis and ascites, but only to those with low protein levels in ascitic fluid in line with our criteria for cirrhosis severity. Survival in the control group was higher than expected (68.1% vs. 40% in the study by Fernandez *et al.*¹³), and the trial may have been underpowered. However, demonstrating an effect of RFX will likely prove challenging, considering the numerically lower survival in the RFX group observed in our trial.

In conclusion, in patients with severe cirrhosis and low protein in ascites, 12 months of RFX did not improve survival or reduce complications of cirrhosis. However, we observed a decrease in the cumulative incidence of first-event liver complications in adherent patients. Consequently, this result needs to be further explored in larger trials, with or without consideration of the protein concentration in ascitic fluid.

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Abbreviations

AMR, antimicrobial resistance; GIB, gastrointestinal bleeding; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; PBO, placebo; RCT, randomized controlled trial; RFX, rifaximin; SAH, severe alcohol-associated hepatitis; SBP, spontaneous bacterial peritonitis.

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Conflict of interest

TT, LE, EBJ, IR, ENK, FL, AL, PN, GR, JPC, VDM received grants from Abbvie and Gilead to support attending meetings. CB received consulting fees from Alfasigma, Gilead, Abbvie and Ipsen. MM received grants from Grifols and Gilead to support attending meetings. FO received grants from Roche, AstraZeneca and Ipsen to support attending meetings. AP received speaking fees from Abbvie and received grants from Sandoz to support attending meetings. LM received grants

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study conception and design: Thévenot T, Hocquet D and Desmarests M; Acquisition of data: Thévenot T, Elkrief L, Bureau C, Bardou-Jacquet E, Rosa I, Nguyen-Khac E, Oberti F, Pitta A, Mallet M, Lebossé F, Louvet A, Meunier A, Nahon P, Ollivier-Hourmand I, Anty R, Francoz C, Riachi G, Cervoni JP, Cure-Martin A, Muller A, Clairet AL, Di Martino V and Weil D. Analysis, interpretation of data and statistical analysis: Tio G, Desmarests M, Ladeira R and Thévenot T; drafting of the manuscript and obtained funding: Thévenot T and Desmarests M. Maxime Desmarests has access to all of the data and can vouch for the integrity of the data analyses.

Data availability

Data are available from the corresponding author upon reasonable request.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2025.06.019>.

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