Clinical trial results:
Efficacy of the combination of simvastatin plus rifaximin in patients with decompensated cirrhosis to prevent ACLF development: a multicenter, double-blind, placebo controlled randomized clinical trial (LIVERHOPE_EFFICACY).

Summary

EudraCT number	2018-001698-25
Trial protocol	ES NL FR GB DE BE IT
Global end of trial date	01 December 2022

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	LIVERHOPE_EFFICACY

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03780673
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer)
Sponsor organisation address	Rosselló, 149 , Barcelona, Spain, 08036
Public contact	Pere Ginés, Hospital Clínic, +34 9322754001713, pgines@clinic.cat
Scientific contact	Pere Ginés, Hospital Clínic, +34 9322754001713, pgines@clinic.cat

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2022
Global end of trial reached?	Yes
Global end of trial date	01 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of oral administration of Simvastatin plus Rifaximin in halting the progression of decompensated cirrhosis as assessed by the time to first incidence of ACLF during treatment period.

Protection of trial subjects:

All participants will provide written informed consent before any study procedures. The trial complies with the Declaration of Helsinki, ICH-GCP, and EU regulations. Ethics Committee and Competent Authority approvals are obtained. Patient confidentiality and data protection are ensured per GDPR. Insurance covers trial-related injuries.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Spain: 95
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Italy: 91
Worldwide total number of subjects	254
EEA total number of subjects	242

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	254
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study recruited 254 patients with decompensated cirrhosis across 14 European hospitals between January 2019 and December 2021. Patients were randomized to receive simvastatin plus rifaximin or placebo for 12 months.

Pre-assignment

Screening details:

772 patients were screened for eligibility. Inclusion criteria included age ≥18 and Child-Pugh class B or C cirrhosis. Key exclusions were ACLF at baseline, severe liver impairment, hepatocellular carcinoma, or ongoing statin/rifaximin therapy.

Period 1

Period 1 title	Randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Simvastatin plus Rifaximin

Arm description:

A total of 126 patients were randomized to receive simvastatin (20 mg/day) plus rifaximin (1200 mg/day) for 12 months. Of these, 117 initiated treatment and were included in the primary analysis.

Arm type	Experimental
Investigational medicinal product name	Simvastatin 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The first cohort will receive one 20 mg tablet of simvastatin every 24 hours at night.

Investigational medicinal product name	Rifaximin 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The first cohort will receive one 400 mg tablet of rifaximin every 8 hours.

Arm title	Placebo

Arm description:

A total of 128 patients were randomized to receive placebo for 12 months. Of these, 120 initiated treatment and were included in the primary analysis.

Arm type	Placebo
Investigational medicinal product name	Simvastatin Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:	
The second cohort will receive one tablet of placebo of simvastatin every 24 hours at night.	
Investigational medicinal product name	Rifaximin Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The second cohort will receive one tablet of placebo of rifaximin every 8 hours.

Number of subjects in period 1	Simvastatin plus Rifaximin	Placebo
Started	126	128
Completed	117	120
Not completed	9	8
Consent withdrawn by subject	1	2
Protocol deviation	8	6

Period 2

Period 2 title	Primary analysis population
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Simvastatin plus Rifaximin

Arm description:

This arm includes 117 patients who initiated treatment with simvastatin plus rifaximin and were included in the primary analysis. Baseline characteristics and outcomes are reported for this population. 81 patients completed the study.

Arm type	Experimental
Investigational medicinal product name	Simvastatin 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The first cohort will receive one 20 mg tablet of simvastatin every 24 hours at night.

Investigational medicinal product name	Rifaximin 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The first cohort will receive one 400 mg tablet of rifaximin every 8 hours.

Arm title	Placebo

Arm description:

This arm includes 120 patients who initiated treatment with placebo and were included in the primary analysis. Baseline characteristics and outcomes are reported for this population. 69 patients completed the study.

Arm type	Placebo
Investigational medicinal product name	Simvastatin Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The second cohort will receive one tablet of placebo of simvastatin every 24 hours at night.

Investigational medicinal product name	Rifaximin Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The second cohort will receive one tablet of placebo of rifaximin every 8 hours.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The first period (“Randomisation”) includes all randomized patients (n=254), regardless of whether they initiated treatment. However, the baseline period was defined as the second period (“Primary analysis population”), which includes only the 237 patients who started treatment and for whom baseline characteristics were collected. This structure reflects the actual conduct of the trial and ensures accurate reporting of baseline data.

Number of subjects in period 2[2]	Simvastatin plus Rifaximin	Placebo
Started	117	120
Completed	81	69
Not completed	36	51
Consent withdrawn by subject	8	10
Physician decision	3	6
Adverse event, non-fatal	17	23
Other	-	1
Lost to follow-up	2	-
Had transplant	3	8
Protocol deviation	3	3

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The trial randomized 254 patients, but only 237 initiated treatment and were included in the primary analysis. Baseline characteristics are reported exclusively for these 237 patients, as they

represent the population that received at least one dose of study medication. The remaining 17 patients were excluded prior to treatment initiation due to protocol violations or other eligibility issues, and therefore do not have baseline data available.

Baseline characteristics

Reporting groups	
Reporting group title	Simvastatin plus Rifaximin
Reporting group description:	
This arm includes 117 patients who initiated treatment with simvastatin plus rifaximin and were included in the primary analysis. Baseline characteristics and outcomes are reported for this population. 81 patients completed the study.	
Reporting group title	Placebo
Reporting group description:	
This arm includes 120 patients who initiated treatment with placebo and were included in the primary analysis. Baseline characteristics and outcomes are reported for this population. 69 patients completed the study.	

Reporting group values	Simvastatin plus Rifaximin	Placebo	Total
Number of subjects	117	120	237
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	58	56	
standard deviation	± 9	± 10	-
Gender categorical Units: Subjects			
Female	29	38	67
Male	88	82	170

End points

End points reporting groups

Reporting group title	Simvastatin plus Rifaximin
Reporting group description:	
A total of 126 patients were randomized to receive simvastatin (20 mg/day) plus rifaximin (1200 mg/day) for 12 months. Of these, 117 initiated treatment and were included in the primary analysis.	
Reporting group title	Placebo
Reporting group description:	
A total of 128 patients were randomized to receive placebo for 12 months. Of these, 120 initiated treatment and were included in the primary analysis.	
Reporting group title	Simvastatin plus Rifaximin
Reporting group description:	
This arm includes 117 patients who initiated treatment with simvastatin plus rifaximin and were included in the primary analysis. Baseline characteristics and outcomes are reported for this population. 81 patients completed the study.	
Reporting group title	Placebo
Reporting group description:	
This arm includes 120 patients who initiated treatment with placebo and were included in the primary analysis. Baseline characteristics and outcomes are reported for this population. 69 patients completed the study.	

Primary: Time to ACLF in the two groups during follow-up

End point title	Time to ACLF in the two groups during follow-up
End point description:	
Efficacy of treatment in halting the progression of decompensated cirrhosis as assessed by time to first ACLF during the treatment period, defined according to criteria by Moreau et al., Gastroenterology 2013. The endpoint is reported as the number of subjects who developed ACLF during the 12-month follow-up.	
End point type	Primary
End point timeframe:	
12 months	

End point values	Simvastatin plus Rifaximin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	120		
Units: Subjects				
Subjects with ACLF	21	17		

Statistical analyses

Statistical analysis title	Primary endpoint analysis: Time to ACLF
Statistical analysis description:	
The primary endpoint was analyzed using a Fine and Gray competing risk model, stratified by Child-Pugh class. This method accounts for competing events such as death and liver transplant. Since Fine and Gray is not available in the selection list, “Regression, cox” has been selected as the closest approximation.	

Comparison groups	Simvastatin plus Rifaximin v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.52 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	2.34

Notes:

[1] - The study aimed to assess whether simvastatin plus rifaximin was superior to placebo in preventing ACLF.

[2] - No statistically significant difference was observed between groups.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 months (duration of treatment and follow-up)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Simvastatin + Rifaximin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Simvastatin + Rifaximin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 117 (37.61%)	50 / 120 (41.67%)	
number of deaths (all causes)	17	17	
number of deaths resulting from adverse events	12	13	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 117 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Craneoencephalic trauma			
subjects affected / exposed	1 / 117 (0.85%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Surgical and medical procedures			
Transplant			
subjects affected / exposed	5 / 117 (4.27%)	12 / 120 (10.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoxic encephalopathy due to stroke			

subjects affected / exposed	1 / 117 (0.85%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Unknown cause of Death	Additional description: Found dead at home and Cause of death not reported		
subjects affected / exposed	2 / 117 (1.71%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Immune system disorders			
Neurosarcoidosis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
ACLF (Acute-on-Chronic Liver Failure)	Additional description: ACLF is a severe decompensation of cirrhosis characterized by failure of one or more organs or systems (including liver, kidney, brain, respiratory, circulatory, and coagulation) and is associated with poor short- and mid-term prognosis. Defined acco		
subjects affected / exposed	21 / 117 (17.95%)	17 / 120 (14.17%)	
occurrences causally related to treatment / all	21 / 21	17 / 17	
deaths causally related to treatment / all	12 / 12	13 / 13	
Complications of cirrhosis	Additional description: New ascites, worsening of ascites, hepatic encephalopathy, acute kidney injury,bacterial infection, and variceal bleeding.		
subjects affected / exposed	10 / 117 (8.55%)	17 / 120 (14.17%)	
occurrences causally related to treatment / all	0 / 111	0 / 132	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	3 / 117 (2.56%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Simvastatin + Rifaximin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 117 (48.72%)	50 / 120 (41.67%)	
Nervous system disorders			
Nervous systemdisorders			
subjects affected / exposed	14 / 117 (11.97%)	7 / 120 (5.83%)	
occurrences (all)	18	7	
Gastrointestinal disorders			
Gastrointestinaldisorders			
subjects affected / exposed	35 / 117 (29.91%)	40 / 120 (33.33%)	
occurrences (all)	53	62	
Hepatobiliary disorders			
Hepatobiliarydisorders			
subjects affected / exposed	44 / 117 (37.61%)	46 / 120 (38.33%)	
occurrences (all)	85	91	
Renal and urinary disorders			
Kidney and urinarydisorders			
subjects affected / exposed	19 / 117 (16.24%)	21 / 120 (17.50%)	
occurrences (all)	31	32	
Musculoskeletal and connective tissue disorders			
Musculoskeletal andconnective tissuedisorders	Additional description: Three patients in the simvastatin plus rifaximin group presented with 1 episode ofrhabdomyolysis (2.5%) vs zero episodes in zero patients in the placebo group.		
subjects affected / exposed	32 / 117 (27.35%)	26 / 120 (21.67%)	
occurrences (all)	39	30	
Infections and infestations			
Infection			
subjects affected / exposed	33 / 117 (28.21%)	33 / 120 (27.50%)	
occurrences (all)	64	45	
Metabolism and nutrition disorders			
Metabolism andnutrition disorders			
subjects affected / exposed	21 / 117 (17.95%)	19 / 120 (15.83%)	
occurrences (all)	33	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2018	Substantial Amendment No. 1
10 January 2020	Substantial Amendment No. 2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Most patients had alcohol-related cirrhosis; findings may not apply to MASLD or viral hepatitis. The statin dose was low, and patients had moderate to severe liver impairment.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/39908052