Clinical trial results:
Safety and tolerability of the combination of simvastatin plus rifaximin in patients with decompensated cirrhosis: a multicenter, double-blind, placebo controlled randomized clinical trial.

Summary

EudraCT number	2016-004499-23
Trial protocol	ES NL GB FR
Global end of trial date	12 March 2018

Results information

Result version number	v1 (current)
This version publication date	22 July 2020
First version publication date	22 July 2020

Trial information

Trial identification

Sponsor protocol code	LIVERHOPE_SAFETY

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03150459
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IDIBAPS
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	02 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2018
Global end of trial reached?	Yes
Global end of trial date	12 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the treatment-related toxicity of oral administration of simvastatin plus rifaximin in patients with decompensated cirrhosis.

Protection of trial subjects:

Not required

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2017
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	United Kingdom: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 16
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	35

From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial subjects were recruited at 9 European European University Hospitals in Spain, Germany, UK, The Netherlands, Italy and France.
Recruitment period:
28-July-2017 to 2-January-2018

Pre-assignment

Screening details:

Having given consent, participants will undergo screening assessments to verify their eligibility to participate in the study according the selection criteria specified in the protocol. Study population was adult patients with decompensated cirrhosis.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

It is a double-blind placebo controlled clinical trial

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo of simvastatin + Placebo of rifaximin

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

Dosage and administration details:

2 tablets every 24 hours at night during 12 weeks

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

Dosage and administration details:

One tablet of Placebo of Rifaximin every 8 hours during 12 weeks

Arm title	Simvastatin 20 mg

Arm description:

Simvastatin 20mg/day + Rifaximin 400mg/8 hours

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: 1 tablet of simvastatin 20 mg every 24 hours at night during 12 weeks	
Investigational medicinal product name	Placebo of simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 2 tablets every 24 hours at night during 12 weeks	
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: One tablet of Rifaximin 400 mg every 8 hours during 12 weeks	
Arm title	Simvastatin 40 mg
Arm description: Simvastatin 40 mg + Rifaximin 400 mg	
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: 1 tablet of simvastatin 20 mg every 24 hours at night during 12 weeks	
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: 1 tablet of Rifaximin 400 mf every 8 hours during 12 weeks	

Number of subjects in period 1	Placebo	Simvastatin 20 mg	Simvastatin 40 mg
Started	14	14	16
Completed	14	14	16

Period 2

Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

It is a double-blind placebo controlled clinical trial

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo of simvastatin + Placebo of rifaximin

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

Dosage and administration details:

2 tablets every 24 hours at night during 12 weeks

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

Dosage and administration details:

One tablet of Placebo of Rifaximin every 8 hours during 12 weeks

Arm title	Simvastatin 20 mg

Arm description:

Simvastatin 20mg/day + Rifaximin 400mg/8 hours

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:

1 tablet of simvastatin 20 mg every 24 hours at night during 12 weeks

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

Dosage and administration details:

2 tablets every 24 hours at night during 12 weeks

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:

One tablet of Rifaximin 400 mg every 8 hours during 12 weeks

Arm title	Simvastatin 40 mg

Arm description:

Simvastatin 40 mg + Rifaximin 400 mg

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:

1 tablet of simvastatin 20 mg every 24 hours at night during 12 weeks

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:

1 tablet of Rifaximin 400 mf every 8 hours during 12 weeks

Number of subjects in period 2	Placebo	Simvastatin 20 mg	Simvastatin 40 mg
Started	14	14	16
Completed	12	12	5
Not completed	2	2	11
Consent withdrawn by subject	1	1	5
Adverse event, non-fatal	1	-	5
Liver transplantation	-	1	-
Prematurely discontinuation (DSMB recommendation)	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo of simvastatin + Placebo of rifaximin	
Reporting group title	Simvastatin 20 mg
Reporting group description:	
Simvastatin 20mg/day + Rifaximin 400mg/8 hours	
Reporting group title	Simvastatin 40 mg
Reporting group description:	
Simvastatin 40 mg + Rifaximin 400 mg	

Reporting group values	Placebo	Simvastatin 20 mg	Simvastatin 40 mg
Number of subjects	14	14	16
Age categorical			
median age 18-64			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	14	11
From 65-84 years	4	0	5
85 years and over	0	0	0
Age continuous			
55.89 (11.58)			
Units: years			
median	59	49	60
standard deviation	± 12	± 11	± 12
Gender categorical			
Units: Subjects			
Female	5	3	4
Male	9	11	12
Etiology of cirrhosis			
Units: Subjects			
Alcohol	9	9	9
Others	5	5	7
CHild Pugh class			
Units: Subjects			
Child B	10	10	12
CHild C	4	4	4

MELD score			
Units: no			
arithmetic mean	13	14	14
standard deviation	± 3	± 3	± 3

Reporting group values	Total		
Number of subjects	44		
Age categorical			
median age 18-64			
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)	35		
From 65-84 years	9		
85 years and over	0		
Age continuous			
55.89 (11.58)			
Units: years			
median			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	12		
Male	32		
Etiology of cirrhosis			
Units: Subjects			
Alcohol	27		
Others	17		
CHild Pugh class			
Units: Subjects			
Child B	32		
CHild C	12		
MELD score			
Units: no			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo of simvastatin + Placebo of rifaximin	
Reporting group title	Simvastatin 20 mg
Reporting group description: Simvastatin 20mg/day + Rifaximin 400mg/8 hours	
Reporting group title	Simvastatin 40 mg
Reporting group description: Simvastatin 40 mg + Rifaximin 400 mg	
Reporting group title	Placebo
Reporting group description: Placebo of simvastatin + Placebo of rifaximin	
Reporting group title	Simvastatin 20 mg
Reporting group description: Simvastatin 20mg/day + Rifaximin 400mg/8 hours	
Reporting group title	Simvastatin 40 mg
Reporting group description: Simvastatin 40 mg + Rifaximin 400 mg	

Primary: Liver toxicity	
End point title	Liver toxicity
End point description: (1) liver toxicity assessed by the development of liver injury defined as 3-fold increase in serum transaminases to a final value at least 3 times the upper normal limit, or 2-fold increase in serum levels of alkaline phosphatase with respect to baseline value to a final value at least 2 times the upper normal limit	
End point type	Primary
End point timeframe: 12 weeks of treatment period	

End point values	Placebo	Simvastatin 20 mg	Simvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	16	
Units: IU/L	14	14	16	

Statistical analyses

Statistical analysis title	primary endpoint liver toxicity
Comparison groups	Simvastatin 20 mg v Placebo v Simvastatin 40 mg

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	50
Confidence interval	
level	90 %
sides	2-sided
lower limit	5
upper limit	95

Primary: Muscle toxicity	
End point title	Muscle toxicity
End point description: 2) muscle toxicity, defined as 5-fold increase in creatinine kinase (CK) levels during treatment.	
End point type	Primary
End point timeframe: 12 weeks treatment period	

End point values	Placebo	Simvastatin 20 mg	Simvastatin 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	16	
Units: IU/l	14	14	16	

Statistical analyses

Statistical analysis title	primary endpoint muscle toxicity
Comparison groups	Placebo v Simvastatin 20 mg v Simvastatin 40 mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	50
Confidence interval	
level	90 %
sides	2-sided
lower limit	5
upper limit	95

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Simvastatina 20
Reporting group description: -	
Reporting group title	Simnvastatina 40
Reporting group description: -	

Serious adverse events	Placebo	Simvastatina 20	Simnvastatina 40
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)	3 / 14 (21.43%)	9 / 16 (56.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hepatitis toxic			
subjects affected / exposed	4 / 14 (28.57%)	3 / 14 (21.43%)	9 / 16 (56.25%)
occurrences causally related to treatment / all	1 / 6	0 / 3	4 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			

subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Peritonitis bacterial			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic encephalopathy			
subjects affected / exposed	2 / 14 (14.29%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fistula			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			

subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	2 / 16 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Simvastatina 20	Simnvastatina 40
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 14 (78.57%)	10 / 14 (71.43%)	15 / 16 (93.75%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Chest pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Fatigue			

subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 14 (7.14%)	2 / 14 (14.29%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Weight increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Paracentesis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural			

complications			
Fall			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hepatitis toxic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Encephalopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hepatic encephalopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Ascites			
subjects affected / exposed	2 / 14 (14.29%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	3	3	0
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)	2 / 14 (14.29%)	3 / 16 (18.75%)
occurrences (all)	1	2	3
Dyspepsia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	2 / 14 (14.29%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Peritonitis bacterial			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Ascites			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	3
Hepatic encephalopathy			

subjects affected / exposed	2 / 14 (14.29%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences (all)	4	1	1
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	4 / 14 (28.57%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Acute kidney injury			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	2 / 16 (12.50%)
occurrences (all)	1	1	2
Musculoskeletal and connective tissue disorders			
Fistula			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	2 / 14 (14.29%)	1 / 14 (7.14%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	3 / 14 (21.43%)	2 / 16 (12.50%)
occurrences (all)	0	3	2
Myopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Myositis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Rhabdomyolysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Infections and infestations			

Furuncle			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	3 / 14 (21.43%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	4	0	1
Escherichia urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Enterocolitis infectious			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	0 / 16 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2017	The objective of the amendment is the correction of some errors detected related to the amount of blood and urine required during the follow-up of the study and their timepoints.
23 October 2017	The aim of the substantial amendment was the introduction of the following modifications: 1. Addition of the definition of women of child-bearing potential. 2. Addition of a urine pregnancy test at baseline. 3. Addition of a telephone contact visit 4 weeks after study completion. 4. Addition of cyclosporine and simeprevir as nonpermitted medication. 5. Correction of the group to which clarithromycin and telithromycin belong. 6. Removal week 2 visit as a timepoint for secondary endpoints 2, 3, 4 and 5 and as a timepoint for collecting samples for storage at the biobank. 7. Replacement of the principal investigator in Bologna University Hospital.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 March 2018	On 13th February 2018, the DSMB concluded during its regular meeting to recommend stopping one of the arms of the LIVERHOPE SAFETY study because of safety concerns. The decision to stop one of the arms of the trial was made because the data indicated that there was a higher prevalence of early study discontinuation (either because of adverse events or patient decision) in this group as compared with the other two groups. After extensive discussion within the executive committee of the LIVERHOPE SAFETY study and the Principal Investigators from the partner centers involved, the 16th February 2018 it was agreed unanimously to support this recommendation. This implied to stop therapy in those patients that were still active, but only in this specific treatment arm. In the other two arms, there were no safety concerns during the trial until that moment. Patients remaining active in the other two arms continued in the study until the end of the 12 week treatment period, the end of study according to the protocol. Only one patient was on treatment with the affected study arm and discontinued the study treatment the 16th February 2018. The blindness was maintained. The affected treatment arm has been identified at the time of the analysis of the results. The study arm concerned was Simvastatin 40mg + Rifaximin 400mg.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31607677