



## 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, pginés@clinic.cat |
| Scientific contact           | Pere Ginés, Hospital Clínic, +34 9322754001713, pginés@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 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     |
| <b>Arm title</b>             | 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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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          |                        |
| <b>Arm title</b>                                                      | 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            |                        |

| <b>Number of subjects in period 1</b> | 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     |
| <b>Arm title</b>             | 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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 2</b>             | 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:<br>Placebo of simvastatin + Placebo of rifaximin  |                   |
| Reporting group title                                                          | Simvastatin 20 mg |
| Reporting group description:<br>Simvastatin 20mg/day + Rifaximin 400mg/8 hours |                   |
| Reporting group title                                                          | Simvastatin 40 mg |
| Reporting group description:<br>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 |

  

|                                                    |       |  |  |
|----------------------------------------------------|-------|--|--|
| <b>Reporting group values</b>                      | 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:<br>Placebo of simvastatin + Placebo of rifaximin  |                   |
| Reporting group title                                                          | Simvastatin 20 mg |
| Reporting group description:<br>Simvastatin 20mg/day + Rifaximin 400mg/8 hours |                   |
| Reporting group title                                                          | Simvastatin 40 mg |
| Reporting group description:<br>Simvastatin 40 mg + Rifaximin 400 mg           |                   |
| Reporting group title                                                          | Placebo           |
| Reporting group description:<br>Placebo of simvastatin + Placebo of rifaximin  |                   |
| Reporting group title                                                          | Simvastatin 20 mg |
| Reporting group description:<br>Simvastatin 20mg/day + Rifaximin 400mg/8 hours |                   |
| Reporting group title                                                          | Simvastatin 40 mg |
| Reporting group description:<br>Simvastatin 40 mg + Rifaximin 400 mg           |                   |

### Primary: Liver toxicity

|                                                                                                                                                                                                                                                                                                                                                         |                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| End point title                                                                                                                                                                                                                                                                                                                                         | Liver toxicity |
| End point description:<br>(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:<br>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 | Simvastatina 40 |
|-----------------------|-----------------|

Reporting group description: -

| Serious adverse events                                              | Placebo         | Simvastatina 20 | Simvastatina 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 %

| <b>Non-serious adverse events</b>                                   | Placebo          | Simvastatina 20  | Simvastatina 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<br>occurrences (all) | 2 / 14 (14.29%)<br>4 | 1 / 14 (7.14%)<br>1 | 1 / 16 (6.25%)<br>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: <ol style="list-style-type: none"><li>1. Addition of the definition of women of child-bearing potential.</li><li>2. Addition of a urine pregnancy test at baseline.</li><li>3. Addition of a telephone contact visit 4 weeks after study completion.</li><li>4. Addition of cyclosporine and simeprevir as nonpermitted medication.</li><li>5. Correction of the group to which clarithromycin and telithromycin belong.</li><li>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.</li><li>7. Replacement of the principal investigator in Bologna University Hospital.</li></ol> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Restart date |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 12 March 2018 | <p>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.</p> <p>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.</p> <p>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.</p> <p>Only one patient was on treatment with the affected study arm and discontinued the study treatment the 16th February 2018. The blindness was maintained.</p> <p>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.</p> | -            |

Notes:

### Limitations and caveats

None reported

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## Online references

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