Clinical trial results:
Intestinal decontamination with rifaximin.
Effects on the inflammatory and circulatory state in patients with cirrhosis and ascites
- A randomised controlled clinical study

Summary

EudraCT number	2012-002890-71
Trial protocol	DK
Global end of trial date	31 December 2019
Results information	
Result version number	v1 (current)
This version publication date	07 April 2022
First version publication date	07 April 2022
Summary attachment (see zip file)	Primary outcomes Hepatology2017 (Hepatology2017vol65no2p592-603.pdf) Secondaryoutcomes_JGH2017 (JGH2017vol33bactDNA.pdf) Secondaryoutcomes_plosone2018 (PlosOne2018.pdf)

Trial information

Trial identification	
Sponsor protocol code	RifaxNK150612
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01739040
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Hvidovre University Hospital
Sponsor organisation address	Kettegaard Alle 30, Hvidovre, Denmark, 2650
Public contact	Department of Gastroenterology , Copenhagen University Hospital Hvidovre , 45 38623862,
Scientific contact	Department of Gastroenterology , Copenhagen University Hospital Hvidovre , 45 38623862,

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	31 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2019
Global end of trial reached?	Yes
Global end of trial date	31 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized clinical trial will be assessing the effect of rifaximin on pathophysiology and haemodynamics in the patient with decompensated liver cirrhosis, and addressing the effect of rifaximin on several organs on marker level.
We hypothesize that intestinal decontamination with rifaximin in patients with cirrhosis and ascites will interrupt bacterial translocation, diminish the following inflammatory response, prevent splanchnic vasodilatation and portal systemic contraction and thereby reduce the risk clinical complications to cirrhosis. Hence, rifaximin:

Will decrease portal pressure, measured as the hepatic venous pressure gradient (HVPG).
Will improve renal function expressed as an increase in glomerular filtration rate,

Protection of trial subjects:

Duration of study period was limited, study medication was distributed by oral administration.

Background therapy:

Standard therapy for decompensated liver cirrhosis, including nutritional support, betablockers and diuretics.

Evidence for comparator:

Comparator was placebo. We investigated the efficacy of rifaximin as add on to standard therapy. The evidence to support a beneficial effect of placebo is well-established.

Actual start date of recruitment	01 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	38
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled between February 2013 and December 2015 from six hospitals in the Capital Region of Denmark. 295 patients were screened for eligibility

Pre-assignment

Screening details:

Inclusion criteria: cirrhosis verified by clinical, biochemical, and ultrasound findings; ascites; age between 18 and 80 years; Portal Hypertension HVPG of 10 mm Hg or higher.
Exclusion criteria: cardiac, kidney or respiratory failure, invasive cancer; infection, atibiotics treatment, HE, hbg <5,5, use of alcohol, expected survival >3 months.

Pre-assignment period milestones

Number of subjects started	54
Number of subjects completed	54

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Patients were randomized in a 2:1 fashion using a computer-generated logarithm provided by our external data manager. Patients were identified by a single
four-digit randomization number. All patients and personnel were blinded to the treatment. Study medication was packed by the Hospital Pharmacy. Rifaximin and placebo
tablets were similar in color, size, shape, and packing. Decoding could only be perfromed by sponsor and PI in unison.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rifaximin

Arm description:

Rifaximin 1 tablet of 550 mg twice a day

Arm type	Experimental
Investigational medicinal product name	Rifaximin
Investigational medicinal product code	A07AA11
Other name	Xifaxan
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of 550 mg twice a day

Arm title	Placebo

Arm description:

Placebo treatment

Arm type	Placebo

Investigational medicinal product name	Rifaximin/placebo
Investigational medicinal product code	A07AA11
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet twice a day

Number of subjects in period 1	Rifaximin	Placebo
Started	36	18
Completed	36	18

Baseline characteristics

Reporting groups	
Reporting group title	Rifaximin
Reporting group description:	
Rifaximin 1 tablet of 550 mg twice a day	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment	

Reporting group values	Rifaximin	Placebo	Total
Number of subjects	36	18	54
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	58.5	52.5	
full range (min-max)	33 to 68	34 to 74	-
Gender categorical			
Units: Subjects			
Female	5	4	9
Male	31	14	45

End points

End points reporting groups

Reporting group title	Rifaximin
Reporting group description:	
Rifaximin 1 tablet of 550 mg twice a day	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment	

Primary: Hepatic venous pressure gradient

End point title	Hepatic venous pressure gradient[1]
End point description:	
we measured hepatic venous pressure gradient at baseline and at 4 weeks after treatment	
End point type	Primary
End point timeframe:	
baseline and 4 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Full data set is posted, published results including statistics are posted

End point values	Rifaximin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	18		
Units: mmHg				
number (not applicable)	16.6	16.4		

Statistical analyses

No statistical analyses for this end point

Primary: Glomerular filtration rate

End point title	Glomerular filtration rate[2]
End point description:	
End point type	Primary
End point timeframe:	
from baseline and 4 weeks	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Full data set is posted, published results including statistics are posted

End point values	Rifaximin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	18		
Units: ml/hour				
number (not applicable)	84.7	77.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from inclusion to end of treatment plus one week. In total 5 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Rifaximin
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Rifaximin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 36 (11.11%)	1 / 18 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 36 (2.78%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Spontaneous bacterial peritonitis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	1 / 36 (2.78%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rifaximin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 36 (88.89%)	16 / 18 (88.89%)	
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	0 / 36 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 36 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	4	2	
Gastrointestinal disorders			
mild abdominal pain			
subjects affected / exposed	6 / 36 (16.67%)	1 / 18 (5.56%)	
occurrences (all)	6	1	
Reflux gastritis			
subjects affected / exposed	1 / 36 (2.78%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	5 / 36 (13.89%)	1 / 18 (5.56%)	
occurrences (all)	5	1	
Constipation			
subjects affected / exposed	4 / 36 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Flatulence			
subjects affected / exposed	1 / 36 (2.78%)	1 / 18 (5.56%)	
occurrences (all)	1	1	

Vomiting			
subjects affected / exposed	2 / 36 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	2 / 36 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
c. diff			
subjects affected / exposed	0 / 36 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hunger			
subjects affected / exposed	0 / 36 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 36 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Haematochezia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Masticatory pain			
subjects affected / exposed	2 / 36 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 36 (2.78%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	0 / 36 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 36 (2.78%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	4 / 36 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	4	2	
fall			
subjects affected / exposed	1 / 36 (2.78%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 36 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28671712

http://www.ncbi.nlm.nih.gov/pubmed/27775818

http://www.ncbi.nlm.nih.gov/pubmed/30183743