Clinical trial results:
A placebo controlled single centre double blind randomised trial to investigate the efficacy of rifaximin versus placebo in improving systemic inflammation and neutrophil malfunction in patients with cirrhosis and chronic hepatic encephalopathy

Summary

EudraCT number	2013-004708-20
Trial protocol	GB
Global end of trial date	29 July 2016

Results information

Result version number	v1 (current)
This version publication date	05 December 2018
First version publication date	05 December 2018
Summary attachment (see zip file)	FINAL STUDY REPORT (RIFSYS Scientific Report_VCP_FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	RIFSYS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02019784
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Debbie Shawcross, King's College London, 44 2032993713, debbie.shawcross@kcl.ac.uk
Scientific contact	Debbie Shawcross, King's College London, 44 2032993713, debbie.shawcross@kcl.ac.uk
Sponsor organisation name	King's College Hospital
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE59RS
Public contact	Debbie Shawcross, King's College Hospital NHS Foundation Trust, 44 2032993713, debbie.shawcross@kcl.ac.uk
Scientific contact	Debbie Shawcross, King's College Hospital NHS Foundation Trust, 44 2032993713, debbie.shawcross@kcl.ac.uk

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	29 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2016
Global end of trial reached?	Yes
Global end of trial date	29 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test if rifaximin reduces neutrophil spontaneous oxidative burst ex vivo in patients with cirrhosis and chronic hepatic encephalopathy after 30 days.

Protection of trial subjects:

Participants eligible for this study with cirrhosis and hepatic encephalopathy may be unable to provide informed consent due to cognitive impairment arising from hepatic encephalopathy or pharmacologic sedation. In this situation where the potential participant is unable to consent, an appropriate legal representative will be sought. The legal representative will most often be a close personal contact of the potential participant e.g. the patient's next of kin. They will be suitable to act as the legal representative by the virtue of their relationship, availability and their willingness to do so. In the process of considering inclusion into the study, the patient's wishes and feelings will be assessed and written information will be provided in the form of a 'legal representative information sheet'. After an appropriate time period (minimum 24 hours) and the opportunity to ask any questions, the legal representative will sign a 'legal representative consent form'.

Background therapy:

None

Evidence for comparator: -

Actual start date of recruitment	10 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from one centre in London UK.

Pre-assignment

Screening details:

Patients with established cirrhosis complicated by hepatic encephalopathy will be recruited to this study. For the purposes of this study a patient will be considered to have cirrhosis if they fulfil two out of the three diagnostic criteria of confirmatory liver histology, biochemistry and/or radiologic findings consistent with cirrhosis/portal hy

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

Blinding implementation details:

The double-blind supplies of Rifaximin-α (TARGAXAN *, manufactured by Alfa-Wasserman, Bologna, Italy) will be in blister packs each containing 14 tablets of 550mg. Matching placebo (manufactured by Alfa-Wasserman, Bologna, Italy) will also be supplied in blister packs each containing 14 tablets with accompanying stability data of appropriate standard. In order to maintain blinding, the study drug and placebo will be packaged in an identical anonymised fashion.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A - Active

Arm description:

Rifaximin-α 550mg BID

Arm type	Experimental
Investigational medicinal product name	Rifaximin-α
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rifaximin-α 550mg BID for 90 days

Arm title	Group B - Placebo

Arm description:

Placebo BID for 90 days

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo BID for 90 days orally.

Number of subjects in period 1	Group A - Active	Group B - Placebo
Started	19	19
Completed	13	13
Not completed	6	6
Death due to disease progression	2	3
Consent withdrawn by subject	2	1
Patient underwent transplant	1	-
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	38	38	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	34	34	
From 65-84 years	4	4	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	11	11	
Male	27	27	

End points

End points reporting groups

Reporting group title	Group A - Active
Reporting group description: Rifaximin-α 550mg BID	
Reporting group title	Group B - Placebo
Reporting group description: Placebo BID for 90 days	

Primary: Clinical Endpoint

End point title	Clinical Endpoint[1]
End point description: A reduction in spontaneous neutrophil oxidative burst of 50% compared to baseline (as measured by the Burstest which measures the spontaneous production of reactive oxygen species) 30 days following the start of rifaximin-α/placebo therapy.	
End point type	Primary
End point timeframe: 30 days following start of IMP	

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: Please see attached documents for results.

End point values	Group A - Active	Group B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: whole	13	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic Inflammation Reduction

End point title	Systemic Inflammation Reduction
End point description: A reduction in systemic inflammation as measured by plasma endotoxaemia, bacterial DNA quantification and plasma pro-inflammatory cytokine profile at 90 days.	
End point type	Secondary
End point timeframe: 90 days post cmmencement of IMP	

End point values	Group A - Active	Group B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: whole	13	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Neutrophil

End point title	Neutrophil

End point description:

An improvement in neutrophil bacteriocidal capacity as measured by the Phagotest which utilises opsonised E. coli at 30 and 90 days.
An improvement in neutrophil phenotype and function including baseline and LPS-induced toll-like receptor 4 expression and intracellular cytokine production at 30 and 90 days.

End point type	Secondary

End point timeframe:

30 and 90 days post commencement of IMP

End point values	Group A - Active	Group B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: whole	13	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Faecal

End point title	Faecal

End point description:

Alterations in faecal microbiota at 90 days.
Reduction in intestinal permeability and changes in faecal biomarkers (calprotectin) at 90 days.

End point type	Secondary

End point timeframe:

90 Days post Commencement of IMP

End point values	Group A - Active	Group B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: whole	13	13		

Statistical analyses

No statistical analyses for this end point

Secondary: plasma metabonomic profile

End point title	plasma metabonomic profile

End point description:

Changes in urinary and plasma metabonomic profile as measured by proton MR spectroscopy at 90 days.

End point type	Secondary

End point timeframe:

90 days post commencement of IMP

End point values	Group A - Active	Group B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: whole	13	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Hepatic Encephalopathy

End point title	Hepatic Encephalopathy

End point description:

Development of recurrent overt hepatic encephalopathy, organ failure and infection during the 90 day follow up.
Improvement in Psychometric Hepatic Encephalopathy Score including Trails A and B neuropsychiatric test scores at 30 and 90 days

End point type	Secondary

End point timeframe:

90 days post IMP commencement

End point values	Group A - Active	Group B - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: whole	13	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Until 30 days post final IMP dose for each patient.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	Group A - Active
Reporting group description: -	
Reporting group title	Group B - Placebo
Reporting group description: -	

Serious adverse events	Group A - Active	Group B - Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	1	0	
Gastrointestinal disorders			
Bowel Perforation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Group A - Active	Group B - Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 19 (89.47%)	19 / 19 (100.00%)	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

Hepatobiliary disorders			
Ascites			
subjects affected / exposed	9 / 19 (47.37%)	17 / 19 (89.47%)	
occurrences (all)	9	17	
Spontaneous bacterial peritonitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Variceal haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Hepatocellular encephalopathy			
subjects affected / exposed	0 / 19 (0.00%)	6 / 19 (31.58%)	
occurrences (all)	0	0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 19 (5.26%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2014	Change to IMP labels.
23 September 2015	change to eligibility criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported