



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