Clinical trial results:
The effect of probiotics on the incidence of spontaneous bacterial peritonitis in patients with cirrhosis and ascites.

Summary

EudraCT number	2010-022886-92
Trial protocol	GB
Global end of trial date	08 October 2014

Results information

Result version number	v1 (current)
This version publication date	25 July 2016
First version publication date	25 July 2016
Summary attachment (see zip file)	10GA021 VSL3 End of Study Report (10GA021_End-of-Study-Report_VSL#3_2010-022886-92_signed.pdf) Appendix 1 - Protocol Deviations (Appendix 1_ Log of protocol deviations.pdf) Appendix 5 - Log of Serious Adverse Events (Appendix 5_Log of Serious Adverse Events.pdf) Appendix 2 - Participant Consent Form (Appendix 2_PCF.pdf) Appendix 3 - Participant Information Sheet (Appendix 3_PIS.pdf) Appendix 4 - Log of AEs (Appendix 4_Log of Adverse Events.pdf) Appendix 6 - Visit Schedule (Appendix 6_Participant Visit Schedule.pdf) Appendix 7 - Participant Data (Appendix 7_Participant Data.pdf)

Trial information

Trial identification

Sponsor protocol code	10GA021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01701297
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nottingham University Hospitals NHS Trust
Sponsor organisation address	QMC, Derby Road, Nottingham, United Kingdom, NG7 2UH
Public contact	Research & Innovation Dept, Nottingham University Hospitals NHS Trust, +44 01159249924, researchsponsor@nuh.nhs.uk
Scientific contact	Research & Innovation Dept, Nottingham University Hospitals NHS Trust, +44 01159249924, researchsponsor@nuh.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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	08 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2014
Global end of trial reached?	Yes
Global end of trial date	08 October 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Do oral probiotics (VSL#3 sachets)or oral antibiotics (cotrimoxazole) reduce the incidence and severity of liver-related complications in cirrhotic patients with ascites?

Protection of trial subjects:

Eligibility criteria ensured that participants were not recruited to the study if there were likely to be an known contra-indications to the IMPs. Safety reporting was adhered to according to Directive 2001/20/EC and the investigator was able to unblind and withdraw participants if necessary.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2013
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: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	7
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

VSL3 was a single centre study open to recruitment at Nottingham University Hospitals NHS Trust only. The first participant consent was taken on 13th March 2013 and the final participant consent was on 9th December 2013. Recruitment ended on the 8th October 2014 when the study was stopped prematurely.

Pre-assignment

Screening details:

Patients having ascitic samples taken to investigate the cause or to exclude infection (SBP) were considered for the study. 334 patient's records were reviewed to consider eligibility. 17 consented to be screened for the study and 10 were randomised. 1 of the 10 patients was withdrawn due to active infection found following the ascitic sample.

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, Data analyst, Carer, Assessor

Blinding implementation details:

Sachets were plain white and indistinguishable from placebo sachets, but labelled with a study/code number, and provided by VSL#3 pharmaceuticals. The study medications were supplied as matched appearance sachets for active and placebo VSL3 and as open label cotrimoxazole tablets. Tablets and sachet counts were confirmed with patients at each study visit to document compliance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Probiotic VSL#3

Arm description:

VSL#3 probiotic preparations. Each packet of VSL#3® contained 450 billion live lactic acid bacteria and bifidobacteria. There are 8 different strains of bacteria contained in VSL#3: Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii subsp. Bulgaricus. Other ingredients included maltose and silicon dioxide.
The prescribed dose was 2 sachets (containing 900 billion bacteria) orally each day. Sachets were plain white and indistinguishable from placebo sachets, but labelled with a study/code number, and provided by VSL#3 pharmaceuticals. Probiotics and placebo sachets should have been opened and the contents stirred into cold water or another non-fizzy cold drink (but not with hot drinks or hot food). Study patients were prohibited from taking any other probiotics during the study (such as Yakult®).

Arm type	Experimental
Investigational medicinal product name	VSL#3®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

The prescribed dose was 2 sachets (containing 900 billion bacteria) orally each day for 48 weeks. Probiotics and placebo sachets should have been opened and the contents stirred into cold water or another non-fizzy cold drink (but not with hot drinks or hot food).

Arm title	VSL#3 Placebo

Arm description:

VSL#3 Placebo. This was two placebo sachets identical to VSL#3 active sachet.

Arm type	Placebo

Investigational medicinal product name	VSL#3 Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

VSL#3 Placebo. This was two placebo sachets identical to VSL#3 active sachet. The prescribed dose was 2 sachets orally each day for 48 weeks. Sachets were plain white and indistinguishable from active sachets, but labelled with a study/code number, and provided by VSL#3 pharmaceuticals. Probiotics and placebo sachets should have been opened and the contents stirred into cold water or another non-fizzy cold drink (but not with hot drinks or hot food).

Arm title	Co-trimoxazole

Arm description:

Cotrimoxazole 960mg orally each day (two 480mg tablets). Cotrimoxazole is a combination of sulfamethoxazole (800mg) and trimethoprim (160mg). This was supplied by NUH clinical trials pharmacy and is the standard dose for prophylaxis of spontaneous bacterial peritonitis in clinical practice. Cotrimoxazole antibiotics were to be taken with food or any drink

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

Dosage and administration details:

960mg orally each day (two 480mg tablets) for 48 weeks. Cotrimoxazole antibiotics were to be taken with food or any drink

Number of subjects in period 1	Active Probiotic VSL#3	VSL#3 Placebo	Co-trimoxazole
Started	4	4	2
Completed	2	2	1
Not completed	2	2	1
Ineligible	1	-	-
Consent withdrawn by subject	-	-	1
Study termination (lack of drug supply)	1	2	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	10	10	
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)	7	7	
From 65-84 years	3	3	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	5	5	
Male	5	5	

End points

End points reporting groups

Reporting group title	Active Probiotic VSL#3

Reporting group description:

VSL#3 probiotic preparations. Each packet of VSL#3® contained 450 billion live lactic acid bacteria and bifidobacteria. There are 8 different strains of bacteria contained in VSL#3: Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii subsp. Bulgaricus. Other ingredients included maltose and silicon dioxide.
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Reporting group title	VSL#3 Placebo

Reporting group description:

VSL#3 Placebo. This was two placebo sachets identical to VSL#3 active sachet.

Reporting group title	Co-trimoxazole

Reporting group description:

Cotrimoxazole 960mg orally each day (two 480mg tablets). Cotrimoxazole is a combination of sulfamethoxazole (800mg) and trimethoprim (160mg). This was supplied by NUH clinical trials pharmacy and is the standard dose for prophylaxis of spontaneous bacterial peritonitis in clinical practice. Cotrimoxazole antibiotics were to be taken with food or any drink

Primary: Liver related mortality

End point title	Liver related mortality[1]

End point description:

End point type	Primary

End point timeframe:

Liver-related mortality from enrolment onto the study until the end of the study period (48 weeks of study treatment)

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 analysis not completed due to premature discontinuation

End point values	Active Probiotic VSL#3	VSL#3 Placebo	Co-trimoxazole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[2]	2[3]	2[4]	
Units: Deaths	1	1	0	

Notes:

[2] - Full analysis not completed due to premature discontinuation.

[3] - Full analysis not completed due to premature discontinuation

[4] - Full analysis not completed due to premature discontinuation

Statistical analyses

No statistical analyses for this end point

Primary: Liver related morbidity

End point title	Liver related morbidity[5]

End point description:

admission for any liver-related complication and the number of days hospitalisation

End point type	Primary

End point timeframe:

From time of enrolment until end of trial (48 weeks of study treatment)

Notes:

[5] - 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 analysis not completed due to premature discontinuation

End point values	Active Probiotic VSL#3	VSL#3 Placebo	Co-trimoxazole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[6]	2[7]	2[8]	
Units: Hospital admissions	1	1	0	

Notes:

[6] - Full analysis not completed due to premature discontinuation

[7] - Full analysis not completed due to premature discontinuation

[8] - Full analysis not completed due to premature discontinuation

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from date of consent until the participant's last visit or date of completion/withdrawal.

Adverse event reporting additional description:

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Active Probiotic VSL#3

Reporting group description:

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The prescribed dose was 2 sachets (containing 900 billion bacteria) orally each day. Sachets were plain white and indistinguishable from placebo sachets, but labelled with a study/code number, and provided by VSL#3 pharmaceuticals. Probiotics and placebo sachets should have been opened and the contents stirred into cold water or another non-fizzy cold drink (but not with hot drinks or hot food). Study patients were prohibited from taking any other probiotics during the study (such as Yakult®).

Reporting group title	VSL#3 Placebo

Reporting group description:

VSL#3 Placebo. This was two placebo sachets identical to VSL#3 active sachet.

Reporting group title	Co-trimoxazole

Reporting group description:

Cotrimoxazole 960mg orally each day (two 480mg tablets). Cotrimoxazole is a combination of sulfamethoxazole (800mg) and trimethoprim (160mg). This was supplied by NUH clinical trials pharmacy and is the standard dose for prophylaxis of spontaneous bacterial peritonitis in clinical practice. Cotrimoxazole antibiotics were to be taken with food or any drink

Serious adverse events	Active Probiotic VSL#3	VSL#3 Placebo	Co-trimoxazole
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	2 / 2 (100.00%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	1	0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 2 (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
Hepatobiliary disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 2 (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
Jaundice			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 2 (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
alcoholic liver disease			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Active Probiotic VSL#3	VSL#3 Placebo	Co-trimoxazole
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	0 / 2 (0.00%)
Surgical and medical procedures			

Tooth extraction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Blood transfusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
acid reflux			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
constipation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	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? Yes

Date	Interruption	Restart date
08 October 2014	The IMP was shipped to NUH at the end of 2013, however the IMP remained in quarantine in Pharmacy pending QP release certification to be issued from the manufacturer (VSL3). Numerous attempts were made to acquire the documentation to no avail and given this had been going on for nine months, the decision has come to close the trial. Premature discontinuation of the trial.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to premature discontinuation of the trial, a full analysis could not be performed.

Notes: