Clinical trial results:
A Prospective, randomised placebo controlled feasibility trial of Faecal Microbiotica Transplantation in cirrhosis

Summary

EudraCT number	2017-003629-13
Trial protocol	GB
Global end of trial date	17 October 2019

Results information

Result version number	v1 (current)
This version publication date	15 October 2020
First version publication date	15 October 2020
Summary attachment (see zip file)	Clinical Study report (PROFIT CSR 17Sep20 final.pdf)

Trial information

Trial identification

Sponsor protocol code	PROFIT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02862249
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	Professor Debbie Shawcross, King's College London, 44 2032993713, debbie.shawcross@kcl.ac.uk
Scientific contact	Professor Debbie Shawcross, King's College London, 44 2032993713, debbie.shawcross@kcl.ac.uk
Sponsor organisation name	King's College Hospital NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 9RS
Public contact	Professor Debbie Shawcross, King's College London, 44 2032993713, debbie.shawcross@kcl.ac.uk
Scientific contact	Professor Debbie Shawcross, King's College London, 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	01 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2019
Global end of trial reached?	Yes
Global end of trial date	17 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether stabilising gut dysbiosis with FMT in patients with advanced cirrhosis is both feasible and safe

Protection of trial subjects:

A trial participant has the liberty to withdraw their consent at any time and for any reason, without penalty or loss of benefits to which the individual would otherwise be entitled. Participants who withdraw consent will discontinue their participation in the trial and no further data will be collected. Prior to giving consent, recipients will be informed that they are able to request the destruction of stored biological samples (e.g. blood/stool) upon withdrawal, and that this will only be possible for samples that have not been tested at the time of withdrawal. Participants will not be able to request the deletion of data generated from tested samples.
The DMEC’s role was to ensure safety of trial participants and review the interim data to ensure safety of trial continuation.

Background therapy:

Patients received 2L of Moviprep®, one litre at 6pm the night before the endoscopy and the second litre at 6am on the morning of the endoscopy. Patients were required to be nil by mouth for 6 hours prior to the endoscopy.

Evidence for comparator: -

Actual start date of recruitment	23 May 2018
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: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	15
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Thirty-two patients were recruited from outpatient clinics and the hepatology wards at King's College Hospital, including two patients who were referred from Kingston Hospital. Subjects were recrited in a 12 month period from 23/05/2018.

Pre-assignment

Screening details:

At the screening visit consent forms signed and bloods checked for the MELD score and HIV serology. If the patient met the inclusion criteria, they attended the baseline visit where they were reviewed in the Clinical Research Facility by the research team. Concomitant medications, medical and surgical histories were confirmed.

Pre-assignment period milestones

Number of subjects started	318[1]
Number of subjects completed	23

Pre-assignment subject non-completion reasons

Reason: Number of subjects	ineligible: 286
Reason: Number of subjects	Consent withdrawn by subject: 9

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Includes screen fails who were not enrolled in the study

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

IMP was delivered out of the patient's sight, so as not to unblind them to the treatment allocation. All efforts were made to maintain blinding of the treatment allocation to the patient, but the study investigators were not blinded as the placebo and FMT solutions were not matched.

Arms

Are arms mutually exclusive?	Yes
Arm title	Faecal microbiota transplantation (FMT)

Arm description:

Faecal microbiota transplantation (FMT) derived from a healthy donor (200mls- less small aliquot for archiving) administered via a gastroscope into the duodenum following preparation of the bowel with 2 sachets of MoviPrep® [PEG-3350, sodium sulphate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution 100g, 7.5g, 2.691g, 1.051g, 5.9g, 4.7g

Arm type	Experimental
Investigational medicinal product name	Faecal Microbiota for Transplantation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastroenteral liquid
Routes of administration	Intraduodenal use

Dosage and administration details:

190ml administered via a gastroscope into the duodenum following preparation of the bowel with 2 sachets of MoviPrep® [PEG-3350, sodium sulphate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution 100g, 7.5g, 2.691g, 1.051g, 5.9g, 4.7g].

Arm title	Placebo

Arm description:

Placebo solution (200mls 0.9% normal saline and 12.5% glycerol) administered via a gastroscope into the duodenum following preparation of the bowel with 2 sachets of MoviPrep®.

Arm type	Placebo
Investigational medicinal product name	200mls 0.9% normal saline and 12.5% glycerol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastroenteral liquid
Routes of administration	Intraduodenal use

Dosage and administration details:

Placebo solution (200mls 0.9% normal saline and 12.5% glycerol) administered via a gastroscope into the duodenum following preparation of the bowel with 2 sachets of MoviPrep®.

Number of subjects in period 1	Faecal microbiota transplantation (FMT)	Placebo
Started	17	6
Completed	15	6
Not completed	2	0
Consent withdrawn by subject	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Faecal microbiota transplantation (FMT)
Reporting group description:	
Faecal microbiota transplantation (FMT) derived from a healthy donor (200mls- less small aliquot for archiving) administered via a gastroscope into the duodenum following preparation of the bowel with 2 sachets of MoviPrep® [PEG-3350, sodium sulphate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution 100g, 7.5g, 2.691g, 1.051g, 5.9g, 4.7g	
Reporting group title	Placebo
Reporting group description:	
Placebo solution (200mls 0.9% normal saline and 12.5% glycerol) administered via a gastroscope into the duodenum following preparation of the bowel with 2 sachets of MoviPrep®.	

Reporting group values	Faecal microbiota transplantation (FMT)	Placebo	Total
Number of subjects	17	6	23
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			
arithmetic mean	57.3	56.8	
standard deviation	± 11.1	± 11.8	-
Gender categorical Units: Subjects			
Female	4	2	6
Male	13	4	17
Ethnicity Units: Subjects			
White	15	3	18
Black	0	1	1
Asian	0	2	2
Mixed	0	0	0
Other	2	0	2
Smoking Status Units: Subjects			
Current	5	1	6
Ex-smoker	5	1	6
Never smoker	7	4	11

Height			
Units: cm			
arithmetic mean	170.9	165.5	
standard deviation	± 10.6	± 11.3	-
Weight			
Units: kg			
arithmetic mean	86.9	73.7	
standard deviation	± 19.7	± 20.9	-

End points

End points reporting groups

Reporting group title	Faecal microbiota transplantation (FMT)

Reporting group description:

Faecal microbiota transplantation (FMT) derived from a healthy donor (200mls- less small aliquot for archiving) administered via a gastroscope into the duodenum following preparation of the bowel with 2 sachets of MoviPrep® [PEG-3350, sodium sulphate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution 100g, 7.5g, 2.691g, 1.051g, 5.9g, 4.7g

Reporting group title	Placebo

Reporting group description:

Placebo solution (200mls 0.9% normal saline and 12.5% glycerol) administered via a gastroscope into the duodenum following preparation of the bowel with 2 sachets of MoviPrep®.

Primary: Assessment of Safety

End point title	Assessment of Safety[1]

End point description:

Assessment of the safety of FMT:
• Incidence of any transmissable bacterial or viral infection that is deemed to have been acquired from the donor including Clostridiodes difficile infection.
• The development of any Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR) that is not pre-specified or is a known consequence of disease progression or complication of cirrhosis that:
Results in death
Is life-threatening
Required hospitalisation or prolongation of existing hospitalisation
Results in persistent or significant disability or incapacity

End point type	Primary

End point timeframe:

Day 1 (endoscopy) to Day 90

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 report for analyses

End point values	Faecal microbiota transplantation (FMT)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	6		
Units: Number of SAEs				
SAE	8	1		
SAR	0	0		
USAR	0	0		
Incidence of any transmissable bacterial or viral	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Assess tolerability of FMT e.g reflux rates

End point title	Assess tolerability of FMT e.g reflux rates[2]

End point description:

End point type	Primary

End point timeframe:

Administration to 2 hours

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: Please see attached report for analyses

End point values	Faecal microbiota transplantation (FMT)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	6		
Units: Subjects				
Vomit within 2 hours	1	0		
Type 6/7 bowel motion within 2 hours	3	0		

Statistical analyses

No statistical analyses for this end point

Primary: Assess recruitment rates

End point title	Assess recruitment rates[3]

End point description:

End point type	Primary

End point timeframe:

Randomization to 90 days

Notes:

[3] - 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 report for analyses

End point values	Faecal microbiota transplantation (FMT)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	6		
Units: Subjects				
Received Intervention	15	6		
Completed 7 day FU	15	6		
Completed 30 day FU	15	6		
Completed 90 day FU	15	5		

Statistical analyses

No statistical analyses for this end point

Secondary: improvement in global liver synthetic function as assessed by the MELD score

End point title	improvement in global liver synthetic function as assessed by the MELD score

End point description:

End point type	Secondary

End point timeframe:

Baseline to 90 days

End point values	Faecal microbiota transplantation (FMT)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	6		
Units: MELD Score				
arithmetic mean (standard deviation)				
Baseline	9.7 (± 2.84)	9.76 (± 3.63)		
90 Days	10.20 (± 3.8)	8.92 (± 3.03)		
Change (90 days-Baseline)	-0.58 (± 2.18)	-1.83 (± 1.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Development of overt hepatic encephalopathy

End point title	Development of overt hepatic encephalopathy

End point description:

The development of organ failure (hypotension requiring inotropic support, respiratory failure requiring ventilator support or the development of acute kidney injury requiring renal replacement therapy) and infection

End point type	Secondary

End point timeframe:

Baseline to 90 days

End point values	Faecal microbiota transplantation (FMT)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	6		
Units: Westhaven Criteria >=grade1				
Baseline	5	1		
90 days	7	1		

Statistical analyses

No statistical analyses for this end point

Secondary: The development of any infection

End point title	The development of any infection

End point description:

The development of any infection during the 90 day follow up including chest, urinary, stool, ascites and blood infection.

End point type	Secondary

End point timeframe:

Baseline to 90 days

End point values	Faecal microbiota transplantation (FMT)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	6		
Units: Number				
7 days	1	0		
30 days	1	0		
90 days	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The development of organ failure

End point title	The development of organ failure

End point description:

The development of organ failure (hypotension requiring inotropic support, respiratory failure requiring

ventilator support or the development of acute kidney injury requiring renal replacement therapy) and infection

End point type	Secondary

End point timeframe:

Baseline to 90 days

End point values	Faecal microbiota transplantation (FMT)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	6		
Units: Number				
by 90 days	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period for AE reporting was from the date of the intervention up until 90 days post intervention.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	FMT- faecal microbiota transplantation
Reporting group description: -	
Reporting group title	PLacebo

Reporting group description: -

Serious adverse events	FMT- faecal microbiota transplantation	PLacebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 15 (26.67%)	1 / 6 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal bleeding			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
lesion			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (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: 0 %

Non-serious adverse events	FMT- faecal microbiota transplantation	PLacebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	6 / 6 (100.00%)	
Nervous system disorders			

neurological disorder			
subjects affected / exposed	4 / 15 (26.67%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
General disorders and administration site conditions			
other			
subjects affected / exposed	13 / 15 (86.67%)	5 / 6 (83.33%)	
occurrences (all)	29	5	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	3 / 6 (50.00%)	
occurrences (all)	1	3	
Constipation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Gastrointestinal disorder			
subjects affected / exposed	2 / 15 (13.33%)	2 / 6 (33.33%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	
occurrences (all)	4	3	
Infections and infestations			
Infection			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2018	IMPD updated to change container

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Mechanistic analyses are in progress and the manuscript is currently being drafted.

Notes: