Clinical trial results:
A randomised placebo controlled trial of follow on Rifaximin for the prevention of relapse of Clostridium difficile associated diarrhoea.

Summary

EudraCT number	2012-003205-10
Trial protocol	GB
Global end of trial date	10 December 2016

Results information

Result version number	v1
This version publication date	31 December 2018
First version publication date	31 December 2018
Summary attachment (see zip file)	RAPID trial published in Gut (Major, 2018 RAPID trial full paper gutjnl-2018-316794.full.pdf)

Trial information

Trial identification

Sponsor protocol code	12072

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	Kingsmeadow campus, Nottingham, United Kingdom, NG7 2NR
Public contact	Spiller, University of Nottingham, 44 01158231090, robin.spiller@nottingham.ac.uk
Scientific contact	Spiller, University of Nottingham, 44 01158231090, robin.spiller@nottingham.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	10 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2016
Global end of trial reached?	Yes
Global end of trial date	10 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To look at whether a course of Rifaximin after a patient has been successfully treated for C.difficile diarrhoeal infection with a standard course of antibiotics can reduce the rate of the infection returning (recurrence)

Protection of trial subjects:

Usual measures Very safe drug so risk small

Background therapy:

None

Evidence for comparator:

Placebo controlled as unclear if intervention was beneficial

Actual start date of recruitment	11 December 2012
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: 151
Worldwide total number of subjects	151
EEA total number of subjects	151

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)	45
From 65 to 84 years	99
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between 11 December 2012 and 7 March 2016. Those eligible for inclusion (see online supplementary file 1) were adults aged 18 years or older with a confirmed case of CDI that was successfully treated with metronidazole or vancomycin. This included primary, recurrent and multiply recurrent CDI episodes.

Pre-assignment

Screening details:

Participants were recruited between 11 December 2012 and 7 March 2016. Those eligible for inclusion (see online supplementary file 1) were adults aged 18 years or older with a confirmed case of CDI that was successfully treated with metronidazole or vancomycin. This included primary, recurrent and multiply recurrent CDI episodes.

Pre-assignment period milestones

Number of subjects started	2157[1]
Number of subjects completed	151

Pre-assignment subject non-completion reasons

Reason: Number of subjects	did not meet eligibility: 736
Reason: Number of subjects	declined to participate: 460
Reason: Number of subjects	other: 443
Reason: Number of subjects	consent unobtainable: 138
Reason: Number of subjects	unable to contact: 136
Reason: Number of subjects	unknown: 93

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: The numbers in the preassignment period were approached to take part but did not and so were not enrolled

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:

Participants were given 126 tablets, containing either rifaximin 200 mg or an identical placebo formulation.

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo

Arm description:

Identical tablets to active

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:

2 tablets t.d.s. for 2 weeks then 1 tablet t.d.s. for 2 weeks

Arm title	Active

Arm description:

The intended treatment regime was two tablets (400 mg rifaximin)
taken three times a day for 14 days, reduced to one tablet
(200 mg) three times a day for a further 14 days.

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

Dosage and administration details:

two tablets (400 mg rifaximin)
taken three times a day for 14 days, reduced to one tablet
(200 mg) three times a day for a further 14 days.

Number of subjects in period 1	Placebo	Active
Started	74	77
Completed	61	69
Not completed	13	8
Consent withdrawn by subject	8	7
death	5	1

Baseline characteristics

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Identical tablets to active	
Reporting group title	Active
Reporting group description:	
The intended treatment regime was two tablets (400 mg rifaximin) taken three times a day for 14 days, reduced to one tablet (200 mg) three times a day for a further 14 days.	
Subject analysis set title	Full set
Subject analysis set type	Full analysis
Subject analysis set description:	
All analyses were conducted according to allocated group (placebo or rifaximin) regardless of the amount of tablets actually taken.	

Primary: CDI recurrence within 12 weeks of randomisation.

End point title	CDI recurrence within 12 weeks of randomisation.
End point description:	
The primary outcome was CDI recurrence within 12 weeks of randomisation. A recurrence was defined as three or more loose stools for two or more days in conjunction with a positive stool toxin assay. The primary outcome was determined by research nurses in each site confirming stool frequency with the study subject by direct questioning, together with the laboratory results.	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	Placebo	Active	Full set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61[1]	69	130	
Units: number of patients in whom CDI recurred				
CDI recurrence within 12 weeks	18	11	29	

Notes:

[1] - 8 withdrew 5 died

Statistical analyses

Statistical analysis title	generalised estimating equation
Statistical analysis description:	
Analyses were carried out using Stata/SE 13.1. All analyses were conducted according to allocated group (placebo or rifaximin) regardless of the amount of tablets actually taken. The primary analysis estimated the difference in percentage CDI recurrence between rifaximin and placebo groups at 12 weeks without imputation of missing outcome data. A generalised estimating equation was used with binomial family, identity link and	

an exchangeable correlation matrix to account for randomisation

Comparison groups	Active v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	-13.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.1
upper limit	0.7
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: weeks 1-8	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15
Reporting groups	
Reporting group title	placebo
Reporting group description: Placebo arm	
Reporting group title	rifaximin
Reporting group description: active treatment arm	

Serious adverse events	placebo	rifaximin	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 74 (20.27%)	12 / 77 (15.58%)	
number of deaths (all causes)	5	1	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
haemorhage	Additional description: GASTROINTESTINAL HAEMORRHAGE		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 74 (1.35%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	5 / 74 (6.76%)	4 / 77 (5.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 74 (2.70%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 74 (2.70%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cellulitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 74 (4.05%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture	Additional description: hip fracture		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	placebo	rifaximin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 74 (24.32%)	21 / 77 (27.27%)	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed occurrences (all)	18 / 74 (24.32%) 18	21 / 77 (27.27%) 21	

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

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

did not achieve intended recruitment numbers which were 180

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30254135