Clinical trial results:
Efficacy and mode of action of mesalazine in the treatment of diarrhoea-predominant irritable bowel syndrome (IBS-D).

Summary

EudraCT number	2010-018340-14
Trial protocol	GB
Global end of trial date	30 May 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	27 April 2016
Summary attachment (see zip file)	MIBS Synopsis (Synopsis Efficacy and mode of action of mesalazine in the treatment of diarrhoea-predominant irritable bowel syndrome (IBS-D)..pdf)

Trial information

Trial identification

Sponsor protocol code	10085

Additional study identifiers

ISRCTN number	ISRCTN76612274
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	Lenton Lane, Nottingham, United Kingdom, NG7 2NR
Public contact	Robin Spiller, University of Nottingham, robin.spiller@nottingham.ac.uk
Scientific contact	Robin Spiller, University of Nottingham, 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	30 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 May 2014
Global end of trial reached?	Yes
Global end of trial date	30 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of mesalazine on stool frequency.

Protection of trial subjects:

n/a

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2011
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: 136
Worldwide total number of subjects	136
EEA total number of subjects	136

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)	136
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants will be recruited from IBS clinics at the investigator's hospital, or from lists of patients who have previously taken part in research studies and have indicated that they would like to be contacted about future relevant research projects. In addition, we will, in conjunction with the local Primary Care Research Network, approach GPs

Pre-assignment

Screening details:

Male or Female patients aged 18-75 years able to give informed consent.
Patients should all have had a colonoscopy or sigmoidoscopy within the last 12 months to exclude microscopic or any inflammatory colitis. (If not, but they have had a negative colonoscopy within 5 years and symptoms are unchanged, then a sigmoidoscopy and mucosal biopsy

Pre-assignment period milestones

Number of subjects started	136
Number of subjects completed	136

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, Assessor

Blinding implementation details:

This is a double blind parallel study. Neither participant nor supervising doctor nor study nurse will be aware of the treatment allocation.
The randomisation will be based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their standard operating procedure (SOP) and held on a secure server. The randomisation will be stratified by the recruiting centre.

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental: Mesalazine Granules

Arm description:

2g oral granules, once a day for 1 week, then 2g oral granules, twice a day for 11 weeks

Arm type	Experimental
Investigational medicinal product name	Mesalazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

2g oral granules, once a day for 1 week, then 2g oral granules, twice a day for 11 weeks

Investigational medicinal product name	Mesalazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

2g oral granules, once a day for 1 week, then 2g oral granules, twice a day for 11 weeks

Arm title	Placebo Comparator: Placebo Granules

Arm description:

Placebo Comparator: Placebo Granules
2g oral granules, once a day for 1 week, then 2g oral granules, twice a day for 11 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Placebo
2g oral granules, once a day for 1 week, then 2g oral granules, twice a day for 11 weeks

Number of subjects in period 1	Experimental: Mesalazine Granules	Placebo Comparator: Placebo Granules
Started	68	68
Completed	68	68

Baseline characteristics

End points

End points reporting groups

Reporting group title	Experimental: Mesalazine Granules
Reporting group description:	
2g oral granules, once a day for 1 week, then 2g oral granules, twice a day for 11 weeks	
Reporting group title	Placebo Comparator: Placebo Granules
Reporting group description:	
Placebo Comparator: Placebo Granules 2g oral granules, once a day for 1 week, then 2g oral granules, twice a day for 11 weeks	

Primary: Average stool frequency during weeks 11-12 of the treatment period.

End point title	Average stool frequency during weeks 11-12 of the treatment period.
End point description:	
End point type	Primary
End point timeframe:	
End of Study	

End point values	Experimental: Mesalazine Granules	Placebo Comparator: Placebo Granules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	68		
Units: Whole Numbers	68	68		

Statistical analyses

Statistical analysis title	Stats Analysis
Statistical analysis description:	
For descriptive purposes continuous data will be summarised in terms of the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. Categorical data will be summarised in terms of frequency counts and percentages. Statistical modelling will be used to evaluate the primary and secondary outcomes, and safety data.	
Comparison groups	Experimental: Mesalazine Granules v Placebo Comparator: Placebo Granules
Number of subjects included in analysis	136
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	Regression, Linear

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In accordance with the Clinical Trials Statutory Instrument 2004 No. 1031

Adverse event reporting additional description:

Reference Safety Information: MEDRA coding dictionary used. Expectedness definitions taken from UK regulations.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	Unrelated

Reporting group description:

Unrelated to IMP

Reporting group title	Possibly related

Reporting group description:

Serious adverse reaction which possibly may be related to IMP

Serious adverse events	Unrelated	Possibly related	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 136 (0.74%)	1 / 136 (0.74%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Chest Pain	Additional description: Had ruled out cardiac event and pulmonary embolism Treated for chest infection. Symptoms improved. Trial medication stopped with no long term sequalae.		
subjects affected / exposed	0 / 136 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	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	Unrelated	Possibly related	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 136 (2.21%)	0 / 136 (0.00%)	
Cardiac disorders			

Loss of consciousness	Additional description: Fainting spell after a planned arthroscopy. Hospitalised for observation and discharged after 24 hours.		
subjects affected / exposed	1 / 136 (0.74%)	0 / 136 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Breast cancer	Additional description: Newly diagnosed with breast cancer and treatment was on going from the date of diagnosis Withdrew from trial as the outcome from this diagnosis may interfere with the trial results		
subjects affected / exposed	1 / 136 (0.74%)	0 / 136 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Anal bleeding	Additional description: Anal pain and small PR bleeding post colonoscopy		
subjects affected / exposed	1 / 136 (0.74%)	0 / 136 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2010	1) Protocol (version 2.0, 25 Nov 2010) a) We have altered inclusion criteria 2 to include any inflammatory colitis, not just microscopic colitis. b) Addition of faecal tryptases as a mechanistic secondary endpoint. The analysis of faecal tryptases was already mentioned in the objectives, but omitted by mistake from the endpoints. Addition of a new secondary endpoint detailing polymorphic DNA analysis of participants with details about sampling and storage of the DNA also added. c) Change of manufacturer from MIA(IMP)19162 to MIA(IMP)17136. This involves the labelling and final assembly of blinding supplies. Several references to the license holder have been amended. d) Expand abbreviation (NUH – Nottingham University Hospitals NHS Trust) e) Addition of details of the Rome III questionnaire and the post-infectious IBS-D questionnaire. 2) Daily Symptom and Stool Diary (version 2.0, 25 Nov 2010) We have altered the layout of this document and changed the scale from which the participants must score their symptoms. We have not detailed the changes below but instead submitted the whole document for review. 3) Post-Infectious IBS-D Criteria Participants will complete 4 questions to help sub-type them with or without post-infectious IBS-D. This is a new document so we have not detailed the changes below but instead submitted the new document in whole. 4) Patient information sheet (version 2.0, 25 Nov 2010) Details regarding the collection, analysis and future use of a DNA sample have been added. 5) Consent Form (version 2.0, 25 Nov 2010) Optional consent for a DNA sample to be collected, analysed and store for future use has been added. Reference to the new version of the PIS has changed 7) Simplified IMP-D (version 1.1, 25 Nov 2010) We have changed the contact details for one of the manufacturer's. The previous were unable to fulfil their commitment. (We have also submitted, to the CA only, a copy of the new manufacturer's license.) 8) Initial
05 May 2011	Altered inclusion criteria 2 to include colonoscopy or sigmoidoscopy, not just colonoscopy. b) Altered inclusion criteria 5 whereby patients with stool frequency of 3 or more per day for 2 or more days per week during the screening phase are eligible to be included into the study. Previously, part of eligibility into the study was patient with average stool frequency of 3 or more per day during the screening phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported