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

SYNOPSIS

Title	Efficacy and mode of action of mesalazine in the treatment of diarrhoea-predominant irritable bowel syndrome (IBS-D)
Acronym	MIBS
Short title	Mesalazine for the treatment of IBS-D
Chief Investigator	Professor R. Spiller
Objectives	Primary objective To assess the effect of mesalazine on stool frequency. Secondary objectives To assess the effect of mesalazine on 1. Overall IBS symptoms 2. Mast cell numbers, mucosal lymphocytes and faecal tryptases. 3. Small bowel tone by measurement of fasting small bowel water content through MRI. 4. To assess ability of biomarkers (mucosal/MRI parameters) to predict treatment response
Trial Configuration	This is a multi-centre randomised, double-blind, placebo-controlled trial using a parallel group design.
Setting	Secondary Care
Sample size estimate	We propose to study 108 patients based on the primary end point of stool frequency. Our previous study on diarrhoea predominant IBS patients gives a mean stool frequency of 3.1 (standard deviation 2.0). Tuteja and colleagues reported mesalazine decreasing stool frequency by 1.4 bowel movements per day[23]. Our study will have an 80% power to detect such an effect at the 1% significance level (90% at 5% significance). Much smaller numbers are needed to assess the effect of mesalazine on mast cell numbers and tryptase release. Corinaldesi *et al* reported a 36% decrease in mast cell numbers from mean 9.2 (standard deviation 2.5) [22] which requires just 12 patients to show such a decrease with a power of 90% at the 1% significance level. There is no data on which to base a power calculation for the MRI data but we have previously shown that IBS patients with diarrhoea have decreased fasting small bowel water content at 50mls (standard deviation 33) significantly less than the 104 (16) for controls. Using n=60 we can detect a 28% increase in fasting small bowel water content towards normal values which we feel would be a clinically minimally significant difference.
Number of participants	108

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Eligibility criteria	Inclusion criteria 1) Male or Female patients aged 18-75 years able to give informed consent. 2) Patients should all have had a colonoscopy or a 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 of the left colon would be sufficient to exclude microscopic or any inflammatory colitis). 3) IBS-D Patients meeting Rome III criteria prior to screening phase. 4) Patients with ≥25% soft (score >4) and <25% hard (score 1 or 2) stools during the screening phase, as scored by the daily symptom and stool diary*. 5) Patients with a stool frequency of 3 or more per day for 2 or more days per week during the screening phase*. 6) Satisfactory completion of the daily stool and symptom diary during the screening phase at the discretion of the investigator. 7) Women of child bearing potential willing and able to use at least one highly effective contraceptive method throughout the study. In the context of this study, an effective method is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly such as: implants, injectables, combined oral contraceptives, sexual abstinence or vasectomised partner. *If inclusion criterion 4 and/or 5 is/are not met but the results are considered atypical (as observed from medical history and patient recall) then the patient can be re-screen on 1 occasion only. Exclusion criteria 1) Women who are pregnant or breast feeding 2) Prior abdominal surgery which may cause bowel symptoms similar to IBS (note appendectomy and cholecystectomy will not be an exclusion) 3) Patients unable to stop anti-muscarinics, anti-spasmodics, high dose tricyclic antidepressants (i.e. above 50 mg/day), opiates / anti-diarrhoeal drugs*, NSAIDs (occasional over the counter use and topical formulations are allowed), long-term antibiotics, other anti-inflammatory drugs or 5-ASA containing drugs. 4) Patients on selective serotonin re-uptake inhibitors and low dose tricyclic antidepressants (i.e. up to 50 mg/day) for at least 3 months previous unwilling to remain on a stable dose for the duration of the trial. 5) Patients with other gastro-intestinal diseases including colitis and Crohn's disease. 6) Patients with the following conditions: Renal impairment, severe hepatic impairment or salicylate hypersensitivity. 7) Patients currently participating in another trial or have been in a trial within the previous 3 months 8) Patients who in the opinion of the investigator are considered unsuitable due to inability to comply with instructions 9) Patients with serious concomitant diseases e.g. cardiovascular, respiratory, neurological etc.

	*Loperamide is allowed as rescue medication through-out the trial, however if >2 doses / week are taken during the screening phase then they are not eligible, though they can be re-screened on 1 occasion only.
Description of intervention	Mesalazine granules or matching placebo for 12 weeks, with the week 1 of treatment at 2g, once a day, then a step increase to 2g, twice a day for the remainder of the 12 weeks.
Duration of study	It is anticipated that patient recruitment will start in January 2011 and will continue for up to 3 years. Study participants will be participating in the study for 14 weeks.
Randomisation and blinding	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. The supervising doctor or study nurse will obtain a randomisation reference number for each participant by means of a remote, internet-based randomisation system developed and maintained by the Nottingham CTU. The sequence and decode of treatment allocations will be concealed until interventions have all been assigned and recruitment, data collection, and all other trial-related assessments are complete.
Outcome measures	***Primary endpoints*** *Clinical endpoint*: Average stool frequency during weeks 11-12 of the treatment period. *Mechanistic endpoint:* Mast cell numbers per mm^2 ***Secondary endpoints*** *Clinical secondary endpoints:* 1) Average daily severity of abdominal pain on a 0-10 scale 2) Days with urgency during weeks 11-12 post-randomisation 3) Mean stool consistency using Bristol Stool Form Score 4) Global satisfaction with control of IBS symptoms as assessed from the answer to the question “Have you had satisfactory relief of your IBS symptoms this week? Yes / No. ” *Mechanistic secondary endpoints:* 1) Mast cell tryptase release during 6 hour biopsy incubation 2) IL-1β, TNF-α, histamine and serotonin secretion during same incubation 3) Small bowel tone assessed by volume of fasting small bowel water 4) Faecal Tryptases 5) Difference in primary outcome measure between those with different TNFSF15 polymorphism will be assessed using ANOVA

	Ancillary secondary endpoints: 1) EQ-5D 2) CDC HRQOL4 3) HADS 4) PHQ-15 *Safety endpoints* 1) Adverse events related to the trial treatment (see page 16 'Known side effects of mesalazine) 2) Withdrawal from the trial treatment due to adverse events.
Statistical methods	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. Tests will be two-tailed, and results will be declared "statistically significant" if $P<0.05$ and 95% confidence intervals will be presented. No formal adjustment for multiple significance testing will be applied