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Treatment of Irritable bowel syndrome with diarrhoea using titrated ondansetron

Submission date 11/09/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 02/10/2017	**Overall study status** Completed	
Last Edited 18/11/2024	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
Irritable bowel syndrome (IBS) with diarrhoea (IBS-D) is a common condition characterised by recurrent abdominal pain with frequent, loose stools passed with urgency. Such patients may have an excess of serotonin (5-hydroxytryptamine [5-HT)) in their intestine which stimulates movement through the bowel (transit) and secretion. Ondansetron is a drug which blocks the 5-HT receptor, which is used to treat nausea, and has an excellent safety record. A pilot study has known that that Ondansetron slows transit and improves IBS-D symptoms so there is a need to find out how this works. Bowel contractions can be measured using a new high resolution system and bowel relaxation by assessing pressure during rectal distension with a balloon to determine whether these changes are related to improved symptoms. Total bile acid concentrations and the amount of pancreatic enzyme can be measured, tryptase, in the stools as these may sensitise the rectum causing urgency. The response to ondansetron may depend upon genetic factors so the variation in the gene controlling the rate of 5HT production needs to be assessed. The aim of this study is to treat patients with Ondansetron or a placebo (a dummy tablet without any effect) and compare the change in symptoms.

Who can participate?
Adults aged 18 and older with IBS

What does the study involve?
Participants are allocated to one of two groups. Those in the first group receive the medication Ondansetron taken by mouth for 12 weeks. Those in the second group receive a placebo (a dummy tablet without any effect). Participants are contacted by researchers to discuss any symptoms. Participants are measured in the 12th week to see the effect of the drug compared to placebo.

What are the possible benefits and risks of participating?
Participants may benefit from a reduction in their symptoms if ondansetron is effective. There are risks such as constipation. Ondansetron is currently licenced for the management of nausea and vomiting post-operatively or following treatment with cancer. In this setting it is used in a much higher dose (32mg) and is administered intravenously. Within its current licenced use, ondansetron has been associated with prolongation of the QT interval. This effect is not

anticipated in the TRITON study giving that patients will be administered a much lower dose (4-8mg) orally. However as safeguard, those with a prolonged QT or taking drugs known to prolong this will be excluded from the study. Ischaemic colitis has been associated with other, similar drugs and therefore those with Ischaemic colitis are excluded from the study. Additionally, if participants develop rectal bleeding whilst on study, they will be recommended to have a sigmoidoscopy. It is likely that bleeding will stem from the anal canal associated with trauma from frequent defecation.

Where is the study run from?
University of Leeds (UK)

When is the study starting and how long is it expected to run for?
February 2017 to August 2020

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Miss Lorna Barnard
triton@leeds.ac.uk

Added 07/02/2019:
Twitter account for trial: @IBSTriton

Contact information

Type(s)
Public

Contact name
Miss Lorna Barnard

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Additional identifiers

Clinical Trials Information System (CTIS)
2017-000533-31

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
33831

Study information

Scientific Title
TReatment of Irritable bowel syndrome using Titrated ONdansetron Trial

Acronym
TRITON

Study objectives
The overall aim of the study is to investigate the effectiveness and mechanism of action of ondansetron, a 5HT3RA, in patients with IBS-D, as assessed by stool frequency, consistency, urgency and abdominal pain.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/11/2017, Yorkshire & The Humber - Leeds West Research Ethics Committee, ref: 17/YH/0262

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Irritable bowel syndrome

Interventions
Participation attend an initial visit where they are registered for the study. Patients are asked to complete a two-week daily paper diary recording:
1. Stool frequency
2. Stool consistency for each stool using the Bristol stool form scale (BSFS)
3. Worst abdominal pain experienced that day (on a scale of 0-100, where 0 is no pain and 100 is worst imaginable pain)
4. Worst bowel movement urgency (on a scale of 0-100, where 0 is no urgency and 100 is worst imaginable urgency)
5. If they have used loperamide that day.
The completed pages of the patient diaries will be collected at each visit by the local study team. This information is used to confirm eligibility at the randomisation visit.

In addition the CTRU will send each patient two text messages to the mobile phone number provided every day. The first will ask if they have passed a stool which has had a consistency 6 or

7 on the BSFS and the patient will need to text back 1 for yes and 0 for no. The second will ask what their worst abdominal pain score was that day, from a scale of 0-100 (where 0 is no pain and 100 is worst imaginable pain) and the patient will need to text back the score from 0-100.

The study nurse will discuss this process with the patients and if it is highlighted that this will be a problem, the patient will complete only the paper diary. The mobile number provided will be verified prior to use. The patient may withdraw from receiving text messages upon request.

Completed diaries will be brought to visit two Eligibility confirmation.

Participants attend a third visit where they are randomised. Participants are randomised on a 1:1 basis to receive either ondansetron or placebo. Participants are randomised based on stratification factors to ensure the treatment groups are well-balanced. Details of which are required at randomisation include the site name, colonic monometry assessment carried out and barostat assessment carried out. This is a double blinded trial and therefore neither the patient nor those responsible for their care (treating team and research team) will know the allocation. Patients are given the opportunity to find out what treatment arm they are allocated to at the end of the study period. Upon randomisation, participants are allocated either 4mg Ondansetron or placebo and instructed to start their treatment on one capsule a day. Depending on the response, participants are asked to increase the dose in 4 mg steps every two days to a maximum of 8 mg three times a day. Treatment lasts for 12 weeks and the follow up visit occurs four weeks from the last dose of trial treatment.

Patients are asked to continue to record the following information until visit 6 (Follow-Up visit) Daily:
1. Stool frequency
2. Stool consistency for each stool - using the Bristol stool form scale (BSFS);
3. Worst abdominal pain experienced that day - on a scale of 0-100, where 0 is no pain and 100 is worst imaginable pain.
4. Worst bowel movement urgency - on a scale of 0-100, where 0 is no urgency and 100 is worst imaginable urgency.
5. Number of trial medication capsules taken.
6. If they have used loperamide that day.

Weekly they record if they feel they have had satisfactory relief from their symptoms that week.

The completed pages of the patient diaries will be collected in at each visit by the local study team.

Text Messaging
Patients will continue to receive two text messages to their mobile phone every day for the next 6 weeks unless they have withdrawn from this aspect. The first will ask if they have passed a stool which has had a consistency 6 or 7 on the BSFS and the patient will need to text back yes or no. The second will ask what their worst abdominal pain score was that day, from a scale of 0-100 (where 0 is no pain and 100 is worst imaginable pain) and the patient will need to text back the score from 0-100.

During the first two week patients will be contacted every 2 days the site team to discuss symptoms. The dose will then be titrated as required.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Current primary outcome measure as of 07/09/2021:
The primary endpoint is measured at 12 weeks post-randomisation and defined, as recommended by the FDA, as a patient being a weekly responder for BOTH pain intensity AND stool consistency for at least 6 weeks in the 12-week treatment period. Weekly responder status is defined as follows:
1. Weekly responder for abdominal pain intensity: at least 30% decrease from baseline in weekly average of worst daily abdominal pain score (abdominal pain score measured on a 0 to 100 point scale in past 24 hours)
2. Weekly responder for stool consistency: decrease of at least 50% in the number of days per week with at least one loose stool consistency (BSFS = 6 or 7) compared with baseline
To achieve success in the primary endpoint, a patient must be a weekly responder for both pain and for consistency during the same 6 weeks within the 12-week treatment period.

Previous primary outcome measure:
FDA defined responder rate (in relation to abnormal defecation and abdominal pain) is measured using weekly responder for Abdominal Pain Intensity and Stool consistency scales at weeks 6 and 12.

Key secondary outcome(s))
Current secondary outcome measures as of 07/09/2021:
1. Treatment effect of ondansetron in relation to:
1.1. Stool frequency (number of stools passed per day) is defined as number of stools per day up to 12 weeks post-randomisation using the patient's diary. The mean number of stools per day over the last month (weeks 9-12) is used.
1.2. Stool consistency (number of days per week with at least 1 loose stool) and average stool consistency (from weeks 9-12) is measured using patient diaries and the Bristol Stool Form Score (BSFS) daily from baseline and week 12. Consistency is assessed daily by Bristol Stool Form Score (BSFS) and a loose stool is defined as BSFS >5.
1.3. Urgency of defecation is measured using patient diaries daily from baseline and week 12. For the endpoint analyses, the mean daily urgency score over last month (weeks 9-12) is used.
1.4. Satisfactory relief of IBS symptoms is measured using patient diaries weekly from baseline and week 12 will be defined as satisfactory relief of IBS symptoms for at least 6 out of 12 weeks. For the endpoint analyses, the proportion of patients with satisfactory relief of symptoms will be used.
1.5. Functional dyspepsia score is measured using the short-form Leeds dyspepsia questionnaire (SF-LDQ) at baseline and week 12.
1.6. IBS severity is measured using the IBS Symptom Severity Scale (IBS-SSS) questionnaire at baseline and week 12
1.7. Use of rescue medication is measured using patient diaries daily from baseline and week 12
1.8. Abdominal pain score is measured using the patient diaries daily from baseline and week 12. For the endpoint analyses, the mean daily pain score over the last month (weeks 9-12) is used.
2. Assessing the patient's mood over 12 weeks following treatment with ondansetron by:
2.1 Anxiety and depression measured using the Hospital Anxiety and Depression Scale (HADS) at baseline and week 12
2.2. Quality of life measured using the IBS-QOL summary score at baseline and 12 weeks
3. Longer-term effects of ondansetron after 12 weeks of treatment (off-treatment):
3.1. Stool frequency longer term is measured using patient diaries daily from weeks 13-16. The

mean number of stools per day over the whole month (weeks 13-16) is used.
3.2. Stool consistency is measured using daily patient diaries from weeks 13 to 16. The mean number of days per week with at least 1 loose stool over the whole month (weeks 13-16) and the mean daily stool consistency over the whole month (weeks 13-16) is used.
3.3. Urgency of defaecation is measured using daily patient diaries from weeks 13 to 16. The mean daily urgency score over the whole month (weeks 13-16) is used.
3.4. Abdominal pain is measured using daily patient diaries from weeks 13 to 16. The mean daily pain score over the whole month (weeks 13-16) is used.

Previous secondary outcome measures:
1. Treatment effect of ondansetron in relation to:
1.1. Stool frequency (number of stools passed per day) is measured using patients diaries daily from baseline and week 12
1.2. Stool consistency (number of days per week with at least 1 loose stool) and average stool consistency (from weeks 9-12) is measured using patient diaries and the Bristol Stool Form Score (BSFS) daily from baseline and week 12
1.3. Urgency of defecation is measured using patient diaries daily from baseline and week 12
1.4. Satisfactory relief of IBS symptoms is measured using patient diaries weekly from baseline and week 12
1.5. Functional dyspepsia score is measured using the short-form Leeds dyspepsia questionnaire (SF-LDQ) at baseline and week 12
1.6. IBS severity is measured using the IBS Symptom Severity Scale (IBS-SSS) questionnaire at baseline and week 12
1.7. Use of rescue medication is measured using patient diaries daily from baseline and week 12
1.8. Abdominal pain score is measured using the patient diaries daily from baseline and week 12
2. Assessing the patient's mood over 12 weeks following treatment with Ondansetron by:
2.1 Anxiety and depression measured using the Hospital Anxiety and Depressison Scale (HADS) at baseline and week 12
2.2. Quality of life measured using the IBS-QOL summary score at baseline and 12 weeks
3. Longer term effects of ondansetron after 12 weeks of treatment (off-treatment):
3.1. Stool frequency longer term is measured using patient diaries daily from weeks 13-16
3.2. Stool consistency is measured using daily patient diaries from weeks 13 to 16
3.3. Urgency of defaecation is measured using daily patient diaries from weeks 13 to 16
3.4. Abdominal pain is measured using daily patient diaries from weeks 13 to 16

Completion date
31/08/2020

Eligibility

Key inclusion criteria
1. Written (signed and dated) informed consent
2. Considered fit for study participation
3. Meeting Rome IV criteria (Appendix 1) for IBS-D
4. Aged ≥ 18 years
5. Undergone standardised workup to exclude the following alternative diagnoses
5.1. Microscopic colitis (colonoscopy or flexible sigmoidoscopy)
5.2. Bile acid diarrhoea (SeHCAT results of > 10% or C4 results of <19 ng/ml or failed 1 week trial of a bile acid binding agent [colestyramine 4g t.d.s., colesevelam 625mg t.d.s. or equivalent]) within previous 5 years)
(Note: Cholecystectomy will not be an exclusion criterion if bile acid diarrhoea has been

excluded. Patients with SeHCAT values of 5-10% will be eligible if they fail to respond to a 1 week trial of bile acid binding agent (see above))
5.3. Lactose malabsorption
5.4. Coeliac disease (tTG or duodenal biopsy)
6. Patients of childbearing potential or with partners of childbearing potential must agree to use methods of medically acceptable forms of contraception during the study and for 90 days after completion of study drug, (e.g. implants, injectable, combined oral contraceptives, barrier methods, true abstinence (when this is in line with the preferred and usual lifestyle of the patient) or vasectomised partners).
7. For women of childbearing potential, a negative pregnancy test should be performed within 72 hours of confirmation of eligibility
8. Weekly average worst pain score during 2-week screening period meets inclusion criteria
9. Stool consistency during 2-week screening period meets inclusion criteria
* Inclusion criteria 8 & 9 will be assessed after the patient has completed the 14-day daily stool and pain diary and returned the results at visit 2

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
80

Key exclusion criteria
1. Gastrectomy
2. Intestinal resection
3. Other known organic GI diseases (e.g. Inflammatory bowel disease – Crohns disease, Ulcerative colitis, coeliac disease)
4. Unable or unwilling to stop restricted medication including regular loperamide, antispasmodics (e.g. buscopan, mebeverine, peppermint oil, alverine citrate), eluxadoline, tricyclic antidepressant doses >30mg/day or other drugs likely in the opinion of the investigator to alter bowel habit. These medicines should be discontinued for a 7 day washout period prior to registration. Intermittent loperamide will be permitted but only as rescue medication
5. QTc interval ≥450msec for men and ≥470msec for women. Assessed within the last 3 months by a 12-lead ECG
6. Previous chronic use of Ondansetron or contraindications to it (rare as per BNF)
7. Pulse, Blood pressure, FBC or LFTs outside the normal ranges according to the site's local definition of normal. Assessed within the last 3 months. Note: Minor rises in ALT (<2 x upper limit of normal) will be acceptable but the patient's GP will be informed if they remain elevated at end of the study

8. Women who are pregnant or breastfeeding
9. Currently participating or who have been in an IMP trial in the previous three months where the use of the IMP may cause issues with the assessment of causality in this study
10. Currently taking SSRIs or tricyclic antidepressants (unless at a stable dose for at least 3 months and with no plan to change the dose during the study)
11. Currently taking and unwilling or unable to stop any of the prohibited medications. (Prohibited medications – Apomorphine and Tramadol which interact with ondansetron Caution should be taken with patients on QT prolonging drugs and cardio toxic drugs. These patients should be reviewed by the PI to determine if they are suitable for the study.
12. Stool consistency during 2-week screening period does not meet inclusion criteria

Date of first enrolment
01/01/2018

Date of final enrolment
11/05/2020

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Nottingham University Hospitals NHS Trust Headquarters
QMC Campus
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
St James's University Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
West Yorkshire
Leeds
United Kingdom
LS9 7TF

Study participating centre

The Royal London Hospital
Barts and the London NHS Trust
Trust Offices
White Chapel
London
United Kingdom
E1 1BB

Study participating centre
St Mary's Hospital
Imperial College Healthcare NHS Trust
Praed Street
London
United Kingdom
W2 1NY

Study participating centre
University College London Hospital NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Wythenshawe Hospital
University Hospital of South Manchester NHS Foundation Trust
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Study participating centre
Salford Royal NHS Foundation Trust
Salford Royal
Stott Lane
Manchester
United Kingdom
M6 8HD

Study participating centre

Darlington Memorial Hospital
County Durham and Darlington NHS Foundation Trust
Hollyhurst Road
Darlington Country
Durham
United Kingdom
DL3 6HX

Study participating centre
City Hospital
Sandwell and West Birmingham Hospitals NHS Trust
Dudley Road
West Midlands
Birmingham
United Kingdom
B18 7QH

Study participating centre
Barnsley Hospital NHS Foundation Trust
Gawber Road
South Yorkshire
Barnsley
United Kingdom
S75 2EP

Study participating centre
North Staffordshire Royal Infirmary
University Hospital of North Staffordshire NHS Trust
Princes Road
Staffordshire
Stoke-on-Trent
United Kingdom
ST4 7LN

Study participating centre
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Crewe Road South
Edinburgh
United Kingdom
EH4 2XU

Study participating centre
Royal Hallamshire Hospital
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Glossop Road
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S10 2JF

Study participating centre
South Tees Hospitals NHS Foundation Trust
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TS4 3BW

Sponsor information

Organisation
Nottingham University Hospitals NHS Trust

ROR
https://ror.org/05y3qh794

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from CTRU-DataAccess@leeds.ac.uk. Data will only be shared for participants who have given consent to use their data for secondary research. Requests to access trial data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		03/03/2023	06/03/2023	Yes	No
Results article		01/10/2023	18/11/2024	Yes	No
Protocol article	protocol	20/08/2019	21/08/2019	Yes	No
Basic results	version 2.0	07/09/2021	07/09/2021	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes