

# Treatment of Irritable bowel syndrome with diarrhoea using titrated ondansetron

<b>Submission date</b> 11/09/2017	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 02/10/2017	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 18/11/2024	<b>Condition category</b> Digestive System	<input type="checkbox"/> Individual participant data

## 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, trypsin, 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

**Study website**  
<https://ctr.leeds.ac.uk/triton/>

## Contact information

**Type(s)**  
Public

**Contact name**  
Miss Lorna Barnard

**Contact details**  
Clinical Trials Research Unit  
Leeds Institute of Clinical Trials Research  
University of Leeds  
Leeds  
United Kingdom  
LS2 9JT  
+44 1133 430555  
triton@leeds.ac.uk

## Additional identifiers

**EudraCT/CTIS number**  
2017-000533-31

**IRAS number****ClinicalTrials.gov number**

Nil known

**Secondary identifying numbers**

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

**Secondary study design**

Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Treatment

**Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

**Health condition(s) or problem(s) studied**

Irritable bowel syndrome

## Interventions

Participants 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 manometry 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 measure**

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.

#### **Secondary outcome measures**

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 Depression Scale (HADS) at baseline and week 12

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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

**Overall study start date**

01/02/2017

**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  $\geq 18$  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., colessevelam 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

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

Planned Sample Size: 400; UK Sample Size: 400

## **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  $\geq 450$ msec for men and  $\geq 470$ msec 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 ( $< 2 \times$  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**

England

Scotland

United Kingdom

### **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****Western General Hospital**

Crewe Road South  
Edinburgh  
United Kingdom  
EH4 2XU

**Study participating centre****Royal Hallamshire Hospital**

Sheffield Teaching Hospitals NHS Foundation Trust  
Glossop Road  
Sheffield  
United Kingdom  
S10 2JF

**Study participating centre****South Tees Hospitals NHS Foundation Trust**

The James Cook University Hospital  
Marton Road  
Middlesbrough  
United Kingdom  
TS4 3BW

## **Sponsor information**

**Organisation**

Nottingham University Hospitals NHS Trust

**Sponsor details**

Trust Headquarters  
Queens Medical Centre  
Derby Road  
Nottingham

England  
United Kingdom  
NG7 2UH

**Sponsor type**

Hospital/treatment centre

**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**

**Publication and dissemination plan**

Planned publication in a high-impact peer-reviewed journal.

**Intention to publish date**

10/09/2021

**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](mailto: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](mailto: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?
<a href="#">Protocol article</a>	protocol	20/08/2019	21/08/2019	Yes	No
<a href="#">Basic results</a>	version 2.0	07/09/2021	07/09/2021	No	No
<a href="#">Results article</a>		03/03/2023	06/03/2023	Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Results article</a>		01/10/2023	18/11/2024	Yes	No