Nottingham University Hospital NHS Trust

The University of Nottingham

Nottingham Digestive Diseases Centre

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TRITON

Queen Mary University of London

TReatment of Irritable bowel syndrome using Titrated Ondansetron Trial

TRIAL STEERING COMMITTEE AND DATA MONITORING AND ETHICS COMMITTEE

INITIAL MEETING 30TH NOVEMBER 2017

Rationale for TRITON

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- 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.

Clinical Aims

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To determine the effectiveness and safety of ondansetron in patients with the symptoms of IBS-D including:

- Urgency
- Looseness of stool
- Frequency of defecation
- Abdominal discomfort.

Study Design

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- TRITON is a multi-site, parallel group, randomised, double-blinded, placebo controlled trial, with embedded mechanistic studies within selected sites.
- 400 patients with IBS-D will be randomised from 13 UK sites on a 1:1 basis to receive either Ondansetron or Placebo.
- Both treatments will be administered in oral doses of between 4-24mg daily for 12 weeks.
- Dose titration will be undertaken in the first two weeks of the study to avoid constipation, which at a standard dose occurs in one quarter of patients.

Primary Endpoint

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- Does 12 weeks of ondansetron increase the FDA defined responder rate (in relation to abnormal defecation and abdominal pain) compared with placebo?

- **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)

- **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.

Secondary Endpoints

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- What is the estimated treatment effect of ondansetron in relation to stool frequency, consistency, urgency of defecation, satisfactory relief of IBS symptoms and use of rescue medication and abdominal pain over 12 weeks of treatment?

- **Where:**

- **Stool frequency** - number of stools per day up to 12 weeks post randomisation.
- **Stool consistency** - number of days per week with at least 1 loose stool.
- **Urgency of defecation** - on a scale 0-100
- **Satisfactory relief of IBS symptoms** - satisfactory relief of IBS symptoms for at least 6 out of 12 weeks
- **Use of rescue medication** - total number of days having to take Loperamide over 12 weeks.
- **Abdominal pain score** - on a scale 0-100
- **Score of Functional Dyspepsia Questionnaire** (Jan Tack) – at 0 and 12 weeks
- **Score of IBS Symptom Severity Scale Questionnaire for IBS** (IBS-SSS) – at 0 and 12 weeks

Secondary Endpoints (cont)

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- Does the treatment with Ondansetron improve patient's mood over 12 weeks of treatment?

- **Hospital Anxiety and Depression Scale (HADS) scores**
- For the endpoint analyses, the HADS anxiety and depression scores at 12 weeks will be used.

- **IBS-QOL summary score**
- For the endpoint analyses, the IBS-QOL summary score at 12 weeks will be used.

Secondary Endpoints (cont)

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- What is longer term (one month) effect of ondansetron after 12 weeks of treatment (off-treatment)?

  - **Stool Frequency** - the mean number of stools per day over the whole month (weeks 13-16).
  - **Stool consistency** - the mean number of days per week with at least 1 loose stool and the mean daily stool consistency over the whole month (weeks 13-16).
  - **Urgency of defaecation** - the mean daily urgency score over the whole month (weeks 13-16).
  - **Abdominal pain** - the mean daily pain score over the whole month (weeks 13-16).

Eligibility -Inclusion Criteria

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- 1. Written (signed & dated) informed consent
- 2. Considered fit for study participation
- 3. Meeting Rome IV criteria for IBS-D
- 4. Aged ≥ 18 years
- 5. Undergone standardised workup to exclude the following alternative diagnoses

a) Microscopic colitis (colonoscopy or flexible sigmoidoscopy),

b) Bile acid diarrhoea (SeHCAT results of > 10% or C4 results of <19 ng/ml), *Note: Cholecystectomy not an exclusion criteria if bile acid diarrhoea excluded,*

c) Lactose malabsorption,

d) Coeliac disease (tTG or duodenal biopsy)

- 6. Contraception use as per protocol
- 7. Negative pregnancy test within 72 hours of eligibility confirmation (childbearing age women)
- 8. Weekly average worst pain score >= 30 on a 0 to 100 point scale
- 9. Any stools with a consistency of 6 or 7 on the Bristol Stool Form score (BSFS) for 2 -6 days per week.^

- ^ 8 & 9 assessed from patient completed 14 day daily stool &pain diary

Eligibility –Exclusion Criteria

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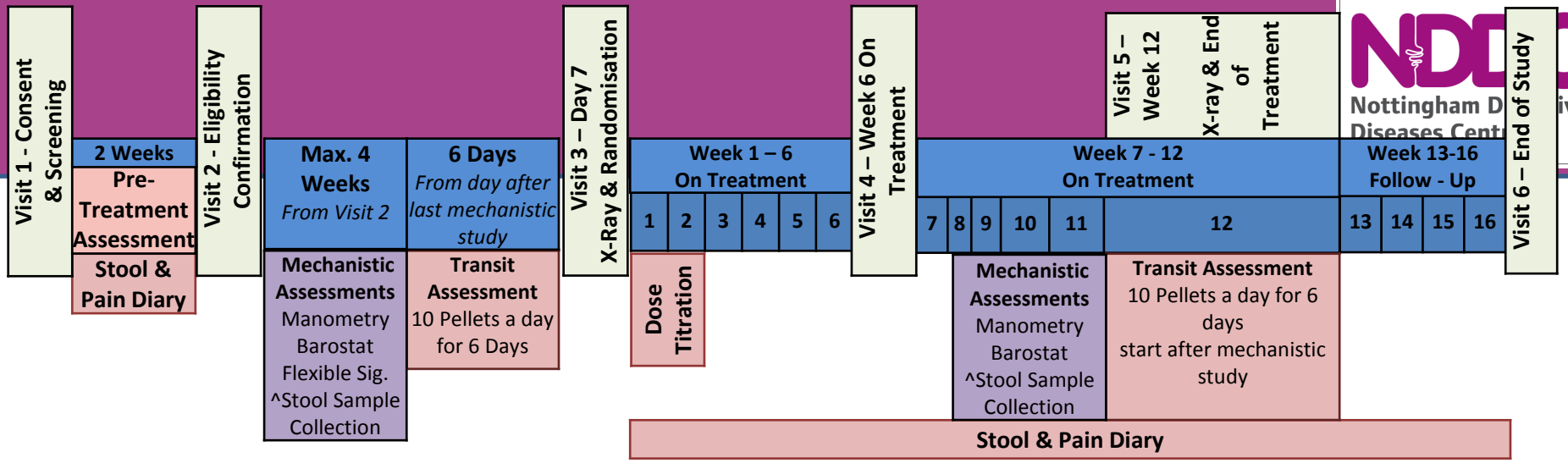
- 1. Gastrectomy
- 2. Intestinal resection
- 3. Other known organic GI diseases (e.g. Inflammatory bowel disease – Crohns disease, Ulcerative colitis.)
- 4. Inability to stop anti-diarrhoeal drugs for the duration of the study
- 5. QTc interval >=420msec. Assessed within the last 3 months by a 12-lead ECG.
- 6. Previous chronic use of Ondansetron or contraindications to it (rare as per BNF)
- 7. Pulse, Blood pressure, FBC or LFTs outside site's normal ranges. Assessed within the last 3 months
- 8. Women who are pregnant or breastfeeding
- 9. IMP trial participation in previous 3 months where IMP may confuse causality assessment
- 10. Patients taking SSRIs or tricyclic antidepressants are not excluded if on stable dose for at least 3 months and with no plan to change the dose during the study
- 11. Patients currently taking any of the restricted medications (Apomorphine, Tramadol & medications likely to alter bowel habit (in investigator opinion). Caution to be taken with patients on QT prolonging & cardio toxic drugs.
- 12. Patients with only stools of consistency 7 on the Bristol Stool Form score (BSFS) for 7 days a week



Visit 1:

- Preliminary Evaluation of Inclusion / Exclusion criteria
- Consent to Main Study
- Consent to Mechanistic Assessments
- Patient registration
- Distribution of Patient diary.
- Book X-ray for Transit Assessment
- Book Mechanistic Assessments

Pre-Treatment Assessments

- Daily Stool Consistency & Pain Diary
- ECG *
- Blood Tests *
- Colonoscopy & Biopsies *
- SeHCAT/C4*
- Physical Exam
- Medical History

** If not previously completed within the protocol defined timelines*

Visit 2:

- Pregnancy Test
- Confirm Eligibility
- Dispense of Transit Pellets
- Confirm X-Ray
- Confirm Mechanistic Appointments

- **If consented** Give out Instructions for Stool Collection

Visit 3:

- Transit X-ray
- Randomisation
- Questionnaire - IBS-SSS, IBS QOL, Functional Dyspepsia, HADS & PHQ-12
- Dispense Treatment
- Dispense Stool & Pain Diary
- **If consented:**
- Collect Research Blood
- Collect Stool Samples if not taken at mechanistic assessments ^.

Dose Titration

- Call to Discuss symptoms & dose titration in week 1
- Confirm dose in week 2

Visit 4:

- Collect Diary
- Collect unused IMP
- Dispense of IMP
- Dispense new diary
- Dispense Transit Marker & Instructions & book X-ray
- Review Con Meds
- Confirm Mechanistic Assessment Appointments

Visit 5:

- Transit X-ray
- Collect diary
- Questionnaire - IBS-SSS, IBS QOL, Functional Dyspepsia & HADS
- Collect unused IMP
- Review Con Meds
- **If consented:**
- Collect Research Blood
- Collect Stool Samples if not taken at mechanistic assessments ^.

Visit 6:

- Review & Collect Diary
- Return unused Medication
- Confirm knowledge of treatment allocation