Study Site Operating Procedure	Title	Dose Titration SSOP				
	Trial Name	TRITON				
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Details:

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Comments:

The purpose of this SSOP is to provide guidance to research staff on dose titration during the TRITON study.

Version Control:

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Contents

Section A Applicability

The Study Site Operating Procedure (SSOP) is applicable to the Principal Investigator (PI), Co-investigators, Research Nurses, and any other authorised research staff at site who will be involved in the TRITON dose titration process, either by overseeing the process or contacting patients directly.

Section B Dose Titration Guidance

1.0 Outline

1.1 Guidance on dose titration in the form of the *Participant Dose Adjustment Instructions* is available for all participating patients and should be issued to them at randomisation.

1.2 Dose Titration will take place during the first two weeks of treatment. Each patient should be contacted a minimum of every two days by a delegated member of the research team. Calls may occur more frequently if required. The first call is to occur in the afternoon of day 2 of treatment. Patients must be called in the afternoon as opposed to the morning as it allows the patients longer to assess the treatment effects.

1.3 The details of each call should be recorded on F10 *Dose Titration*, including those where the patient did not answer. Supplementary pages may be used if necessary.

1.4 At each phone call a check is made as to whether any doses were missed or any Serious Adverse Events experienced.

1.5 At the end of the dose titration period, the original copy of F10 *Dose Titration* CRF is to be sent back to the CTRU and a photocopy retained at site.

2.0 Dosing information

2.1 **Day 1**: Patients will start by taking one capsule (4mg) once a day in the morning before breakfast.

2.2 **Day 2**: Patients will take one capsule in the morning. The research team are to call the patient in the afternoon querying their bowel habits in the past 24 hours. Depending on the individual's response, the following actions should be advised:

2.2.1 No stools or hard stools (Bristol Stool Form Score 1 or 2): Omit the Day 3 dose and if necessary continue to omit doses until the patient has had a bowel movement. Once bowel movement has occurred, the patient can be restarted the following morning on a lower dose of 4mg on alternate days.

2.2.2 Satisfactory bowel habits (Bristol Stool Form Score 3-5): Continue on one capsule per day.

2.2.3 Loose Stools (Bristol Stool Form Score 6 or 7): Increase the dose to 2 capsules (8mg) per day, starting on Day 3.

If Day 2 falls on the weekend, the research team must go through the guidance available to the patient during the randomisation visit and advise them on how to proceed over the weekend.

2.3 The patient must be advised on when to take the capsule(s) throughout the course of the day. This will vary depending on their actual dose. More information can be found under section 3.0 *Dose Timing.*

2.4 **Days 3-12**: Continue to call the patient every two days (days 4, 6, 8, 10, 12) or more as required. During each call, advise the patient on how to proceed based on their bowel habits during the past 24 hours. For guidance on dose titration, see the flowchart in section 6.0.

2.4.1 The steady dose increase should continue after each call if stools remain loose, up to a maximum of 2 x 4mg capsules, three times daily (i.e. 6 capsules daily).

2.4.2 The dose reduction should continue if stools remain hard, down to a minimum of 1 x 4mg capsule every three days. If the patient continues to have hard stools at this dose then treatment should be discontinued. Important information regarding this can be found in section 5.0 *Treatment Discontinuation.*

2.5 **Day 14**: Day 14 marks the end of the dose titration period and site are to call the patient to advise the steady dose to be taken forward for the remainder of the study.

2.5.1 **It is important to explain to the patient that the dose required to control symptoms may alter over time. If they feel the need to adjust the dose because of constipation or worsening symptoms they should contact their research nurse to discuss.**

2.5.2 F10 *Dose Titration* must be used to determine if a kit replenishment is needed at this point. Site can add the recommended titrated dose and calculate the number of remaining capsules. If the patient has reached a steady dose of 4 or more capsules a day, then F16 *Kit Replenishment* should be completed to ensure the patient has enough capsules until their week 6 visit.

3.0 Dose Timing

3.1 Depending on the daily dosage, patients will be required to take a number of capsules at certain times of day as per the table below.

3.2

Total Number of Capsules/Day	Morning	Lunch	Evening
1	1	0	0
2	1	0	1
3	1	1	1
4	2	1	1
5	2	2	1
6	2	2	2

4.0 Treatment Discontinuation

4.1 If the patient continues to have hard stools whilst taking 1 x 4mg capsule every three days then treatment should be discontinued.

4.2 In this case they should continue with further follow up and/or data collection, unless they explicitly withdraw.

4.3 F18 *Treatment Discontinuation & Patient Withdrawal Request* should be completed within 24 hours of the decision to stop trial treatment and the form faxed to the CTRU. The original should be posted within 24 hours.

5.0 Anti-Diarrhoeal medication

5.1 Patients should **not** take **regular** loperamide whilst taking part in the study, as it will make it impossible to assess the effect of treatment.

5.2 However, patients may **exceptionally** take loperamide if their diarrhoea is excessive (i.e. > 7 bowel movements per day). They should not take more than 2mg twice a week which is equivalent to 2 tablets a week.

6.0 Dose Adjustment Flowchart

6.1 The flowchart overleaf should be used as guidance on how to adjust the patient's dose.