# Randomised, placebo-controlled study to assess the safety and efficacy of Enterosgel® in the treatment of functional abdominal pain in children and young people

## STUDY PROTOCOL

| | |
|---|---|
| **Document Description** | Full Study Protocol |
| **Brief Study Title** | **En**terosgel® in the **tr**eatment **o**f functional abdominal **p**ain **i**n **c**hildren and young people |
| **Acronym** | ENTOPIC |
| **Version and Date** | Version 1.0, 07/05/2025 |
| **Protocol Reference (internal)** | ENT08UK |
| **IRAS number** | 356725 |
| **National Institute for Health Research (NIHR) portfolio number** | |
| **International Standard Randomised Controlled Trial Number (ISRCTN)** | ISRCTN |
| **Development Phase** | Investigation for CE marking purposes |
| **Sponsor** | Enteromed Ltd |
| **Chief Investigator** | Professor Stephen Allen |

## Confidentiality Statement

## SIGNATURE PAGE

**Study Name:** Randomised, placebo-controlled multi-centre study to assess the safety and efficacy of Enterosgel® in the treatment of functional abdominal pain in children and young people

**Study Number:** ENT08UK

The Sponsor and Chief Investigator have approved the protocol version v.1.0 dated 07/05/2025 and confirm hereby to conduct the study according to the protocol and the Sponsor's SOPs, the current version of the World Medical Association Declaration of Helsinki, International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements.

**Chief Investigator:**

_____

Name Signature Date

**Sponsor:**

_____

Name Signature Date

**Statistician:**

_____

Name Signature Date

**For Local Principal Investigator (PI) at study site:**

I agree to conduct this trial as set out in this study protocol, and to comply with the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the applicable regulatory requirements.

_____

Site Name

_____

Name Signature Date

## CONTACT DETAILS

**Reporting of Serious Adverse Events (SAEs)**
Sites are responsible for submitting SAEs to the Sponsor within 24 hours by email to research@enteromed.co.uk

| | |
|---|---|
| **Chief Investigator** | Professor Stephen Allen<br>Professor of Paediatrics,<br>Liverpool School of Tropical Medicine, UK<br>Email: Stephen.Allen@lstmed.ac.uk<br>Tel: +44 7584 200611 |
| **Sponsor** | Enteromed Ltd<br>85 Great Portland Street, First Floor, London, W1W 7LT<br>Email: emarkaryan@enteromed.co.uk<br>Tel: +447860 817365 |
| **Funder** | Bioline Products s.r.o<br>Pátkova 831, Libeň, 182 00, Prague 8,<br>Czech Republic.<br>Email: info@enterosgel.eu<br>Phone: +420 702 240 532 |
| **Clinical Trial Manager,** | Dr Carol Howell<br>85 Great Portland Street, First Floor, London, W1W 7LT<br>Email: research@enteromed.co.uk<br>Tel; +447596887046 |
| **Data Manager/Statistician** | Matthew Dodd,<br>London School of Hygiene and Tropical Medicine<br>Email: Matthew.Dodd@lshtm.ac.uk<br>Tel: +44798181930 |
| **CRF, eDiary and Randomisation tool** | Sealed Envelope Ltd<br>Solar House - Pf 915 High Road, North Finchley, London N12 8QJ<br>Email: contact@sealedenvelope.com<br>Tel: +4420 3951 9928 |
| **Data Monitoring Committee** | Professor RM Beattie<br>Consultant Paediatric Gastroenterologist<br>Southampton Children's Hospital<br>Email: Mark.Beattie@uhs.nhs.uk<br>Tel: +442380777222 extn 6888<br><br>Laura Read,<br>London School of Hygiene and Tropical Medicine<br>Email: Laura.Read@lshtm.ac.uk<br>Tel: +447544522435 |

# Table of Contents

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AxMP | Auxiliary Medicinal Product |
| DMC | Data Monitoring Committee |
| eCRF | electronic Case Report Form |
| FAPD | Functional abdominal pain disorder |
| FGID | Functional gastrointestinal disorder |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| IBS | Irritable Bowel Syndrome |
| ICH | International Conference of Harmonisation |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| NHS | National Health Service |
| NICE | The National Institute for Health and Care Excellence |
| PedsQL-3.0-GIS | The Paediatric Quality of Life Inventory™ Gastrointestinal Symptoms Module |
| PI | Principal Investigator |
| REC | Research Ethics Committee |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UADE | Unanticipated Adverse Device Effect |

## TRIAL SUMMARY

| | |
|---|---|
| **Title:** | Randomised, placebo-controlled multi-centre study to assess the safety and efficacy of **Ent**erosgel® in the treatment **o**f functional abdominal **p**ain **i**n **c**hildren and young people |
| **Acronym:** | ENTOPIC |
| **Phase:** | Medical device study for CE marking purposes |
| **Chief Investigator:** | Professor Stephen Allen |
| **Sponsor:** | Enteromed Ltd |
| **Intervention:** | Enterosgel® (Bioline Products s.r.o), which is an intestinal adsorbent categorised as a class IIa medical device |
| **Study Design:** | UK two-centre, parallel arm, randomised, double-blind, placebo-controlled trial to evaluate the efficacy, tolerability and safety of Enterosgel® in the treatment of functional abdominal pain in children and young people age 3-18 years. After an initial 2-week observation phase eligible patients will be randomised 1:1 to receive Enterosgel® or placebo for 4 weeks during the double-blind treatment phase, then all patients will receive open-label Enterosgel® treatment for a further 4 weeks. All children will have the option to increase the dose of the intervention if required to control their symptoms during both phases. The patients then return to standard care.<br><br>The study involves a screening clinic appointment (routine clinical care; week 0) and remote recruitment appointment, a two-week initial observation period (weeks 1-2), a follow-up remote appointment at Baseline week 3 to confirm eligibility and a call at week 4 to check compliance, and follow-up remote appointments at weeks 6 and 10. Patients or carers will complete a daily study diary during 10 weeks (2 weeks of observation and 8 weeks of intervention). In addition, children and parents/carers complete questionnaires (PedsQL 3.0 GIS module, KIDSCREEN-27) at baseline and 6- and 10-weeks. |
| **Objectives:** | **<u>Primary objective</u>**<br><br>The primary objective of this study is to test the efficacy (superiority) of Enterosgel® (Bioline Products s.r.o, Czech Republic) compared with placebo in terms of change in mean abdominal pain score as recorded in the daily diary between the initial observation phase (weeks 1-2) and the double-blind treatment phase (weeks 3-6).<br><br>**<u>Secondary objectives</u>**<br><br>The secondary objectives for the **double-blind treatment phase** are:<br>1. To determine the efficacy of Enterosgel® compared with a parallel placebo group in terms of:<br>• abdominal pain as recorded in the daily diary<br>• change in stomach pain and other gastrointestinal symptoms<br>2. To determine effects of treatment on health-related quality of life<br>3. To evaluate safety of Enterosgel® through reported adverse events potentially related to treatment<br><br>The secondary objectives for the **open-label treatment phase** are:<br>1. In patients who had received placebo as blinded treatment, to compare the study outcome measures (same as for double-blind phase above) over the open-label Enterosgel® treatment period to the preceding placebo treatment period.<br>2. In patients who had received Enterosgel® as the blinded treatment, to test whether the treatment benefits (in terms of study outcome measures; same as for double-blind phase above) can be effectively maintained with Enterosgel®. |

| | |
|---|---|
| | 3. To evaluate safety of Enterosgel® through reported adverse events potentially related to treatment. |
| **Outcome measures:** | **<u>Primary Outcome Measure</u>**<br>Comparison of the change in mean daily Wong-Baker FACES Pain Rating Scale (limited to abdominal pain) during weeks 1-2 (initial observation phase) and the double-blind phase (week 3-6) recorded in the daily diary in the Enterosgel□ versus the placebo arm.<br>**<u>Secondary Outcome Measures</u>**<br>Comparison of the Enterosgel® versus the placebo arm during the double-blind treatment phase and open-label treatment phase:<br>1. Mean daily Wong-Baker FACES Pain Rating Scale recorded in the daily diary<br>2. The proportion of days with any abdominal pain<br>3. The proportion of days missed nursery/school<br>4. Change in the Stomach Pain and Hurt total score (comprised of 6 items) of the PedsQL 3.0 GIS module (parent/carer proxy-report for 3-4-year-olds and child self-report from 5-18 years; by parent/carer proxy-report for 3-18-year-olds)<br>5. Change in other individual components of the PedsQL 3.0 GIS module (parent/carer proxy-report for 3-4-year-olds and child self-report from 5-18 years; by parent/carer proxy-report for 3-18 years olds): stomach discomfort when eating (5 items), food and drink limits (6), trouble swallowing (3), heartburn and reflux (4), nausea and vomiting (4), gas and bloating (7), constipation (14), blood in bowel movement (2), diarrhoea (7), worry about bowel movements (5), medicines (4), communication (5).<br>6. Change in total PedsQL 3.0 GIS module score (parent/carer proxy-report for 3-4-year-olds and child self-report from 5-18 years; by parent/carer proxy-report for 3-18 years olds)<br>7. Change in health-related quality of life KIDSCREEN-27 questionnaire total score for children 8-18 years (child report and parent/carer proxy-report)<br>8. Change in health-related quality of life KIDSCREEN-27 questionnaire for children 8-18 years (child report and parent/carer proxy-report) and “General Mood and Feelings about Yourself” sub-score (7 questions) to assess anxiety and depression<br>9. Acceptability of the study interventions (daily diary)<br>10. Adequate relief during the past 7 days (end of double-blind and open-label phase)<br>11. Use of common analgesics for abdominal pain in the last weeks of the initial observation period (week 2), double blind phase (week 6) and open label phase (week 10)<br>12. Adverse Events |
| **Sample size:** | 154 patients will be enrolled |
| **Inclusion criteria:** | 1. Written informed consent<br>2. Children aged 3-18 years (parent/carer available to provide proxy-report and/or parent/carer report) with a clinical diagnosis of FAPD (Group H2) according to the Rome IV criteria (Functional dyspepsia [H2a], Irritable bowel syndrome [H2b]; Abdominal migraine [H2c] or Functional abdominal pain not otherwise specified [H2d]).<br>3. Normal faecal calprotectin at FAPD diagnosis (≤250 ug/g stool age 3-8 yrs, ≤100 ug/g stool age 9-18 yrs)<br>4. Considered suitable to take part in the study by the consenting investigator<br>5. Diary completed on at least 11 days (≥75%) during the observational period<br>6. Able to complete questionnaires in English<br>7. Able to complete e-diary and questionnaires on-line |
| **Exclusion criteria:** | 1. Previously diagnosed coeliac disease, inflammatory bowel disease or other significant gastro-intestinal disorder |

| | |
|---|---|
| | 2. Average number of stools per week <3<br>3. Previous use of Enterosgel®<br>4. Use of antidepressant agents, unless used at a stable dose for at least 6 weeks<br>5. Use of any probiotic supplements, other intestinal adsorbents, slow-release medications or strong opioids<br>6. Participation in any research where treatment is provided in the last three months<br>7. Pregnancy or not willing to use contraception for the duration of the study in females of childbearing potential defined as any female over 11 years of age and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal |
| **Study schedule:** | **Screening appointment in person/video conference (0 weeks)**<br>• Patient screening<br>• Confirming eligibility<br>• Informed consent<br>• Demographic information<br>• Medical history and concomitant medications<br>• Provide information about the study<br>**Recruitment call – remote (0 weeks)**<br>• **Informed consent**<br>• **Questionnaires (PedsQL 3.0 GIS module, KIDSCREEN-27)**<br>**Initial observation period (weeks 1-2)**<br>• Daily symptom diary (continue for 10 weeks)<br>**Baseline (remote): Start of double-blind phase (beginning of week 3)**<br>• Review of changes in medical history and concomitant medications<br>• Instruction on use of study intervention<br>• Randomisation<br>• Double-blind study treatment received by post<br>**Follow-up call – remote (week 3)**<br>• Ensure participant continuing in the study and discuss any potential issues<br>• Adverse events<br>**Follow-up 1 appointment – remote (end of week 6)**<br>• Questionnaires (PedsQL 3.0 GIS module, KIDSCREEN-27)<br>• Review of changes in medical history and concomitant medications<br>• Record Adverse Events<br>• Adequate relief question<br>• Check compliance and advise on any issues<br>• Open label study treatment received by post<br>**Follow-up 2 appointment – remote (end of week 10)**<br>• Questionnaires (PedsQL 3.0 GIS module, KIDSCREEN-27)<br>• Review of changes in medical history and concomitant medications<br>• Record Adverse Events<br>• Adequate relief question<br>• Check if any arrangements for clinical follow-up as part of routine care |

# 1. BACKGROUND

## 1.1 FUNCTIONAL ABDOMINAL PAIN

Functional abdominal pain disorders (FAPDs), also known as disorders of gut-brain interaction, are estimated to affect 13.5% of children worldwide and 10.5% of European children [1]. They can result in a decreased health related quality of life (HR-QOL) across all factors (emotional, social and physical) [2], school absenteeism and reduced participation in school and after-school activities similar to children with inflammatory bowel disease [3] and have significant health care costs [4]. A recent audit of children attending Alder Hey Gastroenterology Outpatients, showed 23.2% fulfilled the Rome IV criteria [5] for a functional gastrointestinal disorder (FGID). Amongst these children 75.5% had a FAPD (H2), of those 42.9% had irritable bowel syndrome (IBS; H2b); 14.3% functional dyspepsia (H2a); 4.8% functional abdominal pain not otherwise specified (H2d); and 1.6% abdominal migraine (H2c). Furthermore, it is estimated that up to 25% of childhood FGIDs continue into adulthood [6].

Clinical practice highlights the limited treatment options. A recent systematic review and meta-analysis of 91 studies (7226 children) evaluated dietary treatments (n=730), pharmacological treatments (n=2140), probiotic treatments (n=1762), and psychosocial treatments (n=2952) [7]. The study concluded only two treatments with moderate certainty were probably more effective for treatment success than control treatments. These included hypnotherapy and cognitive behavioural therapy, all other treatments were either not effective or the data were of very low certainty. For example, amitriptyline resulted in significant improvement in children in India, but this was an open-label trial and there was a trend to more frequent adverse events in the treatment arm [8]. A small study of melatonin in children with FAPDs also treated with a probiotic showed an initial, modest improvement in abdominal pain but this was not sustained [9]. Another small study of gut-directed hypnotherapy showed decreased pain frequency and intensity in children with functional abdominal pain and IBS but no improvement in quality of life (QOL) or school absence [10]. A recent study of Mebeverine in adolescents showed it was ineffective in the treatment of IBS and functional abdominal pain not otherwise specified [11]. In summary, there is an absence of safe, effective and evidence-based treatments for FAPDs in children.

## 1.2 INTESTINAL ADSORBENTS IN THE TREATMENT OF FAPDs

Enterosgel® is an oral intestinal adsorbent that binds bacterial toxins, viruses, immune chemicals and bile acids in the gut [12,13]. The active component is polymethylsiloxane polyhydrate. It is classified as a medical device class IIA as it is excreted unchanged being neither absorbed nor metabolised [12]. Enterosgel® is free from preservatives, sugar and other additives and considered to be non-allergenic. It is available over the counter as a gel in a tube or sachet. The gel is taken diluted in water and has no taste. The European database of suspected adverse drug reaction reports no adverse reactions in Europe since it was certified in 2008 (http://www.adrreports.eu/en/index.html). It is certified for the treatment of acute diarrhoea and IBS with diarrhoea (IBS-D) for all ages.

Enterosgel® improves stool frequency and consistency in adults [14] and children with diarrhoea [15-18]. A recent UK randomised, placebo-controlled trial evaluated Enterosgel® in 440 adults with IBS-D (age 16-75yrs) recruited from primary and secondary care, and a virtual site [19]. The primary outcome (percentage of responders for abdominal pain and stool consistency score) was higher in the Enterosgel® (37.4%) than the placebo group (24.3%; NNT:8; odds ratio 1.95 [1.28 to 2.99, p=0.0020]). Statistically significant benefits in the Enterosgel® arm were also found for diary-based outcomes of stool consistency/frequency, pain, bloating and urgency. Questionnaire scores showed significant differences for the IBS Severity Scoring System and IBS-QOL questionnaires. Following an open-label phase, 75.9% of patients reported adequate relief of symptoms.

In IBS, Enterosgel® is thought to target several factors including immune proteins, bacterial breakdown products and bile acids and normalise the intestinal microflora [19]. Based on its mechanisms of action and the encouraging findings in adult IBS-D, Enterosgel® could be a safe and effective treatment for childhood FAPDs.

This trial will be the first placebo-controlled randomised trial with Enterosgel® in children and young people with FAPDs.

# 2. AIMS AND OBJECTIVES

## 2.1 AIMS

The aims of this study are:

1. To determine the efficacy of Enterosgel® treatment for 4 weeks in improving FAPD symptoms in children with Functional dyspepsia [H2a], IBS [H2b]; Abdominal migraine [H2c] or Functional abdominal pain not otherwise specified [H2d])
2. To determine the safety and tolerability of Enterosgel® for the treatment of FAPDs
3. Document the effects of treatment up to 8 weeks on symptoms
4. To determine the efficacy in sub-group analysis of children with specific FAPDs.
5. To obtain data to power a larger follow-on study to determine the clinical and cost effectiveness of Enterosgel® for the treatment of FAPDs in children.

## 2.2 OBJECTIVES

### 2.2.1 Primary objective

The primary objective of this study is to test the efficacy (superiority) of Enterosgel® (Bioline Products s.r.o, Czech Republic) compared with placebo in terms of change in mean abdominal pain score as recorded in the daily diary between the initial observation phase (weeks 1-2) and the double-blind treatment phase (weeks 3-6).

### 2.2.2 Secondary objectives

The secondary objectives for the **double-blind treatment phase** (weeks 3-6) are:

1. To determine the efficacy of Enterosgel® compared with a parallel placebo group in terms of:
    - abdominal pain as recorded in the daily diary
    - change in stomach pain and other gastrointestinal symptoms
2. To determine effects of treatment on health-related quality of life
3. To evaluate safety of Enterosgel® through reported adverse events potentially related to treatment

The secondary objectives for the **open-label treatment phase** (weeks 7-10) are:

4. In patients who had received placebo as blinded treatment, to compare the study outcome measures (same as for double-blind phase above) over the open-label Enterosgel® treatment period to the preceding placebo treatment period.
5. In patients who had received Enterosgel® as the blinded treatment, to test whether the treatment benefits (in terms of study outcome measures; same as for double-blind phase above) can be effectively maintained with Enterosgel®.
6. To evaluate safety of Enterosgel® through reported adverse events potentially related to treatment.

# 3. STUDY DESIGN AND OUTCOME MEASURES

## 3.1 STUDY DESIGN

This is a UK two-centre, parallel arm, randomised, double-blind, placebo-controlled trial to evaluate the efficacy, tolerability and safety of a medical device, Enterosgel®, in the treatment of functional abdominal pain in children and young people. (**Figure 1**).

Children aged 3-18 years will be recruited over a 12-month period by review of NHS referrals to general paediatric and paediatric gastroenterology clinics at Alder Hey Children's NHS Foundation Trust, and Bristol Royal Hospital for Children and by review of children previously diagnosed with a FAPD. All children will be reviewed by an experienced paediatrician. A thorough clinical assessment including any appropriate investigations (e.g. gastro-intestinal endoscopy; abdominal ultrasound, faecal calprotectin) will be performed with careful attention to potential alarm features in children with chronic abdominal pain to ensure that other diagnoses are excluded [20]:

- Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease
- Persistent right upper or right lower quadrant pain
- Dysphagia
- Odynophagia
- Persistent vomiting
- Gastrointestinal blood loss
- Nocturnal diarrhoea
- Arthritis
- Perirectal disease
- Involuntary weight loss
- Deceleration of linear growth
- Delayed puberty
- Unexplained fever

Children will only be recruited once a diagnosis of an FAPD has been confirmed according to Rome IV criteria [21] and including the following syndromes:

- H2a. Functional Dyspepsia
- H2b. Irritable bowel syndrome
- H2c. Abdominal Migraine
- H2d. Functional Abdominal Pain Not Otherwise Specified

The study involves a screening clinic appointment (routine clinical care; week 0) and remote recruitment appointment, a two-week initial observation period (weeks 1-2), a follow-up remote appointment at Baseline week 3 to confirm eligibility and a call at week 4 to check compliance, and follow-up remote appointments at weeks 6 and 10. The daily on-line diary will be completed for 10 weeks (Wong-Baker FACES Pain Rating Scale) and questionnaires (PedsQL 3.0 GIS module, KIDSCREEN-27) at screening, 6 and 10 weeks. No further clinic visits or blood, stool or other samples are required for research purposes.

The screening clinic appointment will take place within a routine clinic visit which may be on site or remote. Recruitment during a remote clinic call will only occur where the child has already been clinically assessed and examined by the referring paediatrician. Children previously diagnosed with a FAPD can be considered for invitation to join the study without the need for an additional routine clinic visit. Patients and their parent/carer that have a clinician’s confirmed diagnosis with specific FAPD category (H2a, H2b, H2c or H2d) and deemed eligible to join the study will receive patient information sheets and a pregnancy test kit for those eligible. After 24 hours consideration the Research Nurse will call and book a remote recruitment

appointment or an additional clinic visit. The research nurse will recruit and consent patients during the recruitment appointment for a 2week observational phase.

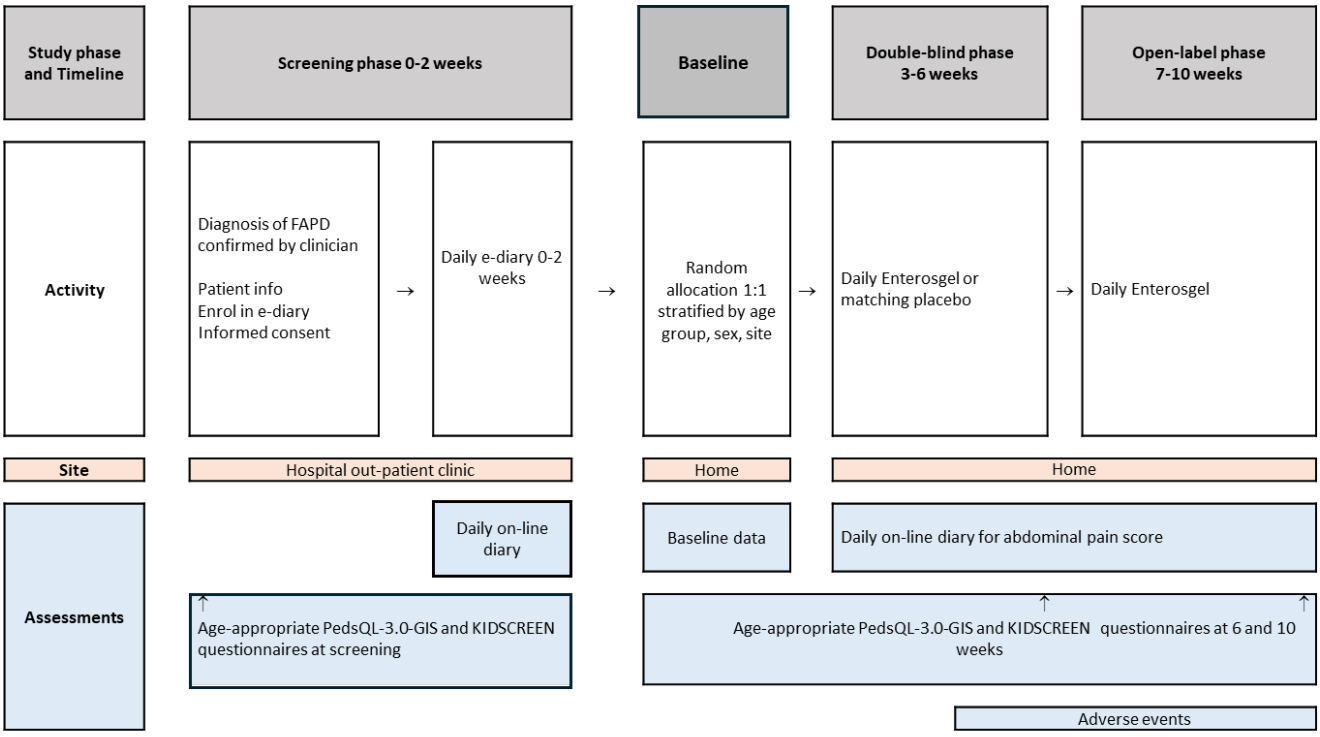
Eligible patients at baseline will be randomised 1:1 to receive Enterosgel® or placebo for 4 weeks during the double-blind treatment phase (weeks 3-6), then all patients will receive open-label Enterosgel® treatment for a further 4 weeks (weeks 7-10). Patients will take a dose in the morning and evening, with an increase in dose from 53% to 80% of the recommended daily dose for diarrhoea at week 3-4 (including in the placebo arm). The purpose of the dose adjustment is two-fold; first, it will maximise the efficacy of the active treatment by making a step-wise increase in dose and second, it will provide us with data to help define the optimal dosage regimen(s) for Enterosgel®.

After the double-blind treatment phase, all patients will receive open-label Enterosgel® treatment for 4 weeks. As in the double-blind phase, patients will take an increase in dose from 53% to 80% of the recommended daily dose for diarrhoea at week 3-4. As the treatment will be open-label, this is a pragmatic part of the trial, allowing us to better understand the optimal dosage regimen(s) for Enterosgel®. After 4 weeks of open-label treatment, the patients will return to standard care.

The study outcomes align with the 8 core outcome set for FAPDs in children as outlined by articles listed on the COMET Core Outcome Measures in Effectiveness Trials database [22].

The initial study design and patient facing documents have been reviewed by the Generation R Liverpool Young Person's Advisory Group, which comment and advise on paediatric trials. The group consists of children and parents and they will continue to be consulted on all aspects of the trial development and delivery and be represented on the Trial Management Group.

**Figure 1.** Study design.




Note: FAPD = functional abdominal pain disorder

## 3.2 STUDY OUTCOME MEASURES

### 3.2.1 Primary Outcome Measure

Comparison of the change in mean daily Wong-Baker FACES Pain Rating Scale (limited to abdominal pain) during weeks 1-2 (initial observation phase) and the double-blind phase (week 3-6) recorded in the daily diary in the Enterosgel® versus the placebo arm.

### 3.2.2 Secondary Outcome Measures

#### 3.2.2.1 Double-blind and Open-label treatment phase

The secondary outcome measures in the Enterosgel® versus the placebo arm during the double-blind and open-label treatment phase are listed in **Table 1**.

**Table 1.** Secondary outcome measures for the double-blind and open-label treatment phase

| Outcome Measure | Time points and method of assessment | Definition |
|---|---|---|
| 1. Abdominal pain score | Daily diary | Mean daily Wong-Baker FACES Pain Rating Scale |
| 2. Frequency of abdominal pain | Daily diary | Proportion of days with any abdominal pain |
| 3. Days missed nursery/school | Daily diary | Proportion of days missed nursery/school |
| 4. Change in the Stomach Pain and Hurt total score | Baseline, weeks 6 and 10 (PedsQL 3.0 GIS module; comprised of 6 items) | Parent/carer proxy-report for 3-4-year-olds and child self-report from 5-18 years; by parent/carer proxy-report for 3-18-year-olds) |
| 5. Change in individual components of the PedsQL 3.0 GIS module | Baseline, week 6, 10 (PedsQL 3.0 GIS module) | Parent/carer proxy-report for 3-4-year-olds and child self-report from 5-18 years; by parent/carer proxy-report for 3-18 years old.<br>Individual components of the PedsQL 3.0 GIS module: stomach discomfort when eating (5 items), food and drink limits (6), trouble swallowing (3), heartburn and reflux (4), nausea and vomiting (4), gas and bloating (7), constipation (14), blood in bowel movement (2), diarrhoea (7), worry about bowel movements (5), medicines (4), communication (5). |
| 6. Change in total PedsQL 3.0 GIS module score | Baseline, week 6,10 (PedsQL 3.0 GIS module) | Parent/carer proxy-report for 3-4-year-olds and child self-report from 5-18 years; by parent/carer proxy-report for 3-18 years old. |
| 7. Change in health-related quality of life KIDSCREEN-27 questionnaire | Baseline, week 6, 10 (Health-related quality of life KIDSCREEN-27) | Total Health-related quality of life KIDSCREEN-27 score (parent reported 3-7 years, child self-report 8-18 years) |
| 8. Change in health-related quality of life KIDSCREEN-27 questionnaire “General Mood and Feelings about Yourself” sub-score | Baseline, week 6, 10 (Health-related quality of life KIDSCREEN-27) | Health-related quality of life KIDSCREEN-27 sub-score for “General Mood and Feelings about Yourself” (7 questions; parent reported 3-7 years, child self-report 8-18 years) |
| 9. Acceptability of the study interventions | Daily (diary) | Compliance with taking study intervention each day* |

| | | |
|---|---|---|
| 10. Adequate relief | Questionnaire | Opinion of the 1) child and 2) parent/carer whether there has been adequate relief of abdominal pain during the previous 7 days (recorded at end of double-blind and open-label phases) |
| 11. Use of common analgesics for abdominal pain | Questionnaire | 1) Use of common analgesics (e.g. paracetamol; ibuprofen) for abdominal pain in the last week of the initial observation period (week 2), double blind phase (week 6) and open label phase (week 10) |
| 12. Adverse Events | When reported | 1) Percentage of patients reporting SAEs and AEs possibly related to treatment<br>2) Total number of SAEs and AEs reported |

*Patients who develop constipation will be advised to stop treatment for a few days as per study treatment instructions. The diary will capture this information which will not be considered as non-compliance.

Data regarding the PedsQL 3.0 GIS module and KIDSCREEN-27 questionnaire will be collected as an online version (for use on mobile devices, laptops and computers). The PedsQL 3.0 GIS module will be a proxy-report completed by the parent/carer for 3-4-year-olds and child self-report from 5-18 years. The KIDSCREEN-27 will be a proxy-report completed by the parent/carer for 3-7 year-olds and child self-report from 8-18 years. The "General Mood and Feelings about Yourself" sub-score (based on 7 questions) will be analysed to assess effects of the intervention on anxiety/depression in addition to the "worry about bowel movements" (5 questions) in the PedsQL 3.0 GIS module. The content of the diary is supplied in Error! Reference source not found.and questionnaires in Error! Reference source not found..

### 3.3 DEFINITION OF END OF TRIAL

End of trial is defined as the last follow-up appointment for the last patient. Patients with unresolved SAEs at the last follow-up appointment would be followed up until SAE resolution or stabilisation.

## 4. STUDY PARTICIPANTS

### 4.1 INCLUSION CRITERIA

1) Written informed consent
2) Children aged 3-18 years (parent/carer available to provide proxy-report and/or parent/carer report) with a clinical diagnosis of FAPD (Group H2a, H2b, H2c, H2d) according to the Rome IV criteria*
3) Normal faecal calprotectin at diagnosis (≤250ug/g stool age 3-8 yrs, ≤100ug/g stool age 9-18 yrs)
4) Considered suitable to take part in the study by the consenting investigator
5) Diary completed on at least 11 of 14 days (≥75%) during the observational period
6) Able to complete questionnaires in English
7) Able to complete e diary and questionnaires on-line

### 4.2 EXCLUSION CRITERIA

1) Previously diagnosed coeliac disease, inflammatory bowel disease or other significant gastro-intestinal disorder
2) Average number of stools per week <3
3) Previous use of Enterosgel®
4) Use of antidepressant agents, unless used at a stable dose for at least 6 weeks
5) Use of any probiotic supplements, other intestinal adsorbents, slow-release medications or strong

opioids

6) Participation in any research where treatment is provided in the last three months
7) Pregnancy or not willing to use contraception for the duration of the study**

** According to the Rome IV criteria for FAPD [H2; 21], the following criteria must be met for the last 3 months:*

*H2a. **Functional Dyspepsia**. Must include one or more of the following bothersome symptoms at least 4 times a month for at least 2 months prior to diagnosis:*

1. *Postprandial fullness*
2. *Early satiation*
3. *Epigastric pain or burning not associated with defecation*
4. *After appropriate evaluation, the symptoms cannot be fully explained by another medical condition*

*Within FD the following subtypes are now adopted:*

*H2a1. **Postprandial distress syndrome** includes bothersome postprandial fullness or early satiation which prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching.*

*H2a2. **Epigastric pain syndrome** which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include (a) burning quality of the pain but without a retrosternal component, (b) commonly induced or relieved by ingestion of a meal but may occur while fasting.*

*H2b. **Irritable Bowel Syndrome**. Diagnostic criteria* Must include all of the following:*

1. *Abdominal pain at least 4 days per month over at least 2 months associated with one or more of the following:*
2. *Related to defecation and/or a change in frequency of stool and/or a change in form (appearance) of stool*
3. *In children with abdominal pain and constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS)*
4. *After appropriate evaluation, the symptoms cannot be fully explained by another medical condition*

**Criteria fulfilled for at least 2 months prior to diagnosis*

*Within IBS the following are subtypes:*

- *Abdominal pain associated with constipation (IBS-C)*
- *Abdominal pain associated with diarrhoea (IBS-D)*
- *Abdominal pain associated with constipation and diarrhoea mixed (IBS-M)*
- *Abdominal pain not otherwise specified (IBS-U)*

*H2c. **Abdominal Migraine.** Diagnostic criteria* Must include all of the following occurring at least twice:*

1. *Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom)*
2. *Episodes are separated by weeks to months*
3. *The pain is incapacitating and interferes with normal activities*
4. *Stereotypical pattern and symptoms in the individual patient*
5. *The pain is associated with two or more of the following:*
    a) *Anorexia*
    b) *Nausea*
    c) *Vomiting*
    d) *Headache*
    e) *Photophobia*
    f) *Pallor*

6. *After appropriate evaluation, the symptoms cannot be fully explained by another medical condition*

**Criteria fulfilled for at least 6 months prior to diagnosis*

*H2d.* ***Functional Abdominal Pain*** *–* ***Not Otherwise Specified*** *Diagnostic criteria* Must be fulfilled at least 4 times per month and include all of the following:*

1. *Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g., eating, menses)*
2. *Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine*
3. *After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition*

**Criteria fulfilled for at least 2 months prior to diagnosis*

*** A pregnancy test will be performed at Baseline on all female patients of child-bearing potential. Females of childbearing potential (over the age of 11 years; not surgically sterile (hysterectomy or bilateral oophorectomy), 12 months postmenopausal or otherwise incapable of pregnancy) and heterosexually active must use contraception throughout the screening period and the 8 weeks when they may be receiving study treatment. Acceptable methods of contraception are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include [23]:*

- *combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:*
  - *oral*
  - *intravaginal*
  - *transdermal*
- *progestogen-only hormonal contraception associated with inhibition of ovulation:*
  - *oral*
  - *injectable*
  - *implantable*
- *intrauterine device (IUD)*
- *intrauterine hormone-releasing system (IUS)*
- *bilateral tubal occlusion*
- *vasectomised partner (Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success)*
- *sexual abstinence (In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.)*

*Method of contraception must be documented in the patient's medical records.*

## 4.3 PATIENT RECRUITMENT

### 4.3.1 Recruitment strategies

#### 4.3.1.1 Research sites

Based on the clinical audit of children attending paediatric gastroenterology clinics, Alder Hey Hospital during 1 month [5], 40 children fulfilled Rome IV criteria [21] for a FAPD (Group H2). A more recent audit at both sites of children attending general paediatric and paediatric gastroenterology clinics estimated each site could recruit 5-10 patients from a potential 20-40 eligible patients.

With the inclusion of patients previously diagnosed with an FAPD and considering difficulties in recruitment to clinical trials especially of older children, recruiting a total of 13 patients per month for 12 months is a realistic target.

Recruitment will be competitive across all sites until the total target of 154 patients has been met. All participating sites will be required to participate in a site initiation and training meeting and regular follow-up meeting to track progress organised by the study Sponsor.

An additional recruitment option will be considered if recruitment rates are slower than estimated. Research nurses will screen for children previously diagnosed with an FAPD and send out an invitation to join the study and include the patient information sheets.

### 4.3.2 Screening process

Potentially eligible patients will be identified by review of NHS referrals to general paediatric and paediatric gastroenterology clinics at Alder Hey Children's NHS Foundation Trust, and Bristol Royal Hospital for Children and also by review of children previously diagnosed with a FAPD. All children will be reviewed by an experienced paediatrician.

The diagnosis of a FAPD and the sub-type will be confirmed by a study paediatrician after undertaking appropriate clinical investigations if required. Participants deemed eligible to join the study and/or their parents/carers will be provided with verbal information regarding the trial and an age-appropriate Patient Information Sheet by the study paediatrician or in the post for previous diagnosed patients. If they are interested in considering joining the trial a pregnancy kit (if required) will be provided for the subject to use, after securing informed consent. They will then be contacted by the Research Nurse after they have had 24 hours to consider the study, to arrange the remote Recruitment appointment. At the remote Recruitment appointment, eligibility will be confirmed, and e-consent and assent will be obtained by the research nurse before any study procedures are conducted. Medical history and list of concomitant medications will be obtained from the screening form and/or medical notes. Information and a demonstration on the e-diary, questionnaires and study treatment will be provided.

Basic information about all screened patients will be documented in a study screening log and/or eCRF at the research site (age, sex, ethnicity). The patient’s GP will be notified of the patient’s participation in the study and will maintain the responsibility for the healthcare of the patient outside the research.

A patient must not be randomised at Baseline before the results from any tests required to exclude other conditions and a negative pregnancy test, if applicable, have been obtained. Eligibility must be confirmed against the patient’s medical notes as stated in section 4.2.

## 4.4 DISCONTINUATION AND WITHDRAWAL CRITERIA

Participants or parents/carers can withdraw consent at any time without providing a reason. This includes during the initial 2-week observation phase and before receiving any interventions. No further data will be collected after a participant withdraws consent or is withdrawn from the study, but data collected before withdrawal can be used. If a participant refuses to continue the use of study treatment, they can continue with follow-up assessments and visits if willing to do so, but a Protocol Deviation for non-compliance to study treatment should be recorded.

In case of the following the participants should be withdrawn from the study by the Principal Investigator:

- Significant deterioration of the participant’s status as assessed by the principal investigator
- Serious Adverse Event (SAE) related to study treatment(s) or procedures
- Pregnancy

- Any other changes in diagnoses or medical conditions that could affect participants safety on the trial and/or scientific quality of the data
- Major protocol violation (affecting participants safety and/or scientific quality of the data)

The reason(s) for withdrawal should be documented in the Continuation Status eCRF as soon as site becomes aware of the patient's withdrawal. If a participant decides to withdraw consent or is lost to follow-up, this should also be documented in the Continuation Status eCRF without delay. Participants should be informed that they might be contacted in the future if any significant new information becomes available regarding the study treatment.

# 5. INTERVENTIONS AND STUDY DEVICE

## 5.1 INTERVENTION

### 5.1.1 Treatment allocation

#### 5.1.1.1 Double-blind phase

For the double-blind treatment phase, patients will be randomised in 1:1 ratio using a computer-based randomisation tool (Sealed Envelope Ltd, UK) to:

**Control Group**: will receive placebo daily for 4 weeks

**Interventional Group**: will receive Enterosgel® daily for 4 weeks

Randomisation will be based on the minimisation method where treatment allocation will be stratified by study centre, sex and age group (15-18 years; 7-14 years and 3-6 years). Minimisation allocates subjects to the treatment group that best maintains balance in stratifying factors. It is effective even at small sample sizes and with multiple stratification variables [24].

#### 5.1.1.2 Open-label phase

For the open-label treatment phase, all patients will receive Enterosgel® daily for 4 weeks in standard 225g tubes, which are identical to those available over-the-counter in the UK.

### 5.1.2 Enterosgel®

#### 5.1.2.1 General description

Enterosgel® is an intestinal adsorbent developed for binding toxins and other harmful substances in the gastrointestinal tract. The commercially available Enterosgel® product contains 30% water and 70% polymethylsiloxane polyhydrate (PP), which is a 3-dimensional crosslinked polymer of methylsiliconic acid formed by polycondensation in which hydroxyl groups form stable siloxane bonds. In solution, these form microglobules via cross-linking of the pentameric cyclic structural units created by the siloxane bonds which connect to each other via strong hydrogen bonds [25]. The microglobules contain porous space filled with water. The overall porous structure of Enterosgel® is formed by connecting the microglobules of approximately 50nm in size, which then associate into larger particles ranging from 5-250μm in size, with over 32% in the 20-50 μm range [26].

Enterosgel® exhibits selective adsorptive activity towards medium and high-molecular weight substances in the gut, including middle-molecular weight toxic metabolites. It effectively binds medium and high molecular weight substances including various bacterial toxins (bacterial endotoxin, *Clostridioides difficile*

toxins A and B, shiga toxin II), while showing a lower binding capacity than carbon-based adsorbents for smaller molecules such as vitamin B12 and certain drug compounds [13,26]. This selectiveness could result from the unique properties of the adsorbent, i.e. its porous structure and the presence of both hydrophilic and hydrophobic groups on the surface.

Enterosgel® does not cross the intestinal barrier and is therefore classified as a medical device. In Europe, it was certified as a medical device class IIA in 2011 and is currently sold over the counter in 30 countries. According to European database of suspected adverse drug reaction reports (http://www.adrreports.eu/en/index.html) there are no reported adverse reactions in Europe since it was certified in 2011. Enterosgel® is available from pharmacies and health stores in the UK and is available in a tube or in a packet of 10 sachets. It is free from preservatives, sugar and other additives, has no distinct taste and is easily suspended in water and taken orally. Enterosgel® can be used in children and adults, including pregnant and breastfeeding women.

#### 5.1.2.2 Description of study treatment

Although there has been extensive research on Enterosgel® in Eastern Europe, so far none of the conducted trials have included a placebo control arm. Any gel-like substances (for example gelatin or starch based) could potentially have effects in the gastrointestinal tract and their suitability for use as a placebo would require validation. However, since Enterosgel® is taken by diluting 1-1.5 tablespoons of the product in 200ml water, a water-based placebo is an alternative to a gel-like placebo. The recent RELIEVE IBS-D trial used water as the placebo and pre-diluted Enterosgel®, both were placed in identical 90g tubes [19], this approach was successful in achieving the first placebo trial of Enterosgel®.

The same approach will be used in this trial. The blinded Enterosgel® will be provided in a pre-diluted form in 90ml tubes containing Enterosgel® in potable water. The dose/weight of Enterosgel® in each tube will vary dependent on age of the child. The appropriate age-related dosed tubes will be provided to each participant. Diluting the Enterosgel® in water will not alter the structural or adsorption properties of Enterosgel® [25].

For the open-label phase, patients will be provided with the standard over-the-counter Enterosgel® in 225g tubes.

### 5.1.3 Placebo

Each placebo tube will contain 90ml of potable water.

### 5.1.4 Treatment dosage

#### 5.1.4.1 Double-blind phase

Both the placebo and Enterosgel® will be provided in 90g tubes, each containing a single dose of treatment (age 7-18 years) or half a dose of treatment (age 3-6 years). Each Enterosgel® tube contains either 8, 12 or 18g of Enterosgel® (Bioline Products s.r.o, Czech Republic) pre-diluted in 65-80ml of potable water. Each placebo tube contains 90ml of potable water.
The age-related treatment dose per day is one dose in the morning 1 hour before or after a meal, and one dose in the evening 1 hour before or after a meal. The daily dose for week 1-2 will be 53% of the recommended age-related daily treatment dose for acute diarrhoea, the dose will increase at week 3-4 to 80% of the dose for acute diarrhoea.
Study-specific age-related dosage instructions for the double-blind treatment period are provided in **APPENDIX C: TREATMENT USE INSTRUCTIONS (DOUBLE-BLIND PHASE)**.

#### 5.1.4.2 Open-label phase

For the open-label treatment phase, all patients will receive Enterosgel® in 225g tubes with the appropriate age-related measuring spoon (5g, 10g or 15g). The age-related dosage morning and evening and the stepwise dose increase at week 3-4 will align with the double-blind phase.
Study-specific dosage instructions are provided in Error! Reference source not found..

### 5.1.5 Labelling, storage, supply and destruction

#### 5.1.5.1 Blinded study treatment

Both the placebo and Enterosgel® dilution will be manufactured in accordance with good manufacturing practice (GMP) by Bioline Products s.r.o. and packed into identical 90g tubes.

In accordance with Annex I of the European Council Directive 93/42/EEC concerning Medical Devices, each study device will be marked with a label containing the text “EXCLUSIVELY FOR CLINICAL INVESTIGATION” and the following information:

1. Content: This tube contains blinded gel drink
2. Manufacturer: Bioline Products s.r.o, Pátkova 831, Libeň, 182 00, Prague 8, Czech Republic.
3. Distributor: Enteromed Ltd, UK
4. Study Sponsor: Enteromed Ltd, UK
5. Study reference: ENT08UK
6. Batch number: Please check crimped top of tube for number
7. Expiry date: Please check crimped top of tube for date
8. Instructions for use: Shake well immediately before use. Add the dose to the volume of room temperature water stated in study treatment instructions. Leave at least 2 hours before and after taking this treatment and taking any oral medications and 1 hour for eating meals.
9. Storage: +4C° to +30C°. Keep away from direct sunlight or heat.
10. Disposal: Contents can be safely disposed into the domestic waste. Packaging can be recycled.

The tubes will be stored at the same warehouse facility as the commercial medical device (Nivtar Distribution Limited, Duxford, UK) contracted by the Sponsor. The study supplies should be clearly separated from any other commercial supplies, and placebo and Enterosgel® will be separated into age groups and treatment arm by product name and barcode, so that they can be identified by the warehouse staff responsible for coordinating the study supplies. After each randomisation, the research team will email using a secure message encryption, a Supplies Request Form with the unique randomisation code and the participant’s name, home address and phone number to a dedicated email address, which is only accessed by two unblinded study coordinators at the Sponsor’s research team. A coordinator will check the randomisation code against a pre-generated randomisation code list provided by Sealed Envelope Ltd, stored in a locked safe only accessible by the unblinded coordinators. The coordinator will determine whether the code corresponds to placebo or Enterosgel® and will log onto the secure study online booking site to request for a shipment of a box (A or B) of tubes of the correct age group corresponding to the randomisation code, to the participant’s home address to be used starting after the Baseline appointment. The online system will generate a unique code which can then be tracked through the system and will confirm dispatch. At the warehouse the patient delivery will be picked, scanned for barcode and a second checking process will re-scan before the delivery is packed and dispatched within 2 calendar days from receiving the request (next day for orders submitted before 2 pm). All parties should delete the request emails once confirmed received by the next party. However, paper copies of the forms should be kept at the sites, and a record of each delivery with barcode checks will be available from the warehouse reporting to allow for treatment accountability. Likewise, the unblinded study coordinators will keep a record on a secure password protected smartsheet containing no patient identifiable information.

The participants can dispose of the empty tubes at home in the domestic waste, as well as any unused tubes remaining at the end of the study. Should the participant run out of study treatment during the 4 weeks, they or their parent/guardian can request for more supplies by contacting the research nurse, who will submit a request to the Sponsor.

#### 5.1.5.2 Open-label study treatment

After a participant has been entered into the open-label phase, the research team will email the participant's name, home address and phone number to a dedicated email address, as described above in section 5.1.5.1. The study coordinators receiving this information will then request a shipment of open-label treatment from the warehouse to the patient's home.

Each study device will be marked with a label containing the text "EXCLUSIVELY FOR CLINICAL INVESTIGATION" and the following information:

1. Content: This tube contains the treatment ENTEROSGEL®
2. Manufacturer: Bioline Products s.r.o, Pátkova 831, Libeň, 182 00, Prague 8, Czech Republic.
3. Distributor: Enteromed Ltd, UK
4. Study Sponsor: Enteromed Ltd, UK
5. Study reference: ENT08UK
6. Batch number: Please check crimped top of tube for number
7. Expiry date: Please check crimped top of tube for date
8. Instructions for use: Shake well immediately before use. Add the correct dose using the measuring spoon to the volume of room temperature water stated in study treatment instructions. Leave at least 2 hours before and after taking this treatment and taking any oral medications and 1 hour for eating meals.
9. Storage: +4C° to +30C°. Keep away from direct sunlight or heat.
10. Disposal: Contents can be safely disposed into the domestic waste. Packaging can be recycled.

Participants can dispose of the empty tubes at home in domestic waste and keep any remaining unused Enterosgel®. Should the participant run out of study treatment during the 4 weeks, they can request for more supplies by contacting the research nurse, who will submit a request to the Sponsor.

## 5.3 CONCOMITANT TREATMENTS

### 5.3.1 Other FGID treatments

Participants will be allowed to continue to take antidepressant agents at a stable dose, provided that they had been taking a stable dose for at least 6 weeks before providing written informed consent.

Use of probiotic supplements, other intestinal adsorbents (activated charcoal, kaoline, diosmectite), slow-release medications or strong opioids during the study will not be permitted and any participants who require slow-release medications, should be withdrawn from the trial. Participants will be advised not to make any changes to their diet while on the trial.

### 5.3.2 Contraindications

The only listed contraindications for Enterosgel® are intestinal atony, use of slow-release medications and intolerance to Enterosgel® based on previous use. The study eligibility criteria will ensure that no participants with these contraindications will be enrolled into the trial.

### 5.3.3 Precautions

To minimise the risk that Enterosgel® could adsorb concomitant medications in the gut, it is recommended to leave at least two hours before and after taking the study treatment and taking any medication. Likewise, to minimise the risk that Enterosgel® could adsorb nutrients from the gut, it is recommended to leave one hour before and after taking the study treatment and eating a meal.

# 6. STUDY SCHEDULE AND PROCEDURES

## 6.1 PATIENT IDENTIFICATION AND SCREENING

Participants recruitment strategies and process are described in **4.3 PATIENT RECRUITMENT**. The participant and/or parent/carer have had sufficient time (at least 24 hours) to consider the information, prior to written or e-consent being secured. Those with a diagnosis of FAPD confirmed by a clinician a negative pregnancy test (if applicable) and meet the inclusion and exclusion criteria will be randomised into the study.

## 6.2 STUDY VISITS AND PROCEDURES

Participants will attend one screening study visit during a routine clinic visit (on site or remote) at the recruiting site followed by a remote Recruitment visit. Informed consent and assent (written or e-consent) will be obtained by the research nurse before any study procedures are conducted. Participants who pass the diagnostic criteria and consent to proceed will be entered into the study. Demographic and clinical data will be collected and questionnaires completed at the recruitment visit and participants entered into the observational phase. Further appointments/calls will be conducted by the research team; at baseline (week 3), week 4 and at the end of the double-blind phase (week 8) and end of the open label phase (week 10).

The schedule of appointments and procedures conducted at each visit are summarised in **Table 3** and described in more detail below. +/- 1 week is allowed around each follow-up appointment. **Table 4** summarises the schedule for completion of study diary and questionnaires. All remote appointments and follow-up calls, can be conducted either via telephone or video call, depending on the participant's preference. At the end of the study (week 10), children will continue under the care of their paediatrician usually including a routine follow-up clinic at week 12 (3 months from the initial screening visit).

**Table 3**. Schedule of events and appointment procedures.

| **Procedure** | **Screening appointment (Recruitment site/remote)**<br><br>**0 weeks** | **Recruitment appointment (remote)** | **Baseline appointment (remote) Week 3** | **Compliance call Week 4** | **Follow-up 1 appointment (remote) 6 weeks** | **Follow-up 2 appointment (remote)10 weeks** |
|---|---|---|---|---|---|---|
| Informed consent | | X | | | | |
| Patient screening | X | | | | | |
| Demographic information | X | | | | | |
| Review of medical history and concomitant medications | X | | | | | |
| Pregnancy test where needed | | | X | | | |
| Instructions on completion of diary | | X | X | | X | |
| Confirming eligibility (based on patient diary data; review of medical notes; pregnancy test) | | | X | | | |
| Randomisation | | | X | | | |
| Instructions on use of study treatment | | | X | | X | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Review of changes in medical history or concomitant medications | | | X | | X | X |
| Adverse Events | | | | X | X | X |
| Checking compliance to study procedures and advising on any issues | | | | X | | |
| Adequate relief question | | | | | X | X |

**Table 4.** Study diary and questionnaire completion schedule. “X” means that the item is completed once that week, except where otherwise specified.

| **Visit/study period** | **Week** | **Diary*** | **PedsQL-3.0-GIS** | **KIDSCREEN** |
|---|---|---|---|---|
| Recruitment appointment | 0 | | X | X |
| Observation phase | 1 | X (daily) | | |
| | 2 | X (daily) | | |
| Blinded treatment period | 3 | X (daily) | | |
| | 4 | X (daily) | | |
| | 5 | X (daily) | | |
| Follow-up 1 appointment | 6 | X (daily) | X | X |
| Open-label treatment period | 7 | X (daily) | | |
| | 8 | X (daily) | | |
| | 9 | X (daily) | | |
| Follow-up 2 appointment | 10 | X (daily) | X | X |

*The daily diary will collect information for the Wong-Baker FACES Pain Rating Scale for 10 weeks and study compliance for 8 weeks (weeks 3-10)

### 6.2.1 Screening/Recruitment appointment

The screening appointment will be held on-site or remotely during a routine clinic visit. This will be followed up by the remote Recruitment appointment where informed e-consent will be obtained before any trial-specific procedures take place. Reviewing eligibility based on clinician diagnosis or medical history will be done prior to consent.

#### 6.2.1.1 Informed consent

A participant or parent/carer should give their written informed consent or e-consent to take part in the study before any trial-specific procedures are conducted. A young person who has sufficient understanding and intelligence to understand fully what is proposed and can use and weigh this information in reaching a decision (i.e. they are 'Gillick competent'), can give consent to treatment. For children or young people not competent, parents (and those with parental responsibility) can consent to medical treatment on their behalf. Consent of only one parent/carer is required. The consent will be taken by the Research Nurse, who has been trained on Good Clinical Practice (GCP) and the study protocol. Before providing consent, the participant and/or parent/carer should have the opportunity to ask any questions they might have. The signed and dated consent form should be printed out and filed in the investigator site file and a copy provided to the participant. Consent must also be documented in the participant’s medical notes, in accordance with GCP.

Participants are free to withdraw from the study at any time without giving a reason, without this affecting the treatment they receive.

#### 6.2.1.2 Eligibility screening

The participants' eligibility will be determined against all criteria. In addition, if a patient is of childbearing potential, a pregnancy test should be conducted at Baseline appointment if a patient is confirmed to be eligible. Any criteria related to medical tests, history or medication use must be confirmed against the participant's medical notes before the patient is randomised at Baseline appointment. The research team should therefore request for the relevant sections of the participant's medical records, including from the patient's GP, if not included in the referral information, prior to the Baseline appointment unless the participant has themselves requested for the information.

During the Screening/Recruitment appointment, the patient should be evaluated against the following study entry criteria:

**Age**

Participants must be aged 3-18 years

**FAPD**

Participants must meet the Rome IV criteria for FAPD (Group H2) [23] (see **4.1 INCLUSION CRITERIA**). FAPD must be either a confirmed existing diagnosis based on Rome IV criteria and recorded in the participant's medical records, or a diagnosis confirmed by the PI or a delegated member of staff. The FAPD (Group H2) sub-type will be recorded.

**Faecal calprotectin level**

Participants must have a normal faecal calprotectin at diagnosis of their FAPD (<250ug/g stool age 3-8 yrs, <100ug/g stool age 9-18 yrs).

**Exclusion of other conditions**

Participants should not be enrolled into the study until any required tests to exclude other conditions have been performed.

**Confirming eligibility and suitability based on medical records**

The patient's medical history and medications should be reviewed to confirm the patient's eligibility and suitability to take part in the trial. If any testing was required to exclude other intestinal conditions, the results from these tests must be obtained before the patient can proceed in the study.

Any patients failing at one or more of the assessments above, should not proceed in the trial and will return to standard-of-care.

**Medical history and concomitant medications**

Patients using probiotic supplements, other intestinal adsorbents (activated charcoal, kaoline, diosmectite), slow-release medications or strong opioids (World Health Organisation Step III) are not eligible to take part in the study. A list of concomitant medications from hospital records should be assessed and eligibility confirmed at Baseline appointment. Patients using antidepressant agents are not eligible unless these were used at a stable dose for at least 6 weeks

**Pregnancy test for women of childbearing potential**

A negative pregnancy test must be obtained from any female participants of childbearing potential at the

Baseline appointment, this will be completed at home on the day of the appointment and confirmed with the investigator.

#### 4.2.1.3. Demographic information

Age, sex and ethnicity should be recorded in the eCRF.

#### 6.2.1.4 Adverse Events (AEs)

Any AEs related to the conduct of the study procedures should be recorded.

#### 6.2.1.5 Randomisation

At Baseline appointment eligible participants will be randomised to blinded treatment by the Research Nurse at each site, who has access to the randomisation tool. The randomisation tool is built into a secure, restricted access web-based eCRF system developed and hosted by Sealed Envelope Ltd. The system will only allow participants to be randomised if they are confirmed to meet all the eligibility criteria listed on the randomisation eCRF.

The randomisation tool will provide a unique randomisation code, which the site research team will record on a treatment request form and email to the Sponsor's unblinded study supplies coordinator. The coordinator will check the code against the randomisation code list to obtain the treatment group allocation and will then schedule a courier shipment of the corresponding treatment to the participant's home address.

At Baseline appointment the Research Nurse will inform the participant if they are eligible to continue in the study or return to standard of care.

#### 6.2.1.6 Treatment instructions

At Recruitment and baseline appointments the Research Nurse will instruct the participant and/or parent/carer on how to use the age-appropriate blinded study treatment during the double-blind phase. Each patient will receive a copy of the written study treatment use instructions (**APPENDIX C: TREATMENT USE INSTRUCTIONS (DOUBLE-BLIND PHASE**).

#### 6.2.1.7 Diary and questionnaires

At Recruitment appointment the Research Nurse will explain the study diary and questionnaires (PedsQL-3.0-GIS and KIDSCREEN-27).

Participants will be enrolled into the study and/or parents/carers will be sent a text and email with a link to the online questionnaires (PedsQL-3.0-GIS and KIDSCREEN-27) to be completed at Recruitment visit. For the duration of the study, each evening at 6 pm a text and email will be sent with a link to that day's diary and questionnaires (recruitment, end of double-blind and open label phases). Participants and/or parents will also be able to complete the previous day's diary if uncompleted.

The content of the diary/questionnaires is provided in Error! Reference source not found..

### 6.2.2 Follow-up appointments

The participants will attend follow-up remote appointments by video or telephone call at week 6 (end of blinded treatment period) and week 10 (end of open-label treatment period). The date and time of the

appointment will be agreed by telephone or email, with email confirmation and attached instructions on accessing the video consultation or call. At both follow-up remote appointments, the following should be conducted:

- Completion of questionnaires (PedsQL-3.0-GIS and KIDSCREEN-27)
- Review of AEs
- Review of any changes in medical history or medications
- Adequate relief question

Additional, visit-specific procedures are described below.

#### 6.2.2.1 Week 6

In addition to the completion of questionnaires and review of AEs and changes in medical history or medications, the following should be conducted:

I. All participants will receive instructions on how to take Enterosgel® for the open-label phase (Error! Reference source not found..

#### 6.2.2.2 Week 10

In addition to the completion of questionnaires and review of AEs and changes in medical history or medications, the following should be conducted:

I. The participants will be explained that they will no longer receive any study treatments and are returning to standard of care.
II. For participants who want to continue to use Enterosgel, they will be advised regarding its availability as an OTC product or through a prescription from their General Practitioner

### 6.2.3 Unscheduled visits

Any unscheduled clinic visits, hospitalisations or visits to the Accident & Emergency department due to FAPD or due to AEs potentially related to study treatment, should be recorded in both medical records and the relevant eCRF.

## 6.3 DESCRIPTION OF ASSESSMENTS

### 6.3.1 Study diary

Data on FAPD symptoms, nursery/school attendance and treatment use will be collected using a study-specific diary, which is available as an electronic diary that can be completed online by following a link provided on daily email and text message notifications. Questions included in the diary are provided in Error! Reference source not found.. No patient identifiable data will be collected using the electronic diary.

### 6.3.2 PedsQL-3.0-GIS

The Pediatric Quality of Life Inventory™ (PedsQL™) Gastrointestinal Symptoms Module for patients is a questionnaire for patients with functional gastrointestinal disorders (FGIDs) and organic GI diseases, hereafter referred to as "GI disorders". The module consists of a patient self-report ages 5-18 and parent proxy-report for ages 2-18 years. PedsQL-3.0-GIS evaluates the intensity of symptoms during the previous one month period [2]. The modules are separated into age categories; teens (13-18yrs), child (8-12 yrs), young child (5-7yrs) and toddlers (2-4 years). It considers fourteen unidimensional scales measuring

stomach pain, stomach discomfort when eating, food and drink limits, trouble swallowing, heartburn and reflux, nausea and vomiting, gas and bloating, constipation, blood, diarrhea, worry, medicines, and communication. The “worry about bowel movements” (5 questions) will be compared to study treatment effects on the intervention on anxiety/depression. Each question is scored on a scale from 0 to 4, and their sum is then calculated to obtain the total score. Higher scores indicate worse symptoms. Data suggests that the PedsQL-3.0-GIS has good measurement properties and can be used as a common metrics to compare GI-specific symptoms in clinical research and practice both within and across patient groups for FGIDs [27].

A copy of PedsQL-3.0-GIS is provided in Error! Reference source not found..

### 6.3.3 KIDSCREEN-27

The KIDSCREEN-27 questionnaires can be used to assess the subjective health and the psychological, mental and social well-being of children and adolescents (HRQoL) between the ages of 8 and 18. The questionnaires can be completed by both healthy and ill children and adolescents themselves as a self-assessment or a corresponding parent version is available for parents for by proxy assessment for age 7 years and below. The questionnaires can be used in hospitals, other medical settings and have been validated in 13 European countries, which allows meaningful cross-cultural comparisons of health-related quality of life. The KIDSCREEN -27 allows a detailed profile of the ten HRQoL dimensions and takes ca. 10 minutes to complete [28]

The questionnaires will be child-self report for participants aged 8-18yrs and parents proxy report for age 3-7yrs. The “General Mood and Feelings about Yourself” sub-score (based on 7 questions) will be compared according to study treatment to assess effects of the intervention on anxiety/depression. A copy of KIDSCREEN-27 is provided in Error! Reference source not found..

## 6.4 EMERGENCY UNBLINDING

Unblinding (code-break) should only be performed during the trial in a situation where information about the patient’s trial treatment is necessary in order to provide the patient with appropriate and optimal medical care. Such emergency unblinding may be requested on the grounds of safety by the Chief Investigator, local PI or authorised delegate or treating physician. A request for unblinding can also come from a patient, carer or GP, for example when an adverse event occurs or there are changes planned to the patient’s regular therapy. Requests for unblinding will first be reviewed by the PI or sub-PI who evaluates the information and the importance of unblinding in the given circumstances. If the PI/sub-PI decides that unblinding is necessary to ensure the patient will receive appropriate medical care, emergency unblinding is performed. Unblinding request can be submitted by any local research team member with access to the eCRF. Following the submission of an unblinding request form in the eCRF, the treatment allocation will be emailed or sent by a text message or fax to the person who had requested unblinding. Following unblinding, a notification will be automatically sent to the trial manager.

In case of emergency unblinding, the PI will be responsible for deciding whether the patient should continue on trial treatment. Unblinded patients should be followed up according to the study protocol until the end of the study. The reason for emergency unblinding should be recorded in the Emergency Unblinding eCRF.

# 7. SAFETY

## 7.1 DEFINITIONS

Types of AEs associated with medical devices and applicable for this study are defined in accordance with the European Commission guidelines on medical devices [29].

### 7.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.
NOTE 1: This includes events related to the investigational device or the comparator.
NOTE 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan).
NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.

### 7.1.2 Adverse Device Effect (ADE)

AE related to the use of an investigational medical device.
NOTE 1: This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2: This includes any event that is a result of a use error or intentional misuse.

### 7.1.3 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious AE.

### 7.1.4 Serious Adverse Event (SAE)

AE that:
a) led to a death,
b) led to a serious deterioration in health that either:
1. resulted in a life-threatening illness or injury, or
2. resulted in a permanent impairment of a body structure or a body function, or
3. required in-patient hospitalisation or prolongation of existing hospitalisation, or
4. resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: This includes device deficiencies that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
NOTE 2: A planned hospitalisation for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a SAE.

### 7.1.5 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or product safety information. NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

### 7.1.6 Expected Adverse Events and Adverse Events of Special Interest

According to the standard Package Information Leaflet, Enterosgel® can cause constipation and nausea. It is normal for patients with IBS-D to feel constipated when diarrhoea symptoms improve. Constipation should only be considered an AE in this study if all of the following are met:
a) patient complains about it to the site research team
b) patient had at least 3 consecutive days without bowel movements
c) clinical intervention is required (i.e. laxative or other treatment)

## 7.2 RECORDING AND REPORTING OF ADVERSE EVENTS

### 7.2.1 Investigational procedures and treatment

AEs will be collected throughout the study from screening appointment until week 10. If an AE is reported by the patient, the relationship of the event to the study treatment or procedures should be assessed by the local PI, or a delegated sub-PI or nurse. The following information will be recorded for all AEs:

- Medical term of the AE (SNOMED CT terminology)
- Start date and date of resolution
- Seriousness
- Severity
- Study treatment action
- Outcome
- Relationship with the study treatment
- Expectedness

**SADEs, SAEs, and USADEs should <u>always</u> be recorded in the eCRF and reported to the Sponsor using the Sponsor's SAE reporting form. Any SAEs that occur during the screening period that resulted from the administration of any study procedures and are unexpected, should also be reported. The form should be emailed to the Trial Manager (**research@enteromed.co.uk**) within 24 hours of the site team becoming aware of the event. If the site does not receive an acknowledgement of the receipt of the report within 24 hours, they should immediately contact the Trial Manager by telephone.**

The Sponsor should immediately inform the CI of any reported SAEs. The CI should review the SAE to confirm causality and expectedness.

The Sponsor should also report all serious adverse events, whether initially considered to be device related to the MHRA (Any SAEs which indicate an imminent risk of death, serious injury or serious illness, and which requires prompt remedial action for other subjects, shall be reported within two calendar days of awareness, any other SAEs shall be reported within seven calendar days). The REC should be notified of any related and unexpected SAEs within 15 days. Reports of related and unexpected SAEs in double-blind trials should be unblinded. Investigators should only receive information on the code-break if it is necessary for the safety of the patient.

SAEs should be followed-up until resolution or a final outcome. All follow-up information should be emailed to the Sponsor as soon as it becomes available. The SAE form and any email correspondence related to the SAE should be filed in the investigator site file and in the electronic Trial Master File.

## 7.3 REPORTING OF PREGNANCIES

Although according to the package information leaflet Enterosgel® can be used in pregnant women and are excluding any pregnant participants from the trial. Any women of childbearing potential should agree to use a medically accepted method of contraception while they are receiving study treatment (i.e. until the end of the open-label period). Should a participant get pregnant while the patient was receiving study treatment, the site should notify the Sponsor within 24 hours of becoming aware of the pregnancy, by emailing the Sponsor's pregnancy reporting form to the Trial Manager ( research@enteromed.co.uk).

In case of a pregnancy while receiving study treatment, a participant should be withdrawn from the study. The pregnancy should be followed for outcome and any adverse outcome of pregnancy should be assessed for causality to the study treatment received. Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus.

# 8. STATISTICS

## 8.1 SAMPLE SIZE CALCULATION

In a previous clinical trial of Mebeverine in the treatment of FAPD in children [30], the mean (SD) change from baseline in the Wong-Baker FACES Pain Rating Scale in the placebo arm was -1.2 (1.5). We consider that a 1-point larger reduction in the Enterosgel arm (a mean change from baseline of -2.2) would be clinically significant. The number of patients required to observe this difference with 80% power and $\alpha$=0.05 is approximately n=130 (or n=65 per arm). We would increase the sample size to n=154 (77 per arm) to allow for 15% drop-outs.

## 8.2 STATISTICAL ANALYSES

This trial will be reported according to the CONSORT guidelines for clinical trials (Consolidated Standards Of Reporting Trials statement (http://www.consort-statement.org/) [31]. Primary data analyses will be based on the intention-to-treat principle. The per-protocol analyses will include children with 80% or greater treatment compliance. Recruitment and attrition rates will be calculated as percentages with 95% CIs. Percentage of patients completing the protocol will be reported and reasons for deviations/study withdrawal collected. Data will inform a power calculation for a definitive clinical and cost-effectiveness study. Descriptive sub analyses, if numbers allow, will be made based on specific FGID diagnoses.

All statistical analyses will be described in detail in the Statistical Analysis Plan.

### 8.2.1 Baseline data

All participant baseline data will be summarised descriptively overall and by trial arm both as randomised and as analysed in the primary analysis. No formal statistical comparisons will be undertaken. Continuous measures will be reported as means and standard deviations while the categorical data will be reported as counts and percentages.

### 8.2.2 Primary analysis

The primary outcome will be analysed using an analysis of covariance (ANCOVA) model with treatment assignment and the baseline Stomach Pain and Hurt score as a covariate. In addition, an adjusted ANCOVA model will be performed by including pre-specified covariates (study site, sex and age group) measured at baseline. The unadjusted and adjusted mean difference between two groups in the primary outcome, together with its 95% confidence intervals (CIs) will be calculated. In addition, subgroup analysis of the primary endpoint will be performed on the pre-specified covariates. Analysis of secondary continuous outcomes will be performed in a similar way.

### 8.2.3 Secondary analysis

Secondary outcome data will be summarised descriptively at each time point, overall and by trial arm. The secondary outcomes will be analysed either by comparing trial arms at week 6 using ANCOVA models adjusting for baseline scores, or by employing mixed effects models for repeated measurements (MMRMs). The baseline scores, treatment group, time point, and treatment group by timepoint interaction terms will be included as covariates. A random effect for participant will be used to account for repeated measurements within participants over time. This will allow efficient use of the data collected, and account for potential within patient correlation.

Further analysis with regards specific FAPD subgroup and ethnicity will also be undertaken and will be described in full in the formal statistical analysis plan [32,33].

### 8.2.4 Handling of missing data

Where appropriate, multiple imputation will be used to impute missing values under a missing at random assumption in order to avoid excluding patients from the analysis. Multiple imputation involves creating multiple copies of the data set, with the missing values replaced by imputed values drawn from their predicted distribution by using the observed data [24].

## 8.3 ANALYSIS POPULATIONS

### 8.3.1 Intention-to-treat population (ITT)

ITT population will include all randomised patients analysed in the groups to which they were randomised to, regardless of whether they received or adhered to the allocated intervention.

### 8.3.2 Per-protocol population (PP)

PP population will include all patients who completed the study without reported protocol violations and with with 80% or greater treatment compliance.

### 8.3.3 Safety population

The safety population is the analysis population based on which AEs will be summarised and reported. This population will include all randomised patients who received at least 1 dose of study treatment. In this population, patients will be analysed according to the treatment they actually received, regardless of the treatment they were randomised to.

# 9. DATA HANDLING

## 9.1 DATA COLLECTION AND SOURCE DATA

Source data means any information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents, which are original documents or certified copies of original documents in which data collected for a clinical trial is first recorded. These include paper questionnaires, study diaries, diagnostic questionnaires, hospital or GP records, or laboratory reports.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data reported in the eCRF derived from source documents, i.e. medical records and the patient diaries, should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

## 9.2 ELECTRONIC CASE REPORT FORMS (eCRF)

All study data will be entered using a validated electronic Case Report Form (eCRF) system developed by Sealed Envelope Ltd. Data recorded in the eCRFs will not contain any patient identifying information; each participant will be identified in the system by a unique study-specific participant number. The eCRF system

can only be accessed by delegated and trained site team personnel, with their individual username and password.

### 9.3 STUDY DIARY

The participants or parents/carers will be requested to complete an online study diary daily during the initial observation, blinded and open-label treatment periods. An electronic diary will be developed for the trial by Sealed Envelope. The diary will be available online for use on any computer or mobile device. No participants identifiable data will be collected using the diary.

### 9.4 PATIENT QUESTIONNAIRES

During the trial, the patients and parents/carers will be asked to complete the PedsQL-3.0-GIS and KIDSCREEN-27 questionnaires on their electronic diary at screening and at each follow-up appointment (week 6 and 10). The diary will have reminders to participants and parents/carers to complete the questionnaires and the electronic format will ensure that all questions are completed correctly. The online questionnaires will input directly into the participant's eCRF.

### 9.5 ARCHIVING

All essential documents and trial data will be held by the Sponsor for a minimum of 5 years after the end of the trial. Investigator site files should be archived at the participating sites for 5 years and should not be destroyed until authorisation to do so has been received from the Sponsor.

## 10. QUALITY ASSURANCE

### 10.1 MONITORING AND QUALITY CONTROL

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. Regular monitoring will be performed in accordance with the ICH GCP and a risk-based Trial Monitoring plan, which will define the monitoring schedule and method (on-site, remote) and the details of targeted monitoring. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Any data issues in the eCRF (such as missing data or data discrepancies), should be primarily addressed by raising data queries in the eCRF. Any unresolved or outstanding queries should be discussed with the site during the remote/on-site monitoring visits.

### 10.2 PROTOCOL DEVIATIONS AND VIOLATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or GCP. The noncompliance may be either on the part of the participant, the investigator, or the study site staff.

Protocol violations are significant deviations that reduce the quality or completeness of the data, make the Informed Consent Form inaccurate, or impact a subject's safety, rights, or welfare [34].

Examples of protocol violations relevant to this study may include the following:

1. Inadequate or delinquent informed consent
2. Inclusion/exclusion criteria not met
3. Unreported SAEs

4. Materially inadequate record keeping
5. Intentional deviation from the protocol, GCP, or regulations by study personnel
6. Subject repeated non-compliance with study requirements
7. Dispensing of incorrect treatment
8. Not using any study treatment
9. Starting on antidepressants, intestinal adsorbents, strong opioids or probiotic supplements
10. Initiating any new treatment during the study that might have a significant impact on abdominal pain, according to the PI's opinion

All deviations/violations must be addressed in study source documents and reported to the Sponsor and the HRA and/or the MHRA as per their guidelines. All protocol violations should be recorded in the Protocol Violation eCRF. The site PI/study staff is responsible for knowing and adhering to these requirements. As a result of deviations and violations, corrective actions are to be developed by the Sponsor and/or site as appropriate and implemented promptly.

Participants with protocol violations will be excluded from the PP population.

# 11. TRIAL MANAGEMENT AND OVERSIGHT

## 11.1 TRIAL MANAGEMENT GROUP

The Trial Management Group (TMG) will be responsible for the set-up and conduct of the trial, including monitoring of recruitment and data. It will include at least one Sponsor's representative, the Chief Investigator, the PI from each site, the trial statistician, the trial manager and a young person from the Generation R Liverpool Young Person's Advisory Group. The TMG will hold a teleconference once a month and two face-to-face meetings a year.

## 11.2 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will monitor data collected during the study for efficacy and safety. If any issues emerge, the DMC will make recommendations regarding the continuation of the study. The DMC will consist of a Chair (Paediatric Gastroenterologist) and a statistician.

# 12. ETHICAL AND REGULATORY CONSIDERATIONS

## 12.1 GENERAL CONSIDERATIONS

This study will be conducted in full accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly of Helsinki (1964), revised at Tokyo (1975), Venice (1983), Hong-Kong (1989), Somerset West (1996), Edinburgh (2000) and Seoul (2008), including the Notes of clarification made by the World Medical Assembly of Washington (2002), Tokyo (2004), Seoul (2008), Fortaleza (2013) and Helsinki (2024) as well as in compliance with ICH GCP Consolidated Guideline (E6) and any applicable national and local laws and regulations, including the Clinical Trials Directive 2001/20/EC and The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments.

The Investigators and the Sponsor are responsible for ensuring that all activities in relation to this study are conducted in accordance with the protocol, GCP guidelines and any other relevant regulations. The

Principal Investigator at each study site has the overall responsibility for the conduct and administration of the study at that site and for ensuring that the site staff conducting any study-related procedures are qualified and appropriately trained to conduct the tasks delegated to them.

The protocol, PIS, informed consent form(s), recruitment materials, and all participant materials will be submitted to the HRA/REC and MHRA for review and approval. Approval of all relevant documents must be obtained before any participant is enrolled. Any substantial amendments to the protocol or other study documents will require review and approval by the relevant authority(ies) before the changes can be implemented to the study.

The Sponsor is responsible for the submissions of SAE reports and annual progress and safety reports to the relevant authority(ies), and for notifying them of the end of the trial.

### 12.2 PATIENT CONSENT

The participant or parent/carer will sign the informed consent document prior to any study-specific procedures being performed. Participants will have the opportunity to carefully review the study information and ask questions prior to providing consent. A copy of the informed consent document will be provided to the participants for their records.

Participants may withdraw consent at any time throughout the course of the trial. The rights and welfare of the participants will be protected by emphasising to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 12.3 PATIENT CONFIDENTIALITY

The Investigators affirm and uphold the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor, a competent authority, or REC may require direct access to parts of the medical records relevant to the study, including participants' medical history.

### 12.4 PAYMENTS TO PATIENTS

Participants will receive an Amazon voucher of £20 at the end of the study as a compensation for any inconvenience.

## 13. PUBLICATION AND DISSEMINATION

This study has been registered with International Standard Randomised Controlled Trial Number (ISRCTN……).

Study results will be submitted for presentation(s) at gastroenterology conference(s) and for publication in international peer-reviewed scientific journal(s). Authors will acknowledge that the study was funded by Bioline Products s.r.o (Czech Republic). Authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and other contributors will be acknowledged.

Results will be disseminated to the patients and the public through the study website and an interactive results webinar for all participants and their parents/carers.

Results will be submitted for inclusion into the National Institute for Health and Care Excellence (NICE) guidance if valuable for NHS.

Any data collected by any healthcare provider under this study is the property of the Sponsor and should not be used for any purposes other than the Sponsor's without the Sponsor's written permission.

## 14. FINANCE AND INSURANCE

This study is funded by Bioline Products s.r.o (Czech Republic). The study Sponsor, EnteroMed Ltd, is the exclusive distributor of Enterosgel® in the UK and holds a Product Liability Insurance for legal liabilities arising from the use of Enterosgel® in the UK.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a patient is harmed whilst taking part in a clinical study as a result of negligence on the part of a member of the study team this liability cover would apply.

## 15. CONFLICTS OF INTEREST

The Sponsor of this study (EnteroMed Ltd) is the exclusive distributor of Enterosgel® in the UK.

The Chief Investigator has no conflicts of interest.

## 16. REFERENCES


1. Korterink JJ et al. Epidemiology of pediatric functional abdominal pain disorders: A meta-analysis. PLoS One 2015;10: e0126982.
2. Varni JW et al. Health-Related Quality of Life in Pediatric Patients with Functional and Organic Gastrointestinal Diseases. J Pediatr 2015;166:85-90.
3. Assa A et al. School attendance in children with functional abdominal pain and inflammatory bowel diseases. J Pediatr Gastroentero Nutr. 2015;61:553–7.
4. Hoekman DR et al. Annual Costs of Care for Pediatric Irritable Bowel Syndrome, Functional Abdominal Pain, and Functional Abdominal Pain Syndrome. J Pediatr 2015;167:1103-1108.e2
5. Golestaneh AK, et al. Diagnosis and management of functional gastrointestinal disorders: a clinical audit. BSPGHAN 2021 online meeting poster presentation. (unpublished)
6. Jarrett M et al. Recurrent abdominal pain in children: forerunner to adult irritable bowel syndrome? J Soc Pediat Nurs 2003;8(3):81–89.
7. Rexwinkel R et al. Pharmacologic treatment in functional abdominal pain disorders in children: A systematic review. Pediatrics 2021;147:e2020042101.
8. Seetharaman J et al. Efficacy of amitriptyline in pediatric functional abdominal pain disorders: A randomized placebo-controlled trial. J Gastroenterol Hepatol 2022;37:685-691.
9. Dipasquale V et al. Randomised controlled trial of melatonin for paediatric functional abdominal pain disorders. J Paediatr Child Health 2023;59:458-463.
10. Vlieger AM et al. Long-term follow-up of gut-directed hypnotherapy vs. standard care in children with functional abdominal pain or irritable bowel syndrome. Am J Gastroenterol 2012;107:627-31.
11. Capozza M et al. Probiotics and Functional Gastrointestinal Disorders in Pediatric Age: A Narrative Review Front. Pediatr 2022;10:805466.

12. Fluer FS et al. A remedy for inhibiting the growth of Staphylococci, suppressing the Staphylococcal enterotoxins production and removing them from biological substrates. Zhurnal mikrobiologii, epidemiologii I immunobiologii (in Russian), 2017;№ 3:71-77
13. Howell CA, Mikhalovsky SV, Markaryan EN, Khovanov AV. 2019. Investigation of the adsorption capacity of the enterosorbent enterosgel for a range of bacterial toxins, bile acids and pharmaceutical drugs. Scientific reports.2019;9:5629.
14. Howell CA et al. Enterosgel® for the treatment of adults with acute diarrhoea in a primary care setting: a randomised controlled trial. BMJ Open Gastroenterology 2019;6:e000287.
15. Ruzhentsova, T.A., et al. Choice of an adequate therapy regimen for acute enteric infections in children: results of a randomized trial. Epidemiology and Infectious Diseases 2016;№4:70-74
16. Markovinovic´ L et al. Enteroadsorbent Polymethylsiloxane Polyhydrate vs. Probiotic Lactobacillus reuteri DSM 17938 in the Treatment of Rotaviral Gastroenteritis in Infants and Toddlers, a Randomized Controlled Trial. Front Pediatr 2020;8:553960.
17. Usenko DV et al. Application of enterosorbents in the treatment of intestinal infections in children with concomitant atopic dermatitis. Pharmateca 2015;N10:31–5.
18. Khavkin AI et al. Polymethylsiloxane Polyhydrate (Enterosgel®) in the Complex Treatment of Diarrhea Syndrome in Children with Diseases of the Digestive System. EC Paediatrics 2020;9.5:17-27.
19. Howell CA et al. Double-blinded randomised placebo controlled trial of enterosgel (polymethylsiloxane polyhydrate) for the treatment of IBS with diarrhoea (IBS-D). Gut 2022;71:2430-2438.
20. Hyams JS, et al. Childhood Functional Disorders: Children and Adolescents. Gastroenterology 2016;15:S0016-5085(16)00181-5.
21. Appendix A: Rome IV Diagnostic Criteria for FGIDs. https://theromefoundation.org/rome-iv/rome-iv-criteria/ (accessed 17/09/2024)
22. Zeevenhooven J, Rexwinkel R, Van Berge VWA, et al. A Core Outcome Set for Clinical Trials in Pediatric Functional Abdominal Pain Disorders. The Journal of Pediatrics 2020;221:115-122
23. Clinical Trial Facilitation Group. 2014. Recommendations related to contraception and pregnancy testing in clinical trials. Final version 2024. Accessed 21/04/2025. Available at: http://efaidnbmnnnibpcajpcglclefindmkaj/https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTCG/2024_HMA_CTCG_Contraception_guidance_Version_1.2__March_2024.pdf
24. Taves DR. 1974. Minimization: a new method of assigning subjects to treatment and control groups. Clin Pharmacol Therapeut. 15:443-53.
25. Yashina NI, Plygan EP, Semenov VG, Martynenko AM, Glushchenko OV. Sol-Gel Methods for Materials Processing. In Sol-Gel Technology of the Mesoporous Methylsilicic Acid Hydrogel: Medicine Aspects of Globular Porous Organosilicon Materials Application. Editors; Plinio Innocenzi, Yuriy L. Zub, Vadim G. Kessle. Springer, Dordrecht 2008. pp 481-488
26. Nikolaev V. Enterosgel: A Novel Organosilicon Enterosorbent with a Wide Range of Medical Applications. In Biodefence - Advanced Materials and Methods for Health Protection. Mikhalovsky, S and Khajibaev, A (Editors). 2011. Springer. Available at: http://www.springer.com/us/book/9789400702165
27. Varni JW, Bendo CB, Denham J, et al. PedsQL Gastrointestinal Symptoms Module Feasibility, Reliability, and Validity. J Paed Gastro Nut. 2014:59(3);347-35528]
28. Ravens-Sieberer U et al. The KIDSCREEN-52 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. Value in Health 2008;11:645-658.
29. European Commission Directorate General for Health and Consumers. 2010. Guidelines on Medical Devices. MEDDEV 2.7/3. December 2010. Available at: http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf
30. Pourmoghaddas Z, Saneian H, Roohafza H, Gholamrezaei A. Mebeverine for Pediatric Functional Abdominal Pain: A Randomized, Placebo-Controlled Trial. BioMed Research International. 2014:first published 25 June 2014. https://doi.org/10.1155/2014/191026

31. Schulz KF, Altman DG, Moher D; CONSORT Group. 2010. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 8:18
32. Gordon M, Benninga MA, Borlack R, et al. ESPGHAN and NASPGHAN 2023 protocol for paediatric FAPD treatment guidelines (standard operating procedure). BMJ Paediatr Open 2023; 7: e002166.
33. Thapar N, Benninga MA, Crowell MD, et al. Paediatric functional abdominal pain disorders. Nat Rev Dis Primers 2020; 6: 89.
34. Bhatt A. 2012. Protocol deviation and violation. Perspect Clin Res. 3:117.

## APPENDICES

APPENDIX A. STUDY DIARY

OBSERVATIONAL PHASE

## Week 1 Day 1 for children to complete

| | |
|---|---|
| 1. Choose the face that best describes the tummy pain you felt today? |  |

| | |
|---|---|
| 2. Did you miss nursery or school today because of your tummy pain? | **YES** **NO** |

DOUBLE-BLIND PHASE

## Week 3 Day 1 for children to complete

Please answer all three questions.

| | |
|---|---|
| 1.Please choose the face that best describes the tummy pain you felt today. |  |

| | |
|---|---|
| 2. How many of the study gel drinks did you have today? | **(dropdown menu)**<br>**2 study drinks**<br>**1 study drink**<br>**None-I forgot**<br>**None-I didn't feel well**<br>**None- I was constipated**<br>**None- study drinks not arrived** |
| 3.Did you miss nursery or school today because of your tummy pain? | **YES** **NO** |

OPEN LABEL PHASE

## Week 7 Day 1 for children to complete

| | |
|---|---|
| 1.Choose the face that best describes the tummy pain you felt today? |  |

| | |
|---|---|
| 2. How many Enterosgel gel drinks did you drink today? | **(dropdown menu)**<br>**2 Enterosgel drinks**<br>**1 Enterosgel drink**<br>**None-I forgot**<br>**None-I didn't feel well**<br>**None- I was constipated**<br>**None- Enterosgel drinks not arrived** |
| 3. Did you miss nursery or school today because of your tummy pain? | **YES** **NO** |

APPENDIX B. STUDY QUESTIONNAIRES- KIDSCREEN 27 QUESTIONNAIRE (child version)


# KIDSCREEN-27

## Health Questionnaire for Children and Young People

Child and Adolescent Version

8 to 18 Years

*Date:* _____ _____
*Month* *Year*

Hello,

How are you? How do you feel? This is what we would like you to tell us.

Please read every question carefully. What answer comes to your mind first? Choose the box that fits your answer best and cross it.

Remember: This is not a test so there are no wrong answers. It is important that you answer all the questions and also that we can see your marks clearly. When you think of your answer please try to remember the last week.

You do not have to show your answers to anybody. Also, nobody who knows you will look at your questionnaire once you have finished it.


KIDSCREEN-27, Child and Adolescent Version
Page 2 of 5

## 1. Physical Activities and Health

1. **In general, how would you say your health is?**

- ○ excellent
- ○ very good
- ○ good
- ○ fair
- ○ poor

**Thinking about the last week...**

| | not at all | slightly | moderately | very | extremely |
|---|---|---|---|---|---|
| 2. Have you felt fit and well? | ○ | ○ | ○ | ○ | ○ |
| 3. Have you been physically active (e. g. running, climbing, biking)? | ○ | ○ | ○ | ○ | ○ |
| 4. Have you been able to run well? | ○ | ○ | ○ | ○ | ○ |

**Thinking about the last week...**

| | never | seldom | quite often | very often | always |
|---|---|---|---|---|---|
| 5. Have you felt full of energy? | ○ | ○ | ○ | ○ | ○ |

## 2. General Mood and Feelings about Yourself

**Thinking about the last week...**

| | not at all | slightly | moderately | very | extremely |
|---|---|---|---|---|---|
| 1. Has your life been enjoyable? | ○ | ○ | ○ | ○ | ○ |

**Thinking about the last week...**

| | never | seldom | quite often | very often | always |
|---|---|---|---|---|---|
| 2. Have you been in a good mood? | ○ | ○ | ○ | ○ | ○ |
| 3. Have you had fun? | ○ | ○ | ○ | ○ | ○ |

| Thinking about the last week... | never | seldom | quite often | very often | always |
|---|---|---|---|---|---|
| 4. Have you felt sad? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |
| 5. Have you felt so bad that you didn't want to do anything? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |
| 6. Have you felt lonely? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |
| 7. Have you been happy with the way you are? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |

## 3. Family and Free Time

| Thinking about the last week... | never | seldom | quite often | very often | always |
|---|---|---|---|---|---|
| 1. Have you had enough time for yourself? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |
| 2. Have you been able to do the things that you want to do in your free time? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |
| 3. Have your parent(s) had enough time for you? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |
| 4. Have your parent(s) treated you fairly? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |
| 5. Have you been able to talk to your parent(s) when you wanted to? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |
| 6. Have you had enough money to do the same things as your friends? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |
| 7. Have you had enough money for your expenses? | never ○ | seldom ○ | quite often ○ | very often ○ | always ○ |

## 4. Friends

**Thinking about the last week...**

| | | never | seldom | quite often | very often | always |
|---|---|---|---|---|---|---|
| 1. | Have you spent time with your friends? | ○ | ○ | ○ | ○ | ○ |
| 2. | Have you had fun with your friends? | ○ | ○ | ○ | ○ | ○ |
| 3. | Have you and your friends helped each other? | ○ | ○ | ○ | ○ | ○ |
| 4. | Have you been able to rely on your friends? | ○ | ○ | ○ | ○ | ○ |

## 5. School and Learning

**Thinking about the last week...**

| | | not at all | slightly | moderately | very | extremely |
|---|---|---|---|---|---|---|
| 1. | Have you been happy at school? | ○ | ○ | ○ | ○ | ○ |
| 2. | Have you got on well at school? | ○ | ○ | ○ | ○ | ○ |

**Thinking about the last week...**

| | | never | seldom | quite often | very often | always |
|---|---|---|---|---|---|---|
| 3. | Have you been able to pay attention? | ○ | ○ | ○ | ○ | ○ |
| 4. | Have you got along well with your teachers? | ○ | ○ | ○ | ○ | ○ |

ID# _____

Date:_____

# PedsQL™

## Gastrointestinal Symptoms Module

Version 3.0

**TEEN REPORT** (ages **13-18**)

**DIRECTIONS**

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

**0** if it is **never** a problem
**1** if it is **almost never** a problem
**2** if it is **sometimes** a problem
**3** if it is **often** a problem
**4** if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

| **STOMACH PAIN AND HURT** *(problems with…)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. I feel pain or hurt in my stomach | 0 | 1 | 2 | 3 | 4 |
| 2. I get stomach aches | 0 | 1 | 2 | 3 | 4 |
| 3. My stomach hurts | 0 | 1 | 2 | 3 | 4 |
| 4. I wake up at night with stomach aches | 0 | 1 | 2 | 3 | 4 |
| 5. I feel sick to my stomach | 0 | 1 | 2 | 3 | 4 |
| 6. I get an upset stomach | 0 | 1 | 2 | 3 | 4 |

| **STOMACH DISCOMFORT WHEN EATING** *(problems with…)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. When I eat I get sick to my stomach | 0 | 1 | 2 | 3 | 4 |
| 2. When I eat my stomach feels bad | 0 | 1 | 2 | 3 | 4 |
| 3. My stomach hurts when I eat | 0 | 1 | 2 | 3 | 4 |
| 4. My stomach feels heavy when I eat | 0 | 1 | 2 | 3 | 4 |
| 5. I feel full as soon as I start to eat | 0 | 1 | 2 | 3 | 4 |

| **FOOD AND DRINK LIMITS** *(problems with…)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. I cannot eat some foods | 0 | 1 | 2 | 3 | 4 |
| 2. I cannot drink some drinks | 0 | 1 | 2 | 3 | 4 |
| 3. I am not able to eat what I want | 0 | 1 | 2 | 3 | 4 |
| 4. I am not able to drink what I want | 0 | 1 | 2 | 3 | 4 |
| 5. I cannot eat some foods because they make me sick | 0 | 1 | 2 | 3 | 4 |
| 6. I cannot eat the foods that my friends eat | 0 | 1 | 2 | 3 | 4 |

| **TROUBLE SWALLOWING** *(problems with…)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. It is hard for me to swallow food | 0 | 1 | 2 | 3 | 4 |
| 2. It hurts when I swallow | 0 | 1 | 2 | 3 | 4 |
| 3. Food gets stuck going down | 0 | 1 | 2 | 3 | 4 |

*In the past **ONE month**, how much of a **problem** has this been for you …*

| HEARTBURN AND REFLUX *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. I get a burning feeling in my throat | 0 | 1 | 2 | 3 | 4 |
| 2. I have pain or hurt in my chest | 0 | 1 | 2 | 3 | 4 |
| 3. I burp a lot | 0 | 1 | 2 | 3 | 4 |
| 4. Food comes back up into my mouth after eating | 0 | 1 | 2 | 3 | 4 |

| NAUSEA AND VOMITING *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. I feel like throwing up | 0 | 1 | 2 | 3 | 4 |
| 2. I feel like throwing up when I eat | 0 | 1 | 2 | 3 | 4 |
| 3. I feel like throwing up after I eat | 0 | 1 | 2 | 3 | 4 |
| 4. I throw up | 0 | 1 | 2 | 3 | 4 |

| GAS AND BLOATING *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. My stomach feels full of gas | 0 | 1 | 2 | 3 | 4 |
| 2. My stomach feels very full | 0 | 1 | 2 | 3 | 4 |
| 3. My stomach gets big and hard | 0 | 1 | 2 | 3 | 4 |
| 4. I have a lot of gas | 0 | 1 | 2 | 3 | 4 |
| 5. I pass a lot of gas | 0 | 1 | 2 | 3 | 4 |
| 6. My stomach feels gassy | 0 | 1 | 2 | 3 | 4 |
| 7. My stomach makes noises | 0 | 1 | 2 | 3 | 4 |

*In the past **ONE month**, how much of a **problem** has this been for you …*

| **CONSTIPATION** *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. I still feel full after I have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 2. I feel like I am not done after I have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 3. I feel like I cannot get all the bowel movement to come out | 0 | 1 | 2 | 3 | 4 |
| 4. It hurts when I have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 5. My bowel movements are hard | 0 | 1 | 2 | 3 | 4 |
| 6. My bowel movements are lumpy | 0 | 1 | 2 | 3 | 4 |
| 7. I have to push hard to have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 8. My poop gets stuck when I have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 9. My bottom hurts after I have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 10. It takes a long time for poop to come out | 0 | 1 | 2 | 3 | 4 |
| 11. I have to work hard to make poop come out | 0 | 1 | 2 | 3 | 4 |
| 12. I do not want to poop because it hurts | 0 | 1 | 2 | 3 | 4 |
| 13. I spend a lot of time on the toilet having a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 14. My stomach hurts when I go poop | 0 | 1 | 2 | 3 | 4 |

| **BLOOD IN BOWEL MOVEMENT** *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. There is blood on my toilet paper after I have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 2. There is blood in my bowel movement | 0 | 1 | 2 | 3 | 4 |

| **DIARRHEA** *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. I need to be near the bathroom a lot | 0 | 1 | 2 | 3 | 4 |
| 2. I have to rush to the bathroom to have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 3. I feel like I am always in the bathroom having a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 4. I wake up at night to have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 5. My bowel movements are watery | 0 | 1 | 2 | 3 | 4 |
| 6. I have poop accidents in my underwear | 0 | 1 | 2 | 3 | 4 |
| 7. I have to have a bowel movement a lot | 0 | 1 | 2 | 3 | 4 |

PedsQL 5

*In the past **ONE month**, how much of a **problem** has this been for you …*

| **WORRY ABOUT BOWEL MOVEMENTS** *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. I worry about having a bowel movement in my pants | 0 | 1 | 2 | 3 | 4 |
| 2. I worry that I will not make it to the bathroom in time | 0 | 1 | 2 | 3 | 4 |
| 3. I worry that it will hurt when I have a bowel movement | 0 | 1 | 2 | 3 | 4 |
| 4. I worry that I will have to use the bathroom at school | 0 | 1 | 2 | 3 | 4 |
| 5. I worry that I will have a bowel movement in my pants at school | 0 | 1 | 2 | 3 | 4 |

| **WORRY ABOUT STOMACH ACHES** *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. I worry about my stomach aches | 0 | 1 | 2 | 3 | 4 |
| 2. I worry that my stomach will hurt in school | 0 | 1 | 2 | 3 | 4 |

| **MEDICINES** *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. It is hard for me to take my medicines | 0 | 1 | 2 | 3 | 4 |
| 2. I forget to take my medicines | 0 | 1 | 2 | 3 | 4 |
| 3. It is hard for me to swallow my medicines | 0 | 1 | 2 | 3 | 4 |
| 4. I do not like having to take my medicines all the time | 0 | 1 | 2 | 3 | 4 |

| **COMMUNICATION** *(problems with...)* | Never | Almost Never | Some-times | Often | Almost Always |
|---|---|---|---|---|---|
| 1. It is hard for me to tell the doctors and nurses how I feel | 0 | 1 | 2 | 3 | 4 |
| 2. It is hard for me to ask the doctors and nurses questions | 0 | 1 | 2 | 3 | 4 |
| 3. It is hard for me to explain my illness to other people | 0 | 1 | 2 | 3 | 4 |
| 4. It is hard for me to explain my illness to my friends | 0 | 1 | 2 | 3 | 4 |
| 5. It is hard for me to talk to my parents about my illness | 0 | 1 | 2 | 3 | 4 |

APPENDIX C. STUDY TREATMENT INSTRUCTIONS DOUBLE-BLIND PHASE

# 4 WEEK DOUBLE-BLIND PHASE (WEEKS 3-6)

## ENTOPIC Treatment instructions for children aged 7-14 years

### IMPORTANT! PLEASE READ BEFORE STARTING THE TREATMENT

Enterosgel® is a safe, drug-free treatment with 30 years of safe use without any reports of serious adverse events. There is no risk of overdose. You may contact your research nurse at any time to discuss any questions.

### HOW TO STORE THE TREATMENT?

- Do not use if the outer tube is damaged
- Keep out of the reach of children
- Store at room temperature (between +4 to +30 °C) and **not** in the fridge

### HOW TO TAKE THE TREATMENT?

- **Take the treatment 2 hours before or after taking oral medications and 1 hour before or after meals**

**Preparing a single dose**

- Add **20ml** room temperature water into the measuring cup
- Shake the tube well before opening and open immediately before use
- Add **all** the contents of the tube into a glass and add the **20ml** of room temperature water, mix well and drink straight away

### HOW MANY TIMES A DAY TO TAKE THE TREATMENT?

***Week 1 and 2***

Use the tubes in the box labelled "**WEEK 1-2: Age 7-14 years, Double blind phase study treatment**"
Take **One DOSE IN THE MORNING & One DOSE IN THE EVENING** for **2 weeks**

***Week 3 and 4***

Use the tubes in the box labelled "**WEEK 3-4: Age 7-14 years, Double blind phase study treatment**"
Take **One DOSE IN THE MORNING & One DOSE IN THE EVENING** for **2 weeks**

**PLEASE NOTE:** ***It is important to know that your child's bowel might start changing its habits, including slowing down and not having any stool for 1-2 days. This is completely normal.***

***If at any time your child does not have a bowel movement (no stool at all) for 2 days, stop the treatment and increase your child's intake of water. After the next bowel movement, continue with a single dose once a day for a few days then return to two doses per day.***

APPENDIX D. STUDY TREATMENT INSTRUCTIONS OPEN LABEL PHASE

# 4 WEEK OPEN-LABEL PHASE (WEEKS 7-10)
## ENTOPIC Treatment instructions for children aged 7-14 years

### IMPORTANT! PLEASE READ BEFORE STARTING THE TREATMENT

Enterosgel® is a safe, drug-free treatment with 30 years of safe use without any reports of serious adverse events. There is no risk of overdose.

### HOW TO STORE THE TREATMENT?

- Do not use if the tube is damaged, once opened it can be used for 30 days
- Keep out of the reach of children
- Store at room temperature (between +4 to +30 °C) and **not** in the fridge

### HOW TO TAKE THE ENTEROSGEL TREATMENT?

- **Take the treatment 2 hours before or after taking oral medications and 1 hour before or after meals**

**Week 1 & 2**

- Shake the Enterosgel tube well before each opening
- For **one dose**: Measure **8 ml** of the gel onto the 10ml measuring spoon provided (just under a level spoonful)
- Fill the measuring cup with **100 ml** of room temperature water
- Add the spoon contents to the measuring cup and mix well, drink straight away

**Week 3 & 4**

- Shake the Enterosgel tube well before each opening
- For **one dose**: Measure **12 ml** of the gel onto the 10ml measuring spoon provided (just over a level spoonful)
- Fill the measuring cup with **100 ml** of room temperature water
- Add the spoon contents to the measuring cup and mix well, drink straight away

### HOW MANY TIMES A DAY TO TAKE THE TREATMENT?

***Weeks 1 - 2***

Take **One DOSE IN THE MORNING & One DOSE IN THE EVENING** (see week 1&2 above for the correct dose)

***Week 3 and 4***

Take **One DOSE IN THE MORNING & One DOSE IN THE EVENING** (see week 3&4 above for the correct dose)

**PLEASE NOTE:** ***It is important to know that your child's bowel might start changing its habits, including slowing down and not having any stool for 1-2 days. This is completely normal.***

***If at any time your child does not have a bowel movement (no stool at all) for 2 days, stop the treatment and increase your child's intake of water. After the next bowel movement, continue with a single dose once a day for a few days then return to two doses per day.***