Randomised, multi-centre study to assess efficacy, tolerability and safety of Enterosgel® in treatment of acute diarrhoea in adults

STUDY PROTOCOL

Document Description	Full Study Protocol
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Sponsor	Enteromed Ltd
Chief Investigator	Dr Preeti Pandya

SIGNATURE PAGE

Study Name: Randomised, multi-centre study to assess efficacy, tolerability and safety of Enterosgel® in treatment of acute diarrhoea in adults

Study Number: ENT02UK

The Sponsor and Chief Investigator have approved the protocol version v.1.4 dated 11th June 2018, and confirm hereby to conduct the study according to the protocol, the current version of the World Medical Association Declaration of Helsinki, International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and the local legally applicable requirements.

Chief Investigator:

_____

Signature

_____ _____

Name Date

Sponsor:

_____

Signature

_____ _____

Name Date

For Local Principal Investigator (PI) at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

_____

Site Name

_____

Signature

_____ _____

Investigator Name Date

CONTACT DETAILS

Sponsor

Enteromed Ltd
85 Great Portland Street, First floor
London, W1W 7LT
Email: emarkaryan@enteromed.co.uk
Phone: 07 860 817 365

Funder

Bioline Products s.r.o.
Krakovska 1338/10
110 00 Praha
Czech Republic
Email: info@enterosgel.eu
Phone: +420 266 317 783

Chief Investigator

Dr Preeti Pandya (MBBS., MD., DFFP. DRSH., MRCGP)
The Village Practice
Thornton Medical Centre
Church Road
Thornton-Cleveleys, FY5 2TZ
Email: drpreetipandya@hotmail.com
Phone: 01253 955561
Mobile: 07 480 470 651

Scientific Advisor

Professor Ramesh Arasaradnam (MB BcH BaO, C Clin Ed., PhD, FRCP, FEBGH)
University Hospitals Coventry & Warwick and Medical School, University of Warwick & Coventry
University
Email: Ramesh.arasaradnam@uhcw.nhs.uk
Phone: 02476 966087

Project Management

Elena Markaryan
Enteromed Ltd
85 Great Portland Street, First floor
London, W1W 7LT
Email: emarkaryan@enteromed.co.uk
Phone: 07 860 817 365

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

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LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference of Harmonisation
ITT	Intention-to-treat
ISRCTN	International Standard Randomised Controlled Trial Number
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
ORS	Oral Rehydration Solution
PI	Principal Investigator
PP	Per-protocol
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect

1 BACKGROUND

Approximately 20% of the UK population develop infectious intestinal disease each year (1). It is characterized by the sudden onset of diarrhoea, with or without vomiting. Other symptoms may include nausea, fever and abdominal pain. Most cases are due to an enteric virus, such as the rotavirus, but some are caused by bacterial or protozoal infections (2). The illness usually resolves without treatment within days; however, symptoms are unpleasant and can affect the whole family. Severe diarrhoea can quickly cause dehydration, which may be life threatening if not treated quickly.

Although intestinal infections are often managed at home without seeking professional advice, they still pose a significant burden on health service resources and the economy with many patients and parents missing time from work and seeking advice from healthcare professionals in primary or secondary care (1,3,4). For example, approximately 10% of children younger than 5 years present to healthcare services with gastroenteritis each year (5) and in the UK diarrhoeal illness has been reported to account for 16% of clinical presentations to a major paediatric emergency department (6). While there appears to be a lack of recent data on the economic and healthcare burden of intestinal infections, data from mid 1990s suggested that around 1 in 5 people in England suffered from infectious intestinal disease every year, with around 35,000 hospital admissions and 300 deaths annually and an estimated annual cost to the nation of £0.75 billion (4,7). The treatments recommended for acute diarrhoea by The National Institute for Health and Care Excellence (NICE) guidance are fluid management and nutritional management (1,3). However, standard rehydration management does not reduce the duration of diarrhoea (8) and the challenge of treating diarrhoea itself remains. There is a need for novel treatments, which can decrease the duration of illness and reduce attendances to primary care or emergency departments.

One potential treatment alternative is the use of intestinal adsorbents, also called enterosorbents, which are frequently used in some countries for treatment of diarrhoea (9). A meta-analysis of 13 randomised clinical trials found that diosmectite, a natural clay adsorbent, significantly decreased the duration of acute diarrhoea in comparison with placebo (10). However, the authors concluded that the evidence was not sufficient and future research was needed. Another study has provided evidence that Enterosgel®, an over-the-counter adsorbent consisting of organic methyl-silicic acid, could be effective in treatment of gastrointestinal disorders (11), but there is a need for randomised studies to further investigate its efficacy.

To address the need for more evidence on the efficacy of intestinal adsorbents in the treatment of diarrhoea, the objective of this randomised, multi-centre study is to assess the efficacy, tolerability and safety of Enterosgel® in treatment of acute

diarrhoea in adult patients. Use of effective over-the-counter treatments could help to reduce NHS costs and economic burden of intestinal infections by decreasing patient visits to primary care and hospitals and by reducing absences from work.

2 OBJECTIVES

To investigate the efficacy, tolerability and safety of the intestinal adsorbent, Enterosgel® (Bioline Products s.r.o, Czech Republic), in treating adult patients with acute diarrhoea.

2.1 PRIMARY OBJECTIVE(S)

The primary objective of this study is to investigate the efficacy of Enterosgel® in reducing the duration of acute diarrhoea.

2.2 SECONDARY OBJECTIVE(S)

The secondary objectives of this study are:

1. To investigate the tolerability and safety of Enterosgel®
2. To investigate the impact of Enterosgel® on:
   a) stool frequency
   b) duration of other symptoms and signs of intestinal infection (i.e. fever, nausea, vomiting, abdominal pain)
   c) diarrhoea complications resulting in hospitalisation, Accident & Emergency room attendance, nurse/GP home visit or unscheduled visit to the medical practice

2.3 EXPLORATORY OBJECTIVE(S)

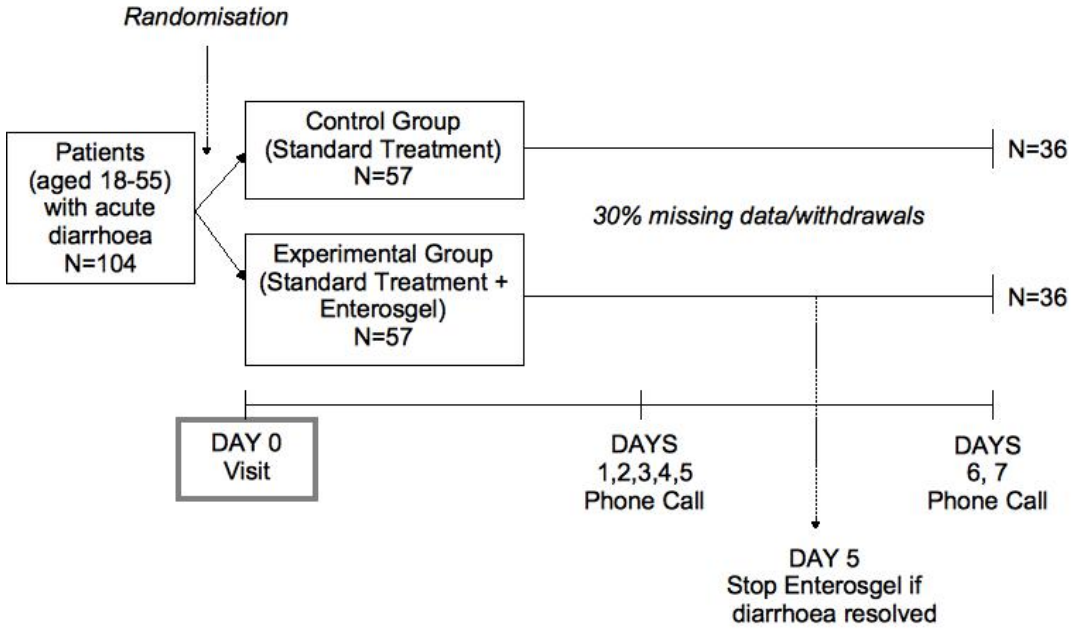
The exploratory objective of this study is to investigate the incidence of Irritable Bowel Syndrome (IBS) -related symptoms and gastrointestinal conditions following an acute diarrhoea episode in the two treatment groups. Our hypothesis is that the use of intestinal adsorbents during an acute diarrhoea episode, could potentially reduce the likelihood that more persistent intestinal problems develop after an acute episode. The data from this study will be used as pilot data to help design larger studies in the future, with the aim of understanding the mechanisms of chronic intestinal conditions such as IBS.

3 STUDY DESIGN AND OUTCOMES

3.1 STUDY DESIGN

This is a 1-week randomised, multi-centre, post-marketing efficacy and safety study of a medical device used within its intended purpose. As in many medical device studies, use of placebo in this trial would be difficult. The exploratory treatment is an orally consumed organosilicon gel-like product, and similar products without any potential impact on the study outcomes and with a demonstrated safety profile would be challenging to develop. As all efficacy and safety data will be recorded in patient diaries, the study outcomes will not be subject to assessor bias. The outcomes have been defined to be as standardised as possible in order to minimise any bias resulting from the participants being unblinded.

Figure 1. Study design.



3.2 STUDY OUTCOMES

3.2.1 Primary Outcome

Duration of diarrhoea defined as time (hours) from randomisation to first non-watery stool (soft or firm)

3.2.2 *Secondary Outcome(s)*

1. Duration of diarrhoea defined as time (hours) from randomisation to last watery stool

2. Percentage of patients with diarrhoea resolved on Day 3 (i.e. first soft or firm stool recorded on Day 0-3)
3. Stool frequency defined as average number of stools/day from randomisation to first soft or firm stool
4. Tolerance and safety of Enterosgel® (assessed via Adverse Event (AE) reporting from start of treatment until end of Day 7)
5. Percentage of patients with diarrhoea-related complications resulting in hospitalisation, Accident & Emergency department visit, nurse/GP home visit or unscheduled visit to the medical practice from randomisation until end of Day 7
6. Duration (days) of the following from randomisation:
   a) Nausea
   b) Vomiting
   c) High body temperature defined as ≥38°C
   d) Abdominal pain

Patient diary is the data source for all efficacy outcomes. Any AEs related to taking study treatment(s) should also be recorded in the patient diary. Any diarrhoea-related complications resulting in hospitalisation, Accident & Emergency department visit, nurse/GP home visit or unscheduled visit to the medical practice, should be reported by the patient during follow-up calls and recorded by the nurse in practice medical notes and the eCRF.

3.2.3 *Exploratory Outcome(s)*

Percentage of patients developing Irritable Bowel Syndrome (IBS) symptoms or other chronic gastrointestinal conditions or acute diarrhoea following the acute diarrhoea episode (within 6 to 20 months).

3.3 DEFINITION OF END OF TRIAL

End of trial is defined as the last follow-up phone contact for the last patient. Patients with unresolved AEs at the last follow-up phone contact would be followed up until AE resolution or stabilisation.

4 STUDY PARTICIPANTS

4.1 INCLUSION CRITERIA

1. Informed consent
2. Patient-reported episode of acute diarrhoea defined as at least 3 watery stools within the last 48 hours
3. Aged 18 to 70

4. Willing and able to comply with the study protocol and evaluation(s) specified in the protocol
5. Considered suitable to take part in the study by the consenting nurse/GP (based on medical history and physical examination)

4.2 EXCLUSION CRITERIA

1. History of intestinal atony (severe constipation due to bowel obstruction)
2. Blood in stools
3. Any underlying condition that could cause chronic diarrhoea (such as gastroduodenal ulcer, ulcerative colitis, or Crohn's disease)
4. Patients with known cancer of any localisation
5. Use of any clinical trial investigational medication within the last 30 days before screening visit
6. Use of antibiotics since the onset of current diarrhoea episode
7. Pregnancy*
8. A history of clinically significant allergic reactions
9. Any underlying condition that could affect the patient's participation in this study or the results of this study in Investigator's opinion

* Patient-reported; last menstrual period date will be recorded.

4.3 PATIENT RECRUITMENT

Patients will be recruited to the study from an estimated 15 GP practices in the UK. GP practices are recruited to the study through the National Institute for Health Research (NIHR) Clinical Research Network (CRN).

Eligible patients will be identified opportunistically when patients contact their GP practice with symptoms of diarrhoea. The research GP or nurse can discuss the opportunity to take part in the trial by phoning the patient before the appointment, or during the appointment. The study can also be advertised to patients on practice notice boards with a poster and on practice websites and newsletters, and in newspapers, the Sponsor's website and social media accounts, public places and at local pharmacies using approved advertising materials, including the study poster in an electronic or printed format. Potentially eligible patients will be provided with the Patient Information Sheet. Patients who are interested to take part in the study after having had sufficient time to consider the information will be seen by the research GP or nurse at the practice to confirm eligibility. Informed consent will then be obtained by the GP or nurse before any study procedures are conducted.

4.4 WITHDRAWAL CRITERIA

Patients can withdraw consent at any time without providing a reason. No further

data will be collected after a patient withdraws consent or is withdrawn from the study, but data collected before withdrawal can be used.

In case of the following the patient should be withdrawn from the study:

1. Refusal to continue the use study treatments
2. Significant deterioration of the patient's status
3. Serious Adverse Event (SAE)
4. Serious adverse reaction
5. Changes in diagnosis
6. Major protocol violation (affecting patient safety and/or scientific quality of the data)

5 INTERVENTIONS AND STUDY DEVICE

5.1 INTERVENTION

Patients in both treatment groups will be prescribed standard of care oral rehydration solution (ORS) treatment.

Patients will be randomised in 1:1 ratio using a computer-based stratified permuted blocks randomisation tool developed by Sealed Envelope Ltd (London, UK) to:

Control Group: will receive a prescription for standard of care ORS treatment
Interventional Group: will receive a prescription for standard of care ORS treatment together with an intestinal adsorbent, over-the-counter medical device, Enterosgel® (Bioline Products s.r.o, Czech Republic) to be taken according to study-specific dosage instructions provided in **Appendix A** for 5-7 days. Patients will be given 2 tubes of Enterosgel® 225 g and a pack of 10 Enterosgel® sachets to provide a more convenient alternative if the patient is not at home.

Randomisation will be stratified by site identifier.

5.2 STUDY DEVICE

5.2.1 Description of study device

Enterosgel® is an over-the-counter intestinal adsorbent developed for binding toxins, harmful substances, pathogens and allergens in the gastrointestinal tract (**Appendix B**). It does not cross the intestinal barrier and is classified as a medical device. In Europe, it was certified as a medical device class IIA in 2008 with an indication for diarrhoea.

Enterosgel® is a polymethylsiloxane based hydrogel produced by polycondensation of methylsilicic acid with the loss of water and formation of siloxane bonds (12). It is completely excreted and exhibits selective sorptive activity towards medium and high-molecular weight substances in the gut, including middle-molecular weight toxic metabolites. Because of the selective adsorption, Enterosgel® is believed not to adsorb medications. However, it is still recommended to leave at least one hour between taking Enterosgel® and other medications. It is free from preservatives, sugar and other additives and is considered to be non-allergenic. It is easily suspended in water and taken orally, and has no taste. Enterosgel® can be used in children and adults, including pregnant and breastfeeding women.

Enterosgel® is used in 30 countries, and in some of them for over 20 years, without reported adverse reactions. 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 2008. Enterosgel® is available from pharmacies and health stores in the UK in a form of gel and is available in a tube or in a packet of 10 sachets.

5.2.2 Labelling, storage and destruction

Study devices will be marked with a label containing the text “FOR RESEARCH PURPOSES” and the following fields:

1. Patient's name
2. Patient's Date of Birth
3. Study reference (i.e. ENT02UK)
4. PI's name

Study devices will be stored at the medical practice in a secure, restricted access room under room temperature conditions. Dispensing of study devices will be recorded in a study dispensing log for device accountability. Unused devices will be returned to the Sponsor for destruction at the end of the study. As the device is an over-the-counter product, the patients can dispose of the empty tubes at home and keep any remaining unused Enterosgel®.

5.3 CONCOMITANT TREATMENTS

All patients will be prescribed standard of care ORS treatment throughout the study. Patients should not use any other diarrhoea medication, such as antidiarrhoeal treatments, during the study unless prescribed by their doctor. During the study the nurse will ask the patients about their diarrhoea medication use, and use of any other diarrhoea medication should be recorded in the eCRF. Any patients who have taken antidiarrhoeal medications (such as loperamide) will be excluded from the analyses.

If the GP decides to add antibiotic therapy, the details including the reason for antibiotic therapy will be recorded in the eCRF and source documents for both groups. Patients in the Interventional group will still take Enterosgel® along with the antibiotic therapy giving 1-2 hours between taking the antibiotic and Enterosgel®.

6 STUDY SCHEDULE AND PROCEDURES

Patients will complete 1 visit at their GP practice with 7 follow-up phone calls after the visit. The patients will not be invited for visits outside their standard of care regime. The schedule of visits/calls, and the procedures conducted and data collected at each visit/call are presented in **Table 1**. A +/- 2-day deviation is allowed for the Day 7 follow-up call.

Table 1. Schedule of procedures and data collection.

Procedure	**Day 0 (Screening Visit)**	**Days 1- 7 (Follow-up calls)**	**End of study**
Patient screening and consent	x		
Demographic information and relevant medical history, symptoms and medication	x		
Randomisation	x		
Prescription for ORS (all patients) and provision of Enterosgel® (Interventional group)	x		
Stool sample	x		
Other symptoms (vomiting, abdominal pain, nausea, fever etc)*	x	x	
Body temperature*		x	
Stool frequency and form*		x	
Medication use*		x	
Adverse Events*		x	
Returning of the diaries			x

*Recorded by the patient in a patient diary from Day 0 (after randomisation) until end of Day 7 (**Appendix C**)

6.1.1 Day 0

On the Day 0 appointment, the patient's eligibility to take part in the study will be confirmed by the GP and written informed consent will be obtained by the GP or nurse before any study procedures take place. Screening will include a physical examination by the GP/nurse to ensure the patient is suitable to take part in the study (including measurement of body temperature, pulse and blood pressure).

The following information is then recorded in the eCRF:

1. Demographic information (age, gender, ethnicity)
2. Relevant medical history:

   a) date of onset of symptoms (diarrhoea, vomiting, nausea, abdominal pain, fever etc.)
   b) contact with suspected infection
   c) details of travel
   d) details of possible food poisoning
   e) any antidiarrheal medication taken during the current episode

The research nurse or GP will then randomise the patient to the intervention group using a computerised randomisation tool. Patients randomised to the Interventional group will be provided with a sufficient amount of Enterosgel® for 5-7 days of treatment and should take Enterosgel® as instructed in the study-specific instructions which will be provided to them (**Appendix A**). Patients randomised to the Control group will not receive any treatment in addition to the standard of care ORS treatment. The details of prescribed ORS treatment and any dietary recommendations will be recorded in the eCRF.

All patients will be provided with a patient diary (**Appendix C**) to record:

1. stool times and consistency
2. diarrhoea medication use
3. other symptoms (fever, nausea, vomiting etc.)
4. any AEs

Patients should fill in the patient diary daily from Day 0 until end of Day 7.

Patients will be asked to take a stool sample on the same day at home in a provided clean container. Patients in the Interventional Group should take the stool sample before taking the first Enterosgel® dose. ORS treatment can be started before taking the stool sample. The sample should be taken to the medical practice by the patient or a family member/friend. It will then be delivered to a local laboratory to test for the presence of rotavirus and diarrhoea causing bacteria (i.e.

Campylobacter, *Clostridium difficile, Escherichia coli*, *Salmonella enterica, Shigella),* in order to identify the likely cause of the episode. If there is a reason to suspect norovirus infection (i.e. outbreak), this will also be tested for. Patients who have recently travelled abroad will be additionally tested for *Pseudomonas* and *Vibrio cholerae*. A stool sample will only be collected in baseline and the results will be summarised in baseline characteristics.

6.1.2 Days 1-7

During the study, the patients will fill the patient diary (**Appendix C**) from Day 0 (after randomisation) until end of Day 7, measure their body temperature twice a day, and take ORS as prescribed and ® according to study-specific instructions provided in **Appendix A**.

Every morning between 8 am to 11am, the research nurse will call the patients to ask about the information recorded in the patient diary and record it in the eCRF. On Day 7, the patients should continue to fill the diary after the call until end of the day. After completing the study, the patients should return the patient diaries to the medical practice. A pre-paid envelope will be provided.

6.1.3 Unscheduled visits

Any unscheduled visits to the medical practice, home visits by nurse/GP, hospitalisations or visits to the Accident & Emergency department due to diarrhoea or related symptoms or due to AEs will be recorded in the eCRF and the source documents.

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 (13).

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.

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.

Serious Adverse Device Effect (SADE)

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

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 fetal distress, fetal 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.

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. NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

7.2 REPORTING

All procedures conducted as part of this study are standard procedures in routine care and/or clinical research. In the unlikely event that an AE occurs during a study

visit, the relationship of the event to the conduct of the study will be assessed by the PI at site. Only AEs which are determined to have resulted (definitely, probably or possibly) from participation in the study will be recorded as AEs in the study records.

All treatments used in this study are standard treatments or licensed over-the-counter products (i.e. Enterosgel®). Throughout the study the patients will be asked about any unusual symptoms or side effects. The PI will review all such events to establish the potential relationship with use of study treatments. AEs which are determined to be definitely, probably or possibly related to the use of Enterosgel® will be recorded as ADEs in the study records.

All SAE/SADE/UADEs need to be reported to the Sponsor within one working day of the site team becoming aware of them.

8 STATISTICS

8.1 POWER CALCULATION

The power calculation for this study is based on demonstrating superiority of the Interventional Group on the primary outcome, duration (days) of diarrhoea. Power was calculated using an online power calculator for continuous outcome superiority trial (Sealed Envelope Ltd. 2012. Available from: https://www.sealedenvelope.com/power/continuous-superiority/).

In line with some previous studies, we assumed a standard deviation for the duration of diarrhoea of 1.3 days (14,15). In order to detect an average decrease of 1 day in the duration of diarrhoea in the Interventional group compared with the Control group, 36 patients in each group are required for 90% power to demonstrate superiority at 5% significance level. Accounting for a combined patient withdrawal and missing data rate of 30%, 52 patients will need to be randomised into each group. Therefore, the total number of patients enrolled will be 104.

8.2 STATISTICAL ANALYSES

A CONSORT flow diagram will show the progress through the parallel randomised trial (that is, enrollment, intervention allocation, follow-up, and data analysis). The baseline characteristics of the groups will be summarised as mean (standard deviation) or n (%). The baseline characteristics will not be compared statistically, in line with CONSORT.

Primary analysis will be conducted on an intention-to-treat basis. The primary outcome will be summarised as mean (standard deviation). The Interventional

group and Control group will be compared using a t-test or Mann Whitney test, as appropriate. A generalised linear model will undertaken to control for an potentially confounding variables, e.g. age and gender.

Secondary outcomes will be summarised as mean (standard deviation) or n(%) median (interquartile range). The Interventional group and Control group will be compared using a t-test or Mann Whitney test for continuous data (e.g. duration of nausea, vomiting and fever) and chi-square tests for categorical data (e.g. complication rate).

A p-value of <0.05 will be considered to indicate statistical significance and all analyses will be undertaken on STATA.

A 30% drop out has been taken into account in the sample size calculation for the primary analysis to allow for missing data. The extent and reasons for missing data will be reported and investigated to see whether the data is missing at random. This will inform which methods to handle missing data will be employed. Sensitivity analyses will be performed as appropriate.

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 (Days 0-7) without reported protocol violations.

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 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 DATA HANDLING AND RECORD KEEPING

All study data will be entered using a validated electronic Case Report Form (eCRF)

system, where the participants will be identified by a study-specific participant number. Data recorded in the eCRFs will not contain any patient identifying information.

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.
Study documents should be retained at site for a minimum of 2 years after the End of Trial. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

9.2 DATA QUALITY

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 according to ICH GCP and a study-specific Trial Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

Following written standard operating procedures, 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.

9.3 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 (16).

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. Use of any prohibited medication (i.e. any antidiarrhoeal medications)

5. Inadequate completion of the patient diary (i.e. data missing systematically, diary missing entirely for one or more days, any data entry issues that compromise the verification of primary outcome data against the source)
6. Materially inadequate record keeping
7. Intentional deviation from the protocol, GCP, or regulations by study personnel
8. Subject repeated non-compliance with study requirements, including not using any Enterosgel®, if randomised to Enterosgel group

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

1. Stool sample not taken, or taken after Day 0
2. One or more calls missed
3. Infrequent missing data in patient diary (however, any missing data affecting the interpretation of the primary outcome would be recorded as a protocol violation)

All deviations/violations must be addressed in study source documents and reported to the Sponsor and Research Ethics Committee (REC) and/or local authorities as per their guidelines. 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.

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

10 ETHICAL CONSIDERATIONS

10.1 GENERAL CONSIDERATIONS

This study will be conducted in 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) and Fortaleza (2013) as well as in compliance with ICH GCP guidelines.

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. All the personnel involved in the

study will be fully informed about the nature of the study and will be subject to protocol procedures concerning their duties in the study.

The protocol, PIS, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REC 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 REC before the changes can be implemented to the study.

10.2 PATIENT CONSENT

The participant will sign the informed consent document prior to any procedures being done specifically for the study. 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 given 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.

10.3 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.

10.4 PAYMENTS TO PATIENTS

Patients will receive £20 to cover travel expenses for delivering the stool sample.

11 PUBLICATION AND DISSEMINATION

This study has been registered with International Standard Randomised Controlled Trial Number (ISRCTN) (ISRCTN20758708).

Study results will be submitted for presentation(s) at gastroenterology conference(s) and for publication in international peer-reviewed scientific journal(s).

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by Enteromed Ltd. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Results will be submitted for inclusion into the NICE guidance if valuable for NHS.

12 FINANCE AND INSURANCE

This study is funded by Bioline Products s.r.o., who is the manufacturer of Enterosgel®. 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.

13 CONFLICTS OF INTEREST

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

The Chief Investigator has no conflicts of interest.

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15 APPENDICES

APPENDIX A: ENTEROSGEL® STUDY USE INSTRUCTIONS

Randomised, multi-centre study to assess efficacy, tolerability and safety of Enterosgel® in treatment of acute diarrhoea in adults

Enterosgel® use instructions for research participants

IMPORTANT:

- **Stop taking Enterosgel® if you did not have any bowel movements for 2 days at any stage of the study**
- **Mix every dose of Enterosgel® in 100-200 ml of room temperature water**
- **Please leave at least 1 hour between taking Enterosgel® and any other medication or meals**

Day 0 (today):

First dose (as soon as possible): 2 tablespoons or 2 sachets of Enterosgel®

After the first dose: 1 tablespoon or 1 sachet of Enterosgel® after every bowel movement up to a total of 6 times and at least 3 times a day

Day 1:

If you have loose stool more than once a day:
1 tablespoon or 1 sachet of Enterosgel® after every bowel movement up to a total of 6 times and at least 3 times a day

If you don't have loose stool or have it just once a day:
1 tablespoon or 1 sachet of Enterosgel® 3 times a day

Days 2, 3, 4 and 5:

If you have loose stool more than once a day:
1 tablespoon or 1 sachet of Enterosgel® 3 times a day

If you don't have loose stool or have it just once a day:
1 tablespoon or 1 sachet of Enterosgel® 1-2 times a day

Days 6 and 7:

If you have loose stool more than once a day:
1 tablespoon or 1 sachet of Enterosgel® 3 times a day

If you don't have loose stool or have it just once a day:
Stop taking Enterosgel®

ENT02UK *Enterosgel® use instructions v.1.0* *12/10/2016*

APPENDIX B: ENTEROSGEL® STANDARD PATIENT INFORMATION LEAFLET

Patient Information Leaflet.

ENTEROSGEL®
Oral suspension

Please read this Leaflet carefully before you start taking Enterosgel®. Keep this Leaflet. You may need to read it again. If you have any further questions, ask your doctor or pharmacist.

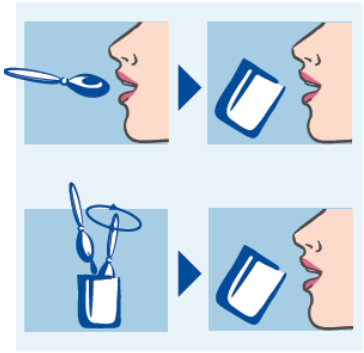
1. What is Enterosgel® and what it is used for?

Enterosgel® is an innovative intestinal adsorbent developed for binding toxins, allergens, pathogens and other harmful substances in the gastrointestinal tract, to help remove them from the body.
ENTEROSGEL® is an ancillary treatment for diarrhoea and is used in children and adults in the following conditions:

- ✓ **Acute diarrhoea (Gastroenteritis).**
- ✓ **Allergies with gastrointestinal symptoms** (Not used for treatment of anaphylactic shock)
- ✓ **Irritable Bowel Syndrome with diarrhoea (IBS-D).**

2. How should I take Enterosgel®

Enterosgel® in a tube:



Enterosgel® in a sachet:

Age	Dosage	How Often
Child 1–6 years old	1 teaspoon or 5g	3 times a day
	or 1/3 of sachet	
Child 7–14 years old	2 teaspoons or 10g	3 times a day
	or 1/2 of sachet	
15+ and adults	1–1,5 tablespoon or 15 to 22.5g	3 times a day
	1–1,5 sachet	

- For babies and children 1 to 3 years old Enterosgel® can be used under advice of a doctor. Enterosgel® should be administered orally 1–2 hours before or after a meal. When this product is taken it is recommended to wash it down with sufficient quantity of water or dilute the dose in water of room temperature prior to its administration (in 200 ml of water for adults and children 7 and over, 50-100 ml of water for children aged 1–6).
- Enterosgel® may affect the absorption of some medicines that are administered orally – use Enterosgel® 1–2 hours before or after taking medication. If you are taking any medication, you may also consult with your doctor or pharmacist regarding taking Enterosgel®.
- If there is blood in the stools, signs of dehydration or symptoms have continued for more than 2 days, seek medical advice especially in the case of children.

3. Contraindications

Intestinal atony (severe constipation due to bowel obstruction). Intolerance, based on prior use of ENTEROSGEL®.

4. Pregnancy and breastfeeding

Enterosgel® can be taken during pregnancy and breastfeeding. It is recommended to speak to your GP or midwife if you are unwell during pregnancy.

5. Additional information

Composition: polymethylsiloxane polyhydrate (methylsilicic acid hydrogel) – 70%, water purified – 30%.
Enterosgel is free from preservatives, colouring, gluten, fat, sugar, lactose, flavours and sweeteners.

Packaging:
Oral suspension in tube 225g, tube 90g, sachet 15g (10 sachets per package).

Note:
Please, shake the tube or a sachet well before use. When squeezing Enterosgel® out of the tube or a sachet some amount of liquid may appear.

Storage parameters:
Store at temperatures of 4–25°C. Keep out of the reach and sight of children.
Avoid drying out after opening the package. Do not freeze! Use the tube within 30 days after opening. Use a sachet within 24 hours after opening.

Shelf life:
Three years. Not to be used beyond the expiry date indicated on the package.

What to do if the package is damaged:
Do not use the product if the package is damaged.

Date of last revision: *10 February 2016*

Explanation of graphic symbols on package:

Certified medical device

Disposable packaging. Dispose of used packaging in appropriate waste receptacle.

Packaging can be recycled

A fee for the national packaging management system has been paid for this packaging.

ZP/EN/NEW/2

Useful information on the mechanism of action of Enterosgel®

The gastrointestinal tract plays an essential role in maintaining good health: delivers necessary nutrients; serves as one of the main routes of elimination of harmful substances and toxins; performs barrier and immune functions.

Causes of diseases and symptoms

Acute exposure of the gastrointestinal tract to pathogens, toxins, allergens, and xenobiotics (pesticides, radionuclides, salts of heavy metals, etc.) results in development of gastrointestinal infections, intoxication and allergic reactions. Vital bodily functions are associated with the production of harmful and toxic metabolites. Part of them having reached the gut are usually eliminated from the body with faeces, but some of harmful substances may be reabsorbed into the bloodstream again and transported back to the liver, remaining in the enterohepatic circulation. The most common symptoms of acute intoxication include a feeling of general malaise, headache, nausea, vomiting, diarrhoea, allergic manifestations, and elevated body temperature.

What can be done?

Detoxification – elimination of toxins and pathogens from the gastrointestinal tract – is an important step towards achieving recovery, optimal health and longevity. The active substance of Enterosgel® is an organosilicon compound -polymethylsiloxane polyhydrate. It has a porous structure, and a gel-like consistency. This allows Enterosgel® to bind harmful substances to its surface and remove them from the body. Detoxification leads to improvement of general well-being, normalization of digestion and augmentation of resistance to infection, and helps the body work under optimal conditions.

Manufacturer:
Bioline Products
Bioline Products s.r.o., Krakovská 1338/10,
110 00 Prague 1, Czech Republic
tel./fax: + 420 266 317 783
e-mail: info@enterosgel.eu
www.enterosgel.eu

Exclusive Distributor in the UK:
EnteroMed Ltd
10 John Street London, WC1N2EB
info@enterosgel.co.uk
www.enterosgel.co.uk

APPENDIX C: PATIENT DIARIES

Randomised, multi-centre study to assess efficacy, tolerability and safety of Enterosgel® in treatment of acute diarrhoea in adults

PATIENT DIARY (CONTROL GROUP)

Patient Identifier:_____ **Date:**_____

DIARRHOEA

After every bowel movement, please write down the time of the movement below.
Please also check one option that best describes the consistency of the stool (by placing a check mark or a cross in the relevant column).

	Time (for example 6.15 am)	Liquid/ Watery/ Loose	Soft	Firm/ Solid
Morning 6 am-12 pm				
Day 12 pm-6 pm				
Evening 6 pm-12 am				
Night 12 am-6 am				

ENT02UK *Patient Diary Control Group v.1.0* *09/10/2016*
1

SYMPTOMS

Please circle all symptoms you have experienced today, or "None" if you did not experience any.

None **Nausea** **Vomiting** **Abdominal pain** **Other**

If other, please describe: _____

Body temperature in the morning: _____°C **Body temperature** in the evening: _____°C

TREATMENTS

Every time after taking your oral rehydration treatment, please write down the time below.

Please also select which treatment you took by placing a cross or check mark in the relevant column and describe if you experienced any side effects which you think could be related to the treatment.

	Time (for example 6.15 am)	**Describe any side effects or complications**
Morning 6 am-12 pm		
Day 12 pm-6 pm		
Evening 6 pm-12 am		
Night 12 am-6 am		

Please list here if you have used any other medication(s) for your diarrhoea today:

PATIENT DIARY (ENTEROSGEL® GROUP)

Patient Identifier:_____ **Date:**_____

DIARRHOEA

After every bowel movement, please write down the time of the movement below.
Please also check one option that best describes the consistency of the stool (by placing a check mark or a cross in the relevant column).

	Time (for example 6.15 am)	Liquid/ Watery/ Loose	Soft	Firm/ Solid
Morning 6 am-12 pm				
Day 12 pm-6 pm				
Evening 6 pm-12 am				
Night 12 am-6 am				

SYMPTOMS

Please circle all symptoms you have experienced today, or "None" if you did not experience any.

None **Nausea** **Vomiting** **Abdominal pain** **Other**

If other, please describe: _____

Body temperature in the morning: _____°C **Body temperature** in the evening: _____°C

TREATMENTS

Every time after taking diarrhoea treatment, please write down the time below.

Please also select which treatment you took by placing a cross or check mark in the relevant column and describe if you experienced any side effects which you think could be related to the treatment.

	Time (for example 6.15 am)	**Enterosgel®**	**Oral rehydration treatment**	**Describe any side effects or complications**
Morning 6 am-12 pm				
Day 12 pm-6 pm				
Evening 6 pm-12 am				
Night 12 am-6 am				

Please list here if you have used any other medication(s) for your diarrhoea today:
