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Enterosgel® in the treatment of Irritable Bowel Syndrome with Diarrhoea

Submission date
14/11/2017

Recruitment status
No longer recruiting

Registration date
15/11/2017

Overall study status
Completed

Last Edited
20/09/2022

Condition category
Digestive System

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Irritable Bowel Syndrome (IBS) is a common condition with symptoms causing around 1 in 10 people to seek help from their GP at some point in their lives. It is a combination of abdominal discomfort or pain and altered bowel habits. Depending on the stool consistency, IBS can be classified as IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), or mixed IBS (IBS-M). IBS is often a chronic condition that can significantly impair quality of life and cause absence from work and school. The emergence of new drugs for IBS has been slow and there is a need for new treatment alternatives, including drug-free treatments, which are easy to use and can safely be used in different types of patients, including in children and pregnant women. Currently available drug-free treatments include Enterosgel®, which is an intestinal adsorbent that has been approved for use in patients with IBS-D and is available over-the-counter in the UK. It is an orally consumed gel-like product classified as a medical device, which has been shown to adsorb harmful substances like bacterial toxins in the gut. There have been studies suggesting that Enterosgel® and other intestinal adsorbents can improve diarrhoea, bloating and abdominal pain in patients with IBS-D. However, larger studies are needed to further investigate the potential benefits of Enterosgel® in the treatment of IBS-D. This study aims to recruit 430 participants with IBS-D. The goal is to investigate whether Enterosgel® can improve IBS-D symptoms, including diarrhoea and abdominal pain. In addition, the study aims to investigate the impact of this treatment on the quality of life, work productivity and activity and general health. The safety and tolerability of Enterosgel® in this condition will also be evaluated.

Who can participate?
Adults aged 16-75 who have been diagnosed with IBS-D and have diarrhoea symptoms

What does the study involve?
The study involves in total four visits and one follow-up call over 26 weeks. At each visit and at given time points between the visits, the participants complete questionnaires asking about their IBS symptoms, quality of life, work productivity and activity and general health. In addition, the participants are asked to complete a study diary throughout the study to record their symptoms and treatment use. The diary is available as an electronic and paper diary. The diary should be completed daily for the first 18 weeks. At the first visit (week 0), potential participants are provided with the study diary to record their diarrhoea and abdominal symptoms for 2

weeks. Those who had sufficientsymptoms over this period are eligible to take part in the study and are randomly allocated to one of two treatment groups at the second visit (week 2). The first group receive dummy treatment and the second group receive Enterosgel® for 8 weeks. Neither the participants nor the research team know which treatment the participant receives. After 8 weeks, the participants attend the third visit (week 10) and all participants are given Enterosgel® for the next 8 weeks. This time, the participants are informed about the treatment they receive. After 8 weeks of treatment with Enterosgel®, the participants attend the fourth study visit (week 18) and return to standard-of-care. A final follow-up call takes place 8 weeks later (week 26).

What are the possible benefits and risks of participating?
To allow all patients to try Enterosgel®, this study includes an 8-week period where all participants receive it. Some participants may find that Enterosgel® helps with their IBS symptoms while others might not experience any benefit. The aim of this study is to evaluate what proportion of participants can benefit from this treatment, and what the benefits are. In the future, this information can be helpful to the patients and healthcare professionals when they are considering different treatment alternatives. Enterosgel® has been available in some countries for 30 years and is commonly used as a treatment for gastrointestinal conditions, including acute diarrhoea and IBS-D. According to the manufacturer, possible known side effects are nausea and constipation. Enterosgel® is completely excreted from the gut and does not get absorbed into the blood circulation.

Where is the study run from?
This study will be conducted at about 30 medical practices, secondary care centres and private clinics in the UK and a virtual site. In addition to the participating research sites, the study is advertised through local pharmacies and through an IBS research register called ContactME-IBS (https://www.contactme-ibs.co.uk)

When is the study starting and how long is it expected to run for?
March 2017 to October 2021

Who is funding the study?
Bioline Products s.r.o

Who is the main contact?
Dr Carol Howell

Study website
https://enteromed.co.uk/research-report/

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
ENT04UK

Study information

Scientific Title
Randomised, double-blind, placebo-controlled multi-centre study to assess the efficacy, tolerability and safety of Enterosgel® in the treatment of Irritable Bowel Syndrome with Diarrhoea (IBS-D) in adults (RELIEVE IBS-D)

Acronym
RELIEVE IBS-D

Study objectives
The hypothesis is that Enterosgel® is superior compared with placebo in terms of patient-reported outcomes for stool consistency and abdominal pain, in patients with IBS-D.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North East - Tyne & Wear South Research Ethics Committee, 19/02/2018, REC ref: 18/NE/0023

Study design
Randomised double-blind placebo-controlled multi-centre trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Irritable Bowel Syndrome with diarrhoea (IBS-D)

Interventions
Using a centralised computer-based randomisation tool, patients will be randomised 1:1 to receive intestinal adsorbent Enterosgel® or placebo. The patients will receive blinded study treatment for 8 weeks according to study-specific dosage instructions, which allow adjusting the dosage based on IBS symptoms. The treatment is provided in 90g tubes, each containing a single treatment dose. The Enterosgel® tubes contain 22.5g Enterosgel® pre-diluted in water. The placebo tubes contain water with chalk added to mimic the appearance and consistency of Enterosgel®. Updated 17/10/2018: The control group will receive identical tubes containing placebo.

Treatments are taken orally up to 6 doses per day, depending on the symptoms.

After 8 weeks of blinded treatment, all patients will receive open-label Enterosgel® treatment for 8 weeks to take if they experience diarrhoea.

Following the open-label treatment period, all patients will return to standard-of-care and will be followed up for 8 weeks.

Intervention Type
Device

Phase
Not Applicable

Primary outcome measure
Percentage of patients defined as responders for abdominal pain and stool consistency based on daily study diary data, during at least 4 weeks in the 8-week blinded treatment period, where:
1. An Abdominal Pain Intensity Weekly Responder is defined as a patient who experiences a decrease in the weekly average abdominal pain score of at least 30 percent compared with baseline. The weekly average abdominal pain score is derived by scoring the worst pain experienced each day and taking the average for one week
AND
2. A Stool Consistency Weekly Responder is defined as a patient who experiences a 50 percent or greater reduction in the number of days per week with at least one stool that has a consistency of Bristol Stool Form Scale (BSFS) Type 6 or 7 compared with baseline

Secondary outcome measures
Original secondary outcome measures:

Double-blind treatment phase and open-label treatment phase:
1. Stool frequency based on daily study diary data; mean over 8 weeks and the last 4 weeks of each treatment period
2. Stool consistency assessed as average number of days/week with Bristol Stool Scale type >5 based on daily study diary data and percentage of responders over 8 weeks and the last 4 weeks of each treatment period
3. Abdominal pain based on daily study diary data; mean on a VAS scale from 0 to 10 over 8 weeks and the last 4 weeks, percentage of responders over 8 weeks and the last 4 weeks of each treatment period
4. Bloating based on weekly study diary data; mean weekly score on a numerical scale from 0 to 6 over 8 weeks and the last 4 weeks of each treatment period
5. Urgency based on weekly study diary data; mean weekly score on a numerical scale from 0 to 6 over 8 weeks and the last 4 weeks of each treatment period
6. Percentage of patients reporting adequate relief of global IBS symptoms based on weekly study diary data weekly from baseline until week 8 of each treatment period
7. Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) score weekly from baseline until week 8 of each treatment period
8. Irritable Bowel Syndrome Quality of Life (IBS-QOL) score every 4 weeks from baseline until week 8 of each treatment period
9. Patient Health Questionnaire-12 Somatic Symptom scale (PHQ-12 SS) score to measure severity of somatic symptoms excluding gastrointestinal symptoms every 4 weeks from baseline until week 8 of each treatment period
10. IBS-related Work Productivity and Activity Impairment (WPAI:IBS) score; weekly from baseline until week 8 of each treatment period
11. Use of rescue medication, i.e. loperamide, based on weekly study diary data; number of days over each 8 weeks of treatment
12. Adverse events over each 8 weeks of treatment

Follow-up:
1. Satisfaction with bowel symptoms based on weekly study diary data; mean weekly score on a numerical scale from 0 to 6, over 8 weeks
2. Satisfaction with abdominal pain based on weekly study diary data; mean weekly score on a numerical scale from 0 to 6, over 8 weeks
3. Loperamide use based on weekly study diary data; mean number of days per week over 8 weeks
4. Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) score at baseline and 8 weeks
5. Patient Health Questionnaire-12 Somatic Symptom scale (PHQ-12 SS) score to measure severity of somatic symptoms excluding gastrointestinal symptoms at baseline and 8 weeks
6. Irritable Bowel Syndrome Quality of Life (IBS-QOL) score at baseline and 8 weeks
7. IBS-related Work Productivity and Activity Impairment (WPAI:IBS) score at baseline and 8 weeks
8. Percentage of patients who maintained treatment benefit over 8 weeks after cessation of treatment based on weekly study diary data over 8 weeks

Updated 17/10/2018:
Follow-up:
In patients who reported adequate relief in the last 4 weeks of open-label period:
1. Maintenance of treatment benefit (percentage of patients who report increased or maintained treatment benefit at 8 weeks)
2. Enterosgel® use (percentage of patients who report having used Enterosgel® during the follow-up period; frequency of use in these patients)
3. Loperamide use (percentage of patients who report having used less loperamide during the

follow-up period than before the trial)
4. Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) score at baseline and 8 weeks
5. Patient Health Questionnaire-12 Somatic Symptom scale (PHQ-12 SS) score to measure severity of somatic symptoms excluding gastrointestinal symptoms at baseline and 8 weeks
6. Irritable Bowel Syndrome Quality of Life (IBS-QOL) score at baseline and 8 weeks
7. IBS-related Work Productivity and Activity Impairment (WPAI:IBS) score at baseline and 8 weeks
8. Percentage of patients who maintained treatment benefit over 8 weeks after cessation of treatment based on weekly study diary data over 8 weeks

Updated 07/01/2020:
Double-blind treatment phase and open-label treatment phase:
1. Stool frequency based on daily study diary data; mean over 8 weeks and the first and last 4 weeks of each treatment period
2. Stool consistency assessed as average number of days/week with Bristol Stool Scale type >5 based on daily study diary data (over 8 weeks and the first and last 4 weeks of each treatment period) and percentage of responders
3. Abdominal pain based on daily study diary data; mean on a VAS scale from 0 to 10 over 8 weeks and the last 4 weeks, percentage of responders over 8 weeks and the last 4 weeks of each treatment period
4. Bloating based on weekly study diary data; mean weekly score on a numerical scale from 0 to 6 over 8 weeks and the last 4 weeks of each treatment period
5. Urgency based on weekly study diary data; mean weekly score on a numerical scale from 0 to 6 over 8 weeks and the last 4 weeks of each treatment period
6. Percentage of patients reporting adequate relief of global IBS symptoms based on weekly study diary data over 8 weeks and the first and last 4 weeks of each treatment period
7. Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) score average over 8 weeks and the first and last 4 weeks
8. Irritable Bowel Syndrome Quality of Life (IBS-QOL) 4-weekly score average over 8 weeks and week 4 and week 8 scores
9. Patient Health Questionnaire-12 Somatic Symptom scale (PHQ-12 SS) score to measure severity of somatic symptoms excluding gastrointestinal symptoms 4-weekly score average over 8 weeks and week 4 and week 8 scores
10. IBS-related Work Productivity and Activity Impairment (WPAI:IBS) weekly score average over 8 weeks of each treatment period
11. Use of rescue medication, i.e. loperamide, based on weekly study diary data; number of days over 8 weeks and the last 4 weeks
12. Adverse events over each 8 weeks of treatment

Overall study start date
01/03/2017

Completion date
31/10/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 04/04/2019:
1. Written informed consent
2. Irritable Bowel Syndrome with diarrhoea (IBS-D) according to Rome IV criteria

3. Aged 16-75
4. Considered suitable to take part in the study by the consenting doctor/nurse
5. Diary completed on at least 11 of 14 days (≥75%) during the screening period

Previous inclusion criteria from 17/10/2018 to 04/04/2019:
1. Written informed consent
2. Irritable Bowel Syndrome with diarrhoea (IBS-D) according to Rome IV criteria
3. Aged 18-75
4. Considered suitable to take part in the study by the consenting doctor/nurse
5. Diary completed on at least 11 of 14 days (≥75%) during the screening period

Original inclusion criteria:
1. Irritable Bowel Syndrome with diarrhoea (IBS-D) according to Rome IV criteria
2. Negative calprotectin test or adequate exclusion of Inflammatory Bowel Disease (IBD)
3. Aged 18+
4. Considered suitable to take part in the study by the consenting physician

Participant type(s)
Patient

Age group
Mixed

Lower age limit
16 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
430

Total final enrolment
439

Key exclusion criteria
Current exclusion criteria as of 07/01/2020:
1. Loose stools (BSFS 6 or 7) on less than 3 days during the 14 days after Screening Visit
2. Average abdominal pain <2.5 during the 14 days after Screening Visit (scale 0–10: 0 = no pain; 10 = worst possible pain)
3. Previously diagnosed coeliac disease
4. Previously diagnosed Inflammatory Bowel Disease
5. Previous bowel cancer or bowel resection
6. Other previously known gastrointestinal disorder contributing to the diarrhoea
7. Unexplained weight loss
8. Unexplained rectal bleeding
9. Previous use of Enterosgel®
10. Use of antidepressant agents, unless used at a stable dose for at least 6 weeks

11. Use of any probiotic supplements, other intestinal adsorbents, slow-release medications or strong opioids
12. Participation in any research where treatment is provided, or was provided in the last three months
13. Pregnancy

Previous exclusion criteria from 04/04/2019 to 07/01/2020:
1. Loose stools (BSFS 6 or 7) on less than 3 days during the 14 days after Screening Visit
2. Average abdominal pain <3 during the 14 days after Screening Visit (scale 0–10: 0 = no pain; 10 = worst possible pain)
3. Previously diagnosed coeliac disease
4. Previously diagnosed Inflammatory Bowel Disease
5. Previous bowel cancer or bowel resection
6. Other previously known gastrointestinal disorder contributing to the diarrhoea
7. Unexplained weight loss
8. Unexplained rectal bleeding
9. Previous use of Enterosgel®
10. Use of antidepressant agents, unless used at a stable dose for at least 6 weeks
11. Use of any probiotic supplements, other intestinal adsorbents, slow-release medications or strong opioids
12. Participation in any research where treatment is provided, or was provided in the last three months
13. Pregnancy

Previous exclusion criteria from 17/10/2018 to 04/04/2019:
1. Loose stools (BSFS 6 or 7) on less than 3 days during the 14 days after Screening Visit
2. Average abdominal pain <3 during the 14 days after Screening Visit (scale 0–10: 0 = no pain; 10 = worst possible pain)
3. IBS-SSS≥400
4. Previously diagnosed coeliac disease
5. Previously diagnosed Inflammatory Bowel Disease
6. Previous bowel cancer or bowel resection
7. Other previously known gastrointestinal disorder contributing to the diarrhoea
8. Unexplained weight loss
9. Unexplained rectal bleeding
10. Previous use of Enterosgel®
11. Use of antidepressant agents, unless used at a stable dose for at least 6 weeks
12. Use of any probiotic supplements, other intestinal adsorbents, slow-release medications or strong opioids
13. Participation in any research where treatment is provided, or was provided in the last three months
14. Pregnancy

Original exclusion criteria:
1. Loose stools (BSFS 6 or 7) on less than 3 days during the last 14 days before Baseline
2. IBS-SSS≥400
3. Organic gastrointestinal disorder
4. Celiac disease (existing diagnosis)
5. Lactose malabsorption (existing diagnosis)
6. Bile acid malabsorption (existing diagnosis)
7. Bowel cancer
8. Previous use of Enterosgel®

9. Pregnancy
10. Diary completed on at least 11 of 14 days (≥75%) during the screening period

Date of first enrolment
15/10/2018

Date of final enrolment
21/04/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospital of North Durham
United Kingdom
DH1 5TW

Study participating centre
Newcastle Upon Tyne Hospitals
United Kingdom
NE7 7DN

Study participating centre
Bodey Medical Centre
United Kingdom
M14 6WP

Study participating centre
The Village Practice
United Kingdom
FY5 2TZ

Study participating centre
Blackpool Victoria Hospital
United Kingdom
FY3 8NR

Study participating centre
Vauxhall Primary Health Care
United Kingdom
L5 8XR

Study participating centre
Ashgate Medical Practice
United Kingdom
S40 4AA

Study participating centre
Newton Place Surgery
United Kingdom
ME13 8FH

Study participating centre
Pound Hill Medical Group
United Kingdom
RH10 7DX

Study participating centre
West Walk Surgery
United Kingdom
BS37 4AX

Study participating centre
Pickering Medical Centre
United Kingdom
YO18 8BL

Study participating centre
Functional Gut Clinic
United Kingdom
W1G 6NB

Study participating centre
University Hospital Coventry and Warwickshire
United Kingdom
CV2 2DX

Study participating centre
Warrington Hospital
United Kingdom
WA5 1QG

Study participating centre
Queen's Road Surgery
United Kingdom
DH8 0BW

Study participating centre
Well Close Medical Group
United Kingdom
TD15 1LL

Study participating centre
Well Close Medical Group
United Kingdom
TD15 1LL

Study participating centre
Redburn Park Medical Centre
United Kingdom
NE29 6HT

Study participating centre
Derriford Hospital
United Kingdom
PL6 8DH

Study participating centre

Royal Stoke University Hospital
United Kingdom
ST4 6QG

Study participating centre
Hadrian Primary Care Alliance
United Kingdom
NE43 7LL

Study participating centre
Castlegate and Derwent Surgery
United Kingdom
CA13 9HT

Study participating centre
Carmel Medical Practice
United Kingdom
DL3 8SQ

Study participating centre
Stepping Hill Hospital
United Kingdom
SK2 7JE

Study participating centre
Royal Bournemouth Hospital
United Kingdom
BH7 7DW

Study participating centre
St George's University Hospital
United Kingdom
SW17 0QT

Study participating centre

King's College Hospital
United Kingdom
SE5 9RS

Study participating centre
Doncaster Royal Infirmary
Armthorpe Road
Doncaster
United Kingdom
DN2 5LT

Study participating centre
Wythenshawe Hospital
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Sponsor type
Industry

Website
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ROR
https://ror.org/013bz8f47

Funder(s)

Funder type

Industry

Funder Name
Bioline Products s.r.o

Results and Publications

Publication and dissemination plan
Current publication and dissemination plan as of 15/09/2022:
Study results were submitted for presentation(s) at the British Society for Gastroenterology Conference (June 2022) and published in the scientific journal GUT online on 27/06/2022 (doi: 10.1136/gutjnl-2022-327293). Results were disseminated to patients at an interactive webinar which is now available on the study website for patients and the public to view. The protocol will be made available immediately following publication with no end date.

Previous publication and dissemination plan:
Study results will be submitted for presentation(s) at gastroenterology conference(s) and for publication in international peer-reviewed scientific journal(s). Results will be disseminated to the patients and the public through the study website. The protocol will be made available immediately following publication with no end date.

Intention to publish date
31/03/2022

Individual participant data (IPD) sharing plan
After publication, individual anonymised participant data that underlie the results reported in the publication will be available to researchers upon request from Dr Carol Howell at Enteromed Ltd. Participants have provided their consent for the sharing of anonymised data for research purposes.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		30/01/2020	19/10/2021	Yes	No
Results article		27/06/2022	28/06/2022	Yes	No
Protocol file		29/06/2020	20/09/2022	No	No
HRA research summary			28/06/2023	No	No