Original research

Double-blinded randomised placebo controlled trial of enterosgel (polymethylsiloxane polyhydrate) for the treatment of IBS with diarrhoea (IBS-D)

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ABSTRACT

Objective Irritable bowel syndrome with diarrhoea (IBS-D) is a common and challenging condition that significantly reduces quality of life. Enterosgel (polymethylsiloxane polyhydrate) is an intestinal adsorbent which sequesters harmful molecules and is safe and effective in acute infective diarrhoea. This randomised controlled multicentre trial aimed to investigate its safety and efficacy in patients with IBS-D.

Design After a 2-week screening phase, participants were randomised into an 8-week double-blind phase, followed by an 8-week open-label and follow-up phase. Participants recorded stool consistency, pain and global symptoms in e-diaries and questionnaires. The primary outcome was the percentage of responders on a composite abdominal pain (≥30% decrease in the weekly score) and stool consistency (50% reduction in days per week with at least one stool of BSFS type 6 or 7) score during at least 4 weeks of the treatment period.

Results 440 patients with IBS-D were randomised to the double-blind phase with 393 continuing to the open-label phase. The Primary outcome responder rate by intention-to-treat for enterosgel versus placebo was 37.4% vs 24.3% (OR 1.95, NNT 8, p=0.002). Enterosgel also improved stool consistency (48.5% vs 32.5%, p<0.0001) abdominal pain (53.3% vs 40.2%, p=0.003), stool frequency (treatment effect −0.32 (−0.62 to −0.02)) and urgency (treatment effect −0.59 (−0.85 to −0.33)). 60% of patients reported adequate relief of symptoms after open-label treatment. Adverse event frequency was similar in both groups, with no serious events attributable to enterosgel.

Conclusion Enterosgel is safe and effective in IBS-D, providing an alternative to the limited current treatment options.

Trial registration number ISRCTN17149988.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Current treatments for irritable bowel syndrome (IBS) focus on symptom control and satisfaction with treatment is low.
⇒ Based on previous small studies in IBS and other conditions, enterosgel maybe beneficial for the treatment of IBS-D symptoms.

WHAT THIS STUDY ADDS

⇒ Enterosgel showed significantly higher treatment response rate versus placebo for combined symptoms of abdominal pain and stool consistency.
⇒ Enterosgel also showed significant treatment benefit for bloating, stool frequency, urgency and adequate relief.
⇒ A high percentage of participants reported adequate relief after open-label phase, and 74.1% showed continued treatment benefit during the follow-up phase.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Enterosgel is a readily available over-the-counter treatment option that could improve global symptoms in patients with IBS-D .

INTRODUCTION, BACKGROUND AND OBJECTIVES

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders seen by clinicians in both primary and secondary care.[1] The condition is categorised by symptoms of abdominal pain or discomfort accompanied with altered bowel habit and bloating.[2 3] According to patients, the most important factors in the symptomatic treatment of diarrhoea predominant IBS (IBS-D) are the relief of diarrhoea, urgency and abdominal pain. Studies have shown that patients with IBS-D have a significantly higher median pain episode frequency per month,[4] greater stool frequency and looser stool consistency[5] and urgency,[6] than other subtypes.

IBS is a heterogeneous disorder which makes management challenging, with IBS-D therapies focusing on treating predominant symptoms. Recent guidelines[1] recommend patients with IBS are provided with dietary advice and take regular exercise. Other approaches for IBS-D include psychological interventions, the low FODMAP diet, multistrain probiotics and pharmacological interventions. However, evidence to support their
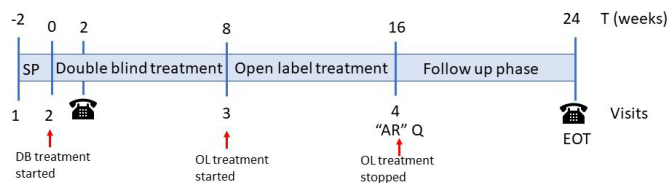
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Figure 1 Study design. After a 2-week screening phase, eligible participants were randomised in the 8 week double-blind treatment phase where participants received either placebo or Enterosgel, followed by the open-label phase where all participants received Enterosgel. Participants who answered Yes for adequate relief at the end of the open-label phase, were included in the 8 week follow-up phase. "Ar" Q, adequate relief question; DB, double-blind; EOT, end of trial; OL, open-label; SP, screening phase.

use is mixed with some drugs providing only poor relief of all IBS symptoms or have safety concerns. More effective therapies are required as less than one third of patients with IBS are satisfied with their current therapy[7] and 34% report no symptom control.[8]

Intestinal adsorbents such as diosmectite a mineral clay, which are classified as medical devices as they have no pharmacological action, have shown promise for the treatment of gastrointestinal conditions including IBS.[9 10] The basis for their use in IBS is not completely understood but is likely due to their capacity to adsorb endogenous and exogenous substances such as bacterial break-down products (eg, lipopolysaccharides), immune proteins and bile acids, thereby inactivating their effects in the gut.

Enterosgel is a CE certified over-the-counter (OTC) intestinal adsorbent currently indicated for acute diarrhoea and chronic diarrhoea associated with IBS-D. It can bind bacterial products, bile acids and other harmful substances in the gastrointestinal tract.[11] A recent UK study has shown its effectiveness in acute diarrhoea in adults,[12] however, to date studies have not included a placebo control. Our aim was to investigate the efficacy, tolerability and safety of Enterosgel as a treatment for IBS-D symptoms, through a robust, pragmatic multicentre randomised placebo-controlled study.
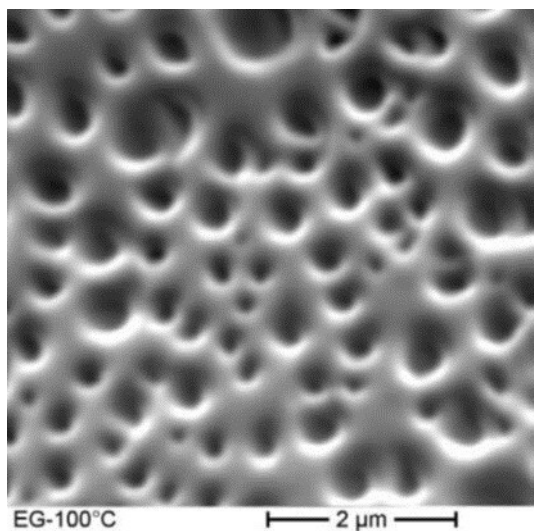

Figure 2 SEM image of the porous surface of polymethylsiloxane polyhydrate xerogel.

METHODS
Trial design

A multicentre, parallel arm, randomised, double-blind, placebo controlled trial design was used to evaluate the efficacy, tolerability and safety of Enterosgel in the treatment of IBS-D in adults.[13] The study was designed in line with FDA guidance for clinical trials in IBS,[14] which allows direct comparison with other products. Following a 2-week screening phase, eligible subjects were randomised to receive either enterosgel or placebo for 8 weeks. An incremental dosage schedule was employed starting at 15 g two times a day for the first 5 days, working up to 30 g three times per day, depending on symptom relief. Following the double-blind phase, all participants received open-label enterosgel treatment for 8 weeks, followed by a return to standard care; however, those who responded to open-label treatment received a follow-up call 8 weeks later. Initially, there were four face-to-face visits (week −2, 0, 8 and 16) with additional telephone visits at week 2 to ensure compliance, and at week 24 at the end of the follow-up phase (figure 1). Participants recorded symptoms in an electronic or paper diary daily from screening visit until end of open-label phase.

Adult patients aged 16–75 years diagnosed with IBS-D were initially recruited at 14 primary, 13 secondary care sites and a private clinic located across England, with the first participant enrolled on 20 November 2018. The study was suspended due to COVID-19 in March 2020 and the protocol amended to allow remote visits to enable enrolled subjects to continue and the recruitment of new participants. The National Institute for Health and Care Research (NIHR) Patient Recruitment Centre—Newcastle, was converted to a virtual site, recruiting via the ContactME-IBS registry, from anywhere in the UK.

Participants

Patients were required to meet the Rome IV criteria for IBS-D.[15] Exclusion criteria were: previously diagnosed coeliac disease, inflammatory bowel disease, bowel cancer or bowel resection, other gastrointestinal disorder contributing to the diarrhoea, unexplained weight loss or rectal bleeding, use of probiotic supplements, other intestinal adsorbents, slow-release medications or strong opioids,[16] previous use of enterosgel and average abdominal pain score of <3 during screening, this was reduced to <2.5 in response to screening failures after 44% of participants were recruited. Patients who had been on a stable dose of antidepressant for at least 6 weeks were eligible. All female patients of childbearing potential were required to provide a negative pregnancy test at baseline and continue contraception use. Patients were not allowed to take loperamide during the screening period, but after randomisation loperamide was provided as a rescue medication.

Investigational medical device

Enterosgel is a CE certified class IIa medical device composed of polymethylsiloxane polyhydrate and 30% water by weight. The porous hydrogel is amorphous thus insoluble in water, with pores 2–100 nm in diameter, and a large surface area with highest adsorption capacity towards larger molecular weight molecules (figure 2).

Enterosgel is a colourless gel and achieving an identical placebo proved challenging. Any gel-like substances used as a placebo could potentially have an effect in the gut; their use as a placebo would require separate validation. Dilution with 200 mL water adequately disguised the active component but the
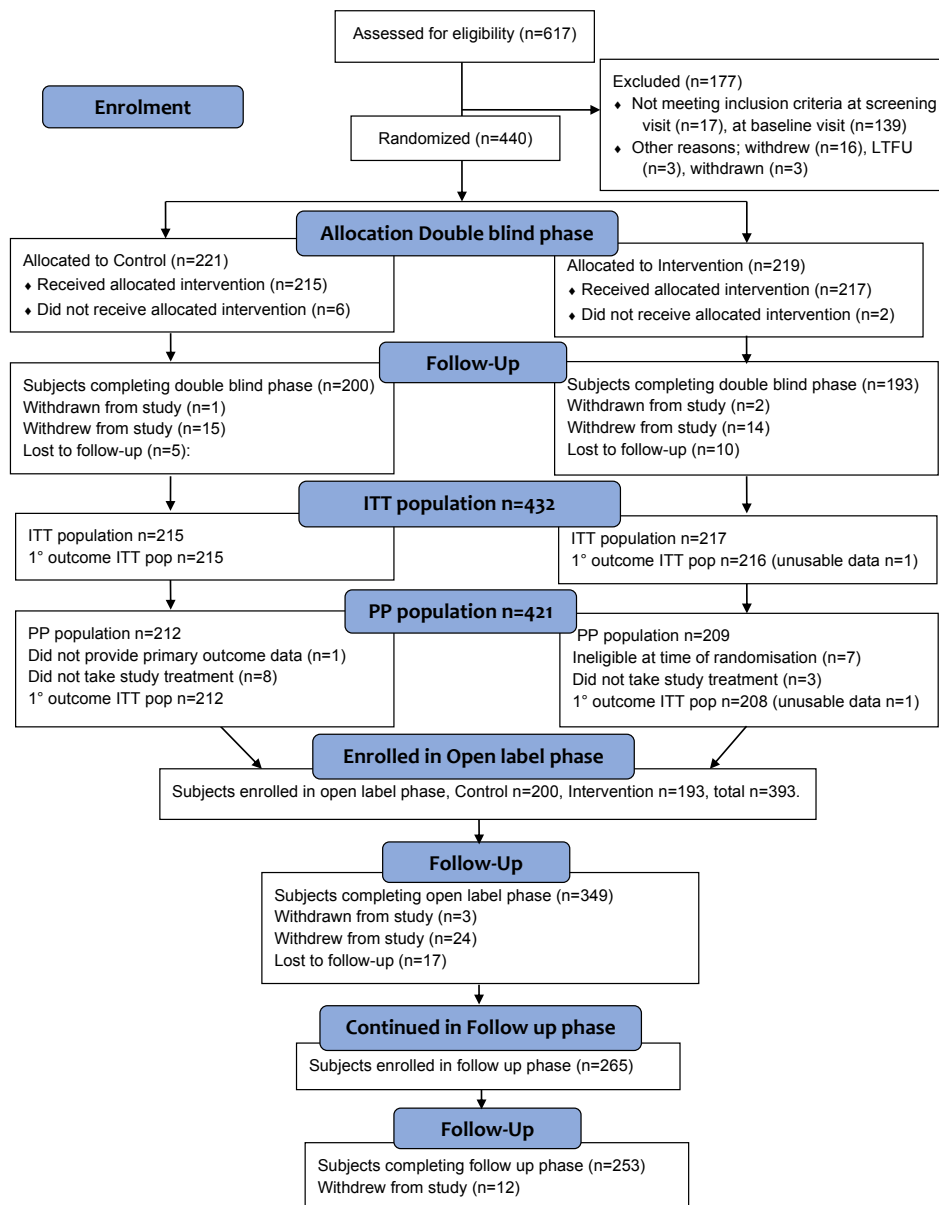
Figure 3 Study CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials; ITT, intention-to-treat; LFTU, lost to follow-up; PP, per-protocol.

volume and weight of packaging was excessive. Thus, blinded enterosgel was prediluted in tubes containing 15 g enterosgel (Bioline Products s.r.o., Czech Republic) in 67.5 mL potable water, forming a tasteless, colourless slightly opaque liquid, with 90 mL water used as the placebo comparator. To maintain blinding, Enterosgel and placebo were packaged into identical, opaque, study-specific labelled tubes, which were mixed in 100 mL water by patients before administration. For the open-label phase, OTC enterosgel 15 g sachets were provided.

Data collection

Participant baseline demographics and medical information were collected at screening visit (week −2). From week −2 to 16, participants completed a daily e-diary to record stool consistency (BSFS), abdominal pain (score 0=no pain at all, score 10=worst possible pain patient can imagine), bowel movements and doses of study treatment and a weekly diary to record adequate relief over the last week, urgency and bloating score (score 0=not at all, 6=a very great deal) and loperamide use. Participants also completed weekly IBS Severity Scoring System (IBS-SSS)[17] and Work Productivity and Activity Impairment[18][19] and 4-weekly IBS Quality of Life (IBS-QOL)[20][21] and Patient Health Questionnaire-12 Somatic Symptom Scale[22] paper questionnaires. Patients who reported adequate relief of IBS symptoms in the last 4 weeks of the open-label period, were included in the follow-up phase.

Outcomes

The composite primary outcome was the percentage of patients defined as responders for both abdominal pain and stool consistency during at least 4 weeks in the 8-week treatment period.[14][23] An abdominal pain intensity weekly responder was defined as a patient who experienced ≥30% decrease in the weekly average abdominal pain score compared with the screening period. A

Table 1 Baseline characteristics of study participants in the ITT population

Characteristic	Placebo (n=221)	Enterosgel (n=219)
Age, years (IQR)	44.0 (33.3–55.0)	40.0 (29.0–55.0)
Female gender, n (%)	162 (73.3)	161 (73.5)
Ethnicity, n (%)		
Asian/Asian British	4 (1.8)	3 (1.4)
Black/African/Caribbean/Black British	0 (0.0)	1 (0.5)
White	212 (95.9)	213 (97.3)
Mixed	3 (1.4)	1 (0.5)
Other	2 (0.9)	1 (0.5)
Days ≥1 stool of BSFS 6 or 7, (IQR)*†	4.5 (3.5–6.0)	4.4 (3.0–6.0)
Abdominal pain score, (IQR)*	5.1 (4.1–6.4)	5.0 (3.9–6.1)
IBS-SSS score, (SD)	352.3 (80.8)	334.4 (80.3)

*Collected during screening phase.
†Median number of days per week with at least one stool of BSFS type 6 or 7
BSFS, Bristol Stool Form Scale; IBS-SSS, Irritable Bowel Syndrome Severity Scoring System total score; ITT, intention-to-treat.

stool consistency weekly responder was defined as a patient experiencing a ≥50% reduction in the number of days per week with at least one stool that has a consistency of BSFS type 6 or 7 compared with the screening period.

Secondary outcomes of abdominal pain, stool consistency and frequency, bloating, urgency, loperamide use and questionnaire scores were compared between randomised groups and adjusted for baseline values. Adequate relief was defined by a 'yes' response to the question 'With regard your IBS symptoms, compared with the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms'. At week 24 follow-up, the secondary outcomes were maintenance of treatment benefit and use of enterosgel and loperamide.

Randomisation and blinding
Treatment allocation was masked for both participants and investigators in the double-blind phase. Randomisation used a proprietary tool, built into the restricted access web-based eCRF hosted by Sealed Envelope, to generate a unique code. Investigators sent the code to the Sponsor's unblinded supplies coordinator, who checked against the randomisation code list to obtain treatment allocation and shipped unlabelled treatment to the patient's home. The randomisation algorithm was based on the minimisation method where treatment allocation was stratified by site.

Statistical methods
We sought to demonstrate that enterosgel treatment improves stool consistency and reduces abdominal pain in patients with IBS-D. Sample size calculation was based on demonstrating superiority for the primary composite outcome with 90% power at 5% significance level. Assuming a placebo response rate of 20% based on previous studies[24 25] and 35% in the active treatment group, 182 patients per treatment group were required. Assuming 15% drop-out rate, we sought to randomise 430 patients. However, due to fewer participants failing the screening phase towards the end of recruitment, we allowed these patients to continue and recruited 440 participants.

Analysis and presentation of data was in accordance with Consolidated Standards of Reporting Trials guidance, using STATA IC V.15.1. Primary analyses were conducted following the intention-to-treat (ITT) principle with patient outcomes analysed according to their original randomised group irrespective of deviations based on non-compliance. Per-protocol (PP) analyses were also performed, where participants who were ineligible at randomisation, did not take any study treatment or provide any primary outcome measures, were excluded. The primary outcome measure was analysed using both observed data and multiple imputation by chained equations to impute missing daily scores. Missing values were imputed on a weekly basis, with the following variables included in the imputation models: treatment group, baseline measure of the outcome, age and sex. The primary outcome was summarised descriptively by trial arm and the proportions compared using a logistic regression model. Proportions categorised as study period responders for stool consistency and abdominal pain were also compared using logistic regression.

Secondary outcomes were compared between trial arms using either a linear mixed effects model for repeated measures or a mixed effects logistic regression model. Unstructured variance-covariance matrices were used to allow for the anticipated correlation between repeated outcome measurements. For open-label analysis all outcomes were analysed separately for patients receiving placebo or enterosgel in the double-blind phase. Where necessary, multiple imputation was used to impute missing values and conditional logistic regression applied to compare the proportions with the primary outcome in both phases. Proportions categorised as study

Table 2 Analysis of study period responders in double-blind phase (ITT population): the table shows responder rates for composite (primary outcome) and individual stool consistency and abdominal pain

Study period responder	Placebo	Enterosgel	OR (95% CI)*	P value
Primary outcome				
Observed data (excluding weeks with <4 values)	52/214 (24.3)	80/214 (37.4)	1.95 (1.28 to 2.99)	0.0020
Observed data (excluding weeks with <7 values)	37/206 (18.0)	61/204 (29.9)	2.03 (1.26 to 3.25)	0.0035
Stool consistency				
Observed data (excluding weeks with <4 values)	91/214 (42.5)	125/214 (58.4)	1.97 (1.33 to 2.92)	0.0007
Observed data (excluding weeks with <7 values)	67/206 (32.5)	99/204 (48.5)	2.02 (1.34 to 3.05)	0.0007
Abdominal pain				
Observed data (excluding weeks with <4 values)	86/214 (40.2)	114/214 (53.3)	1.80 (1.22 to 2.67)	0.0034
Observed data (excluding)	70/206 (34.0)	94/204 (46.10)	1.76 (1.16 to 2.65)	0.0074

Data are reported as number of patients, proportion (%), and OR (95% CI).
*Adjusted for age and sex.

Table 3 Analysis of the secondary outcomes in double-blind phase (ITT population)

Model	Placebo	Enterosgel	Treatment effect (95% CI)*	P value
Stool consistency (excluding weeks with <4 values)				
Days ≥1 stool of BSFS 6/7 (week 1–8)†	3.16 (1.89)	2.46 (1.82)	−0.58 (−0.87 to −0.28)	0.0001
Days ≥1 stool of BSFS 6/7 (week 1–4)†	3.33 (1.85)	2.70 (1.85)	−0.50 (−0.79 to −0.21)	0.0007
Days ≥1 stool of BSFS 6/7 (week 5–8)†	2.92 (2.13)	2.08 (1.86)	−0.67 (−1.02 to −0.32)	0.0002
Abdominal pain (excluding weeks with <4 values)				
Mean score (week 1–8)	4.02 (1.85)	3.59 (1.84)	−0.35 (−0.62 to −0.09)	0.0086
Mean score (week 5–8)	3.70 (1.99)	3.10 (1.96)	−0.50 (−0.83 to −0.18)	0.0026
Stool consistency (excluding weeks with <7 values)				
Days ≥1 stool of BSFS 6/7 (week 1–8)†	3.14 (1.89)	2.47 (1.83)	−0.53 (−0.82 to −0.24)	0.0004
Days ≥1 stool of BSFS 6/7 (week 1–4)†	3.30 (1.87)	2.65 (1.83)	−0.50 (−0.80 to −0.21)	0.0009
Days ≥1 stool of BSFS 6/7 (week 5–8)†	2.94 (2.16)	1.96 (1.89)	−0.76 (−1.13 to −0.39)	<0.0001
Abdominal pain (excluding weeks with <7 values)				
Mean score (week 1–8)	4.02 (1.85)	3.56 (1.83)	−0.36 (−0.63 to −0.10)	0.0079
Mean score (week 5–8)	3.64 (1.99)	2.93 (1.91)	−0.61 (−0.96 to −0.25)	0.0008
Stool frequency				
Mean no daily stools (week 1–4)	2.96 (2.74–3.18)	2.67 (2.45–2.89)	−0.30 (−0.60 to 0.01)	0.0554
Mean no daily stools (week 5–8)	2.81 (2.59–3.03)	2.47 (2.25–2.69)	−0.35 (−0.66 to 0.04)	0.0251
Bloating				
Mean bloating score (week 1–8)	3.14 (2.95–3.33)	2.73 (2.54–2.92)	−0.42 (−0.69 to 0.15)	0.0021
Mean bloating score (week 5–8)	3.06 (2.86–3.25)	2.50 (2.30–2.69)	−0.57 (−0.85 to 0.29)	<0.0001
Urgency				
Mean urgency score (week 1–8)	3.08 (2.89–3.27)	2.51 (2.32–2.70)	−0.59 (−0.85 to 0.33)	<0.0001
Mean urgency score (week 5–8)	2.99 (2.79–3.19)	2.29 (2.09–2.48)	−0.72 (−0.99 to 0.44)	<0.0001
Adequate relief				
Adequate relief (week 1–8)‡	0.22 (0.16–0.31)	0.56 (0.46–0.65)	4.44 (2.49 to 7.91)	<0.0001
Adequate relief (week 1–4)‡	0.16 (0.10–0.23)	0.45 (0.34–0.56)	4.40 (2.34 to 8.28)	<0.0001
Adequate relief (week 5–8)‡	0.30 (0.21–0.40)	0.69 (0.58–0.77)	5.21 (2.74 to 9.89)	<0.0001
Loperamide use				
Loperamide use (week 1–8)§	1.46 (1.21–1.71)	0.97 (0.73–1.22)	−0.51 (−0.86 to −0.15)	0.0049
Loperamide use (week 5–8)§	1.55 (1.29–1.81)	0.97 (0.72–1.23)	−0.59 (−0.95 to −0.23)	0.0014

Data are reported as mean (SD or range) and treatment effect (95% CI).
*Adjusted for age, sex and the baseline measure of the outcome.
†Mean number of days per week with at least one stool of BSFS type 6 or 7 over.
‡Proportion of patients reporting adequate relief (95% CI).
§Mean number of days per week loperamide used.
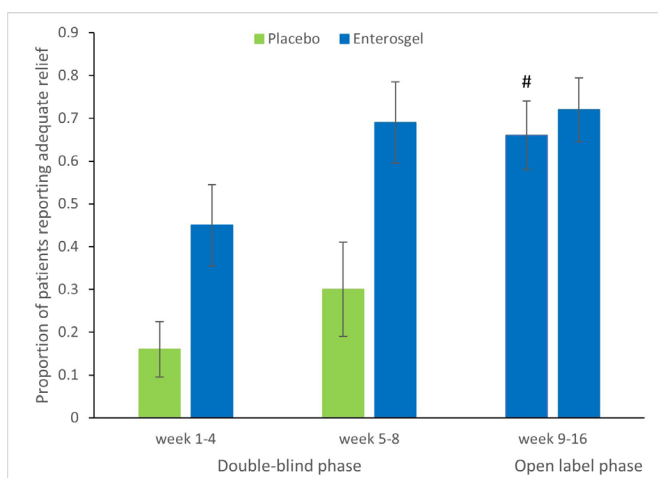BSFS, Bristol Stool Form Scale; ITT, intention-to-treat.

Figure 4 Proportion of patients reporting adequate relief of their symptoms over the double-blind phase (week 1–4 and week 5–8) and open-label phase (week 9–16), for the enterosgel allocated group and placebo allocated group (mean±95% CI). #Allocated placebo in the double-blind phase.

period responders for stool consistency and abdominal pain were also compared between phases using conditional logistic regression. Other secondary outcomes were analysed using equivalent mixed effects models to those implemented in the double-blind phase. All models were adjusted for the baseline measurement of the outcome, patient age and sex. Analysis of the follow-up phase and exploratory outcomes was descriptive only. The safety population included all randomised participants who took at least one dose of the study treatment.

Patient involvement

Patients were involved at all stages of the trial including review of the protocol and trial materials and testing the diaries and questionnaires. A survey of 55 patients from the Chief Investigator's outpatient clinic supported the use of an electronic diary with daily text reminders, and the dosage structure. Patient feedback was instrumental in the overall design, burden of patient reporting, and subsequent virtual trial set up, it was also collected at the 2-week visit and participants were approached for an interview about their experience. On request we included an open-label phase so participants could

Table 4 Adverse events (AEs) during the double-blind phase in the safety population; possibly, probably or definitely related to treatment

Adverse event	Placebo (n=213)	Enterosgel (n=214)
Nausea	8 (3.8%) (1 s, 2 mo, 5 m)*	8 (3.7%) (2 mo, 6 m)
Abdominal pain	4 (1.9%) (2 mo, 2 m)	3 (1.4%) (1 mo, 2 m)
Bloating	3 (1.4%) (2 mo, 1 m)	6 (2.8%) (3 mo, 3 m)
Constipation	2 (0.9%) (1 s, 1 m)	2 (0.9%) (1 s, 1 m)
Headache	2 (0.9%) (2 m)	2 (0.9%) (1 s,1 m)
Dry mouth	2 (0.9%) (1 mo, 1 m)	1 (0.5%) (1 m)
Backpain	0 (0%)	2 (0.9%) (1 s,1 mo)
Loss of appetite	0 (0%)	2 (0.9%) (2 m)

AE listed in descending order of frequency in the placebo group. The AEs listed were reported in two or more cases in either treatment group.
*AE severity; s=severe, mo=moderate, m=mild.

try treatment. We also disseminated the trial results to participants via an interactive webinar.

RESULTS
Study participants
Overall, 617 patients were screened and 440 (71.3%) were randomised (122 at general practitioner and 140 at hospital sites and 170 via virtual site) 1:1 to receive either enterosgel (n=219) or placebo (n=221). In total, 393 (89.3%) participants completed the double-blind phase and were enrolled in the open-label phase, of whom 349 (88.8%) completed the open-label phase, and 265 (75.9%) entered the follow-up phase (figure 3). Primary outcome data were available for 215 participants in the placebo arm and 216 in the enterosgel arm. One patient from the enterosgel arm was excluded from analyses as their screening phase diary data were unusable. Thus, 431 patients were included in the ITT population for the primary endpoint analysis. Two patients in each arm did not take at least one dose of study treatment and were excluded from the safety population (n=427).

Demographics and baseline characteristics of randomised patients in the ITT population were similar between the treatment groups at baseline (table 1). Diary completion and adherence to study treatment were high in both the double-blind and open-label phases and were comparable between treatment groups. Median number of treatment doses taken was two doses in both arms and phases (online supplemental files S1 and S2).

Primary outcome
Following 8 weeks of double-blind treatment, in the ITT population, the percentage of treatment responders was higher in the enterosgel group than the placebo group (table 2). Excluding weeks with data for <4 days, 37.4% of patients in the enterosgel group and 24.3% in the placebo group were classified as responders (Number needed to treat (NNT):8; OR 1.95 (95% CI 1.28 to 2.99, p=0.0020)). Similar results were seen when excluding weeks with data for <7 days, in the multiple imputation analyses, and in the PP population (online supplemental files S3 and S4), indicating that missing data had little impact on results.

Secondary outcomes for double-blind phase
Table 2 shows categorical response rates for stool consistency were higher for the enterosgel than placebo group (58.4% vs 42.5%, NNT 6, OR 1.97). Mean number of days per week with at least one stool of BSFS type 6 or 7 was reduced by the

intervention (2.46 vs 3.16 days) (table 3). The treatment effect for the latter endpoint was larger in magnitude in weeks 4–8 of the 8-week double-blind phase (-0.67 vs −0.50). Similarly, analysis of abdominal pain showed higher response rates in the enterosgel than placebo group (53.3 vs 40.2%, NNT 8, OR 1.80); this was also manifest as lower mean abdominal pain scores (3.59 vs 4.02). The treatment effect for pain score was also larger in magnitude in the later 4 weeks compared with the overall 8 weeks (−0.50 vs −0.35). Similar to the primary outcome, results were consistent when analysed using multiple imputation (online supplemental files S3 and S5).

Statistically significant differences were also found for the other diary-based outcomes of stool frequency, bloating, urgency, and loperamide use, all indicating more improvement in the enterosgel group compared with the placebo group (table 3). Questionnaire data over the 8 weeks showed significant differences for the IBS-SSS questionnaire score (207.29 vs 255.17, treatment effect −37.27, p=0.0002) and the IBS-QOL questionnaire score (60.88 vs 55.24, treatment effect 5.01, p=0.0024), indicating greater improvement in the enterosgel group compared with the placebo, that was also higher for week 5–8, than weeks 1–4 (online supplemental file S6). There was no statistically significant difference in the WPA:IBS questionnaire for work time missed due to IBS symptoms, low statistical significance for impairment while working and overall work impairment, however, activity impairment was significant (p=0.0005), in favour of enterosgel.

Adequate relief of symptoms
The proportion of patients reporting adequate relief over 8 weeks was greater in the enterosgel compared with placebo group (0.56 vs 0.22). Figure 4 shows adequate relief was higher in the enterosgel group for week 5–8 of the double-blind phase (0.69 vs 0.45) and continued to improve further for both groups in the open-label phase (weeks 9–16).

Open-label and follow-up phase outcomes
Following 8 weeks of open-label treatment, 349 patients completed the open-label phase. Comparison with secondary outcome data reported during the double-blind phase confirmed continued treatment effect for the same observed variables (online supplemental files S7–S10). Mean days per week loperamide use fell in the Enterosgel group in contrast to the placebo (week 1: 0.83 vs 1.14, week 8: 0.77 vs 1.47) and continued to fall during open label (week 16: 0.68 vs 0.87), suggesting patients experienced a continued improvement in symptoms.

At the completion of the open-label phase 264 (75.9%) (week 16, figure 2) of patients reported adequate relief of symptoms over the previous 4 weeks and continued into the follow-up phase, representing 60% of all patients that began the trial. 253 patients completed the follow-up phase of whom 186 (74.1%) reported an increased or maintained treatment benefit, with 203 (80.6%) reporting they chose to continue treatment with enterosgel (using left-over supplies from the open-label phase or purchased OTC product). Most patients that continued treatment reported using it on most days (106 (52.2%)) and 133 (53.2%) said they used less loperamide than before the trial (online supplemental file 11).

Safety data
Similar proportions of patients reported at least one AE during the double-blind phase in the placebo group compared with the enterosgel group (24.4% vs 21.0%). AEs considered by the

investigators as possibly, probably or definitely related to treatment were reported by 8.9% in the Placebo group and 7.0% in the enterosgel group (table 4). Total number of AEs was similar (33 enterosgel vs 32 placebo) and there were no clear differences in event terms between the groups. All other AEs, and those reported during the open-label phase, are listed in the online supplemental file 12. There were six serious adverse events reported in five patients, but none were considered related to enterosgel.

DISCUSSION

Despite IBS-D being common and causing much suffering, treatments for this condition are limited, and patient satisfaction with treatment is low.[26] The current trial is the largest to date investigating the efficacy and safety of enterosgel in the treatment of patients with IBS-D and represents the first multicentre, double-blind RCT. In accordance with Food and Drug Administration (FDA) guidance,[14] efficacy was evaluated over an 8-week treatment period. We included further 8-week open-label and follow-up phases to match treatment duration to other IBS-D trials,[27] evaluate any cumulative treatment benefit and for safety assessment.

The study showed that enterosgel significantly improved the composite primary endpoint of abdominal pain and stool consistency, compared with placebo. Analysis was conducted on both observed data and using multiple imputation, though there were no distinguishing differences in outcomes. Treatment effect was lower for abdominal pain alone than for the composite endpoint, or for stool consistency alone, consistent with the hypothesised mode of action in IBS-D, which is the binding and removal of diarrhoea-inducing molecules from the gut. At baseline the mean number of days per week with loose stool was 4.4 days, which fell to 2.1 days for weeks 5–8 in the enterosgel group, that is, more than 50% reduction.

As with many IBS trials,[28] we observed a significant placebo effect (18%–24.5%) in the observed data, although this was comparable to a recent meta-analysis (16.2%) for the same composite endpoint[29] and matched the 20% rate used to estimate sample size.

Significant improvement with enterosgel treatment was also seen in the outcomes of stool frequency, bloating and urgency, compared with the placebo group, as well as in the IBS symptoms, QOL and activity measurements recorded in the IBS-SSS and IBS-QOL questionnaires. The WPA:IBS showed less effect, apart for activity impairment, the COVID-19 pandemic which occurred during ~50% of the trial and working from home may have impacted results. These individual outcomes support the composite primary outcome and suggest that, unlike loperamide, the array of IBS-D symptoms can benefit from this treatment. In the open-label phase, primary and secondary endpoints confirmed that treatment effect was improved further in the treatment allocated arm, and that in the placebo allocated arm significant improvement in endpoints followed the expected response. Being un-blinded, these improvements could represent physiological treatment responses, or represent the power of belief in treatment has on outcome.

The composite primary outcome measure was developed in response to historically high placebo response rates in IBS trials[30] and sets a high threshold. Although this measure succeeds in lowering placebo response, it does not reflect overall patient satisfaction.[29 31] Adequate relief is a binary measure, shown to correlate with multiple endpoints[32] and can provide a valid secondary outcome to support efficacy of IBS therapies.[33] We showed that proportion of adequate relief was considerably higher in the treatment arm in the double-blind phase (0.56) and open-label phase (0.66 and 0.72), than the composite responder rate suggested (37.4%). Adequate relief analysis over the three phases showed there was a progressive benefit over time and suggests that other symptoms such as urgency have a greater impact on QOL. During the follow-up phase, a significant proportion of patients (80.9%) chose to continue with OTC enterosgel after the trial treatment had ended, indicating patients' overall satisfaction and tolerance of the treatment.

Enterosgel exhibited a favourable safety profile, demonstrated by a low percentage of patients with adverse events. This is not surprising as there are over 10 years postmarket surveillance for this treatment in Europe, where it is used in young children and pregnancy, with no adverse event signals.

Limitations

Since eligibility was assessed according to the current Rome IV criteria, the applicability of our findings to the estimated 50% of patients with IBS not matching the Rome IV criteria,[34] including those with milder pain, is not known. We may, however, have mitigated for these patients by recruiting a proportion of cases directly from the community setting and when we reduced the eligibility abdominal pain score at screening to lower screening failures.

Medical device studies commonly lack a placebo arm, although we used a placebo arm, we recognised that even when using the diluted treatment, it was not possible to exactly replicate with an identical placebo. We mitigated for this by excluding any patients with previous enterosgel use, who might recognise a difference, however, it is possible that there has been some un-blinding for patients initially on placebo once they entered the open label phase. We failed to ask patients if they were on treatment or placebo to assess the degree of unblinding.

This was a pragmatic study with flexible treatment instructions in an incremental dosing pattern, to allow participants to find the most appropriate dose to treat their symptoms. Such flexibility hindered our ability to find a set dosage scheme for maximal treatment benefit and as median treatment dose was only two doses per day across the study, this may have prevented patients from taking sufficient treatment to be classified as a responder. At the outset we recognised that this may be a limitation, but we wanted to provide as 'real world' a scenario as possible where patient treatment adherence varies, and IBS symptoms fluctuate over time.

Our primary outcome analysis used multiple imputation for missing diary entries for both stool consistency and abdominal pain. Although this method has been widely adopted to handle missing data[35] it can introduce bias, but it is reassuring that the resulting ORs were comparable to the observed data.

Although we followed FDA guidance with an 8week blinded phase, several recently published IBS-D trials have 12-week treatment durations,[36 37] which could limit comparisons.

CONCLUSION

The results from this study show that enterosgel is safe and effective for treatment of the main IBS-D symptoms, especially urgency which is so incapacitating. Although the primary action is on stool consistency, it provides benefit to global symptoms and improvement in QOL and potentially provides a valid alternative to the few treatment options currently available for patients with this condition.

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