Supplementary data.

METHODS

Participants

To be eligible for randomisation, patients were required to have completed the daily diary on at least 11 of 14 days (≥75%) during the screening period. Exclusion criteria were loose stools (BSFS 6 or 7) on less than 3 days during screening period, and average abdominal pain <2.5 during the 14-day screening period. This was amended from an initial average abdominal pain score of <3, in response to the relatively high numbers of patients failing this criterion.

Trial management

A trial management group was set up to manage the trial from design to implementation. The group held regular meetings to monitor trial progress and to decide on any other management issues. A trial steering committee (TSC) was also set up to provide scientific advice during protocol development and throughout the trial. An Independent Data Monitoring Committee held two meetings during the trial to review blinded safety and efficacy data.

Multiple imputation

The number of weeks requiring at least one missing value of abdominal pain or stool consistency to be imputed were;

- Placebo = 462/1,720 (26.9%)
- Enterosgel = 489/1,728 (28.3%)

For weeks that required at least one missing value of abdominal pain or stool consistency to be imputed, the average number of missing values was:

- Placebo (median and interquartile range) = 4 (2 to 6)
- Enterosgel (median and interquartile range) = 6 (4 to 8)

The maximum permissible number of missing values within a week was 14 (7 for abdominal pain and 7 for stool consistency).

Table S1. Diary completion and adherence to study treatment during double-blind phase

	Placebo (n=221)		**Enterosgel (n=219**	
Number of days patient diary was completed	55	(47 to 56)	54	(48 to 56)
Number of days study treatment was used	50	(42 to 53)	49	(41 to 52)
Number of days that doses of study treatment were used, n (%)				
0 doses	283	(2.8)	546	(5.5)
1 dose	1137	(11.3)	1849	(18.5)
2 doses	3972	(39.5)	4535	(45.4)
3 doses	1487	(14.8)	1016	(10.2)
4 doses	2535	(25.2)	1616	(16.2)
5 doses	90	(0.9)	94	(0.9)
6 doses	543	(5.4)	338	(3.4)
7+ doses	13	(0.1)	6	(0.1)

Data are reported as Median (IQR) and range, out of 56-day double-blind phase

Table S2. Diary completion and adherence to study treatment during open-label phase

	Placebo (n=221)		**Enterosgel (n=219**	
Number of days patient diary was completed	52	(39 to 56)	51	(40 to 56)
Number of days study treatment was used	49	(32 to 53)	47	(33 to 53)
Number of days that doses of study treatment were used, n (%)				
0 doses	406	(4.5)	470	(5.3)
1 dose	1755	(19.3)	1978	(22.2)
2 doses	4231	(46.4)	3900	(43.8)
3 doses	1078	(11.8)	819	(9.2)
4 doses	1136	(12.5)	1356	(15.2)
5 doses	61	(0.7)	139	(1.6)
6 doses	418	(4.6)	244	(2.7)
7+ doses	28	(0.3)	6	(0.1)

Data are reported as Median (IQR) and range, out of 56-day double-blind phase

Table S3. Analysis of study period responders in double-blind phase (ITT population) by multiple imputation: the table shows responder rates for composite (primary outcome) and individual stool consistency and abdominal pain.

Study period responder	Placebo	Enterosgel	Odds ratio (95%CI)*	p value
Primary outcome	n=215	n=216	1.89 (1.21-2.97)	0.0054
Primary outcome (excluding Weeks with <4 values)	n=214	n=214	1.94 (1.25-3.00)	0.0030
Stool consistency				
All weeks	n=215	n=216	2.0 (1.31 to 3.06)	0.0014
Excluding Weeks with <4 values	n = 214	n = 214	1.93 (1.30 to 2.85)	0.0011
Abdominal pain				
All weeks	n=215	n=216	1.62 (1.08 to 2.45)	0.0207
Excluding Weeks with <7 values	n = 214	n = 214	1.72 (1.16 to 2.56)	0.0074

Data are reported as number of patients, and odds ratio (range)
*Adjusted for age and sex

Table S4. Analysis of the primary outcome in double-blind phase (PP population)

Study period responder	Placebo	Enterosgel	Odds ratio (95%CI)*	p value
Observed data (excluding Weeks with <4 values)	52/212 (24.5)	80/208 (38.5)	2.02 (1.32 to 3.10)	0.00129
Observed data (excluding Weeks with <7 values)	37/206 (18.0)	61/199 (30.7)	2.11 (1.31 to 3.39)	0.00216
Multiple imputation	n=212	n=208	1.96 (1.25 to 3.07)	0.00340
Multiple imputation (excluding Weeks with <4 values)	n=212	n=208	2.00 (1.29 to 3.10)	0.00198

Data are reported as number of patients, proportion (%), and odds ratio (range)
*Adjusted for age and sex

Table S5. Analysis of the stool consistency and abdominal pain in double-blind phase (ITT population) by multiple imputation

Model	Placebo	Enterosgel	Treatment effect (95%CI)*	p value
Stool consistency				
Days ≥ 1 stool of BSFS 6/7 (week 1-4)#	n=215	n=216	-0.52 (-0.79 to -0.25)	0.0002
Days ≥ 1 stool of BSFS 6/7 (week 5-8)ǂ	n=215	n=216	-0.68 (-1.00 to -0.36)	<0.0001
Abdominal pain				
Mean score (week 1-8)	n=215	n=216	-0.38 (-0.63 to -0.13)	0.0027
Mean score (week 5-8)	n=215	n=216	-0.51 (-0.81 to -0.20)	0.0011
Stool consistency (excluding weeks with <4 values)				
Days ≥ 1 stool of BSFS 6/7 (week 1-4)#	n = 214	n = 214	-0.50 (-0.79 to -0.21)	0.00079
Days ≥ 1 stool of BSFS 6/7 (week 5-8)ǂ	n = 198	n = 198	-0.67 (-1.01 to -0.33)	0.00014
Abdominal pain (excluding weeks with <4 values)				
Mean score (week 1-8)	n = 214	n = 214	-0.35 (-0.62 to -0.09)	0.00835
Mean score (week 5-8)	n = 198	n = 198	-0.49 (-0.82 to -0.17)	0.00314

Data are reported as mean (SD) and treatment effect (mean days, mean pain score)

* Adjusted for age, sex, and the baseline measure of the outcome

ǂ Mean number of days per week with at least one stool of BSFS type 6 or 7 over

Table S6. Analysis of the secondary questionnaire outcomes in double-blind phase (ITT population)

Model	Placebo	Enterosgel	Treatment effect (95%CI)*	p value
IBS-SSS				
Total score over 8 weeks	255.17 (239.60 to 270.74)	207.29 (191.64 to 222.94)	-37.27 (-57.08 to -17.46)	0.00023
Total score during weeks 1-4	270.26 (254.27 to 286.24)	231.40 (215.33 to 247.47)	-28.63 (-49.09 to -8.17)	0.00610
Total score during weeks 5-8	240.84 (224.90 to 256.78)	184.49 (168.47 to 200.51)	-45.69 (-66.08 to -25.30)	0.00001
IBS-QoL				
Total score over 8 weeks	55.24 (52.02 to 58.47)	60.88 (57.64 to 64.12)	5.01 (1.78 to 8.24)	0.00238
Total score during weeks 1-4	52.14 (48.72 to 55.56)	56.41 (52.95 to 59.86)	3.60 (-0.03 to 7.22)	0.05162
Total score during weeks 5-8	57.67 (54.33 to 61.02)	64.00 (60.65 to 67.35)	5.77 (2.30 to 9.23)	0.00110
PHQ-12 SS				

Mean total score over 8 weeks	6.68 (6.16 to 7.20)	6.54 (6.02 to 7.07)	-0.19 (-0.74 to 0.37)	0.51295
Mean total score at week 4	7.19 (6.62 to 7.76)	7.18 (6.60 to 7.75)	-0.08 (-0.72 to 0.56)	0.80618
Mean total score at week 8	6.28 (5.73 to 6.83)	6.11 (5.56 to 6.66)	-0.21 (-0.82 to 0.39)	0.48872
Mean headache score over 8 weeks	0.72 (0.63 to 0.81)	0.75 (0.66 to 0.84)	0.01 (-0.09 to 0.12)	0.79332
Mean headache score at week 4	0.79 (0.68 to 0.89)	0.80 (0.69 to 0.91)	0.00 (-0.13 to 0.13)	0.97179
Mean headache score at week 8	0.67 (0.57 to 0.76)	0.71 (0.61 to 0.81)	0.03 (-0.09 to 0.15)	0.62198
Mean tiredness score over 8 weeks	1.28 (1.19 to 1.37)	1.28 (1.19 to 1.37)	-0.01 (-0.12 to 0.10)	0.83306
Mean tiredness score at week 4	1.37 (1.27 to 1.47)	1.44 (1.34 to 1.55)	0.05 (-0.08 to 0.18)	0.46297
Mean tiredness score at week 8	1.20 (1.10 to 1.30)	1.16 (1.06 to 1.26)	-0.05 (-0.17 to 0.07)	0.43875
Mean sleep score over 8 weeks	1.10 (1.00 to 1.20)	1.07 (0.97 to 1.17)	-0.06 (-0.18 to 0.06)	0.31410
Mean sleep score at week 4	1.20 (1.08 to 1.31)	1.16 (1.05 to 1.28)	-0.06 (-0.21 to 0.08)	0.39173
Mean sleep score at week 8	1.02 (0.91 to 1.13)	1.00 (0.89 to 1.11)	-0.05 (-0.19 to 0.08)	0.44957
WPA:IBS				
Mean % of work time missed due to IBS symptoms over 8 weeks	3.82 (2.02 to 5.61)	2.86 (1.01 to 4.71)	-1.50 (-3.90 to 0.90)	0.22123
Mean % impairment while working due to IBS symptoms over 8 weeks	35.66 (31.78 to 39.54)	29.98 (25.99 to 33.97)	-5.51 (-10.72 to -0.30)	0.03813
Mean % overall work impairment due to IBS over 8 weeks	36.72 (32.74 to 40.70)	30.97 (26.88 to 35.07)	-5.38 (-10.69 to -0.06)	0.04752
Mean % activity impairment due to IBS symptoms over 8 weeks	41.30 (37.75 to 44.84)	34.80 (31.25 to 38.35)	-7.42 (-11.61 to -3.24)	0.00051

Data are reported as Mean (SD) or treatment effect (range)

* Adjusted for age, sex, and (for continuous outcomes) the baseline measure of the outcome

ǂ Proportion of patients reporting adequate relief (range)

^ Mean number of days per week loperamide used

Table S7. Analysis of study period responders in open-label phase (ITT population): the table shows responder rates for composite (primary outcome) and individual stool consistency and abdominal pain.

Study period responder	Open-label phase	Odds ratio (95%CI)*	p value
Randomised to placebo			
Primary outcome observed data (excluding Weeks with <7 values)	68/175 (38.9)	4.56 (2.21-9.37)	<0.0001
Stool consistency observed data (excluding weeks with <7 values)	94/175 (53.7)	3.80 (1.89 to 7.63)	0.0002
Abdominal pain observed data (excluding weeks with <7 values)	87/175 (49.7)	2.38 (1.25 to 4.56)	0.0085
Randomised to Enterosgel			
Primary outcome observed data (excluding Weeks with <7 values)	72/173 (41.6)	2.00 (1.03-3.89)	0.0413
Stool consistency observed data (excluding weeks with <7 values)	88/173 (50.9)	0.68 (0.35 to 1.31)	0.25271
Abdominal pain observed data (excluding weeks with <7 values)	98/173 (56.6)	1.35 (0.72 to 2.53)	0.34462

Data are reported as number of patients, proportion (%), and odds ratio (range)
*Odds ratio for the open-label phase versus the double-blind phase

Table S8. Analysis of the stool consistency and abdominal pain in open label phase (ITT population) by multiple imputation

Model	Placebo	Odds Ratio (95%CI)*	p value	Enterosgel	Odds Ratio (95%CI)*	p value
Stool consistency						
Study period responder	n = 196	9.18 (3.81 to 22.13)	<0.00001	n = 188	2.04 (1.04 to 4.00)	0.03786
Abdominal pain						
Study period responder	n=196	7.40 (2.92 to 18.76)	0.00003	n = 188	4.34 (2.07 to 9.13)	0.00012

Data are reported as number of patients, and odds ratio (range)
* Effect for the open-label phase versus the double-blind phase;

Table S9. Analysis of the secondary outcomes in open label phase

Model	Placebo allocation	Time effect (95%CI)*	p value	Enterosgel allocation	Time effect (95%CI)*	p value
Stool consistency						
Days ≥ 1 stool of BSFS 6/7 (week 1-8)ǂ	1.85 (1.63 to 2.07)	-1.04 (-1.14 to -0.93)	<0.00001	1.78 (1.57 to 1.99)	-0.42 (-0.52 to -0.32)	<0.00001
Abdominal pain						
Mean score (week 1-8)	3.17 (2.92 to 3.41)	-0.86 (-0.91 to -0.81)	<0.00001	2.84 (2.59 to 3.08)	-0.76 (-0.81 to -0.71)	<0.00001
Stool frequency						
Mean number daily stools (week 1-8)	2.48 (2.26 to 2.70)	-0.41 (-0.46 to -0.37)	<0.00001	2.34 (2.16 to 2.52)	-0.24 (-0.28 to -0.20)	<0.00001
Bloating						
Mean bloating score (week 1-8)	2.50 (2.30 to 2.69)	-0.65 (-0.73 to -0.56)	<0.00001	2.31 (2.12 to 2.50)	-0.42 (-0.51 to -0.34)	<0.00001
Urgency						
Mean urgency score (week 1-8)	2.29 (2.10 to 2.47)	-0.81 (-0.89 to -0.72)	<0.00001	2.18 (2.00 to 2.37)	-0.33 (-0.41 to -0.24)	<0.00001
Adequate relief						
Proportion (week 1-8) #	0.66 (0.57 to 0.73)	5.43 (4.35 to 6.78)	<0.00001	0.72 (0.64 to 0.79)	2.11 (1.70 to 2.63)	<0.00001
Loperamide use						
Mean number of days (week 1-8)^	1.11 (0.84 to 1.37)	-0.35 (-0.44 to -0.27)	<0.00001	0.91 (0.70 to 1.13)	-0.06 (-0.14 to 0.02)	0.1204

Data are reported as Mean (range) and time effect (95% CI)

* Effect for the open-label phase versus the double-blind phase separated into treatment allocation in double-blind phase, adjusted for age, sex, and (where possible, for continuous outcomes) the baseline measure of the outcome

ǂ Mean number of days per week with at least one stool of BSFS type 6 or 7 over

Proportion of patients reporting adequate relief (range)

^ Mean number of days per week loperamide used

Table S10. Analysis of the secondary questionnaire outcomes in open-label phase (ITT population)

Model	Placebo allocation	Time effect (95%CI)*	p value	Enterosgel allocation	Time effect (95%CI)*	p value
IBS-SSS						
Total score over 8 weeks	186.65 (171.00 to 202.30)	-67.38 (-73.62 to -61.14)	<0.00001	164.71 (149.78 to 179.65)	-43.82 (-49.76 to -37.87)	<0.00001
IBS-QoL						
Total score over 8 weeks	65.06 (61.93 to 68.19)	9.68 (7.99 to 11.37)	<0.00001	68.69 (65.41 to 71.97)	7.69 (5.94 to 9.45)	<0.00001
PHQ-12 SS						
Mean total score over 8 weeks	5.94 (5.41 to 6.47)	-0.74 (-1.07 to -0.40)	0.00002	5.79 (5.25 to 6.33)	-0.76 (-1.07 to -0.46)	<0.00001
Mean headache score over 8 weeks	0.67 (0.58 to 0.76)	-0.05 (-0.13 to 0.03)	0.19111	0.69 (0.59 to 0.78)	-0.06 (-0.13 to 0.01)	0.09232
Mean tiredness score over 8 weeks	1.11 (1.02 to 1.20)	-0.17 (-0.25 to -0.10)	0.00001	1.23 (1.13 to 1.32)	-0.05 (-0.13 to 0.02)	0.17102
Mean sleep score over 8 weeks	0.99 (0.89 to 1.09)	-0.11 (-0.19 to -0.03)	0.00783	1.05 (0.94 to 1.15)	-0.02 (-0.09 to 0.06)	0.65376
WPA:IBS						
Mean % of work time missed due to IBS symptoms over 8 weeks	2.87 (1.09 to 4.65)	-0.94 (-1.88 to -0.00)	0.04885	1.54 (0.26 to 2.82)	-1.54 (-2.56 to -0.52)	0.00306
Mean % impairment while working due to IBS symptoms over 8 weeks	27.57 (23.77 to 31.37)	-8.51 (-10.19 to -6.82)	<0.00001	23.57 (19.79 to 27.35)	-6.95 (-8.58 to -5.32)	<0.00001
Mean % overall work impairment due to IBS over 8 weeks	28.32 (24.44 to 32.20)	-8.79 (-10.52 to -7.06)	<0.00001	24.13 (20.26 to 28.00)	-7.53 (-9.25 to -5.82)	<0.00001
Mean % activity impairment due to IBS symptoms over 8 weeks	31.34 (27.85 to 34.83)	-9.98 (-11.30 to -8.65)	<0.00001	27.57 (24.19 to 30.94)	-7.63 (-8.94 to -6.31)	<0.00001

Data are reported as Mean (range) and time effect (95% CI)

* Effect for the open-label phase versus the double-blind phase separated into treatment allocation in double-blind phase, adjusted for age, sex, and (where possible, for continuous outcomes) the baseline measure of the outcome

Table S11. Outcomes during the follow-up phase.

Outcomes assessed during follow-up phase (ITT population)	N, % (95% CI)
Number of patients reporting adequate relief at the start of the follow-up phase	264/348 75.9%
Percentage of patients who report an increased or maintained	186/251 74.1% (68.3 to 79.2)

treatment benefit at 8 weeks			
Percentage of patients who report having used Enterosgel in the last 8 weeks	203/252	80.6%	(75.2 to 85.0)
Frequency of use of Enterosgel in the last 8 weeks			
Occasionally	52/203	25.6%	(20.1 to 32.1)
1-2 days per week	22/203	10.8%	(7.2 to 15.9)
2-3 days per week	23/203	11.3%	(7.6 to 16.5)
Most days	106/203	52.2%	(45.3 to 59.0)
Percentage of patients who report having used less Loperamide in the last 8 weeks than before the trial	133/250	53.2%	(47.0 to 59.3)

Table S12. Adverse Events during the double-blind and open label phase in the safety population; possibly, probably or definitely related to treatment

Adverse event term	**Placebo***	**Enterosgel***	**Open label**
Nausea	8	8	0
abdominal pain	4	3	4
bloating	3	6	3
flatulence	0	1	3
Constipation	2	2	2
dry mouth	2	1	0
backpain	0	2	1
loss of appetite	0	2	0
headache	2	2	0
upset stomach/indigestion	0	0	2
burning sensation in throat	1	0	0
diarrhoea and vomiting	1	0	1
increased frequency of defecation	0	1	1
vomiting symptom	0	1	1
diarrhoea	1	0	0
faeces colour: yellow	1	0	0
haemorrhoidal bleeding due to constipation	1	0	0
heartburn	1	0	0

increased frequency of defecation	1	0	0
perianal bleeding	1	0	0
right flank pain	1	0	0
suicidal thoughts	1	0	0
thirst post dosing	1	0	0
cough	0	1	0
lethargy	0	1	0
nocturnal diarrhoea	0	1	0
sensation of incomplete emptying of bowel	0	1	0
heartburn	0	0	1
faecal urgency	0	0	1

Data presented is for AE terms that are possibly, probably or definitely related to treatment.
*Double-blind phase