Clinical trial results:
A Phase 2 Randomised, Double Blind, Placebo Controlled, Parallel Group, Multicentre Study to Evaluate the Safety and Efficacy of Repeated Oral Doses of Blautix™ in Adult Subjects with Irritable Bowel Syndrome (IBS) Subtypes IBS-C and IBS-D

Summary

EudraCT number	2018-001203-36
Trial protocol	IE GB PL
Global end of trial date	13 May 2020

Results information

Result version number	v1 (current)
This version publication date	24 September 2021
First version publication date	24 September 2021

Trial information

Trial identification

Sponsor protocol code	BHT-II-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03721107
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	4D Pharma Plc
Sponsor organisation address	9 Bond Court, Leeds, United Kingdom, LS1 2JZ
Public contact	Clinical Trials Department, 4D Pharma Plc, 44 0113895 0130, clinicaltrials@4dpharmaplc.com
Scientific contact	Clinical Trials Department, 4D Pharma Plc, 44 0113895 0130, clinicaltrials@4dpharmaplc.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the efficacy of repeated twice daily doses of Blautix > 1*10^10 most probable number (MPN) for 8 weeks in adult subjects with either IBS-C (Cohort C) or IBS-D (Cohort D).

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice (GCP) as required by Food and Drug Administration (FDA) regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and standard operating procedures (SOPs) for clinical investigation and documentation provided by the sponsor, Parexel and Synteract. Compliance with these requirements also indicates conformity with the ethical principles that have their origins in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 122
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	United States: 237
Worldwide total number of subjects	366
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	335
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 366 subjects were randomised across 30 study centers in Ireland, United Kingdom, and United States between 11 October 2018 (first subject enrolled) and 13 May 2020 (last subject completed study).

Pre-assignment

Screening details:

Subjects who met the eligibility criteria were randomised to receive Blautix or Placebo in either Cohort C or Cohort D depending on classification of IBS subtype by the study doctor.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort C: Blautix

Arm description:

Subjects diagnosed with Irritable Bowel Syndrome Subtype-C (IBS-C) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of Blautia hydrogenotrophica) was 10^10 to 10^11 most probable number (MPN).

Arm type	Experimental
Investigational medicinal product name	Blautix
Investigational medicinal product code	MRx1234
Other name	Blautia hydrogenotrophica, DSMZ nº14294
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects diagnosed with IBS-C received two capsules of Blautix orally, twice daily for 8 weeks.

Arm title	Cohort C: Placebo

Arm description:

Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

Arm title	Cohort D: Blautix

Arm description:

Subjects diagnosed with Irritable Bowel Syndrome Subtype-D (IBS-D) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of Blautia hydrogenotrophica) was 10^10 to 10^11 MPN.

Arm type	Experimental

Investigational medicinal product name	Blautix
Investigational medicinal product code	MRx1234
Other name	Blautia hydrogenotrophica, DSMZ nº14294
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects diagnosed with IBS-D received two capsules of Blautix orally, twice daily for 8 weeks.

Arm title	Cohort D: Placebo

Arm description:

Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

Number of subjects in period 1[1]	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix
Started	80	84	97
Completed	75	81	83
Not completed	5	3	14
Consent withdrawn by subject	1	1	5
Physician decision	-	1	-
Adverse event, non-fatal	1	1	6
Unspecified	1	-	-
Lost to follow-up	2	-	3
Inclusion/Exclusion Criteria not Met	-	-	-

Number of subjects in period 1[1]	Cohort D: Placebo
Started	104
Completed	92
Not completed	12
Consent withdrawn by subject	5
Physician decision	-
Adverse event, non-fatal	5
Unspecified	1
Lost to follow-up	-
Inclusion/Exclusion Criteria not Met	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 366 subjects were enrolled, out of which 365 subjects were treated and presented in subject disposition and baseline characteristics.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort C: Blautix
Reporting group description:	
Subjects diagnosed with Irritable Bowel Syndrome Subtype-C (IBS-C) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of Blautia hydrogenotrophica) was 10^10 to 10^11 most probable number (MPN).	
Reporting group title	Cohort C: Placebo
Reporting group description:	
Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.	
Reporting group title	Cohort D: Blautix
Reporting group description:	
Subjects diagnosed with Irritable Bowel Syndrome Subtype-D (IBS-D) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of Blautia hydrogenotrophica) was 10^10 to 10^11 MPN.	
Reporting group title	Cohort D: Placebo
Reporting group description:	
Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.	

Reporting group values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix
Number of subjects	80	84	97
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	44.6	45.3	43.1
standard deviation	± 13.04	± 13.41	± 13.65
Gender categorical Units: Subjects			
Female	67	69	60
Male	13	15	37
Ethnicity Units: Subjects			
Hispanic or Latino	20	21	10
Not Hispanic or Latino	60	63	87
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	2
Asian	1	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	30	33	7
White	48	50	86
More than one race	0	0	0
Unknown or Not Reported	1	1	0

Reporting group values	Cohort D: Placebo	Total	
Number of subjects	104	365	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	44.9		
standard deviation	± 14.40	-	
Gender categorical Units: Subjects			
Female	73	269	
Male	31	96	
Ethnicity Units: Subjects			
Hispanic or Latino	10	61	
Not Hispanic or Latino	94	304	
Unknown or Not Reported	0	0	
Race Units: Subjects			
American Indian or Alaska Native	0	2	
Asian	1	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	11	81	
White	90	274	
More than one race	1	1	
Unknown or Not Reported	1	3	

End points

End points reporting groups

Reporting group title	Cohort C: Blautix
Reporting group description:	
Subjects diagnosed with Irritable Bowel Syndrome Subtype-C (IBS-C) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of Blautia hydrogenotrophica) was 10^10 to 10^11 most probable number (MPN).	
Reporting group title	Cohort C: Placebo
Reporting group description:	
Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.	
Reporting group title	Cohort D: Blautix
Reporting group description:	
Subjects diagnosed with Irritable Bowel Syndrome Subtype-D (IBS-D) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of Blautia hydrogenotrophica) was 10^10 to 10^11 MPN.	
Reporting group title	Cohort D: Placebo
Reporting group description:	
Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.	

Primary: Percentage of Subjects With Overall Response

End point title	Percentage of Subjects With Overall Response
End point description:	
Overall responder was a subject who has at least 7 evaluable weeks of data and has reported an improvement in their weekly symptoms (abdominal pain intensity [API] and stool frequency [SF] or consistency [SC]) for greater than or equal to (>=) 50 percent (%) of the treatment period. API: decrease in weekly average of worst abdominal pain in the past 24 hours score of at least 30% compared with baseline for Cohort C and D; SF: increase of 1 or more CSBM per week compared with baseline for Cohort C; SC: decrease at least 50% in the proportion of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline for Cohort D. Subjects with <4 weeks available were considered non-responders. Full Analysis Set (FAS): all subjects in the safety analysis set who were appropriately randomized into the study. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline up to Week 8	

End point values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix	Cohort D: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	82	94	101
Units: Percentage of subjects				
number (not applicable)	25.0	17.1	23.4	17.8

Statistical analyses

Statistical analysis title	Cohort C: Blautix, Cohort C: Placebo
Comparison groups	Cohort C: Placebo v Cohort C: Blautix
Number of subjects included in analysis	158
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.152 [1]
Method	Chi-squared corrected
Parameter estimate	Difference in Percentage
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	21.9

Notes:

[1] - P-value is from a 1-sided Pearson chi-square test with Yates' correction with null hypothesis that the difference in proportions Blautix – placebo <=0 versus the difference is >0. The significance level for rejection of the null hypotheses is 0.10.

Statistical analysis title	Cohort D: Blautix, Cohort D: Placebo
Comparison groups	Cohort D: Blautix v Cohort D: Placebo
Number of subjects included in analysis	195
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.216 [2]
Method	Chi-squared corrected
Parameter estimate	Difference in Percentage
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	18

Notes:

[2] - P-value is from a 1-sided Pearson chi-square test with Yates' correction with null hypothesis that the difference in proportions Blautix - placebo <=0 versus the difference is >0. The significance level for rejection of the null hypotheses is 0.10.

Secondary: Number of Subjects With Treatment-Related Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Related Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject administered study medication and which does not necessarily have a causal relationship with this treatment. TEAE was defined as an AE that started or worsened in severity on or after the start date of the study treatment and includes all AEs recorded through the follow-up visit. A treatment-related TEAE is a TEAE possibly related to the study treatment. Safety analysis set (SAF) included all subjects randomised into the study who received at least one dose of Blautix or Placebo.

End point type	Secondary

End point timeframe:

Baseline up to follow-up visit (up to Week 14)

End point values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix	Cohort D: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	84	97	104
Units: Subjects	5	4	16	14

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Response to Subject Global Assessment of Relief

End point title	Number of Subjects With Response to Subject Global Assessment of Relief

End point description:

The Subject Global Assessment of Relief was collected weekly through the electronic clinical outcome assessment (eCOA) system. It was a comparison of how the subject has felt over the past week with regards to their IBS to the way they felt before entering the study. It was measured on a 5-point Likert scale with the following responses: Completely relieved; considerably relieved; somewhat relieved; unchanged; worse. The total score ranged from 0-20, where higher scores indicated worsening of condition. FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 1, 4, 8, follow-up visit (Week 12, 13 and 14)

End point values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix	Cohort D: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	70	84	86
Units: Subjects				
Week 1: Completely Relieved	0	2	2	0
Week 1: Considerably Relieved	1	3	1	0
Week 1: Somewhat Relieved	6	6	3	8
Week 1: Unchanged	58	56	72	76
Week 1: Worse	1	3	6	2
Week 4: Completely Relieved	1	1	2	1
Week 4: Considerably Relieved	13	7	13	14
Week 4: Somewhat Relieved	31	31	26	24
Week 4: Unchanged	17	19	28	28
Week 4: Worse	1	5	4	4
Week 8: Completely Relieved	2	3	5	3
Week 8: Considerably Relieved	20	13	14	16
Week 8: Somewhat Relieved	24	23	22	26
Week 8: Unchanged	18	19	21	20

Week 8: Worse	1	2	6	5
Week 12: Completely Relieved	5	5	5	2
Week 12: Considerably Relieved	6	11	10	5
Week 12: Somewhat Relieved	13	17	14	16
Week 12: Unchanged	14	16	19	24
Week 12: Worse	2	3	2	5
Week 13: Completely Relieved	4	4	4	3
Week 13: Considerably Relieved	9	12	4	3
Week 13: Somewhat Relieved	12	9	12	14
Week 13: Unchanged	7	12	15	18
Week 13: Worse	1	4	5	4
Week 14: Completely Relieved	2	0	0	1
Week 14: Considerably Relieved	2	2	0	1
Week 14: Somewhat Relieved	2	1	3	1
Week 14: Unchanged	0	5	8	4
Week 14: Worse	0	0	0	3

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Stool Consistency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14)

End point title	Change From Baseline in Stool Consistency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14)

End point description:

Stool consistency of each bowel movement was assessed by subjects using the 7-point BSFS from 1 to 7 where Type 1 = separate hard lumps, like nuts (hard to pass), Type 2 = sausage-shaped but lumpy, Type 3 = like a sausage but with cracks on the surface, Type 4 = like a sausage or snake, smooth and soft, Type 5 = soft blobs with clear-cut edges (passed easily), Type 6 = fluffy pieces with ragged edges, a mushy stool, Type 7 = watery, no solid pieces; entirely liquid. A score of 1 or 2 indicates constipation and a score of 6 or 7 indicates diarrhea. FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n=number analysed" signifies subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 4, 8, follow-up visit (Week 12, 13 and 14)

End point values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix	Cohort D: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64	73	83	94
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Change at Week 1 (n=64, 73, 83, 94)	0.13 (± 22.859)	3.38 (± 24.412)	-25.67 (± 28.078)	-23.70 (± 30.730)
Change at Week 4 (n=57, 63, 74, 76)	-4.23 (± 24.470)	-1.99 (± 24.077)	-32.43 (± 33.627)	-33.73 (± 33.615)

Change at Week 8 (n=53, 56, 67, 70)	-5.93 (± 26.705)	-0.10 (± 22.852)	-40.36 (± 37.595)	-36.91 (± 35.753)
Change at Week 12 (n=33, 46, 51, 57)	-5.66 (± 23.063)	1.06 (± 27.027)	-34.09 (± 41.128)	-42.13 (± 31.500)
Change at Week 13 (n=7, 15, 17, 25)	10.88 (± 26.517)	-5.16 (± 19.868)	-29.38 (± 35.002)	-32.21 (± 39.679)
Change at Week 14 (n=2, 2, 4, 6)	-15.48 (± 1.684)	-2.98 (± 15.994)	-40.00 (± 36.216)	-38.10 (± 36.608)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Stool Consistency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14)

End point title	Percent Change From Baseline in Stool Consistency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14)

End point description:

Stool consistency of each bowel movement was assessed by subjects using the 7-point BSFS from 1 to 7 where Type 1 = separate hard lumps, like nuts (hard to pass), Type 2 = sausage-shaped but lumpy, Type 3 = like a sausage but with cracks on the surface, Type 4 = like a sausage or snake, smooth and soft, Type 5 = soft blobs with clear-cut edges (passed easily), Type 6 = fluffy pieces with ragged edges, a mushy stool, Type 7 = watery, no solid pieces; entirely liquid. A score of 1 or 2 indicates constipation and a score of 6 or 7 indicates diarrhea. Lower numbers represented more formed stools and higher numbers represented less formed stools. FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n=number analysed" signifies subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 4, 8, follow-up visit (Week 12, 13 and 14)

End point values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix	Cohort D: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	70	83	94
Units: Percent Change				
arithmetic mean (standard deviation)				
Percent Change at Week 1 (n=63, 70, 83, 94)	15.05 (± 126.940)	27.65 (± 129.217)	-32.30 (± 36.887)	-27.27 (± 38.590)
Percent Change at Week 4 (n=57, 61, 74, 76)	-6.36 (± 122.165)	-7.18 (± 112.425)	-40.14 (± 42.757)	-40.60 (± 40.128)
Percent Change at Week 8 (n=52, 54, 67, 70)	-12.00 (± 145.174)	-4.64 (± 103.202)	-49.32 (± 45.798)	-42.64 (± 39.801)
Percent Change at Week 12 (n=33, 44, 51, 57)	-7.45 (± 125.537)	14.75 (± 144.064)	-36.96 (± 50.023)	-49.94 (± 34.638)
Percent Change at Week 13 (n=7, 14, 17, 25)	41.07 (± 143.017)	-40.31 (± 89.914)	-33.29 (± 40.067)	-35.91 (± 44.635)
Percent Change at Week 14 (n=2, 2, 4, 6)	-100.00 (± 0.000)	-25.00 (± 106.066)	-52.50 (± 49.319)	-43.53 (± 44.353)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Average Stool Frequency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14)

End point title	Change From Baseline in Weekly Average Stool Frequency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14)

End point description:

Stool frequency was defined as a sum of weekly CSBMs. Stool types were assessed using the 7-point BSFS where 1 = separate hard lumps, like nuts, 2 = sausage-shaped but lumpy, 3 = like a sausage but with cracks on the surface, 4 = like a sausage or snake, smooth and soft, 5 = soft blobs with clear-cut edges, 6 = fluffy pieces with ragged edges, a mushy stool, 7 = watery, no solid pieces; entirely liquid. Score of 1 or 2 indicates constipation and 6 or 7 indicates diarrhea. Weekly stool frequency based on the daily stool frequency (DSF) which was calculated as follows: if there was 1 or more entry for BSC, the number of BSC entries was summed up. If on that day laxative was used, daily stool frequency was set to 0. If an answer to CSBMs, but no BSC entry was provided, the DSF was set to 0 on that day. FAS Analysis. "Number of subjects analysed" signifies subjects were evaluable for this endpoint; "n=number analysed" signifies subjects were evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 4, 8, follow-up visit (Week 12, 13 and 14)

End point values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix	Cohort D: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64	73	83	94
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Change at Week 1 (n=64, 73, 83, 94)	1.33 (± 2.202)	1.61 (± 2.416)	-1.07 (± 2.441)	-1.02 (± 3.119)
Change at Week 4 (n=57, 63, 74, 76)	2.14 (± 2.348)	1.87 (± 2.809)	-1.60 (± 2.543)	-1.83 (± 3.389)
Change at Week 8 (n=53, 56, 67, 70)	2.00 (± 2.289)	2.42 (± 2.751)	-2.59 (± 3.012)	-1.97 (± 3.048)
Change at Week 12 (n=33, 46, 51, 57)	1.76 (± 2.547)	2.18 (± 2.762)	-2.29 (± 2.599)	-2.43 (± 3.299)
Change at Week 13 (n=7, 15, 17, 25)	2.09 (± 2.489)	1.98 (± 2.539)	-2.05 (± 3.242)	-1.77 (± 2.804)
Change at Week 14 (n=2, 2, 4, 6)	2.56 (± 0.507)	1.19 (± 0.860)	-4.71 (± 2.626)	-3.54 (± 4.063)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in IBS Quality of Life (IBS-QOL) Questionnaire Subscale and Total Scores at Week 4, 8, and Follow-up Visit (Weeks 12-14)

End point title	Change From Baseline in IBS Quality of Life (IBS-QOL) Questionnaire Subscale and Total Scores at Week 4, 8, and Follow-up Visit (Weeks 12-14)

End point description:

Subjects were asked to complete a QOL questionnaire of 34 items each with an individual 5-point response on an ordinal scale. Responses to these items were summed and averaged for a total score (TS) and then transformed to a 100-point scale for ease of interpretation. Sub-scales included dysphoria score (DS [8 items]), interference of activity (IAS [7items]), body image (BIS [4 items]), health worry (HWS [3 items]), food avoidance (FAS [3 items]), social reaction (SRS [4 items]), sexual (SS [2 items]) and relationship (RS [3 items]) were numbered as 1-5 with: 1 = not at all, 2 = slightly, 3 = moderately, 4 = quite a bit, 5 = extremely or a great deal. IBS-QOL was measured on a scale range of 0-100 with (0=worst; 100=better). Higher scores indicates better IBS-specific quality of life. FAS analysis population. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint; "n=number analysed" signifies subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, follow-up visit (Week 12-14)

End point values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix	Cohort D: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	41	47	64
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Change at Week 4: TS (n=41, 41, 45, 64)	5.67 (± 16.858)	5.79 (± 21.908)	5.62 (± 18.087)	5.93 (± 13.113)
Change at Week 4: DS (n=41, 41, 45, 64)	5.95 (± 20.561)	5.34 (± 22.881)	9.17 (± 22.627)	5.81 (± 17.429)
Change at Week 4: IAS (n=41, 41, 45, 64)	4.79 (± 16.952)	6.71 (± 22.633)	7.54 (± 18.230)	8.26 (± 16.008)
Change at Week 4: BIS (n=41, 41, 45, 64)	4.88 (± 23.779)	7.62 (± 23.239)	5.83 (± 20.703)	4.10 (± 17.860)
Change at Week 4: HWS (n=41, 41, 45, 64)	10.98 (± 23.082)	10.57 (± 26.940)	6.85 (± 19.727)	7.55 (± 19.056)
Change at Week 4: FAS (n=41, 41, 45, 64)	6.50 (± 20.625)	4.88 (± 29.461)	5.56 (± 19.624)	7.55 (± 19.960)
Change at Week 4: SRS (n=41, 41, 45, 64)	4.12 (± 16.922)	2.44 (± 24.402)	0.42 (± 23.963)	6.64 (± 14.935)
Change at Week 4: SS (n=41, 41, 45, 64)	7.32 (± 29.445)	1.52 (± 24.716)	-0.56 (± 20.288)	0.39 (± 19.284)
Change at Week 4: RS (n=41, 41, 45, 64)	2.85 (± 21.214)	5.89 (± 26.170)	1.30 (± 23.500)	2.73 (± 17.509)
Change at Week 8: TS (n=38, 35, 47, 53)	12.27 (± 20.969)	8.09 (± 18.318)	11.89 (± 20.933)	8.37 (± 18.043)
Change at Week 8: DS (n=38, 35, 47, 53)	13.40 (± 21.044)	7.59 (± 20.085)	14.23 (± 26.241)	12.21 (± 20.403)
Change at Week 8: IAS (n=38, 35, 47, 53)	10.15 (± 26.120)	10.31 (± 21.529)	15.12 (± 22.944)	8.96 (± 20.247)
Change at Week 8: BIS (n=38, 35, 47, 53)	12.83 (± 22.696)	8.93 (± 18.890)	13.70 (± 22.217)	7.43 (± 23.096)
Change at Week 8: HWS (n=38, 35, 47, 53)	17.32 (± 27.834)	12.38 (± 22.810)	7.80 (± 22.947)	7.23 (± 19.614)

Change at Week 8: FAS (n=38, 35, 47, 53)	17.54 (± 27.522)	7.38 (± 29.412)	14.01 (± 22.327)	6.60 (± 24.534)
Change at Week 8: SRS (n=38, 35, 47, 53)	10.69 (± 21.401)	3.21 (± 17.960)	8.78 (± 24.473)	7.55 (± 20.669)
Change at Week 8: SS (n=38, 35, 47, 53)	10.53 (± 24.406)	3.57 (± 22.600)	3.46 (± 26.797)	3.30 (± 26.420)
Change at Week 8: RS (n=38, 35, 47, 53)	6.36 (± 19.800)	9.05 (± 22.721)	7.45 (± 21.858)	5.35 (± 20.155)
Change at Follow-up: TS (n=34, 36, 37, 38)	15.55 (± 21.368)	8.09 (± 16.647)	7.93 (± 23.919)	10.80 (± 19.950)
Change at Follow-up: DS (n=34, 36, 37, 38)	15.99 (± 23.957)	8.07 (± 17.236)	10.47 (± 30.336)	11.43 (± 21.236)
Change at Follow-up: IAS (n=34, 36, 37, 38)	14.50 (± 23.195)	12.00 (± 21.278)	9.75 (± 25.417)	14.94 (± 26.243)
Change at Follow-up: BIS (n=34, 36, 37, 38)	17.10 (± 21.777)	9.38 (± 17.772)	8.95 (± 24.409)	9.38 (± 25.200)
Change at Follow-up: HWS (n=34, 36, 37, 38)	19.36 (± 28.701)	9.26 (± 23.382)	10.14 (± 23.663)	14.25 (± 18.371)
Change at Follow-up: FAS (n=34, 36, 37, 38)	16.91 (± 23.524)	9.72 (± 21.776)	7.43 (± 24.594)	9.21 (± 26.408)
Change at Follow-up: SRS (n=34, 36, 37, 38)	13.79 (± 24.942)	1.04 (± 15.917)	6.59 (± 27.676)	9.38 (± 23.554)
Change at Follow-up: SS (n=34, 36, 37, 38)	15.07 (± 26.253)	3.13 (± 23.599)	-1.69 (± 27.507)	4.93 (± 25.425)
Change at Follow-up: RS (n=34, 36, 37, 38)	12.25 (± 22.774)	7.18 (± 22.900)	2.03 (± 24.799)	5.26 (± 22.041)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in IBS Symptom Severity Score (IBS-SSS) at Week 4, 8 and Follow-up Visit (Weeks 12-14)

End point title	Change From Baseline in IBS Symptom Severity Score (IBS-SSS) at Week 4, 8 and Follow-up Visit (Weeks 12-14)

End point description:

Subjects were asked to complete a questionnaire on the severity of abdominal distension and pain, frequency of abdominal pain, dissatisfaction with bowel habits, and interference of IBS symptoms with daily life. The IBS-SSS was measured on a Visual Analog Scale (VAS scale) in combination with reported numeric values which equated to an overall score. The scale range was from 0 (no symptoms) to 500 (maximum severity). Subjects were categorized as having mild (74-174), moderate (175-299), or severe (greater than [>] 300) IBS symptoms based on symptomology. Higher scores were indicative of greater disease severity (worse outcome). FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n=number analysed" signifies subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, follow-up visit (Week 12-14)

End point values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix	Cohort D: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	77	81	83	93
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Change at Week 4 (n=77, 81, 83, 93)	-128.87 (± 143.885)	-141.30 (± 139.439)	-125.75 (± 135.258)	-100.97 (± 114.939)
Change at Week 8 (n=73, 79, 81, 85)	-168.46 (± 157.300)	-173.53 (± 155.253)	-143.55 (± 143.781)	-133.63 (± 139.290)
Change at Follow up visit (n=77, 80, 83, 90)	-142.49 (± 149.678)	-160.66 (± 150.174)	-113.47 (± 135.064)	-104.76 (± 146.447)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hospital Anxiety and Depression (HADS) Total Score at Week 4, 8 and Follow-up Visit (Weeks 12-14)

End point title	Change From Baseline in Hospital Anxiety and Depression (HADS) Total Score at Week 4, 8 and Follow-up Visit (Weeks 12-14)

End point description:

Subjects were asked to complete the HADS which was a 14-item scale that generated ordinal data. Seven of the items were related to anxiety and seven were related to depression. Each item on the questionnaire was scored from 0-3 which means that a subject total score (TS) ranges from 0 and 21 each are derived by summing the individual scores under each category for anxiety or depression. Total Scores are interpreted as: 0-7 = Normal, 8-10 = Borderline abnormal and 11-21 = Abnormal. Higher HADS scores were indicative of more severe depression and anxiety. FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n=number analysed" signifies subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, follow-up visit (Week 12-14)

End point values	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix	Cohort D: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	41	47	64
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Change at Week 4: Anxiety TS (n=41, 41, 45, 64)	-0.02 (± 2.612)	0.22 (± 2.954)	0.09 (± 2.827)	-0.27 (± 3.243)
Change at Week 4: Depression TS (n=41, 41, 45, 64)	0.24 (± 3.527)	-0.29 (± 3.303)	0.22 (± 2.566)	0.00 (± 2.410)
Change at Week 8: Anxiety TS (n=38, 35, 47, 53)	0.08 (± 2.981)	-0.09 (± 3.320)	-0.32 (± 3.251)	-0.40 (± 3.213)
Change at Week 8: Depression TS (n=38, 35, 47, 53)	-0.18 (± 3.432)	-0.06 (± 3.556)	0.19 (± 2.787)	-0.36 (± 3.169)
Change at Follow-up: Anxiety TS (n=34, 36, 37, 38)	-0.53 (± 3.360)	0.06 (± 2.714)	-0.14 (± 3.029)	-0.55 (± 3.375)

Change at Follow-up: Depression TS(n=34,36,37,38)	-0.85 (± 3.735)	-0.14 (± 2.939)	0.51 (± 3.024)	-0.68 (± 2.886)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to follow-up visit (up to Week 14)

Adverse event reporting additional description:

SAF included all subjects randomized into the study who received at least one dose of Blautix or Placebo.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Cohort C: Blautix

Reporting group description:

Subjects diagnosed with IBS-C received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of Blautia hydrogenotrophica) was 10^10 to10^11 MPN.

Reporting group title	Cohort C: Placebo

Reporting group description:

Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

Reporting group title	Cohort D: Blautix

Reporting group description:

Subjects diagnosed with IBS-D received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of Blautia hydrogenotrophica) was 10^10 to 10^11 MPN.

Reporting group title	Cohort D: Placebo

Reporting group description:

Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

Serious adverse events	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort D: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 104 (0.96%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort C: Blautix	Cohort C: Placebo	Cohort D: Blautix
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 80 (21.25%)	19 / 84 (22.62%)	41 / 97 (42.27%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1

Early satiety			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 80 (0.00%)	3 / 84 (3.57%)	0 / 97 (0.00%)
occurrences (all)	0	3	0
Influenza like illness			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Thirst			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	2 / 97 (2.06%)
occurrences (all)	0	0	2
Rhinitis allergic			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0

Insomnia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	2 / 97 (2.06%)
occurrences (all)	0	0	2
Irritability			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Post-traumatic stress disorder			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	1	0	1
Muscle strain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Post-traumatic pain			

subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Road traffic accident			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Thermal burn			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Wrist fracture			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 80 (1.25%)	2 / 84 (2.38%)	4 / 97 (4.12%)
occurrences (all)	1	2	4
Hypoaesthesia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Normocytic anaemia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Thrombocytosis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	2 / 80 (2.50%)	1 / 84 (1.19%)	2 / 97 (2.06%)
occurrences (all)	2	1	2
Abdominal pain upper			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Abnormal faeces			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Anal fissure			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Anorectal discomfort			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	1 / 97 (1.03%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	5 / 97 (5.15%)
occurrences (all)	1	0	5
Dyspepsia			

subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	3 / 97 (3.09%)
occurrences (all)	0	0	3
Flatulence			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Frequent bowel movements			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 80 (1.25%)	2 / 84 (2.38%)	0 / 97 (0.00%)
occurrences (all)	1	2	0
Glossodynia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 80 (0.00%)	2 / 84 (2.38%)	0 / 97 (0.00%)
occurrences (all)	0	2	0
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	3 / 97 (3.09%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Vomiting			

subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Brachioradial pruritus			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Urine odour abnormal			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Musculoskeletal pain			

subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Rotator cuff syndrome			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	4 / 97 (4.12%)
occurrences (all)	0	1	4
Herpes zoster			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 80 (1.25%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	1	0	1
Lice infestation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0

Lower respiratory tract infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 80 (2.50%)	1 / 84 (1.19%)	5 / 97 (5.15%)
occurrences (all)	2	1	5
Oral herpes			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 80 (5.00%)	3 / 84 (3.57%)	3 / 97 (3.09%)
occurrences (all)	4	3	3
Urinary tract infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	1 / 97 (1.03%)
occurrences (all)	0	1	1
Vaginal infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	0	1	0

Viral infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Viral rhinitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Vulvovaginal candidiasis			
subjects affected / exposed	2 / 80 (2.50%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	2	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 84 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 80 (1.25%)	1 / 84 (1.19%)	0 / 97 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Cohort D: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 104 (41.35%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Early satiety			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		

Fatigue			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		

Irritability			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Post-traumatic stress disorder			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Muscle strain			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Post-traumatic pain			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Radius fracture			

subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Road traffic accident			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Thermal burn			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Wrist fracture			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	5 / 104 (4.81%)		
occurrences (all)	5		
Hypoaesthesia			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Normocytic anaemia			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Thrombocytosis			

subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Abnormal faeces			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Anal fissure			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Anorectal discomfort			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Flatulence			

subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Frequent bowel movements			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Glossodynia			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Irritable bowel syndrome			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Rectal haemorrhage			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			

Brachioradial pruritus subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0		
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0		
Rash subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1		
Rash macular subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0		
Haematuria subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0		
Pollakiuria subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0		
Urine odour abnormal subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1		
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1		
Back pain subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0		
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0		
Neck pain			

subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Rotator cuff syndrome			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	4 / 104 (3.85%)		
occurrences (all)	4		
Herpes zoster			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 104 (0.00%)		
occurrences (all)	0		
Lice infestation			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences (all)	1		

Nasopharyngitis				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences (all)	1			
Oral herpes				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences (all)	0			
Tonsillitis				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences (all)	0			
Tooth infection				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences (all)	1			
Upper respiratory tract infection				
subjects affected / exposed	4 / 104 (3.85%)			
occurrences (all)	4			
Urinary tract infection				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences (all)	1			
Vaginal infection				
subjects affected / exposed	0 / 104 (0.00%)			
occurrences (all)	0			
Viral infection				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences (all)	1			

Viral rhinitis subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1		
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0		
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 104 (0.96%) 1		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 104 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2018	Protocol Version 1.1: - Amended an administrative error regarding the timing of the dosing by adding approximately 30 minutes to be consistent with other sections of the protocol. - Removal of erythrocyte sedimentation rate and replacement with C-reactive protein [CRP] test within the haematology panel as this is a more accurate measurement for investigator review. - Additional testing for hepatitis B surface antigen, a hepatitis B surface antibody, and a hepatitis core antibody test was added for all subjects at the Screening Visit. - Removal of bile acid analysis of fasting serum from the planned per-protocol assessments.
31 May 2018	Protocol Version 2.0: - Changed the primary endpoint responder symptom definition for stool consistency from number of days per week to proportion of days per week. - Changed the timing for the collection of stool samples from within 48 hours before or on the morning of baseline to the night before or the morning of the next clinic visit. - Added a 24-hour window for completion of IBS QOL before the clinic visit. - Re-added hepatitis C to the safety assessment as it was removed in error during the changes to Version 1.1. - Added the requirement for the subject to record stool frequency of up to 10 bowel movements daily to ensure data required to meet the primary endpoint is sufficient.
13 February 2019	Protocol version 3.0: - Added text to inclusion criterion 4 for clarity: Have a moderate or severe IBS symptom severity score: >175 at the Screening Visit as defined by IBS-SSS. A tolerance of -10% (>= an IBS-SSS score of 157.5) will be allowable at the baseline (Visit 1). - Added a definition for the ranges of mild, moderate, and severe IBS symptom scores.
31 March 2020	Protocol version 3.1: - Planned futility analysis following the randomisation of approximately 250 subjects was cancelled as the study had stopped enrolment before the interim analysis was reported. - An informal interim analysis was conducted once all recruited subjects had completed the primary efficacy analysis 8-week treatment period. - This interim analysis was planned to enable 4D pharma plc to expedite the clinical development strategy based on the outcome of the interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported