Clinical trial results:
A double-blind, randomised, placebo-controlled study on the efficacy of Iberogast® (STW 5) in patients with irritable bowel syndrome

Summary

EudraCT number	2011-002613-10
Trial protocol	DE
Global end of trial date	25 October 2017

Results information

Result version number	v1 (current)
This version publication date	09 November 2018
First version publication date	09 November 2018

Trial information

Trial identification

Sponsor protocol code	BAY98-7411/17063

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01940848
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	25 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to show the efficacy of STW 5 (Iberogast, BAY98-7411) on pain related symptoms of subjects with irritable bowel syndrome (IBS).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 243
Worldwide total number of subjects	243
EEA total number of subjects	243

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)	205
From 65 to 84 years	36

85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 19 active study centers in Germany, between 11 October 2013 (first subject first visit) and 05 July 2017 (last subject last visit).

Pre-assignment

Screening details:

Overall, 320 subjects were screened, of them 77 subjects failed screening: 68 did not fulfil eligibility criteria, 3 lost to follow up, 5 withdrew informed consent and 1 due to other reason. A total of 243 subjects were randomized and received at least one dose of study medication.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	STW 5 (Iberogast)

Arm description:

Subjects received STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).

Arm type	Experimental
Investigational medicinal product name	STW 5
Investigational medicinal product code	BAY98-7411
Other name	Iberogast
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Oral use

Dosage and administration details:

Subjects received STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).

Arm title	Placebo

Arm description:

Subjects received placebo matched to STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).

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

Dosage and administration details:

Subjects received placebo matched to STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).

Number of subjects in period 1	STW 5 (Iberogast)	Placebo
Started	167	76
Completed	152	72
Not completed	15	4
Eligibility criteria not fulfilled	-	1
Lack of therapeutic response	1	1
Adverse event, other reason	1	-
Adverse event	4	-
Other reason	2	1
Withdrawal of informed consent	3	1
Subject lost to follow up	4	-

Baseline characteristics

Reporting groups	
Reporting group title	STW 5 (Iberogast)
Reporting group description:	
Subjects received STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).	

Reporting group values	STW 5 (Iberogast)	Placebo	Total
Number of subjects	167	76	243
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	46.7	46.9	
standard deviation	± 16.59	± 17.24	-
Gender categorical			
Units: Subjects			
Female	129	61	190
Male	38	15	53
IBS type			
IBS is chronic, relapsing gastrointestinal disorder, characterized by abdominal pain, bloating and changes in bowel habit. IBS regarding ROME III is associated with recurrent abdominal pain or discomfort at least 3 days /month in last 3 months is associated with two or more of following: 1)improvement with defecation, 2)onset associated with change in frequency of stool, 3)onset associated with change in form (appearance) of stool. Diarrhoea-predominant IBS (IBS-D), Constipation-predominant- IBS (IBS-C) were included in the study.			
Units: Subjects			
IBS-C	50	25	75
IBS-D	63	27	90
Not classifiable	54	24	78
Time from date of first diagnosis of IBS			
Time from date of first diagnosis of IBS until date of informed consent was described by statistical characteristics according to the nature and distribution of the data.			
Units: years			
arithmetic mean	8.1	7.4	
standard deviation	± 9.80	± 7.47	-
Irritable bowel syndrome-quality of life measure (IBS-QoL) total score			
IBS-QoL is a self-report QoL measure to assess impact of IBS and its treatment. It consists of 34 items, each with a 5-point response scale. Individual responses to 34 items were summed up, averaged for total score, then transformed to 0-100 scale. Higher scores indicate better IBS specific quality of life. The number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n=225, STW 5 = 154, placebo = 71).			
Units: score on a scale			
arithmetic mean	59.19	55.21	
standard deviation	± 19.184	± 17.629	-

Feeling of complete evacuation			
Evacuation is defined as mean daily number of defecations during analyzed period multiplied by 7 for the weekly standardization. The FAS (N=237) included all randomized subjects who received at least one dose of study medication and whose post randomization assessment of data of efficacy were available at least.			
Units: number of defecations per day*7			
arithmetic mean	5.05	5.29	
standard deviation	± 4.226	± 6.190	-
Feeling of incomplete evacuation			
Evacuation is defined as mean daily number of defecations during analyzed period multiplied by 7 for the weekly standardization. The FAS (N=237) included all randomized subjects who received at least one dose of study medication and whose post randomization assessment of data of efficacy were available at least.			
Units: number of defecations per day*7			
arithmetic mean	5.73	5.10	
standard deviation	± 5.729	± 4.792	-
Stool consistency in IBS-C subgroup			
Stool consistency was assessed in subjects with constipation-predominant IBS by the bristol stool form scale (BSS). The BSS provides a pictorial and verbal description of stool consistency, and form and is an appropriate instrument for capturing stool consistency. As per BSS: types 1-2, hard (suggestive of constipation); types 3-5, normal; types 6-7, loose/liquid (associated with diarrhoea). IBS-C (N=74) included all subjects with constipation-predominant IBS in the FAS.			
Units: stool consistency			
arithmetic mean	2.88	2.49	
standard deviation	± 0.613	± 0.796	-
Stool consistency in IBS-D subgroup			
Stool consistency was assessed in subjects with diarrhoea-predominant IBS by the BSS. The BSS provides a pictorial and verbal description of stool consistency, and form and is an appropriate instrument for capturing stool consistency. As per BSS: types 1-2, hard (suggestive of constipation); types 3-5, normal; types 6-7, loose/liquid (associated with diarrhoea). IBS-D (N=88) included all subjects with diarrhoea-predominant IBS in the FAS.			
Units: stool consistency			
arithmetic mean	5.15	5.04	
standard deviation	± 0.671	± 0.663	-
Weekly usage of bisacodyl tablets			
Subjects were instructed to use bisacodyl only in case of absence of bowel movements for more than three days. Investigators dispensed the rescue medication bisacodyl for treatment of severe constipation. The FAS (N=237) included all randomized subjects who received at least one dose of study medication and whose post randomization assessment of data of efficacy were available at least.			
Units: number of tablets			
arithmetic mean	0.18	0.47	
standard deviation	± 0.591	± 1.425	-
Weekly usage of loperamid tablets			
Subjects were instructed to use loperamide only in case of three consecutive bowel movements with type 6 according to BSS or in case of first bowel movement with type 7 according to BSS. As per BSS: types 1-2, hard(suggestive of constipation); types 3-5, normal; types 6-7, loose/liquid (associated with diarrhoea). Investigators dispensed the rescue medication loperamide for treatment of severe diarrhoea. The FAS (N=237) included all randomized subjects who received at least one dose of study medication and whose post randomization assessment of data of efficacy were available at least.			
Units: number of tablets			
arithmetic mean	0.22	0.16	
standard deviation	± 1.060	± 0.616	-
Birmingham IBS symptom questionnaire total score			
Birmingham IBS symptom score comprises a self-completed questionnaire which consists of 11 questions based on frequency of IBS related symptoms. Birmingham IBS symptom questionnaire completed by subjects provides assessment in 3 dimensions pain, constipation and diarrhoea based on frequency of symptoms. All single items of questionnaire were then transformed to a total score ranging from 0 (no symptoms) to 100 (all symptoms). The number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n=230, STW 5 = 158, placebo =72).			

Units: score on a scale			
arithmetic mean	37.62	36.31	
standard deviation	± 11.810	± 11.295	-
Birmingham IBS symptom pain sub scale			
Birmingham IBS symptom score comprises a self-completed questionnaire. This questionnaire completed by the subjects provides assessment in three dimensions pain, constipation and diarrhoea based on the frequency of symptoms. Pain subscale included questions related to 'Pain', 'Pain after eating' and 'Sleep problem.' The items within each dimension were summed up and transformed to a scale ranging from 0 (no symptoms) to 100 (all symptoms). The number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n=236, STW 5 = 161, placebo =75).			
Units: score on a scale			
arithmetic mean	55.20	54.04	
standard deviation	± 16.197	± 16.424	-
Birmingham IBS symptom constipation sub scale			
Birmingham IBS symptom score comprises a self-completed questionnaire. Questionnaire completed by subjects provides assessment in 3 dimensions pain, constipation, diarrhoea based on frequency of symptoms. Constipation subscale included questions related to 'hard bowel motions', 'straining', 'constipation'. Items within each dimension were summed up, transformed to a scale ranging from 0 (no symptoms) to 100 (all symptoms). The number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n = 235, STW 5 = 162, placebo = 73).			
Units: score on a scale			
arithmetic mean	33.29	35.53	
standard deviation	± 25.958	± 32.031	-
Birmingham IBS symptom diarrhoea sub scale			
Birmingham IBS symptom score comprises a self-completed questionnaire. Questionnaire completed by subjects provides assessment in 3 dimensions pain, constipation and diarrhoea based on frequency of symptoms. Diarrhoea subscale included questions related to Loose, watery stools, diarrhoea, leaked or soiled, urgency, mucus or slime. Items within each dimension were summed up, transformed to a scale ranging from 0 (no symptoms) to 100 (all symptoms). Number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n= 231, STW 5 = 158, placebo =73).			
Units: score on a scale			
arithmetic mean	29.39	26.41	
standard deviation	± 18.126	± 19.087	-
IBS-C: Birmingham IBS symptom questionnaire total score			
Birmingham IBS symptom score comprises a self-completed questionnaire. It consists of 11 questions based on frequency of IBS related symptoms. Questionnaire completed by subjects provides assessment in 3 dimensions pain, constipation, diarrhoea based on frequency of symptoms. All single items of questionnaire were then transformed to a total score ranging from 0 (no symptoms) to 100 (all symptoms). Number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n= 73, STW 5 = 48, placebo =25).			
Units: score on a scale			
arithmetic mean	37.61	37.75	
standard deviation	± 10.204	± 11.645	-
IBS-D: Birmingham IBS symptom questionnaire total score			
Birmingham IBS symptom score comprises a self-completed questionnaire. It consists of 11 questions based on frequency of IBS related symptoms. This questionnaire completed by the subjects provides assessment in three dimensions pain, constipation and diarrhoea based on the frequency of symptoms. All single items of the questionnaire were then transformed to a total score ranging from 0 (no symptoms) to 100 (all symptoms). Number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n= 84, STW 5 = 59, placebo =25).			
Units: score on a scale			
arithmetic mean	39.91	37.75	
standard deviation	± 11.785	± 9.305	-
IBS-C: Birmingham IBS symptom pain			

dimension sub scale			
Birmingham IBS symptom score comprises a self-completed questionnaire. This questionnaire completed by subjects provides assessment in three dimensions pain, constipation, diarrhoea based on frequency of symptoms. Pain subscale included questions related to 'Pain', 'Pain after eating' and 'Sleep problem.' The items within each dimension were summed up and transformed to a scale ranging from 0 (no symptoms) to 100 (all symptoms). Number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n= 73, STW 5 = 48, placebo =25).			
Units: score on a scale arithmetic mean standard deviation	 54.86 ± 18.412	 56.53 ± 16.791	 -
IBS-C: Birmingham IBS symptom constipation dimension sub scale			
Birmingham IBS symptom score comprises a self-completed questionnaire. Questionnaire completed by subjects provides assessment in three dimensions pain, constipation and diarrhoea based on frequency of symptoms. Constipation subscale included questions related to hard bowel motions, straining, constipation'. Items within each dimension were summed up and transformed to a scale ranging from 0 (no symptoms) to 100 (all symptoms). IBS-C (N=74, STW 5 = 49, placebo =25) included all subjects with constipation-predominant IBS in the FAS.			
Units: score on a scale arithmetic mean standard deviation	 50.34 ± 23.494	 62.67 ± 30.852	 -
IBS-C: Birmingham IBS symptom diarrhea dimension sub scale			
Birmingham IBS symptom score comprises a self-completed questionnaire. Questionnaire completed by subjects provides assessment in 3 dimensions pain, constipation, diarrhoea based on frequency of symptoms. Diarrhoea subscale included questions related to Loose, watery stools, diarrhoea, leaked or soiled, urgency, mucus or slime. Items within each dimension were summed up, transformed to a scale ranging from 0 (no symptoms) to 100 (all symptoms). The number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n= 74, STW 5 = 48, placebo =25).			
Units: score on a scale arithmetic mean standard deviation	 19.58 ± 12.922	 11.52 ± 11.450	 -
IBS-D: Birmingham IBS symptom pain dimension sub scale			
Birmingham IBS symptom score comprises a self-completed questionnaire. This questionnaire completed by subjects provides assessment in three dimensions pain, constipation, diarrhoea based on frequency of symptoms. Pain subscale included questions related to Pain, Pain after eating and Sleep problem. The items within each dimension were summed up and transformed to a scale ranging from 0 (no symptoms) to 100 (all symptoms). IBS-D (N=88, STW 5=61, placebo= 27) included all subjects with diarrhoea-predominant IBS in the FAS.			
Units: score on a scale arithmetic mean standard deviation	 57.70 ± 14.084	 56.05 ± 16.357	 -
IBS-D: Birmingham IBS symptom constipation dimension sub scale			
Birmingham IBS symptom score comprises a self-completed questionnaire. Questionnaire completed by subjects provides assessment in three dimensions pain, constipation and diarrhoea based on frequency of symptoms. Constipation subscale included questions related to hard bowel motions, straining, constipation'. Items within each dimension were summed up and transformed to a scale ranging from 0 (no symptoms) to 100 (all symptoms). Number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n= 87, STW 5 = 61, placebo =26).			
Units: score on a scale arithmetic mean standard deviation	 20.44 ± 20.399	 14.36 ± 12.746	 -
IBS-D: Birmingham IBS symptom diarrhea dimension sub scale			
Birmingham IBS symptom score comprises a self-completed questionnaire. Questionnaire completed by subjects provides assessment in 3 dimensions pain, constipation, diarrhoea based on frequency of symptoms. Diarrhoea subscale included questions related to Loose, watery stools, diarrhoea, leaked or soiled, urgency, mucus or slime. Items within each dimension were summed up, transformed to a scale ranging from 0 (no symptoms) to 100 (all symptoms). Number of subjects analysed signifies subjects			

who were evaluable for this parameter, for each arm respectively, (n= 85, STW 5 = 59, placebo =26).			
Units: score on a scale			
arithmetic mean	40.68	41.54	
standard deviation	± 17.983	± 14.841	-

End points

End points reporting groups

Reporting group title	STW 5 (Iberogast)
Reporting group description:	
Subjects received STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF (N= 243) included all randomized subjects who received at least one dose of study medication.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS (N=237) included all randomized subjects who received at least one dose of study medication and whose post randomization assessment of data of efficacy were available at least. The FAS includes subjects with treatment effects measured, according to the intention-to-treat principle.	
Subject analysis set title	IBS with predominant constipation (IBS-C)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
IBS-C (N=74) included all subjects with constipation-predominant IBS in the FAS.	
Subject analysis set title	IBS with predominant diarrhoea (IBS-D)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
IBS-D (N=88) included all subjects with diarrhoea-predominant IBS in the FAS.	

Primary: Response Rate for Abdominal Pain Intensity After 4 Weeks of Treatment

End point title	Response Rate for Abdominal Pain Intensity After 4 Weeks of Treatment
End point description:	
The abdominal pain intensity was evaluated by using an 10 centimeters (cm) visual analogue scale (VAS) ranging from no pain to worst pain that asked subjects daily to rate their 'worst abdominal pain over the past 24-hours'. Rate of responders with decrease of worst abdominal pain in past 24 hours score of greater than or equal to (>=) 30 percentage (%) compared with baseline for at least 14 single days within the first 4 weeks of study treatment determined by daily assessment on a VAS was measured.	
End point type	Primary
End point timeframe:	
From start of study drug administration up to 4 weeks of treatment	

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[1]	75[2]		
Units: percentage of subjects				
number (not applicable)	40.7	42.7		

Notes:
[1] - FAS
[2] - FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Within a Cochran-Mantel-Haenszel chi-square test controlling for centre, the odds ratio for the treatment comparison was determined together with the respective 95% confidence interval two-sided and the respective p-value.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8678
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.68

Secondary: Response Rate for Abdominal Pain Intensity After 2 Weeks of Treatment

End point title	Response Rate for Abdominal Pain Intensity After 2 Weeks of Treatment

End point description:

The abdominal pain intensity was evaluated using a 10 cm VAS ranging from no pain to worst pain that asked subjects daily to rate their "worst abdominal pain over the past 24-hours". Rate of responders with decrease of worst abdominal pain in past 24 hours score of >= 30% compared with baseline for at least 7 single days within the first 2 weeks of study treatment determined by daily assessment on a VAS was measured.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 2 weeks of treatment

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[3]	75[4]		
Units: percentage of subjects				
number (not applicable)	39.5	42.7		

Notes:
[3] - FAS
[4] - FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Within a Cochran-Mantel-Haenszel chi-square test controlling for centre, the odds ratio for the treatment comparison was determined together with the respective 95% confidence interval two-sided and the respective p-value.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6552
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.54

Secondary: Irritable Bowel Syndrome - Quality of Life Measure (IBS-QoL): Change From Baseline for the Transformed Total Score at Week 4

End point title	Irritable Bowel Syndrome - Quality of Life Measure (IBS-QoL): Change From Baseline for the Transformed Total Score at Week 4

End point description:

IBS-QoL is a self-report QoL measure to assess impact of IBS and its treatment. It consists of 34 items, each with a 5-point response scale. Individual responses to 34 items were summed up, averaged for total score, then transformed to 0-100 scale. Higher scores indicate better IBS specific quality of life.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141[5]	66[6]		
Units: score on a scale				
arithmetic mean (standard deviation)	10.13 (± 15.365)	9.98 (± 16.010)		

Notes:

[5] - FAS with number of evaluable subjects for this specific end point.

[6] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

IBS-QoL was tested using an analysis of covariance (ANCOVA) model with treatment, center and underlying IBS type as fixed effects and the baseline value as covariate. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3607
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	6

Secondary: Responders Regarding Stool Frequency in IBS-C Subgroup After 4 Weeks of Treatment

End point title	Responders Regarding Stool Frequency in IBS-C Subgroup After 4 Weeks of Treatment

End point description:

Stool frequency responder in constipation-predominant-IBS sub group is defined as subject with increase of one or more complete spontaneous bowel movements (CSBM) per week compared with baseline for at least 50% of analyzed weeks.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 4 weeks of treatment

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[7]	25[8]		
Units: count of subjects				
number (not applicable)	20	11		

Notes:

[7] - IBS-C subgroup of FAS.

[8] - IBS-C subgroup of FAS.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Within a Cochran-Mantel-Haenszel chi-square test controlling for centre, the odds ratio for the treatment comparison was determined together with the respective 95% confidence interval two-sided and the respective p-value.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9753
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	2.9

Secondary: Responders Regarding Stool Consistency in IBS-D Subgroup After 4 Weeks of Treatment

End point title	Responders Regarding Stool Consistency in IBS-D Subgroup After 4 Weeks of Treatment

End point description:

Stool consistency responder in IBS with diarrhoea-predominant sub group is defined as subject with decrease in weekly average of greater than (>) 1 in terms of BSS for at least 50% of analyzed weeks. Stool consistency was assessed by Bristol Stool Form Scale (BSS). The BSS provides a pictorial and verbal description of stool consistency and form. It is an appropriate instrument for capturing stool consistency in IBS trials. As per BSS: types 1-2, hard (suggestive of constipation); types 3-5, normal; types 6-7, loose/liquid (associated with diarrhoea).

End point type	Secondary

End point timeframe:

From start of study drug administration up to 4 weeks of treatment

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[9]	27[10]		
Units: count of subjects				
number (not applicable)	16	10		

Notes:

[9] - IBS-D subgroup of FAS.

[10] - IBS-D subgroup of FAS.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Within a Cochran-Mantel-Haenszel chi-square test controlling for centre, the odds ratio for the treatment comparison was determined together with the respective 95% confidence interval two-sided and the respective p-value.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2952
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	1.6

Secondary: Responders Regarding Stool Frequency for IBS-C Subgroup After 2 Weeks of Treatment

End point title	Responders Regarding Stool Frequency for IBS-C Subgroup After 2 Weeks of Treatment

End point description:

Stool frequency responder in constipation-predominant-IBS sub group is defined as subject with increase of one or more CSBM per week compared with baseline for at least 50% of analyzed weeks.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 2 weeks of treatment

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[11]	25[12]		
Units: count of subjects				
number (not applicable)	22	11		

Notes:

[11] - IBS-C subgroup of FAS.

[12] - IBS-C subgroup of FAS.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Within a Cochran-Mantel-Haenszel chi-square test controlling for centre, the odds ratio for the treatment comparison was determined together with the respective 95% confidence interval two-sided and the respective p-value.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7125
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	3.35

Secondary: Responders Regarding Stool Consistency in IBS-D Subgroup After 2 Weeks of Treatment

End point title	Responders Regarding Stool Consistency in IBS-D Subgroup After 2 Weeks of Treatment

End point description:

Stool consistency responder in IBS with diarrhoea-predominant sub group is defined as subject with decrease in weekly average of >1 in terms of BSS for at least 50% of analyzed weeks. Stool consistency was assessed by Bristol Stool Form Scale (BSS). The BSS provides a pictorial and verbal description of stool consistency and form. It is an appropriate instrument for capturing stool consistency in IBS trials. As per BSS: types 1-2, hard (suggestive of constipation); types 3-5, normal; types 6-7, loose/liquid (associated with diarrhoea).

End point type	Secondary

End point timeframe:

From start of study drug administration up to 2 weeks of treatment

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[13]	27[14]		
Units: count of subjects				
number (not applicable)	20	10		

Notes:

[13] - IBS-D subgroup of FAS.

[14] - IBS-D subgroup of FAS.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Within a Cochran-Mantel-Haenszel chi-square test controlling for centre, the odds ratio for the treatment comparison was determined together with the respective 95% confidence interval two-sided and the respective p-value.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6279
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	2.08

Secondary: Change of Pain Intensity From Baseline to Week 4

End point title	Change of Pain Intensity From Baseline to Week 4

End point description:

The abdominal pain intensity was evaluated by using the 10 cm VAS ranging from no pain to worst pain that asked subjects daily to rate their 'worst abdominal pain over the past 24-hours'.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[15]	69[16]		
Units: centimeter (cm)				
arithmetic mean (standard deviation)	-1.91 (± 2.599)	-2.29 (± 3.009)		

Notes:

[15] - FAS with number of evaluable subjects for this specific end point.

[16] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Change of pain intensity was tested using an ANCOVA model with last VAS value at Week 4 adjusted for treatment, center and underlying IBS type and last VAS baseline value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo

Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5943
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.81

Secondary: Change of Pain Intensity From Baseline to Week 2

End point title	Change of Pain Intensity From Baseline to Week 2

End point description:

The abdominal pain intensity was evaluated by using an 10 cm VAS ranging from no pain to worst pain that asked subjects daily to rate their 'worst abdominal pain over the past 24-hours'.

End point type	Secondary

End point timeframe:

Baseline, Week 2

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158[17]	73[18]		
Units: centimeter (cm)				
arithmetic mean (standard deviation)	-1.57 (± 2.589)	-1.62 (± 2.568)		

Notes:

[17] - FAS with number of evaluable subjects for this specific end point.

[18] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Change of pain intensity was tested using an ANCOVA model with last VAS value at Week 2 adjusted for treatment, center and underlying IBS type and last VAS baseline value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5637
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	0.45

Secondary: Response Rate for Abdominal Pain Intensity After First 7 Days of Treatment (Early Responders)

End point title	Response Rate for Abdominal Pain Intensity After First 7 Days of Treatment (Early Responders)

End point description:

Early responders were defined as subjects responding regarding pain intensity for at least 4 days during the first 7 days of the treatment period. The abdominal pain intensity was evaluated by using an 10 cm VAS ranging from no pain to worst pain that asked subjects daily to rate their 'worst abdominal pain over the past 24-hours'.

End point type	Secondary

End point timeframe:

From the start of study drug administration until first 7 days of treatment

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[19]	75[20]		
Units: percentage of subjects				
number (not applicable)	30.2	28.0		

Notes:

[19] - FAS

[20] - FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Within a Cochran-Mantel-Haenszel chi-square test controlling for centre, the odds ratio for the treatment comparison was determined together with the respective 95% confidence interval two-sided and the respective p-value.

Comparison groups	STW 5 (Iberogast) v Placebo

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5692
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	2.26

Secondary: Response Rate for Abdominal Pain Intensity in the Last 14 Days of Treatment (Late Responders)

End point title	Response Rate for Abdominal Pain Intensity in the Last 14 Days of Treatment (Late Responders)

End point description:

Late responders were defined as subjects responding regarding pain intensity for at least 7 days during the last 14 days of the treatment period. The abdominal pain intensity was evaluated by using an 10 cm VAS ranging from no pain to worst pain that asked subjects daily to rate their 'worst abdominal pain over the past 24-hours'.

End point type	Secondary

End point timeframe:

From the start of study drug administration until last 14 days of treatment

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[21]	75[22]		
Units: percentage of subjects				
number (not applicable)	50.6	53.3		

Notes:

[21] - FAS

[22] - FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Within a Cochran-Mantel-Haenszel chi-square test controlling for centre, the odds ratio for the treatment comparison was determined together with the respective 95% confidence interval two-sided and the respective p-value.

Comparison groups	STW 5 (Iberogast) v Placebo

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7926
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.65

Secondary: Feeling of Completed Evacuation - Change From Baseline to Week 4

End point title	Feeling of Completed Evacuation - Change From Baseline to Week 4

End point description:

Evacuation is defined as mean daily number of defecations during analyzed period multiplied by 7 for the weekly standardization.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[23]	71[24]		
Units: number of defecations per day*7				
arithmetic mean (standard deviation)	0.54 (± 2.554)	0.68 (± 3.485)		

Notes:

[23] - FAS with number of evaluable subjects for this specific end point.

[24] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v STW 5 (Iberogast)
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4411
Method	Wilcoxon rank sum test

Secondary: Feeling of Incomplete Evacuation – Change From Baseline to Week 4

End point title	Feeling of Incomplete Evacuation – Change From Baseline to

	Week 4

End point description:

Evacuation is defined as mean daily number of defecations during analyzed period multiplied by 7 for the weekly standardization.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[25]	71[26]		
Units: number of defecations per day*7				
arithmetic mean (standard deviation)	-1.33 (± 3.731)	-1.45 (± 4.722)		

Notes:

[25] - FAS with number of evaluable subjects for this specific end point.

[26] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5169
Method	Wilcoxon rank sum test

Secondary: Stool Consistency in IBS-C and IBS-D Subgroups-Change From Baseline to Week 4

End point title	Stool Consistency in IBS-C and IBS-D Subgroups-Change From Baseline to Week 4

End point description:

Stool consistency was assessed by the BSS. The BSS provides a pictorial and verbal description of stool consistency and form and is an appropriate instrument for capturing stool consistency. As per BSS: types 1-2, hard (suggestive of constipation); types 3-5, normal; types 6-7, loose/liquid (associated with diarrhoea). In the below table, ‘n’ signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[27]	27[28]		
Units: score on BSS scale				
arithmetic mean (standard deviation)				
IBS-C (n= 47, 22)	0.53 (± 1.020)	0.39 (± 0.705)		
IBS-D (n= 52, 27)	-0.43 (± 0.752)	-0.51 (± 1.076)		

Notes:

[27] - FAS with number of evaluable subjects for this end point.

[28] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Usage of Bisacodyl Tablets

End point title	Change From Baseline in Weekly Usage of Bisacodyl Tablets

End point description:

Subjects were instructed to use bisacodyl only in case of absence of bowel movements for more than three days. Investigators dispensed the rescue medication bisacodyl for treatment of severe constipation. The weekly usage of rescue medication was analysed descriptively and differences between the treatment groups were additionally assessed with a Wilcoxon rank sum test. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 3 and 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[29]	75[30]		
Units: number of tablets				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 161,75)	-0.02 (± 0.474)	-0.20 (± 0.737)		
Change at Week 2 (n= 160,73)	-0.06 (± 0.630)	-0.22 (± 0.821)		
Change at Week 3 (n= 155,73)	-0.01 (± 0.938)	-0.28 (± 1.096)		
Change at Week 4 (n= 151,71)	-0.09 (± 0.431)	-0.29 (± 1.171)		

Notes:

[29] - FAS with number of evaluable subjects for this end point.

[30] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Usage of Loperamid Tablets

End point title	Change From Baseline in Weekly Usage of Loperamid Tablets

End point description:

Subjects were instructed to use loperamide only in case of three consecutive bowel movements with type 6 according to BSS or in case of first bowel movement with type 7 according to BSS. As per BSS: types 1-2, hard (suggestive of constipation); types 3-5, normal; types 6-7, loose/liquid (associated with diarrhoea). Investigators dispensed the rescue medication loperamide for treatment of severe diarrhoea. The weekly usage of rescue medication was analysed descriptively and differences between the treatment groups were additionally assessed with a Wilcoxon rank sum test. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 3 and 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[31]	75[32]		
Units: number of tablets				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 161,75)	-0.01 (± 0.981)	0.01 (± 0.822)		
Change at Week 2 (n= 160,73)	-0.04 (± 0.563)	-0.03 (± 0.616)		
Change at Week 3 (n= 155,73)	-0.01 (± 0.983)	-0.07 (± 0.486)		
Change at Week 4 (n= 151,71)	0.03 (± 0.660)	0.04 (± 0.881)		

Notes:

[31] - FAS with number of evaluable subjects for this end point.

[32] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Birmingham IBS Symptom Questionnaire – Change Between Week 1 and Week 4 for the Total Score

End point title	Birmingham IBS Symptom Questionnaire – Change Between Week 1 and Week 4 for the Total Score

End point description:

The Birmingham IBS symptom score comprises a self-completed questionnaire which consists of 11 questions based on the frequency of IBS related symptoms. The Birmingham IBS symptom questionnaire completed by the subjects provides assessment in the three dimensions pain, constipation and diarrhoea based on the frequency of symptoms. All single items of the questionnaire were then transformed to a total score ranging from 0 (no symptoms) to 100 (all symptoms).

End point type	Secondary

End point timeframe:

Week 1 (Baseline), Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143[33]	64[34]		
Units: score on a scale				
arithmetic mean (standard deviation)	-11.04 (± 13.011)	-10.80 (± 13.571)		

Notes:

[33] - FAS with number of evaluable subjects for this end point.

[34] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Birmingham IBS Symptom Questionnaire – Change Between Week 1 and Week 4 for the 3 Dimensions

End point title	Birmingham IBS Symptom Questionnaire – Change Between Week 1 and Week 4 for the 3 Dimensions

End point description:

Birmingham IBS symptom score comprises a self-completed questionnaire. It consists of 11 questions based on frequency of IBS related symptoms. This questionnaire completed by the subjects provides assessment in three dimensions pain, constipation and diarrhoea based on the frequency of symptoms. All single items of the questionnaire were then transformed to a total score ranging from 0 (no symptoms) to 100 (all symptoms). In the below table 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Week 1 (Baseline), Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[35]	68[36]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Birmingham IBS symptom pain sub scale (n=151,68)	-18.06 (± 20.332)	-16.57 (± 20.329)		
BirminghamIBSsymptomconstipationsub scale(n=151,68)	-8.57 (± 20.431)	-8.14 (± 19.474)		
Birmingham IBSsymptom diarrhoea subscale(n=144,67)	-8.14 (± 15.520)	-8.96 (± 16.508)		

Notes:

[35] - FAS with number of evaluable subjects for this end point.

[36] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Birmingham IBS Symptom Questionnaire – Change Between Week 1 and Week 4 for the 3 Single Items of Questionnaire

End point title	Birmingham IBS Symptom Questionnaire – Change Between Week 1 and Week 4 for the 3 Single Items of Questionnaire

End point description:

The Birmingham IBS symptom score comprises a self-completed questionnaire which consists of 11 questions based on the frequency of IBS related symptoms. Each question has a standard response scale with symptoms all being measured on a 6-point Likert scale ranging from 0=none of the time to 5=all of the time. The Birmingham IBS symptom questionnaire completed by the subjects provides assessment in the three dimensions pain, constipation and diarrhoea based on the frequency of symptoms. Birmingham IBS questionnaire three single items 'Diarrhoea', 'Constipation' and 'Urgency' were provided. In the below table, shifts in the scores from the baseline were analysed and reported. 'n' signifies those subjects who were evaluable for this measure at given time points for each group. '99999' signifies no subjects fall under the below mentioned criteria in the category for the given time points for respective reporting groups.

End point type	Secondary

End point timeframe:

Week 1 (Baseline), Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152[37]	70[38]		
Units: count of subjects				
Diarrhoea item score -4 (n= 149,68)	99999	1		
Diarrhoea item score -3 (n= 149,68)	4	1		
Diarrhoea item score -2 (n= 149,68)	13	13		
Diarrhoea item score -1 (n= 149,68)	41	15		
Diarrhoea item score 0 (n= 149,68)	69	30		
Diarrhoea item score 1 (n= 149,68)	19	7		
Diarrhoea item score 2 (n= 149,68)	1	1		
Diarrhoea item score 3 (n= 149,68)	2	99999		
Constipation item score -5 (n= 152,68)	99999	1		
Constipation item score -4 (n= 152,68)	1	99999		
Constipation item score -3 (n= 152,68)	7	5		
Constipation item score -2 (n= 152,68)	17	3		
Constipation item score -1 (n= 152,68)	34	16		
Constipation item score 0 (n= 152,68)	66	36		
Constipation item score 1 (n= 152,68)	23	5		
Constipation item score 2 (n= 152,68)	4	2		
Urgency item score -5 (n= 152,70)	2	99999		
Urgency item score -4 (n= 152,70)	4	4		
Urgency item score -3 (n= 152,70)	3	3		
Urgency item score -2 (n= 152,70)	24	8		
Urgency item score -1 (n= 152,70)	50	16		
Urgency item score 0 (n= 152,70)	46	18		
Urgency item score 1 (n= 152,70)	16	16		
Urgency item score 2 (n= 152,70)	5	2		
Urgency item score 3 (n= 152,70)	1	2		
Urgency item score 4 (n= 152,70)	1	1		

Notes:

[37] - FAS with number of evaluable subjects for this end point.

[38] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Birmingham IBS Symptom Questionnaire in IBS-C and IBS-D Subgroups – Change Between Week 1 and Week 4 for the Total Score

End point title	Birmingham IBS Symptom Questionnaire in IBS-C and IBS-D Subgroups – Change Between Week 1 and Week 4 for the Total Score

End point description:

Birmingham IBS symptom questionnaire was evaluated in IBS-C and IBS-D subgroups for the total score. Birmingham IBS symptom score comprises a self-completed questionnaire. It consists of 11 questions based on frequency of IBS related symptoms. This questionnaire completed by the subjects provides assessment in three dimensions pain, constipation and diarrhoea based on the frequency of symptoms. All single items of the questionnaire were then transformed to a total score ranging from 0 (no symptoms) to 100 (all symptoms). In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Week 1 (Baseline), Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[39]	25[40]		
Units: score on a scale				
arithmetic mean (standard deviation)				
IBS-C (n= 44, 22)	-10.45 (± 13.205)	-9.34 (± 12.181)		
IBS-D (n= 48, 25)	-13.98 (± 12.258)	-14.47 (± 13.941)		

Notes:

[39] - FAS with number of evaluable subjects for this end point.

[40] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Birmingham IBS Symptom Questionnaire in IBS-C and IBS-D Subgroups – Change Between Week 1 and Week 4 for the 3 Dimensions

End point title	Birmingham IBS Symptom Questionnaire in IBS-C and IBS-D Subgroups – Change Between Week 1 and Week 4 for the 3 Dimensions

End point description:

Birmingham IBS symptom questionnaire was evaluated in IBS-C and IBS-D subgroups for the 3 dimensions (pain, constipation, diarrhoea sub scales). Birmingham IBS symptom score comprises a self-completed questionnaire. It consists of 11 questions based on frequency of IBS related symptoms. This questionnaire completed by the subjects provides assessment in three dimensions pain, constipation and diarrhoea based on the frequency of symptoms. All single items of the questionnaire were then transformed to a total score ranging from 0 (no symptoms) to 100 (all symptoms). In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Week 1 (Baseline), Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[41]	27[42]		
Units: score on a scale				
arithmetic mean (standard deviation)				
IBS-C: IBS pain subscale (n=47,22)	-20.57 (± 21.120)	-16.67 (± 23.254)		
IBS-C: IBS constipation subscale(n=47,23)	-13.19 (± 23.488)	-14.49 (± 24.997)		
IBS-C: IBS diarrhoea subscale (n=45,23)	-2.58 (± 12.363)	-1.04 (± 8.199)		
IBS-D: IBS pain subscale (n=52,27)	-21.54 (± 17.092)	-22.22 (± 17.735)		
IBS-D: IBS constipation subscale (n=52,26)	-6.67 (± 14.995)	-1.54 (± 12.119)		
IBS-D: IBS diarrhoea subscale (n=48,26)	-13.92 (± 18.761)	-18.00 (± 17.933)		

Notes:

[41] - FAS with number of evaluable subjects for this end point.

[42] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Birmingham IBS Symptom Questionnaire in IBS-C and IBS-D Subgroups –Change Between Week 1 and Week 4 for 3 Single Items of Questionnaire

End point title	Birmingham IBS Symptom Questionnaire in IBS-C and IBS-D Subgroups –Change Between Week 1 and Week 4 for 3 Single Items of Questionnaire

End point description:

Birmingham IBS symptom questionnaire was evaluated in IBS-C and IBS-D subgroups for 3 single items of questionnaire (diarrhoea, constipation, urgency items). The Birmingham IBS symptom score comprises a self-completed questionnaire which consists of 11 questions based on the frequency of IBS related symptoms. Each question has a standard response scale with symptoms all being measured on a 6-point Likert scale ranging from 0=none of the time to 5=all of the time. The Birmingham IBS symptom questionnaire completed by the subjects provides assessment in the three dimensions pain, constipation and diarrhoea based on the frequency of symptoms.In the below table, shifts in the scores from the baseline were analysed and reported. ‘n’ signifies those subjects who were evaluable for this measure at given time points for each group. '99999' signifies no subjects fall under the below mentioned criteria in the category for the given time points for respective reporting groups.

End point type	Secondary

End point timeframe:

Week 1 (Baseline), Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[43]	27[44]		
Units: count of subjects				
number (not applicable)				
IBS-C: Diarrhoea item score -2 (n= 47,23)	2	1		
IBS-C: Diarrhoea item score -1 (n= 47,23)	7	4		
IBS-C: Diarrhoea item score 0 (n= 47,23)	28	14		
IBS-C: Diarrhoea item score 1 (n= 47,23)	7	3		
IBS-C: Diarrhoea item score 2 (n= 47,23)	1	1		
IBS-C: Diarrhoea item score 3 (n= 47,23)	2	99999		
IBS-C: Constipation item score -5 (n= 48,23)	99999	1		
IBS-C: Constipation item score -3 (n= 48,23)	5	3		
IBS-C: Constipation item score -2 (n= 48,23)	6	3		
IBS-C: Constipation item score -1 (n= 48,23)	14	5		
IBS-C: Constipation item score 0 (n= 48,23)	12	9		
IBS-C: Constipation item score 1 (n= 48,23)	8	1		
IBS-C: Constipation item score 2 (n= 48,23)	3	1		
IBS-C: Urgency item score -5 (n= 48,23)	1	99999		
IBS-C: Urgency item score -4 (n= 48,23)	99999	1		
IBS-C: Urgency item score -2 (n= 48,23)	7	1		
IBS-C: Urgency item score -1 (n= 48,23)	9	6		
IBS-C: Urgency item score 0 (n= 48,23)	23	7		
IBS-C: Urgency item score 1 (n= 48,23)	6	6		
IBS-C: Urgency item score 2 (n= 48,23)	2	2		
IBS-D: Diarrhoea item score -4 (n= 50,27)	99999	1		
IBS-D: Diarrhoea item score -3 (n= 50,27)	2	99999		
IBS-D: Diarrhoea item score -2 (n= 50,27)	8	9		
IBS-D: Diarrhoea item score -1 (n= 50,27)	17	6		
IBS-D: Diarrhoea item score 0 (n= 50,27)	17	8		
IBS-D: Diarrhoea item score 1 (n= 50,27)	6	3		
IBS-D: Constipation item score -3 (n= 52,26)	1	99999		
IBS-D: Constipation item score -2 (n= 52,26)	4	99999		
IBS-D: Constipation item score -1 (n= 52,26)	12	7		

IBS-D: Constipation item score 0 (n= 52,26)	31	16		
IBS-D: Constipation item score 1 (n= 52,26)	4	3		
IBS-D: Urgency item score -4 (n= 52,27)	4	3		
IBS-D: Urgency item score -3 (n= 52,27)	1	3		
IBS-D: Urgency item score -2 (n= 52,27)	12	5		
IBS-D: Urgency item score -1 (n= 52,27)	16	5		
IBS-D: Urgency item score 0 (n= 52,27)	10	5		
IBS-D: Urgency item score 1 (n= 52,27)	6	5		
IBS-D: Urgency item score 2 (n= 52,27)	3	99999		
IBS-D: Urgency item score 3 (n= 52,27)	99999	1		

Notes:

[43] - FAS with number of evaluable subjects for this end point.

[44] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Global Assessment of Tolerability on a 5-point Likert Scale by Investigator and Subject

End point title	Number of Subjects with Global Assessment of Tolerability on a 5-point Likert Scale by Investigator and Subject

End point description:

The investigator and subjects assessed the tolerability of the study treatment by using a five point Likert scale (1 = very good, 2 = good, 3 = moderate, 4 = poor, 5 = very poor). In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group, and '99999' signifies no subjects fall under the below mentioned criteria in the category for the given time points for respective reporting groups.

End point type	Secondary

End point timeframe:

Weeks 2 and 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159[45]	74[46]		
Units: count of subjects				
Investigator: Week 2 (n=159,74): very good	71	33		
Investigator: Week 2 (n=159,74): good	75	38		
Investigator: Week 2 (n=159,74): moderate	11	3		
Investigator: Week 2 (n=159,74): poor	1	99999		
Investigator: Week 2 (n=159,74): very poor	1	99999		
Investigator: Week 4 (n=153,72): very good	63	34		
Investigator: Week 4 (n=153,72): good	77	35		

Investigator: Week 4 (n=153,72): moderate	9	3		
Investigator: Week 4 (n=153,72): poor	4	99999		
Investigator: Week 4 (n=153,72): very poor	99999	99999		
Subject: Week 2 (n=159,74): very good	72	32		
Subject: Week 2 (n=159,74): good	73	36		
Subject: Week 2 (n=159,74): moderate	12	6		
Subject: Week 2 (n=159,74): poor	1	99999		
Subject: Week 2 (n=159,74): very poor	1	99999		
Subject: Week 4 (n=153,72): very good	62	31		
Subject: Week 4 (n=153,72): good	77	36		
Subject: Week 4 (n=153,72): moderate	10	5		
Subject: Week 4 (n=153,72): poor	1	99999		
Subject: Week 4 (n=153,72): very poor	3	99999		

Notes:

[45] - SAF with number of evaluable subjects for this specific end point.

[46] - SAF with number of evaluable subjects for this specific end point.

Statistical analyses

No statistical analyses for this end point

Secondary: IBS-QoL for IBS-C and IBS-D Subgroups: Change From Baseline for the Transformed Total Score at Week 4

End point title	IBS-QoL for IBS-C and IBS-D Subgroups: Change From Baseline for the Transformed Total Score at Week 4

End point description:

IBS-QoL is a self-report Qol measure to assess impact of IBS and its treatment. It consists of 34 items, each with a 5-point response scale. Individual responses to 34 items were summed up, averaged for total score, then transformed to 0-100 scale. Higher scores indicate better IBS specific quality of life. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[47]	27[48]		
Units: score on a scale				
arithmetic mean (standard deviation)				
IBS-C (n= 44, 21)	9.88 (± 17.772)	10.36 (± 12.595)		
IBS-D (n= 48, 27)	13.01 (± 16.092)	12.96 (± 19.277)		

Notes:

[47] - FAS with number of evaluable subjects for this specific end point.

[48] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

Statistical analysis title	Statistical analyis 1: IBS-C

Statistical analysis description:

IBS-QoL transformed total score was tested based on ANCOVA model with transformed total score at Week 4 adjusted for treatment, center and week 1 value. Results were presented by differences in LS mean difference together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5276
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.74
upper limit	11.07

Statistical analysis title	Statistical analyis 2: IBS-D

Statistical analysis description:

IBS-QoL transformed total score was tested based on ANCOVA model with transformed total score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in LS mean difference together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.792
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.37
upper limit	8.32

Secondary: IBS-QoL: Change From Baseline for the 8 Transformed Subscale Scores at Week 4

End point title	IBS-QoL: Change From Baseline for the 8 Transformed Subscale Scores at Week 4

End point description:

IBS-QoL is a self-report Qol measure to assess impact of IBS and its treatment. It consists of 34 items, each with a 5-point response scale. Individual responses to 34 items were summed up, averaged for total score, then transformed to 0-100 scale. Higher scores indicate better IBS specific quality of life. There were also eight subscale scores for the IBS-QOL (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual relationships). In the below table, TS means transformed subscale, and here, 'n' signifies those subjects who were evaluable for this measure

at given time points for each group.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150[49]	70[50]		
Units: score on a scale				
arithmetic mean (standard deviation)				
TS dysphoria (n=149,68)	12.84 (± 17.919)	12.13 (± 20.977)		
TS interference with activity (n= 146, 68)	8.34 (± 18.500)	10.24 (± 19.725)		
TS body image (n=148,69)	11.06 (± 19.752)	10.24 (± 17.709)		
TS health worry (n=149,68)	10.91 (± 18.682)	10.78 (± 21.016)		
TS food avoidance (n=147,70)	9.52 (± 25.359)	12.50 (± 22.556)		
TS social reaction (n=150,68)	9.00 (± 17.143)	9.38 (± 20.417)		
TS sexual (n=148,69)	6.67 (± 21.499)	4.35 (± 20.654)		
TS relationships (n=150,66)	7.00 (± 18.723)	6.82 (± 20.564)		

Notes:

[49] - FAS with number of evaluable subjects for this specific end point.

[50] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

Statistical analysis title	IBS-QoL: Transformed subscale dysphoria

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center, underlying IBS type and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3021
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.31
upper limit	7.41

Statistical analysis title	Transformed subscale interference with activity

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center, underlying IBS type and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6357
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.63
upper limit	5.94

Statistical analysis title	IBS-QoL: Transformed subscale body image

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center, underlying IBS type and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5711
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.39
upper limit	6.12

Statistical analysis title	IBS-QoL: Transformed subscale health worry

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center, underlying IBS type and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-

values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4424
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.99
upper limit	6.82

Statistical analysis title	IBS-QoL: Transformed subscale food avoidance

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center, underlying IBS type and week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8031
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.38
upper limit	5.72

Statistical analysis title	IBS-QoL: Transformed subscale social reaction

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center, underlying IBS type and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo

Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.592
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.54
upper limit	6.18

Statistical analysis title	IBS-QoL: Transformed subscale sexual

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center, underlying IBS type and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2725
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.34
upper limit	8.24

Statistical analysis title	IBS-QoL: Transformed subscale relationships

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center, underlying IBS type and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5177
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	6.24

Secondary: IBS-QoL for IBS-C and IBS-D Subgroups: Change From Baseline for the 8 Transformed Subscale Scores at Week 4

End point title	IBS-QoL for IBS-C and IBS-D Subgroups: Change From Baseline for the 8 Transformed Subscale Scores at Week 4

End point description:

IBS-QoL is a self-report Qol measure to assess impact of IBS and its treatment. It consists of 34 items, each with a 5-point response scale. Individual responses to 34 items were summed up, averaged for total score, then transformed to 0-100 scale. Higher scores indicate better IBS specific quality of life. There were also eight subscale scores for the IBS-QOL (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual relationships). In the below table, TS means transformed subscale, and here, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[51]	27[52]		
Units: score on a scale				
arithmetic mean (standard deviation)				
IBS-C: TS dysphoria (n=47,22)	13.30 (± 20.476)	15.06 (± 18.791)		
IBS-D: TS dysphoria (n=50,27)	17.38 (± 17.303)	14.93 (± 25.155)		
IBS-C: TS interference with activity (n=46,22)	7.07 (± 18.725)	8.60 (± 14.691)		
IBS-D: TS interference with activity (n=49,27)	12.54 (± 21.343)	13.89 (± 23.216)		
IBS-C: TS body image (n=45,22)	8.61 (± 23.548)	10.80 (± 13.933)		
IBS-D: TS body image (n=51,27)	14.58 (± 17.707)	13.43 (± 21.350)		
IBS-C: TS health worry (n=47,22)	12.59 (± 21.343)	15.15 (± 21.461)		
IBS-D: TS health worry (n=51,27)	11.60 (± 18.187)	12.65 (± 18.253)		
IBS-C: TS food avoidance (n=46,23)	8.33 (± 25.154)	11.23 (± 20.506)		
IBS-D: TS food avoidance (n=51,27)	13.40 (± 24.099)	17.59 (± 19.657)		
IBS-C: TS social reaction (n=47,22)	9.18 (± 18.145)	11.08 (± 17.565)		
IBS-D: TS social reaction (n=51,27)	9.19 (± 18.301)	10.88 (± 24.119)		

IBS-C: TS sexual (n=45,23)	8.89 (± 23.929)	7.07 (± 21.594)		
IBS-D: TS sexual (n=51,27)	7.11 (± 24.142)	6.94 (± 21.183)		
IBS-C: TS relationships (n=46,21)	6.34 (± 17.496)	7.94 (± 20.152)		
IBS-D: TS relationships (n=52,27)	10.26 (± 23.257)	7.41 (± 23.721)		

Notes:

[51] - FAS with number of evaluable subjects for this end point.

[52] - FAS with number of evaluable subjects for this end point.

Statistical analyses

Statistical analysis title	IBS-C: TS dysphoria

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.51
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.66
upper limit	13.26

Statistical analysis title	IBS-D: TS dysphoria

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6331
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.59
upper limit	10.75

Statistical analysis title	IBS-C: TS interference with activity

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9393
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.17
upper limit	8.82

Statistical analysis title	IBS-D: TS interference with activity

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6475
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	11.34

Statistical analysis title	IBS-C: TS body image

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8943
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.51
upper limit	10.87

Statistical analysis title	IBS-D: TS body image

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9489
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.57
upper limit	8.07

Statistical analysis title	IBS-C: TS health worry

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale

score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4863
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	3.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.56
upper limit	13.63

Statistical analysis title	IBS-D: TS health worry

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7329
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.02
upper limit	6.37

Statistical analysis title	IBS-C: TS food avoidance

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8417
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.07
upper limit	12.32

Statistical analysis title	IBS-D: TS food avoidance

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8468
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.02
upper limit	9.89

Statistical analysis title	IBS-C: TS social reaction

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4717
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	3.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.51
upper limit	11.77

Statistical analysis title	IBS-D: TS social reaction

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5524
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.84
upper limit	6.39

Statistical analysis title	IBS-C: TS sexual

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4729
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	3.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.57
upper limit	14

Statistical analysis title	IBS-D: TS sexual

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7376
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.19
upper limit	11.51

Statistical analysis title	IBS-C: TS relationships

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	Placebo v STW 5 (Iberogast)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6652
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.09
upper limit	11.02

Statistical analysis title	IBS-D: TS relationships

Statistical analysis description:

IBS-QoL transformed subscale score was tested based on ANCOVA model with transformed subscale

score at Week 4 adjusted for treatment, center and Week 1 value. Results were presented by differences in least-square means (LS mean difference) together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9849
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.75
upper limit	8.58

Secondary: Change of Pain Intensity From Baseline to Week 4 in the Subgroups IBS-C and IBS-D

End point title	Change of Pain Intensity From Baseline to Week 4 in the Subgroups IBS-C and IBS-D

End point description:

Pain intensity was assessed in subjects suffering from diarrhoea-predominant IBS and constipation-predominant IBS in the evening. The abdominal pain intensity was evaluated by using an 10 cm VAS ranging from no pain to worst pain that asked subjects daily to rate their 'worst abdominal pain over the past 24-hours'. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[53]	25[54]		
Units: centimeter (cm)				
arithmetic mean (standard deviation)				
IBS-C (n= 47,22)	-1.52 (± 2.683)	-2.22 (± 3.142)		
IBS-D (n= 51,25)	-2.43 (± 2.562)	-2.81 (± 2.701)		

Notes:

[53] - FAS with number of evaluable subjects for this specific end point.

[54] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

Statistical analysis title	Statistical analysis 1: IBS-C

Statistical analysis description:

Change of pain intensity from baseline to week 4 was tested using an ANCOVA model with treatment, center and underlying IBS type as fixed effects and the baseline value as covariate. Results are presented by LS mean difference together with the corresponding p-values and 95% confidence intervals.

Comparison groups	Placebo v STW 5 (Iberogast)
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7802
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1.2

Statistical analysis title	Statistical analysis 1: IBS-D

Statistical analysis description:

Change of pain intensity from baseline to week 4 was tested using an ANCOVA model with treatment, center and underlying IBS type as fixed effects and the baseline value as covariate. Results are presented by LS mean difference together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3497
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	1.46

Secondary: Change of Pain Intensity From Baseline to Week 2 in the Subgroups IBS-C and IBS-D

End point title	Change of Pain Intensity From Baseline to Week 2 in the Subgroups IBS-C and IBS-D

End point description:

Pain intensity was assessed in subjects suffering from diarrhoea-predominant IBS and constipation-predominant IBS in the evening. The abdominal pain intensity was evaluated by using an 10 cm VAS ranging from no pain to worst pain that asked subjects daily to rate their ‘worst abdominal pain over the past 24-hours’. In the below table, ‘n’ signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Baseline, Week 2

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[55]	27[56]		
Units: centimeter (cm)				
arithmetic mean (standard deviation)				
IBS-C (n= 49,23)	-1.28 (± 2.730)	-1.26 (± 2.002)		
IBS-D (n= 59,27)	-2.14 (± 2.412)	-2.36 (± 2.705)		

Notes:

[55] - FAS with number of evaluable subjects for this specific end point.

[56] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

Statistical analysis title	Statistical analysis 1: IBS-C

Statistical analysis description:

Change of pain intensity from baseline to week 2 was tested using an ANCOVA model with treatment, center and underlying IBS type as fixed effects and the baseline value as covariate. Results are presented by LS mean difference together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1891
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	0.42

Statistical analysis title	Statistical analysis 2: IBS-D

Statistical analysis description:

Change of pain intensity from baseline to week 2 was tested using an ANCOVA model with treatment, center and underlying IBS type as fixed effects and the baseline value as covariate. Results are presented by LS mean difference together with the corresponding p-values and 95% confidence intervals.

Comparison groups	STW 5 (Iberogast) v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8358
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	1.14

Secondary: Number of Subjects with Treatment Emergent Adverse Events

End point title	Number of Subjects with Treatment Emergent Adverse Events

End point description:

An adverse event (AE) was any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. A treatment-emergent adverse event (TEAE) was defined as any event with onset or worsening after the start of investigational medicinal product administration.

End point type	Secondary

End point timeframe:

Baseline up to Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[57]	76[58]		
Units: count of subjects	37	18		

Notes:

[57] - SAF

[58] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Abnormal Changes in Vital Signs

End point title	Number of Subjects with Clinically Significant Abnormal Changes in Vital Signs

End point description:

The vital signs such as blood pressure, pulse and body weight were assessed for the clinically abnormal significant changes and reported.

End point type	Secondary

End point timeframe:

Baseline up to Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[59]	76[60]		
Units: count of subjects	0	0		

Notes:

[59] - SAF

[60] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Abnormal Changes in Laboratory Parameters

End point title	Number of Subjects with Clinically Significant Abnormal Changes in Laboratory Parameters

End point description:

The laboratory parameters such as haematology, blood chemistry, urinalysis were assessed for the clinically significant abnormal changes and reported.

End point type	Secondary

End point timeframe:

Baseline up to Week 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[61]	76[62]		
Units: count of subjects	3	2		

Notes:

[61] - SAF

[62] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Global Assessment of Efficacy on a 5-point Likert Scale by Investigator and Subject

End point title	Number of Subjects with Global Assessment of Efficacy on a 5-point Likert Scale by Investigator and Subject

End point description:

The investigator and the subjects assessed the efficacy of the study treatment separately by using a five point Likert scale (1 = very good, 2 = good, 3 = moderate, 4 = poor, 5 = very poor). In the below table, ‘n’ signifies those subjects who were evaluable for this measure at given time points for each group, and '99999' signifies no subjects fall under the below mentioned criteria in the category for the given time points for respective reporting groups.

End point type	Secondary

End point timeframe:

Weeks 2 and 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159[63]	74[64]		
Units: count of subjects				
Investigator: Week 2 (n=159,74): very good	5	3		
Investigator: Week 2 (n=159,74): good	61	21		
Investigator: Week 2 (n=159,74): moderate	46	30		
Investigator: Week 2 (n=159,74): poor	43	18		
Investigator: Week 2 (n=159,74): very poor	4	2		
Investigator: Week 4 (n=153,72): very good	11	9		
Investigator: Week 4 (n=153,72): good	59	26		
Investigator: Week 4 (n=153,72): moderate	38	22		
Investigator: Week 4 (n=153,72): poor	42	15		
Investigator: Week 4 (n=153,72): very poor	3	99999		
Subject: Week 2 (n=159,74): very good	5	3		
Subject: Week 2 (n=159,74): good	57	23		
Subject: Week 2 (n=159,74): moderate	53	27		
Subject: Week 2 (n=159,74): poor	40	17		
Subject: Week 2 (n=159,74): very poor	4	4		
Subject: Week 4 (n=153,72): very good	16	7		
Subject: Week 4 (n=153,72): good	56	27		
Subject: Week 4 (n=153,72): moderate	38	23		
Subject: Week 4 (n=153,72): poor	37	14		
Subject: Week 4 (n=153,72): very poor	6	1		

Notes:

[63] - FAS with number of evaluable subjects for this specific end point.

[64] - FAS with number of evaluable subjects for this specific end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly Usage of Bisacodyl Tablets

End point title	Weekly Usage of Bisacodyl Tablets

End point description:

Subjects were instructed to use bisacodyl only in case of absence of bowel movements for more than three days. Investigators dispensed the rescue medication bisacodyl for treatment of severe constipation. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3 and 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[65]	75[66]		
Units: number of tablets				
arithmetic mean (standard deviation)				
Week 1 (n= 161,75)	0.15 (± 0.577)	0.27 (± 1.057)		
Week 2 (n= 160,73)	0.12 (± 0.552)	0.26 (± 1.041)		
Week 3 (n= 155,73)	0.18 (± 1.197)	0.21 (± 0.927)		
Week 4 (n= 151,71)	0.08 (± 0.382)	0.21 (± 1.081)		

Notes:

[65] - FAS with number of evaluable subjects for this end point.

[66] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly Usage of Loperamid Tablets

End point title	Weekly Usage of Loperamid Tablets

End point description:

Subjects were instructed to use loperamide only in case of three consecutive bowel movements with type 6 according to BSS or in case of first bowel movement with type 7 according to BSS. As per BSS: types 1-2, hard (suggestive of constipation); types 3-5, normal; types 6-7, loose/liquid (associated with diarrhoea). Investigators dispensed the rescue medication loperamide for treatment of severe diarrhoea. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3 and 4

End point values	STW 5 (Iberogast)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[67]	75[68]		
Units: number of tablets				
arithmetic mean (standard deviation)				
Week 1 (n= 161,75)	0.20 (± 1.092)	0.17 (± 0.665)		
Week 2 (n= 160,73)	0.18 (± 1.113)	0.14 (± 0.535)		
Week 3 (n= 155,73)	0.22 (± 0.811)	0.10 (± 0.414)		
Week 4 (n= 151,71)	0.24 (± 1.105)	0.21 (± 0.747)		

Notes:

[67] - FAS with number of evaluable subjects for this end point.

[68] - FAS with number of evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 4	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subject received placebo matched to STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).	
Reporting group title	STW5 (Iberogast)
Reporting group description:	
Subjects received STW 5 orally 20 drops three times daily (3*20 drops per day) before or during the meals for 4 weeks (from Day 1 to Day 29).	

Serious adverse events	Placebo	STW5 (Iberogast)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 76 (0.00%)	0 / 167 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	STW5 (Iberogast)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 76 (23.68%)	37 / 167 (22.16%)	
Vascular disorders			
Varicose vein			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Drug intolerance			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Influenza like illness			

subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Soft tissue inflammation			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Investigations			
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	2 / 76 (2.63%)	1 / 167 (0.60%)	
occurrences (all)	2	1	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 76 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	3	
Abdominal pain upper			
subjects affected / exposed	1 / 76 (1.32%)	6 / 167 (3.59%)	
occurrences (all)	1	6	
Diarrhoea			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Enteritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 76 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 76 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Irritable bowel syndrome			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 76 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 76 (2.63%)	3 / 167 (1.80%)	
occurrences (all)	2	3	
Muscle spasms			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 76 (2.63%)	2 / 167 (1.20%)	
occurrences (all)	2	2	
Cystitis			
subjects affected / exposed	0 / 76 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	3	
Gastroenteritis			
subjects affected / exposed	0 / 76 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Herpes simplex			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	

Nasopharyngitis			
subjects affected / exposed	5 / 76 (6.58%)	8 / 167 (4.79%)	
occurrences (all)	5	8	
Salpingo-oophoritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Sinobronchitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 167 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 167 (0.60%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	1 / 76 (1.32%)	1 / 167 (0.60%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

'99999' signifies that no subjects fall under the mentioned criteria in the category for the given time points for respective reporting groups.

Notes: