# 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<br>arithmetic mean<br>standard deviation | <br>54.86<br>± 18.412 | <br>56.53<br>± 16.791 | <br><br>- |
| 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<br>arithmetic mean<br>standard deviation | <br>50.34<br>± 23.494 | <br>62.67<br>± 30.852 | <br><br>- |
| 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<br>arithmetic mean<br>standard deviation | <br>19.58<br>± 12.922 | <br>11.52<br>± 11.450 | <br><br>- |
| 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<br>arithmetic mean<br>standard deviation | <br>57.70<br>± 14.084 | <br>56.05<br>± 16.357 | <br><br>- |
| 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<br>arithmetic mean<br>standard deviation | <br>20.44<br>± 20.399 | <br>14.36<br>± 12.746 | <br><br>- |
| 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: