The Efficacy of Symbion™ In The Treatment Of Irritable Bowel Syndrome: A Randomized, Double-Blind Placebo Controlled Clinical Trial

A Study Sponsored by Pharmabiotix Inc

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INTRODUCTION

Irritable Bowel Syndrome (IBS) is a functional illness, which is characterized by abdominal pain or discomfort associated with change in bowel habits and characteristics of disrupted defecation (1). IBS is one of the most common gastrointestinal (GI) disorders with one tenth to one fifth of the general adult population, with female predominance, reporting IBS symptoms (1).

IBS is associated with a huge financial burden represented by direct medical cost and loss of productivity associated absenteeism of work (2), as well as deterioration of the individual's quality of life both socially and professionally (3).

Fifteen percent of the North American population is suffering from IBS representing one of the highest rates in the world (4). One of the major problems associated with IBS is that there is no approved medication to treat IBS, the treatment that the IBS patient receives aims to address his/her concerns and relief of his/her symptoms (5).

Probiotics are living microscopic organisms, or microorganisms, that scientific research has shown to benefit human health. Most often they are bacteria, but they may also be other organisms such as yeasts. In some cases, they are similar, or the same, as the "good" bacteria already in a human body, particularly those in the gut. The most common probiotic bacteria come from two groups, *Lactobacillus* or *Bifidobacterium*, although it is important to remember that there are many other types of bacteria that are also classified as probiotics (eg, *Streptococcus, E. coli*). The exact mechanism by which probiotics may function is not known.

Probiotics are most often used to promote digestive health. Irritable bowel syndrome is one disorders of the gut that may respond to probiotics, particularly *Bifidobacterium infantis*, *Sacchromyces boulardii, Lactobacillus plantarum* and combination probiotics to regulate stool frequency. Probiotics may also help relieve bloating from gas. A systematic review by Moayyedi and colleagues in 2008 concluded that probiotics appear to be beneficial for patients with IBS, but it is not clear which bacteria are most effective.

Symbion ™ is a probiotic which is composed of the following microorganisms contained in a veggie capsule: *Bacillus coagulans* (33.64 mg) , *Bacillus subtilis* (16.67 mg), *Enterococcus faecium* (16.67 mg), Fructo-oligosacharride (600 mg). *Bacillus coagulans* is a non-pathogenic, Gram positive, spore forming bacteria that produces lactic acid. Though not normally found in the gut, Bacillus coagulans strains have been used as general nutritional supplements and agents to control constipation and diarrhea in humans and animals. *Bacillus subtilis* is a Gram-positive, endospore-forming soil bacteria comprising aerobic and a few facultatively anaerobic rod shaped bacteria. Bacillus subtilis was historically used to treat dysentery. *Enterococcus faecium* is a facultative

(growing with or without oxygen) anaerobic, Gram positive cocci that produces lactic acid. The Enterococcus faecium strain is a natural inhabitant of the mammalian GI tract.

The *primary objective* of this randomized trial was to compare the effect of Symbion™ (PX0612) to placebo, administered over 12 weeks, in diarrhea predominant IBS (IBS-D)-patients on bowel movements using patient's reported stool frequency (number of stools).

Secondary objectives were to compare the effect of Symbion™ (PX0612) to placebo using the patient's rating for IBS symptoms based on the assessment of the overall symptom relief including: stool frequency; abdominal pain; stool consistency; straining; urgency; feeling of incomplete defecation; bloating; and passage of mucus. In addition, the study evaluated changes in changes in upper GI symptoms (i.e. heartburn, early satiety, postprandial fullness, sensation of prolonged digestion, nausea and vomiting) over the study period; IBS severity score; and changes in the patient's assessment of their quality of life using SF-36.

METHODS

A randomized double-blind parallel group placebo-controlled study was conducted in Edmonton, Alberta, Canada. Participants were recruited through advertising to the general public using traditional (i.e. flyers, radio, and local newspaper) as well as a social media campaign.

Inclusion Criteria: Participants were adults between the ages of 18 and 65 years who had mild to moderate diarrhea related to IBS as per the Functional Bowel Disorder Severity Index (FBDSI)). IBS was defined per the Rome criteria with persistent symptoms for at least 3 months including: (1) abdominal pain or discomfort which is relieved by defecation, and/or associated with a change in frequency of stool and/or consistency of stool; and (2) at least two of the following, at least a quarter of occasions or days (25%): (a) altered stool frequency ($\geq$ 3 bowel movements/day or < 3 bowel movements/week); (b) altered stool form (lumpy/hard or loose/watery stools); (c) altered stool passage (straining, urgency or feeling of incomplete evacuation); (d) passage of mucus; (e) bloating or feeling of abdominal distention. Diarrhea is defined as having loose watery stools at least three times per day.

Exclusion Criteria: Patient were excluded if by there was evidence for other medical or surgical conditions revealed in a pre-study medical assessment including history, physical examination or evaluation of existing laboratory assessments that would interfere with the administration or assessment of the study product; especially patients presenting with rectal bleeding, weight loss, nausea, vomiting, fever, iron deficiency anemia, nocturnal symptoms and a family history of colorectal cancer, inflammatory bowel disease, and celiac disease.. In addition, pregnant or lactating women; females of child bearing age without acceptable birth control measures; patients using other

medications or natural health products[1]; untreated lactose intolerance; allergy to milk or soy products; using a catheter; or constipation predominant IBS.. In addition patients were excluded if exceeding the limits of permitted medications (more than 2 days/week during the study period)[2]; new diagnosis of IBS over age 50without a colonoscopy in the previous 5 years; allergies for the active ingredients or any of the excipients; immunosuppression (such as AIDS, lymphoma, long term corticosteroid treatment).

Study Procedures: A two-week run-in period was followed by 12 weeks of active treatment (Figure 1). At visit 1 inclusion/exclusion criteria were assessed, study procedures explained, informed consent obtained, as well as the following: (a) baseline demographics; (b) medical history and examination; and (c) pregnancy test. During the run-in period, participants were asked to keep a symptom diary (Table 1) based on the recommendations of the Rome committee (7); to follow certain dietary recommendations[3]; to stop non-permitted medications; and to reduce permitted medications beings used more than 2 times per week.

Following the run-in period, participants underwent a baseline assessment at visit 2 for exclusion criteria based on the diary, completion of the diary; incapacitating abdominal pain at least twice during the 'run-in' period; abdominal pain/discomfort for more than

1 5-HT3 antagonist, spasmolytics, anticholinergics, cholestyramine, anti-flatulence agents, metoclopramide, gastric-anti secretory agents (proton pump inhibitors; for indications other than Gastroesophageal Reflux Disease (GERD)), narcotics, anti-diarrheal drugs, and systemic steroids; patients requiring the use of antibiotics either in medicine form of natural (e.g. grapefruit seed extract, olive leaf extract, oil of oregano, colloidal silver and highly concentrated garlic preparations); peppermint oil, cognitive behavior therapy

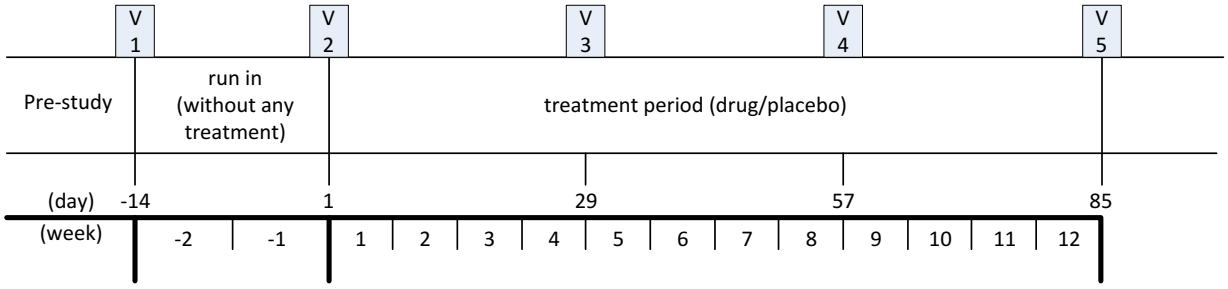
2 alginate, antacids and analgesics (limited to acetaminophen ≤ 1000 mg/day, acetylsalicylic acid or NSAIDS no more than 2 tablets/day), (stable dose throughout the study period, anti-depressants (must be on a stable dose > 3 months), fiber supplements, psyllium hydrophilic mucilloid, gastric anti secretory agents (only for GERD patients who are on a stable dose > 3 months; patients should be able to differentiate between IBS and GERD symptoms), acetylsalicylic acid ≤ 325 mg/day, sedatives. Deliverance medications: Mild laxatives only if necessary.]. Any other medications can be used without limits based on the clinical judgment of the treating investigator.

3 Eliminate or reduce sugars including refined sugar, brown sugar, syrups, molasses, agave, cane juice and honey. The rationale is that sugars play a major role in the overgrowth of small intestinal bacteria and other pathogens such as fungi; avoid known trigger foods, such as fatty fried foods and spicy foods, and any foods that the patient has a known allergy or intolerance to; and to reduce the consumption of processed foods.

50% of the 'run-in' period; and the absence of bowel movement for more than 4 days (either consecutive or non-consecutive) during the 'run-in' period. Participants meeting inclusion/exclusion criteria were then randomized 1:1 basis using a centralized secure website to ensure allocation concealment. Baselines assessments included the SF-36 for quality of life, medication review, and report of subjective upper GI symptoms including frequency of vomiting per week, heartburn, early satiety, postprandial fullness, sensation of prolonged digestion and nausea on a scale of 0-4 (0 is none, 1 mild, 2 moderate, 3 severe and 4 is incapacitating).

During the 12-week active treatment period, participants were provided study product; asked to maintain the daily symptom diary; and underwent 3 more assessments at weeks 4, 8, and 12. At each visit, participants were assessed for exclusion criteria and compliance using pill counts; review of other medications; asked about adverse events; and to report upper GI symptoms (as described above). In addition, the SF-36 was re-administered at week 12 as well as the Functional Bowel Disorder Severity Index (FBDSI) evaluation. Participants were withdrawn from the study if at any time they developed any of the exclusion criteria. Participants were also permitted to drop-out of the study for any reason.

Figure 1: Overall Study Design



V = patients visit

Table 1: Daily symptom diary

Feature	**Scale/assessment**
Stool frequency	Number of stools/day
Abdominal pain	Scale of 0-4 (0 is none, 1 mild, 2 moderate, 3 severe and 4 is incapacitating)
Stool consistency	Scale of 1-7 according to the Bristol stool form scale (1 is separate hard lumps, 2 is sausage shaped but lumpy, 3 is like a sausage or a snake but with cracks on the surface, 4 is like a sausage or a snake, smooth and soft, 5 is soft blobs with clear-cut edges, 6 is fluffy pieces with ragged edges, a mushy stool and 7 is watery, no solid pieces)
Straining	Yes/No
Urgency	Yes/No
Feeling of incomplete defecation	Yes/No
Bloating	Yes/No
Passage of mucus	Yes/No
Any medication taken for bowel movement	Either for diarrhea or constipation
Food frequency and kind to assess the ingestion of potential symptom-exacerbating foods	

Study product and dosing regimen

Participants in the 'intervention' group received PX0612 which is a probiotic composed of the following ingredients contained in a veggie capsule, being one dose:

Bacillus coagulans	200 million CFU	33.34mg
Bacillus subtilis	100 million CFU	16.67mg
Enterococcus faecium	100 million CFU	16.67mg
Fructo-oligosacharride	a nutrient for the packaged product	600.0mg
	Total	668.68 mg

Patients in the 'placebo' group will received capsules in which the main ingredient was Di-Calcium Phosphate.

Participants were instructed to take 1 capsule per day with any meal. At the beginning of week 3, they were instructed to take one capsule with breakfast and one with their evening meal. At the beginning of week 7, they were instructed to take one capsule in the morning, one at lunch and one at the evening meal.

Efficacy Outcomes:
primary outcome is the difference in change in the mean number of bowel movements (stool frequency) between the 'intervention' group and the 'placebo' group comparing the run-in period of 2 weeks with the last 2 weeks of active treatment (weeks 11 and 12).

Secondary outcome measures were assessed comparing means/proportions during the 2 week run-in period with the last 2 weeks of active treatment for the following variables: (1) the difference in the overall symptoms relief between the 'intervention' group and the 'placebo' group over the study period; (2) differences in abdominal pain/discomfort; (3) stool consistency; (4) stool frequency; (5) straining; (6) urgency; (7) bloating; (8) feeling of incomplete defecation; and (9) passage of mucus. The differences from baseline to week 12 in quality of life using SF-36 was also assessed comparing the two groups.

Adverse events: Serious adverse event (SAE) or serious adverse reaction were classified as any untoward medical occurrence at any dose including death, life-threatening event, inpatient hospitalization, persistent disability, congenital anomaly, or medically important as determined by a medical adjudication. SAE were considered related if there was a reasonable possibility according to the treating investigator that the study product may have caused the event.

Sample Size Calculation: Using the information from Dolin (2009) (approximate reduction of 0.47 in the bowel movements in the placebo group versus 0.8 in the treatment group), power of 80% and 95% confidence interval, 78 patients (39 in each group) are required to be able to detect a minimum difference of 0.33 in change in the number of daily bowel movements between the 'intervention' group and the 'placebo' group over the study period.

Statistical Analyses: An interim analysis was planned after a minimum of 20 patients in each study group have completed the trial. The interim analysis included all safety and efficacy data. For the interim analysis, the study data was unblinded to the biostatistician or sponsor representative. All analysis will be conducted on 'Intention to Treat' basis. A comparison of baseline characteristics will be performed using t-tests or Mann-Whitney U tests when sample populations were not normal for continuous variables and chi-squared test for categorical variables. Since the analysis was conducted on 'Intention to Treat' basis, the last available data from drop-outs was carried forward in the analysis.

RESULTS

Baseline characteristics

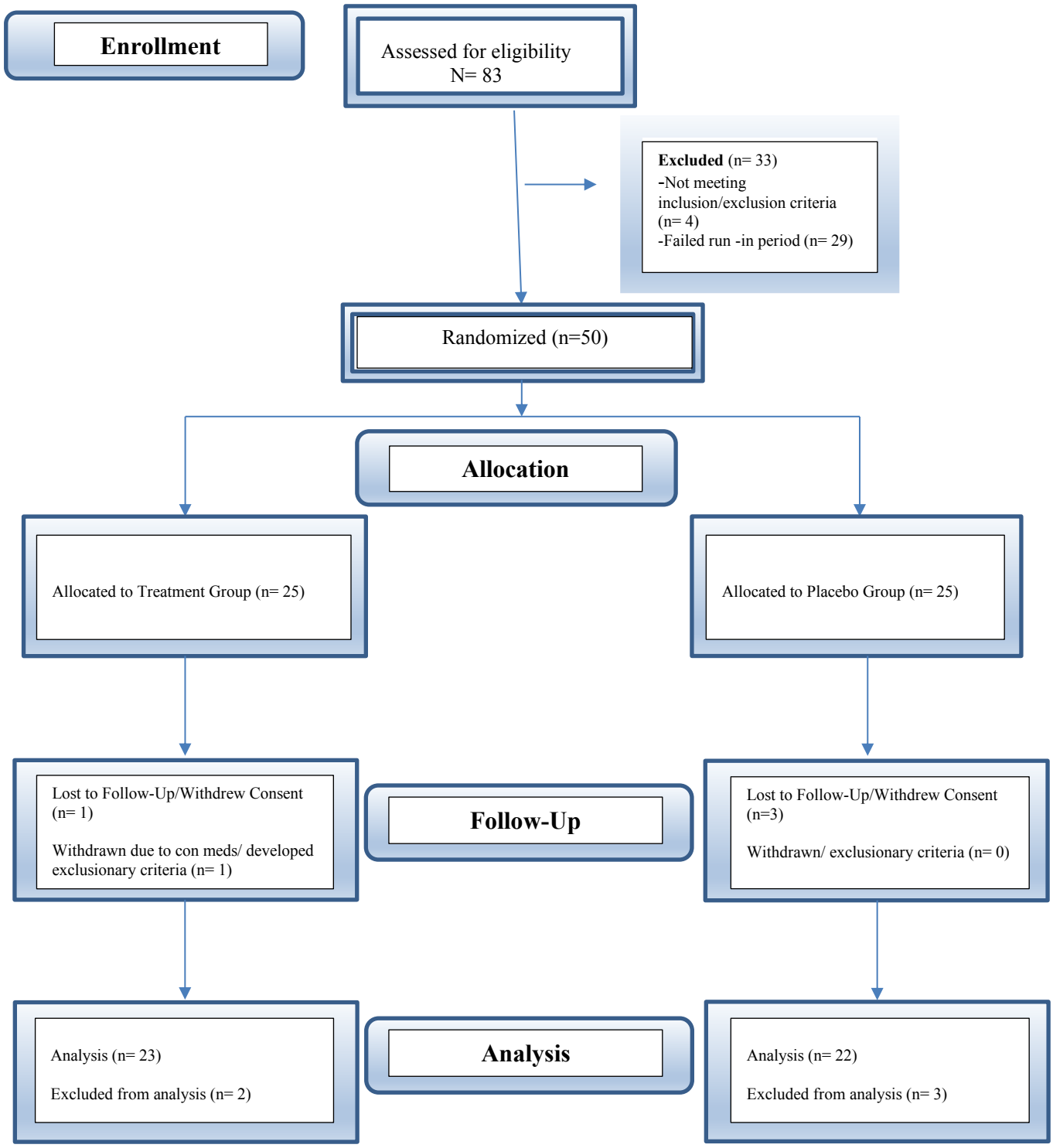
A total of 50 participants were randomized with a mean age of 35 years (SD 1.6) of which 27 (54%) were female. Included in the intention to treat analysis were 45 participants (Figure 2: CONSORT diagram). The groups had very similar baseline characteristics for key outcome measures (Table 2)

Table 1: Baseline Characteristics and Symptoms

Characteristics and Symptoms	**A Group (Mean (95% CI))**	**B Group (Mean (95% CI))**
Stool frequency/day (2-week run-in)	2.35 (1.96- 2.73)	2.39 (1.87 - 2.73)
Abdominal pain severity (2-week run-in; scale 0-4)	1.34 (1.13 - 1.55)	1.2 (1.03 - 1.38)
Stool consistency (2-week run-in)	5.08 (4.72 - 5.43)	4.73 (4.39 - 5.06)
FBDSI IBS Severity Score	272 (243-301)	234 (196-271)
SF 36 PCS Score baseline timepoint	48.92 (45.80-52.04)	50.49 (47.35-53.63)

Compliance varied with a mean range of missed doses between 0 and 10 for each participant and an overall mean of 3.2 missed doses (SD 0.3).

Figure 2: Symbion- PX0612 CONSORT Flow Diagram



Primary Efficacy Outcome: Difference in change in the bowel movements (stool frequency)

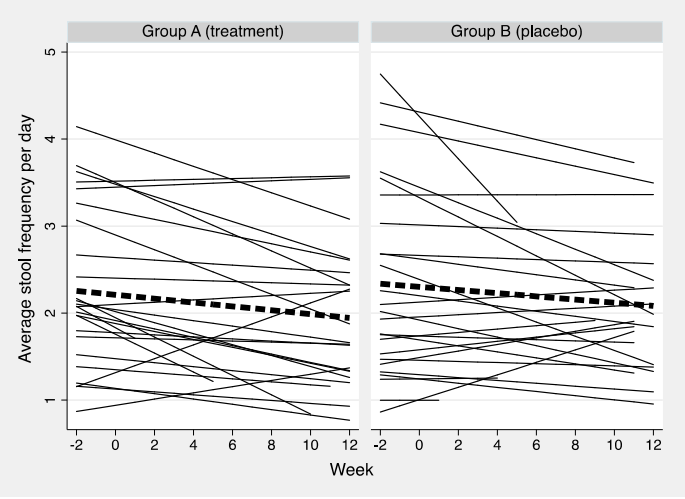
The stool frequency at baseline (day 1-14) was similar between the two groups (Table 1). The average stool frequency during the last two weeks of treatment was 1.92 (95% CI 1.55 - 2.29) for the group A (treatment) and 2.12 (95% CI 1.77 - 2.47) for the group B (placebo). The difference from baseline in the group A (treatment) was a reduction in stool frequency of 0.46 (95% CI 0.25 - 0.67) and 0.21 (95% CI -0.04 - 0.46) in the group B (placebo). The primary outcome measure of the difference in change of average stool frequency between group A (treatment) and group B (placebo) was not statistically significant (p = 0.48) using the Mann Whitney U test since the distribution of the variable was not normal. The post-hoc achieved power was 34.3%.

Recalculation of sample size requirement based on observed data (unplanned analysis)

Group	N	Mean	Std Dev	95% CI for mean		Median	Lower Quartile	Upper Quartile	Minimum	Maximum
				Upper	Lower					
A	23	0.46	0.49	0.25	0.67	0.36	0.07	0.86	-0.43	1.50
B	22	0.21	0.55	-0.04	0.46	0.14	-0.14	0.43	-0.80	1.43

Based on the observed data above and based on the same planned analysis for the primary outcome, the estimated sample size required would be 64 participants per group (total 128) to achieve a power of 80% and alpha error of 5%.

Mean daily stool frequency by week



Secondary Outcomes

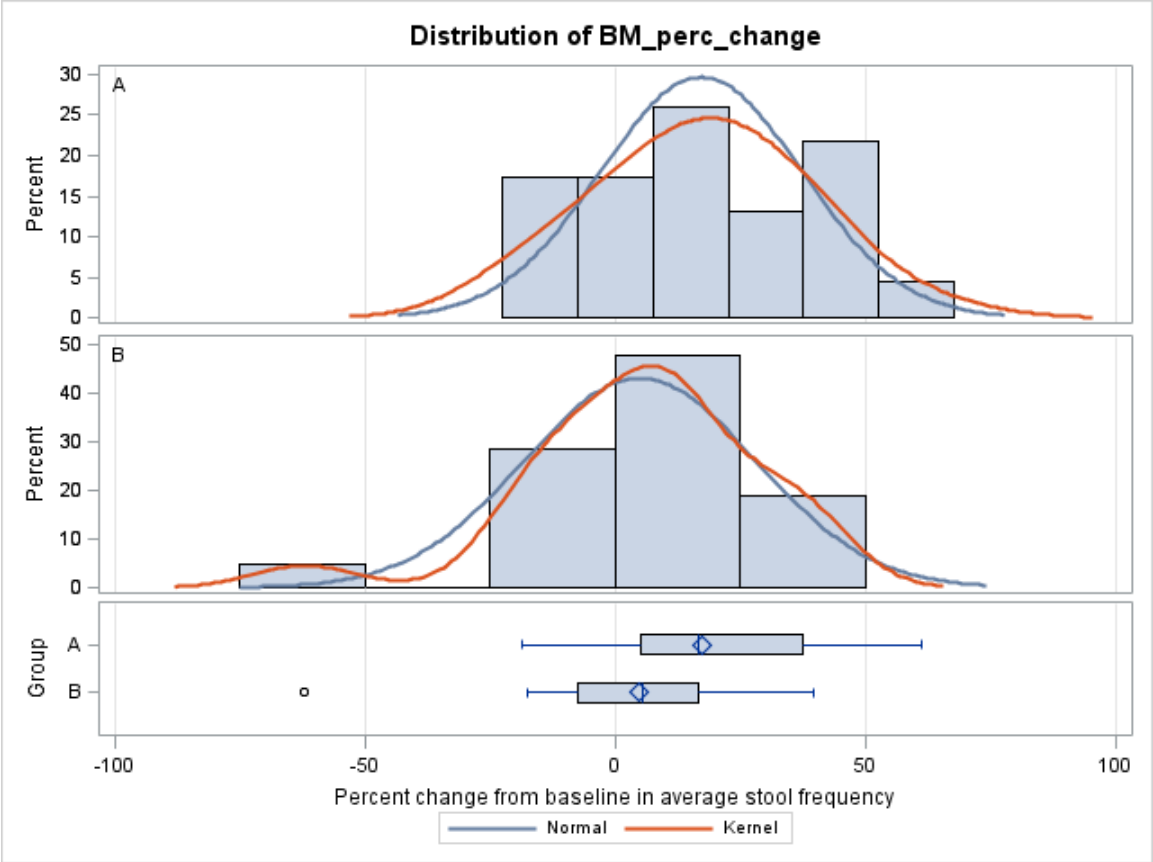
Stool Frequency – Percent Change from Baseline

For each patient stool frequency was estimated as a number of bowel movements per day. The average for the first 2 run-in weeks (day 1 – day 14) and the last 2 weeks (day 78 – day 91) was calculated. To compare stool frequency before and after the treatment, percent change from the baseline was computed as a difference between the average stool frequency for the first 2 weeks and average stool frequency for the last 2 weeks relative to the average stool frequency for the first 2 weeks in percentage, i.e.

$$stool\ frequency\ percent\ change\ from\ baseline = \frac{average\ stool\ frequency\ for\ the\ first\ 2\ weeks - average\ stool\ frequency\ for\ the\ last\ 2\ weeks}{average\ stool\ frequency\ for\ the\ first\ 2\ weeks} * 100\%$$

Percent change from baseline in average stool frequency (in %)

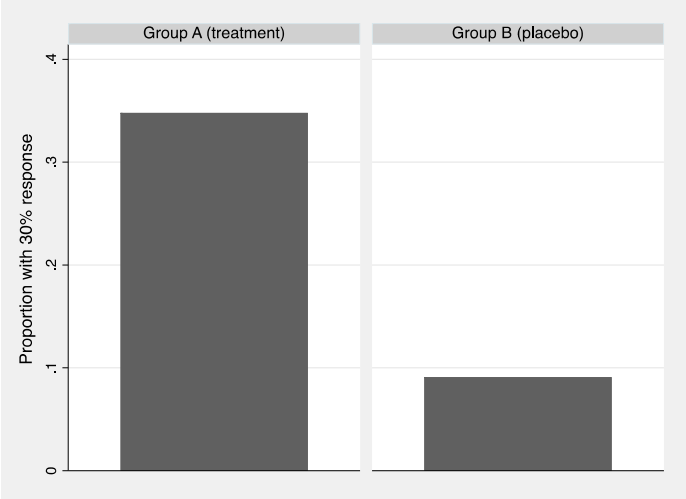
Group	N	Mean	Std Dev	95% CI for mean		Median	Lower Quartile	Upper Quartile	IQR	Minimum	Maximum
				Lower	*Upper*						
A	23	17.10	20.17	8.37	25.82	16.67	5.00	37.50	32.50	-18.75	61.11
B	22	4.86	23.13	-5.67	15.39	5.56	-7.69	16.67	24.36	-62.04	39.47



While the mean percent change from the baseline is larger for the treatment group (group A) then for the control group, the spread in values (IQR) in group A (treatment) is quite wide.

Proportion with response defined as 30% or greater reduction in stool frequency (unplanned analysis)

Comparing the last 2 weeks of active with the run-in non-treatment period, a significant difference was observed in those reporting a 30% or more reduction in stool frequency (p=0.05): in the treatment group 35% (n=8/23) reported at least 30% reduction in stool frequency (95% CI 18-56%) versus 9% (n=2/22) for the placebo group (95% CI 2.1-31%). An equal number of 7 in each group reported worsening in stool frequency greater than 10% over the baseline frequency.

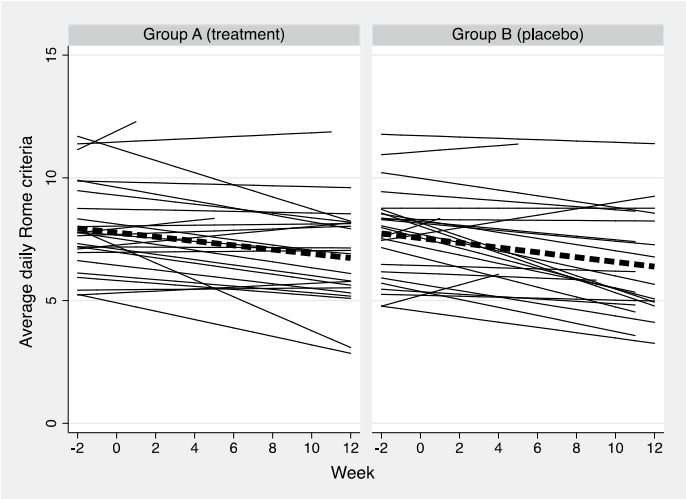


There was no significant change (increase or decrease) in overall Rome criteria, abdominal pain severity, bloating, urgency, or stool consistency.

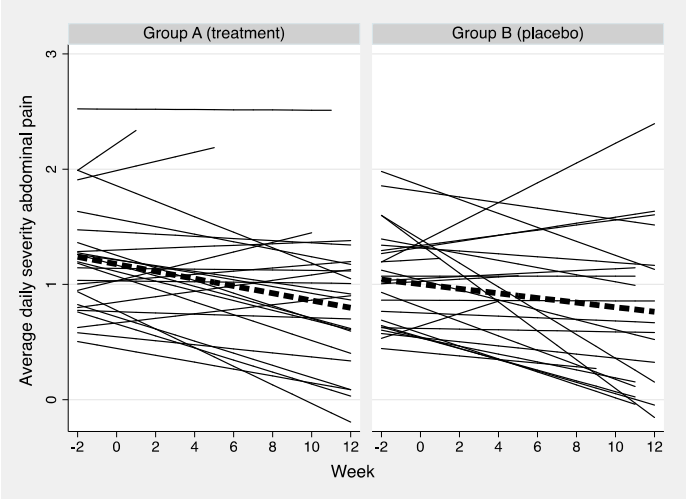
Spaghetti plots

The difference comparing the first two and the last two weeks of active treatment are presented here as a spaghetti plot for each of the following outcome measures:

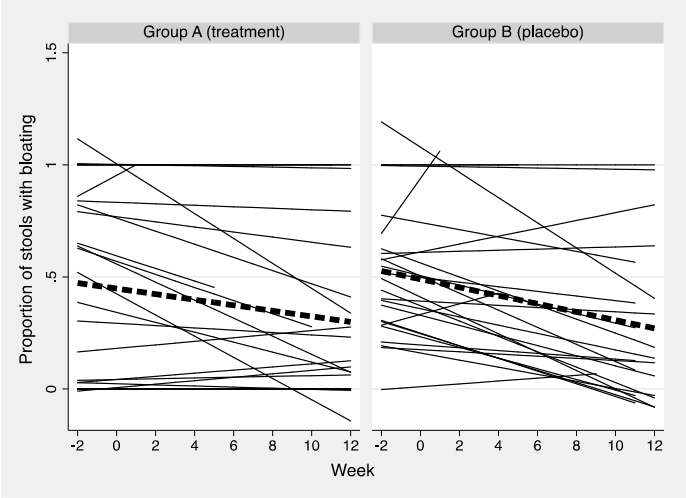
Mean daily Rome Criteria by week



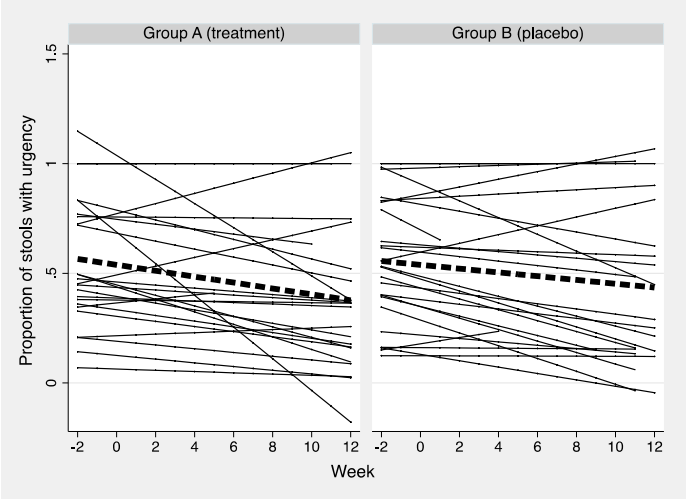
Mean daily abdominal pain severity by week



Proportion of stools with bloating by week



Proportion of stools with urgency by week



Change from baseline and 30% response for FBDSI Score

The mean decrease from baseline in the FBDSI score was 17 (95% CI -33-67) for group A (treatment) while the mean increased by 47 (95% CI 144 to -20) in group B (placebo), but the difference was not statistically significant (p=0.064). However, when examining response as defined as a 30% reduction from baseline in the FBDSI score, 10 of 23 (43%) had reached this outcome in group A (treatment) and 3 of 22 (14%) in group b (placebo) with a statistically significant p-value of 0.032.

Differences in stool frequency based on IBS Severity score (unplanned analysis)

The cohort was divided into three relative equal groups based on the IBS Severity score as follows:

IBS severity category	IBS baseline score	N	%
Low	0 - 279	14	28.0
Moderate	280 - 329	18	36.0
High	330 and more	18	36.0

Analysis of the change in stool frequency for group A (treatment) and group B (placebo) are summarized below:

IBS severity	Group	N	Mean	Std Dev	95% CI for mean		Median	Lower Quartile	Upper Quartile	Min	Max
					Lower	Upper					
Low	**A**	8	2.28	1.29	1.20	3.35	2.21	1.04	3.43	0.93	3.93

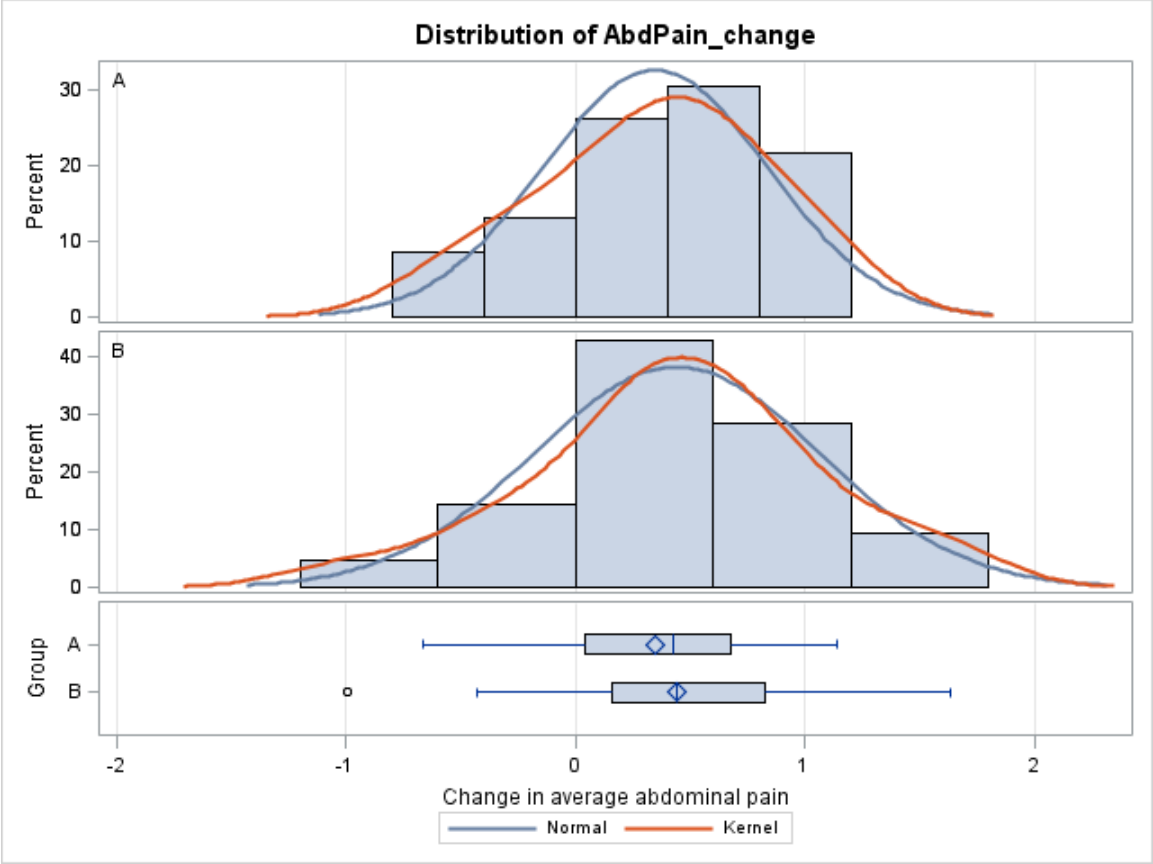
IBS severity	Group	N	Mean	Std Dev	95% CI for mean		Median	Lower Quartile	Upper Quartile	Min	Max
					Lower	Upper					
	B	6	2.17	1.08	1.03	3.30	1.96	1.29	2.71	1.21	3.86
Moderate	**A**	9	2.25	0.54	1.83	2.66	2.29	1.93	2.43	1.50	3.29
	B	9	2.51	1.24	1.55	3.46	2.00	1.86	3.57	1.00	4.36
High	**A**	8	2.53	1.00	1.69	3.36	2.21	1.93	3.07	1.29	4.50
	B	10	2.20	0.89	1.56	2.84	2.00	1.64	2.86	1.00	4.00

Overall the stool frequency was not significantly different between the low, moderate, and severe IBS severity groups. The change in stool frequency was not significantly different between the treatment and placebo groups at any level of IBS severity.

Differences in abdominal pain/discomfort and stool consistency between the 'intervention' group and the 'placebo' group over the study period.

The mean *abdominal pain scores (scale 0-4)* for the last 2 weeks of treatment in the group A (treatment) was 0.93 (95% CI 0.68 - 1.19) and 0.80 (95% CI 0.52 - 1.07) for the group B (placebo). The change from baseline in mean *abdominal pain scores (scale 0-4)* for the group A (treatment) was 0.35 (95% CI 0.13 - 0.56) and 0.44 (95% CI 0.16 - 0.72) for the group B (placebo). The difference in mean scores between the two groups was not statistically significant (p = 0.58).

Abdominal pain



The mean *stool consistency score (scale 1-7)* for the last 2 weeks of treatment in the group A (treatment) was 4.56 (95% CI 4.11 - 5.02) and 4.25 (95% CI 3.78 - 4.72) for the group B (placebo). The change from baseline in mean *stool consistency score* for the group A (treatment) was 0.51 (95% CI 0.16 - 0.86) and 0.46 (95% CI 0.14 - 0.78) for the group B (placebo). The difference in mean scores between the two groups was not statistically significant (p = 0.98).

Differences in quality of life using SF-36 between the 'intervention' group and the 'placebo' group over the study period

The baseline score of the SF 36 PCS was a mean of 48.92 for group A (treatment) and 50.49 for group B (placebo). At visit 5 the scores were 52.08 as the mean for group A (treatment) and 52.36 for group B (placebo).

The difference in quality of life as measured by the SF-36 PCS score from baseline to visit 5 was -2.27 (95% CI -4.35 to -0.19) for the group A (treatment) and -2.05 for the group B (placebo) (95% CI -4.53 to 0.43). The difference between group A (treatment) and group B (placebo) was not statistically significant (p = 0.61).

Adverse events: Reported minor adverse events included upper GI symptoms such as heartburn (n=4; n=3 in group A (treatment)) and increased bloating or gas (n=3; n=1 in group A (treatment)). Other reported adverse events included hives (n=1), sleep disturbance (n=1), anxiety/mood changes (n=1), chest pain (n=1), upper respiratory tract symptoms (n=3), increased Restless Leg Syndrome (n=1), lower back pain (n=2), migraine/headache (n=1), thyroiditis (n=3), vomiting (n=3 all in the group A (treatment)), weight gain (n=1), ear pain/dizziness (n=1),

DISCUSSION

The sample of participants recruited in this clinical trial with IBS-D was comparable in severity or more severe to most other intervention clinical trials of probiotics in this population (1). The mean stool frequency was over 2 per day in each group and the mean IBS severity score over 200.

We observed no significant difference between placebo and the study product PX0612 in the mean change in daily stool frequency over the 12-week active treatment period. However, when response as defined as a 30% reduction in stool frequency was examined, significantly more participants in the treatment group (PX0612) reached this outcome. Since stool frequency in IBS-D patients can vary greatly from day to day, the mean of bowel movements may not accurately reflect the actual changes, i.e. worsening in stool frequency will reduce the mean change in frequency, but not the proportion of responders. A similar response was observed when defined as a 30% reduction in the baseline FBDSI score.

No statistically significant differences were observed in the other secondary outcome measures, including abdominal pain and stool consistency. Measures of changes in quality of life using SF-36 over the active treatment period of 12 weeks were also not different between groups. While IBS severity scores were decreased from baseline by 100 or more in both groups, there was no statistically significant difference between groups.

No serious adverse events were reported during this study for either group. Common adverse events included bloating and heartburn, but these were considered not serious and did not leave to discontinuation of the treatment.

The primary weakness of the study lies in the small sample size. The sample size calculation was based on a previous study of Dolin (2009) where a difference in stool frequency of 0.47 was observed in the placebo group and 0.8 in the treatment group for a difference between groups of 0.33. With the current sample size, there is a high probability that these differences were observed by chance. However, it is possible that with a larger sample size, the smaller than expected difference between groups could be detected with statistical significance. The current post-hoc achieved power is 34.3% where a power of at least 80% is typically deemed critical to reject the null hypothesis

(i.e. to conclude there is no treatment effect). Re-calculation of the sample size based on the observed mean stool frequency and standard deviation, a total sample size of 128 participants (i.e. 64 per group) would achieve a power of 80% to detect a difference between groups of 0.2 stools per day.

Another potential weakness of the study was the use of Di-Calcium Phosphate as the placebo intervention. Calcium salts may have a laxative or constipating effect (https://www.healthstatus.com/health_blog/wellness/vitamins-and-irritable-bowel-syndrome/; accessed Oct 25, 2018) and has been reported to reduce diarrhea in other intervention studies (http://www.thebody.com/content/art2006.html; accessed Oct 25, 2018).

In summary, while we observed no statistically significant difference in the primary or secondary outcome measures comparing PX0612 and placebo, additional analyses demonstrated an encouraging response to treatment as defined as a 30% reduction in stool frequency and IBS severity as measured by the FBDSI score. No serious adverse events were reported, with minor reported adverse events of bloating and heartburn that may be associated with treatment. An increased sample size of another 80 participants will achieve a higher power to detect a difference in stool frequency between groups. The use of other outcome measures that more accurately reflects the episodic nature of IBS-D, such as global symptoms in each patient and not a mean score of the entire patient population, or response defined as a percent reduction from baseline in stool frequency, abdominal pain, or global scores may also be considered.

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