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Effect of a prebiotic galactooligosaccharide mixture (B-GOS®) on gastrointestinal symptoms in adults selected from a general population who suffer with bloating, abdominal pain, or flatulence

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Funding information

Clasado Ltd

Abstract

Background: Prebiotics exert beneficial effects upon gastrointestinal (GI) environment, but this is not always accompanied with a positive effect on GI symptoms. B-GOS® is a prebiotic with high selectivity toward bifidobacteria and a variety of other beneficial effects in humans. Here, we investigated its effect on GI symptoms in adults who suffer with bloating, abdominal pain, and flatulence.

Methods: In a double-blind, placebo-controlled, crossover study, 83 subjects from the general population who presented with GI symptoms during screening period and had a predicted probability of functional bowel disorder of more than 75% were randomized to receive either a placebo or the B-GOS® treatment (2.75 g/d). Subjects were screened for the presence of GI symptoms for 1 week, they consumed the treatments for 2 weeks, and then went through a 2-week washout period, before switching to the other treatment for the final 2 weeks. GI symptoms, bowel movements, and stool consistency were assessed in daily and weekly questionnaires. Quality of life was assessed weekly and depression and anxiety at the end of each treatment period.

Results: B-GOS® resulted in significantly ($P < 0.001$) lower scores for bloating, flatulence, and abdominal pain both from baseline and placebo at the end of first week. The effect was sustained at the end of second week. It had no effect on the number of bowel movements, consistency of stools, quality of life, or mood throughout the study.

Conclusion: Results suggest that B-GOS® could possibly be used in the management of bloating, flatulence, or abdominal pain and warrant further investigation.

KEYWORDS

Bimuno, bloating, flatulence, galactooligosaccharides, intestinal discomfort, prebiotic

Abbreviations: ANOVA, analysis of variance; BDQ, bowel disease questionnaire; B-GOS®, Bimuno®-galactooligosaccharides; FBD, functional bowel disorder; FODMAPS, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; FOS, fructooligosaccharides; GI, gastrointestinal; HAD, hospital anxiety and depression; IBS, irritable bowel syndrome; QOL, quality of life; SGA, subjective global assessment.

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1 | INTRODUCTION

Prebiotics are substrates that are selectively utilized by host microorganisms conferring a health benefit.¹ What distinguishes prebiotics from other undigested dietary ingredients is their selective fermentation, whereby very few groups or even species of bacteria (mainly belonging to beneficial groups of bifidobacteria or lactobacilli) should be able to utilize them. Current confirmed prebiotic status in humans, with the most evidence, belongs to inulin, fructooligosaccharides (FOS), and *trans*-galactooligosaccharides (GOS).¹ Inulin and FOS occur naturally in some types of fruits and vegetables while GOS do not. They are derivatives of lactose that resemble both structural and functional similarities with human breast milk oligosaccharides.²

Bacterial fermentation of carbohydrates (including some prebiotics) can result in increased production of gas and it can also promote symptoms similar to those of irritable bowel syndrome (IBS), that is, bloating, flatulence, abdominal pain, and irregular defecation pattern. This may especially be relevant in individuals with IBS, other functional bowel disorders (FBD) or those that suffer with these symptoms. These individuals are known to have altered GI environment such as motility,³ increased fermentation,⁴ visceral hypersensitivity,⁵ abnormal gas transit,⁶ and dysbiosis of the GI microbiota.⁷ Exclusion of fermentable substrates from the diet has attracted some interest lately, as a potential treatment of IBS symptoms. Studies show that the removal of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPS) can be effective in repressing symptoms in IBS sufferers.⁸ However, this strategy may be criticized for its negative effects on GI environment, in terms of metabolism^{9,10} and altered composition of GI microbiota.^{11–13} Almost without exception, all FODMAPS contain fructose and the symptom induction after ingestion of these substrates is well documented in both uncontrolled^{14,15} and controlled^{16,17} trials. Similarly, prebiotics such as inulin and FOS also contain fructose and, regardless of their positive effect upon GI environment, have been shown to either result in side effects such as increased bloating, flatulence, or abdominal pain or to have no impact on these GI symptoms in healthy adults and those with IBS.^{18–22}

B-GOS (Bimuno®) is composed of galactose chains and it has been shown to have a potent prebiotic effect with high selectivity toward bifidobacteria and a variety of other beneficial effects in humans.^{23–27} In IBS sufferers, it reduced bloating and abdominal pain without changes to their diets,²⁸ and in healthy adults, it was shown not to result in GI symptoms.^{29,30} The aim of the current study was to understand the effect of B-GOS® administration to adults selected from the general population who often suffer with bloating, abdominal pain, or flatulence but who are not formally diagnosed with IBS or other forms of FBD, in a double-blind, placebo-controlled, cross-over study.

2 | METHODS

2.1 | Study population

The participants were selected from the University of Reading database that holds some medical, demographic, lifestyle, and medication

Key Points

- Prebiotics are beneficial to GI environment but those that contain fructose sometimes result in discomfort. B-GOS is a galactose-based prebiotic, highly selective toward beneficial bifidobacteria and its effect on GI symptoms was tested in symptomatic but not formally diagnosed adults with functional bowel disorder.
- More than 90% of subjects experienced significant relief of bloating, abdominal pain, and flatulence following 2 weeks supplementation with B-GOS.
- B-GOS might be a potential candidate for use in dietary management of bloating, flatulence, or abdominal pain.

information about volunteers in the general population who are willing to participate in various trials undertaken by the university. One hundred and twenty subjects aged 18–65 years suffering often (at least three times per month) from GI symptoms were invited into the study. They were selected on the following exclusion criteria: history/diagnosis of GI disease, surgical resection of the bowel, history of malignancy within previous five years, use of antibiotics in the 4 weeks before the study, consumption of pre/probiotic preparations on the regular basis (three or more times per week) in the 2 weeks before the study, former participation in another similar study within the previous month, severe allergy or history of allergic reaction, drug or alcohol use, pregnant/lactating, and regular use of any medication with the exception of hormonal replacement therapy or contraception. Subjects (n = 91) who presented with moderate to severe GI symptoms (bloating, flatulence, abdominal pain) assessed using a 4-point Likert scale (0 = none, 1 = present but tolerated, 2 = present interfering but not preventing activities, 3 = preventing daily activities) for a minimum of 2 days during 1 week of screening period and had a Bowel Disease Questionnaire (BDQ)³¹ predicted the probability of FBD of more than 75% (score ≥ 629) were randomized. Of these, eight subjects did not complete the trial (one used antibiotics, one was hospitalized due to a broken leg, one relocated, five failed to make contact with investigators). The sample size required to give a power of 95% for detecting a treatment difference at a two-sided 0.05 significance level for the intestinal symptoms (bloating, abdominal pain, flatulence), if the true difference between treatments is 0.4 units, was calculated to be 77 subjects.

2.2 | Study design

Eligible subjects were enrolled into a prospective, single-center, randomized, double-blind, placebo-controlled, crossover study. The study lasted 7 weeks and consisted of four periods: a screening period for the presence of symptoms and BDQ score of 1 week, subjects consumed treatments for 2 weeks, followed by a 2-week washout period (without consuming any treatments), before switching onto the other treatment for the final 2 weeks (Figure 1). The

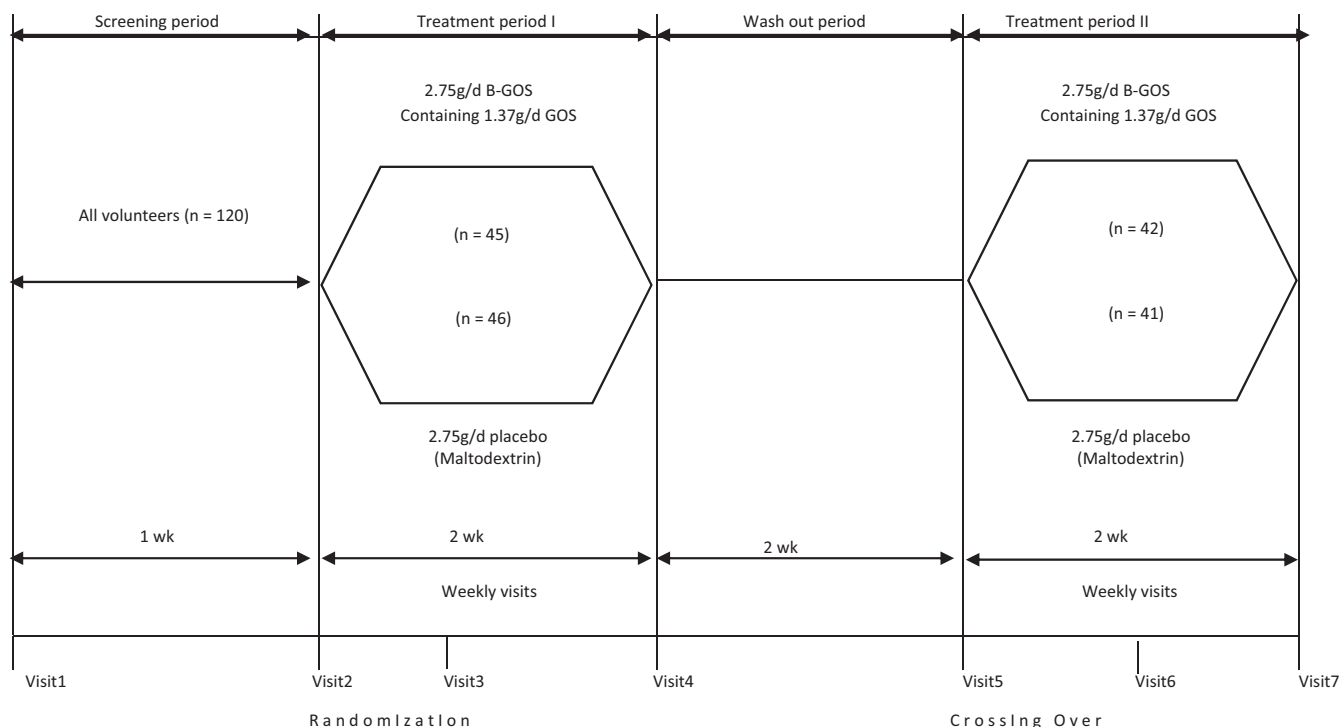


FIGURE 1 Study flow design

study included seven visits: a screening (visit 1) prior to enrolment, randomization and baseline for treatment 1 (visit 2), after 1 week of treatment (visits 3 and 6), at the end of 2 weeks treatment (visit 4 and 7), baseline for treatment 2 (visit 5).

Subjects were stratified by gender using a block size of 10 and randomly assigned, using a random number generator (<https://www.random.org>), in a 1:1 ratio into two groups. One group ($n = 45$) started with a prebiotic B-GOS (Bimuno®) and the other ($n = 46$) with a placebo (Maltodextrin). Both were supplied in powder-containing sachets (2.75 g) and provided by Clasado Ltd, UK. Subjects were asked to reconstitute contents of the sachets immediately before consumption by mixing the powder with water and to consume the product every day at approximately the same time. They were also instructed not to alter their diet or fluid intake during the study. The daily dose of the active ingredient (GOS) provided in a 2.75 g sachet was 1.37 g.

The study was conducted according to the ethical principles stated in the Declaration of Helsinki. Ethical approval for the protocol was obtained from the University of Reading (UK) Review Board, and all participants gave written informed consent to participate in the trial and prior to any assessments.

2.3 | Outcomes

The effect on GI symptoms (bloating, abdominal pain, flatulence, urgency) was assessed daily using a self-report questionnaire with a 4-point Likert scale (0 = none, 1 = present but tolerated, 2 = present interfering but not preventing activities, 3 = preventing daily activities). It was also assessed at the end of each week using the

Subjective Global Assessment (SGA) of relief (1 = completely relieved, 2 = considerably relieved, 3 = somewhat relieved, 4 = unchanged, 5 = worse). The number of bowel movements per day and stool consistency was also assessed daily in a self-report questionnaire. Bowel movement frequency was recorded as numbers per day, and consistency was scored on a 7-point scale and evaluated using the Bristol Stool Scale.

Quality of life (QOL) was assessed at the end of each week using the IBS-36 questionnaire, with scores symptoms on a 7-point Likert scale (0 = never and 6 = always). Anxiety and depression were assessed at the end of each treatment period using the Hospital Anxiety and Depression (HAD) scale, which detects the states of anxiety and depression with score ranges for “non’case,” “doubtful” case, and “definite” case.

Participants also recorded daily in their diary about the consumption of the study products, medications started during the study as well as any adverse events.

2.4 | Statistics

Baseline demographic data (end of week 1 and end of week 5) were compared between groups using Student’s t test, χ^2 test, or Fisher’s exact test, when appropriate.

All data were analyzed by an analysis of variance (ANOVA) model of repeated measurements taking into account the crossover design. In the ANOVA model, treatment period, treatment, and subject were introduced as fixed effects and measurements as random effect. The efficacy for GI symptom scores was the average of the daily repeated measurements recorded over a week (or a number of

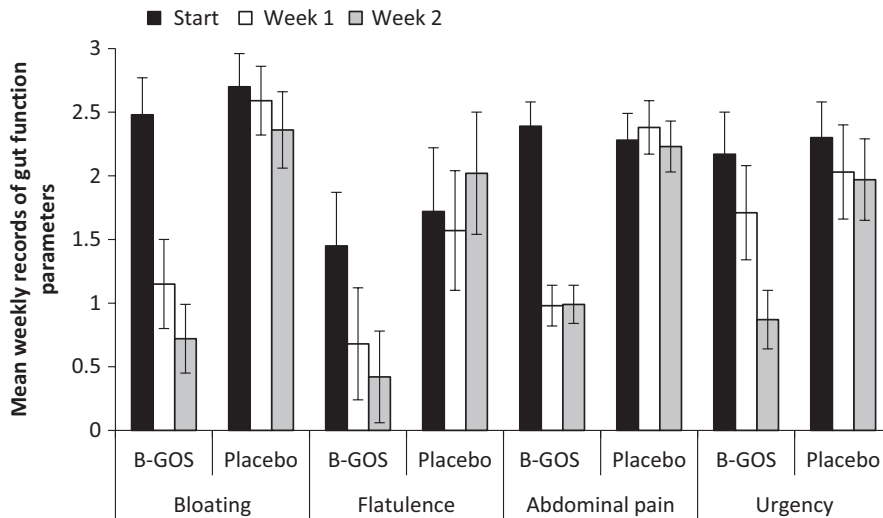


FIGURE 2 Mean daily scores \pm SD ($n = 83$) for bloating, flatulence, abdominal pain, and urgency in subjects with gastrointestinal (GI) symptoms during the trial period with a prebiotic galactooligosaccharide (B-GOS[®]) and a placebo. The mean scores in the B-GOS[®] group were significantly ($P < 0.05$) different from the placebo group and the baseline at week 2 for all symptoms shown and for all except urgency at week 1 too. Assessed with a 4-point Likert scale (0 = none; 1 = present but tolerated; 2 = present interfering but not preventing activities; 3 = preventing daily activities)

recorded days in a week) and calculated in the ‘per protocol’ population. Significant differences between treatments were established by using Dunnett’s least significant difference test (two-tailed). All statistical tests were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL, USA).

3 | RESULTS

3.1 | Baseline characteristics

The average age of subjects in the study was 35.5 ± 8.4 years and the average BDQ score was 635.4 ± 7.4 . A slightly higher population of women (57%) than men (43%) were included overall, but there were no differences between their measurements. These characteristics at baseline did not differ significantly between groups.

3.2 | Compliance with product consumption

The self-reported levels of product consumption did not differ significantly between the groups (97.2 ± 5.9 for the B-GOS[®] and 96.3 ± 6.7 for the placebo treatment).

3.3 | Analysis of GI symptoms

Weekly interval averages, calculated from a self-report questionnaire of daily GI symptoms, did not differ significantly at baseline (Figure 2). However, after 1 week of supplementation, B-GOS[®] resulted in significantly ($P < 0.001$) lower scores for bloating, flatulence, and abdominal pain both from baseline and placebo. This effect was also significant ($P < 0.001$) after 2 weeks compared to baseline and placebo but not compared to week 1 of B-GOS[®] treatment (Figure 2). There was no effect of the treatments on urgency after week 1, but a significantly ($P < 0.001$) lower score in the B-GOS[®] group was achieved after week 2 compared to baseline and placebo (Figure 2).

Additionally, Figure 3 shows the proportion of subjects in the B-GOS[®] group who experienced a significant relief to or below the

“present but tolerated” level of GI symptoms (calculated as a weekly average of recorded daily responses from a self-report questionnaire) during the trial period. All these values were significantly different from the placebo group, where only flatulence was reduced in 17% of subjects (4% below “present but tolerated”) after the first week. However, at the end of week 2, only 2% experienced relief of flatulence to “present but tolerated” levels (data not shown). Bloating, flatulence, and abdominal pain in subjects receiving B-GOS[®] were relieved in a large majority (51% bloating, 80% flatulence, 76% abdominal pain) after week 1 and in almost all (98% bloating, 96% flatulence, 92% abdominal pain) by the end of week 2 (Figure 3). A quarter of subjects had bloating and abdominal pain relieved below the “present but tolerated” level after week 1 and bloating was further improved in 72% of subjects at the end of week 2 (Figure 3). Flatulence was relieved below the “present but tolerated” level in 72% of subjects after first week and in 84% after week 2 (Figure 3). Urgency was reduced to or below the “present but tolerated” level in 7% of subjects after week 1 and in 87% at the end of week 2, however, no subjects experienced complete relief in urgency at the end of week 1, but 57% did at the end of week 2 (Figure 3).

3.4 | Stool characteristics, QOL, HAD, and SGA

Stool characteristics, QOL, HAD, and SGA scores did not differ significantly at baseline. Both treatments appeared to have no effect on the number of bowel movements, consistency of stools, QOL, or HAD (Table 1). However, SGA was significantly ($P < 0.05$) lower after both week 1 and 2 in the B-GOS[®] group compared to baseline and placebo, but it did not differ between the weeks (Table 1).

4 | DISCUSSION

The effect of a prebiotic B-GOS[®] against a placebo on GI symptoms in undiagnosed adults, selected from a general population on the presence of GI symptoms and with a probability of FBD, was investigated in this study. The results showed an overall significant

FIGURE 3 A proportion (% total) of subjects with gastrointestinal (GI) symptom relief to (1) and below (<1) “present but tolerated” level during the trial period with a prebiotic galactooligosaccharide (B-GOS®). All values were significantly ($P < 0.05$) different from the placebo group where only flatulence was reduced to “present but tolerated” level in 17% and 2% of subjects at the end of week 1 and 2, respectively (data not shown). Assessed with a 4-point Likert scale (0 = none; 1 = present but tolerated; 2 = present interfering but not preventing activities; 3 = preventing daily activities)

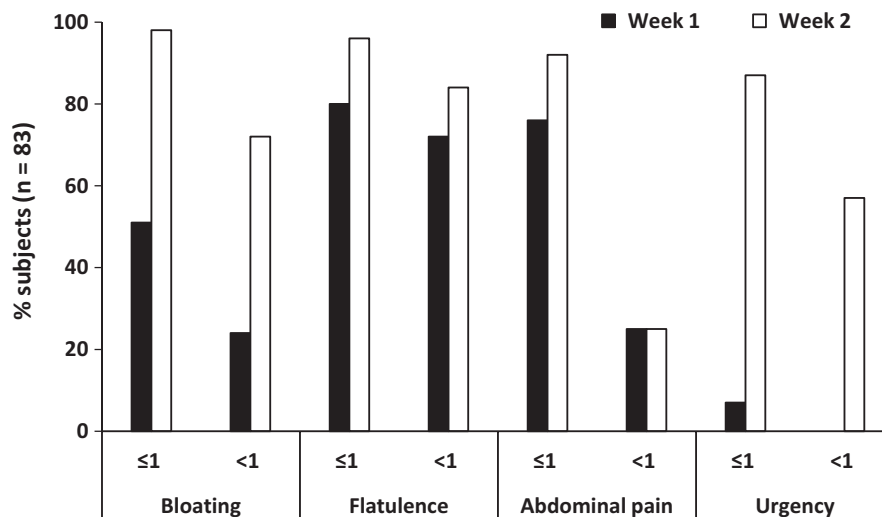


TABLE 1 Comparison of Self Global Assessment (SGA), Quality of Life (QoL), Hospital Anxiety and Depression (HAD), and stool characteristics during the trial period with a prebiotic galactooligosaccharide (B-GOS®) and a placebo

	B-GOS® (n = 83)			Placebo (n = 83)		
	Baseline	Week 1	Week 2	Baseline	Week 1	Week 2
SGA ^a	4.3 ± 0.7	2.7 ± 0.7 ^e	2.1 ± 0.5 ^e	4.1 ± 0.5	3.9 ± 0.6	4.2 ± 0.6
QoL ^b	73.8 ± 40.9	77.4 ± 38.5	79.1 ± 40.2	72.6 ± 41.4	73.8 ± 38.5	75.2 ± 36.6
HAD ^c	5.6 ± 2.8	5.4 ± 2.3	5.7 ± 2.2	6.0 ± 2.6	5.7 ± 2.9	5.8 ± 2.6
Stool frequency per wk ^d	11.9 ± 4.7	11.5 ± 4.0	11.6 ± 4.1	10.6 ± 5.0	9.8 ± 3.9	10.7 ± 3.4
Stool consistency ^d	3.7 ± 1.1	3.5 ± 1.0	3.7 ± 1.1	3.4 ± 1.1	3.5 ± 1.1	3.3 ± 1.1

All data are expressed as mean ± SD. No significant differences were found between treatments at baseline in shown variables.

^aAssessed with a 5-point Likert scale (1 = completely relieved, 2 = considerably relieved, 3 = somewhat relieved, 4 = unchanged, 5 = worse).

^bAssessed using IBS-36 questionnaire.

^cAssessed using the Hospital Anxiety and Depression (HAD) scale.

^dAssessed using the Bristol stool scale.

^eSignificantly different from baseline and placebo.

improvement in bloating, flatulence, and abdominal pain to or below the “present but tolerated” level after 1 week of B-GOS® administration. This improvement was not accompanied with an effect on stool consistency or frequency, but it was sustained during the second week of the study, when the urgency scores were improved too.

B-GOS® is a prebiotic metabolized or fermented by GI bacteria, making it a FODMAP by the current definition. The removal of FODMAPS from the diet has received considerable attention recently, because of a growing number of studies confirming its therapeutic effect in managing IBS symptoms.⁸ Their mechanism of symptom induction is related to an increase in intestinal water content, alteration in motility, and colonic gas production. However, this type of diet reduces daily intake of fermentable carbohydrates by more than 50%¹¹ and not surprisingly results in a significant reduction in bacterial saccharolytic fermentation, undoubtedly shifting the GI environment to a less favourable state for health. Strategies that could be added to low FODMAP diet

or offer an alternative dietary approach, to individuals that suffer with GI symptoms, are therefore of interest. Since administration of B-GOS® in the current study did not result in symptom induction but an improvement in more than 90% of subjects for bloating, flatulence, and abdominal pain at the end of study period, it appears that its mechanism of action may not be similar to FODMAPS.

The present study did not enroll diagnosed IBS or FBD populations, known to have a more sensitive GI environment than healthy subjects.³⁻⁷ However, persons were enrolled from the general population with a predicted FBD probability of more than 75% (score ≥ 629) based on a previously validated BDQ questionnaire.³¹ The BDQ was extensively tested and found to be reliable (0.81) with adequate content and predictive and construct validity.³² More importantly, subjects were enrolled experiencing bloating, flatulence, or abdominal pain at the start of the study. Reports suggest that between 20% and 45% of general western population experiences these symptoms, and in more than 75% of

cases symptoms are moderate to severe.^{33,34} Furthermore, studies also suggest that almost half of FBD patients are not formally diagnosed, so the majority are self-treated.³⁵ As such, since bloating, flatulence, or abdominal pain were present in the subjects enrolled in the current study, regardless of the validity of the BDQ questionnaire, and thus, the possibility of FBD diagnosis in these individuals which was not the aim of the study, a significant reduction in symptoms is of relevance.

The current study used a relatively low daily dose of 2.75 g B-GOS (1.37 g per day of an active ingredient) compared to much higher doses of 10–20 g per day of other previously tested prebiotics (eg, inulin and FOS) that resulted in a FODMAP effect.^{18–20} Higher doses of prebiotics are likely to lose their selectivity on the microbiota and thus possibly increase motility and small intestinal water content. However, these prebiotics have been tested in IBS population at much lower dose of 2–5 g per day, when worsening of the symptoms was not observed but neither was an improvement.^{21,22} At the same dose of 1.37 g per day of an active ingredient, B-GOS® was previously shown to reduce bloating, flatulence, and abdominal pain, with no effect on stool consistency, in IBS populations after 4 weeks of supplementation.²⁸ The treatment period was shorter here than in the IBS study, however selective increases in bifidobacteria, and at much higher rate than other types of GOS, after 1 week of supplementation with B-GOS in healthy adults was previously shown.²³ A selective increase in bifidobacteria was also confirmed in other populations such as IBS patients,²⁸ elderly,²⁴ and overweight.²⁵ Bifidobacteria lack a number of key enzymes involved in the Emden-Meyerhof-Parnas pathway, so instead they metabolize carbohydrates through a metabolic pathway named the “bifid shunt” which does not involve generation of gas.³⁶ Thus, substrates such as B-GOS® that are highly selective toward bifidobacteria, are unlikely to contribute to increase in gas production when used at an appropriate dose. Indeed, gas homeostasis occurring within a week of administration with B-GOS®, as a result of metabolic and compositional microbiota changes was previously shown in adults.^{29,30} Thus, it is not unreasonable to suggest that its positive effect in reducing the GI symptoms in the current study, can be contributed to its positive effect on microbiota and specifically bifidobacteria.

Alterations in the composition of microbiota and specifically reduced numbers of bifidobacteria have been reported in FBD.³⁷ Some key factors involved in the pathogenesis or symptom generation in FBD population are known to be influenced by microbiota. For example, visceral hypersensitivity or reduced intestinal motility are associated with low counts of bifidobacteria and higher levels of other, less beneficial, members of the GI microbiota.³⁸ Positive effects of an appropriate microbiota composition has also been shown in other aspects relevant to FBD, such as reduction in stress, improved intestinal permeability, and the effect on immune activation.³⁷ It is not surprising, therefore, that some of most successful probiotics used in the management of bloating, flatulence, and abdominal pain belong to species of bifidobacteria.³⁹ However, the efficacy of probiotics is not only strain but also individual dependent and therefore, multistrain preparations

may have better effect in reducing symptoms than single species. Prebiotics have an advantage over probiotics in that they support the growth of host's own, well-established, beneficial microbiota—usually at the genus level. However, in some cases as mentioned above, they contribute to exacerbation of symptoms due to their chemistry or fermentative nature, particularly at high doses.

In conclusion, the present study showed a significant reduction in bloating, flatulence, and abdominal pain in an undiagnosed, adult, population that often suffers with these symptoms. The effect was evident after a week of supplementation with B-GOS® and sustained during the second week of the study when 92%, 96%, and 98% of subjects experienced relief to or below the “present but tolerated” level for abdominal pain, flatulence, and bloating, respectively. Although it might be more appropriate to assess the effect of B-GOS® on these symptoms in a diagnosed population, or for a longer period, it is possible to suggest its potential in the management of these symptoms and to warrant further investigations.

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DISCLOSURES

JV and AJ had no conflicts of interest at the time of the study nor during the analyses of samples and data, but are currently employed by Clasado Research Services, Ltd. GT was employed by Clasado Research Services, Ltd. GRG, no conflicts of interest.

AUTHOR CONTRIBUTION

JV, GT, and GRG designed the research; JV wrote the article; AJ conducted the research.

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