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An Open-label, Multicenter Study to Assess the Efficacy and Safety of a Novel Probiotic Blend in Patients With Functional Gastrointestinal Symptoms

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Goal: A novel 5-strain (Bl-04, Bi-07, HN019, NCFM, and Lpc-37) probiotic blend was developed and its safety and efficacy were evaluated in patients with functional gastrointestinal (GI) symptoms.

Background: These strains administered together have not previously been investigated.

Study: Patients aged 18 to 75 years with functional GI symptoms were eligible for inclusion in a single-arm, open-label, multicenter study (NCT04155801). An oral capsule containing the novel probiotic blend was administered once daily for 30 days. The primary efficacy endpoint was patient-reported improvement in overall GI well-being at day 30. Secondary efficacy endpoints included changes in GI symptoms assessed using the GI Health Symptom Questionnaire. Incidence of treatment-emergent adverse events was recorded at all visits.

Results: Of 188 enrolled patients, 72.3% were female and mean (SD) age was 44.1 (13.4) years. At day 30, 85.1% of patients achieved the primary endpoint, a positive response signifying improvement in overall GI well-being. Improvements from baseline were reported at day 30 in diarrhea frequency (baseline frequency $\geq$ 3 to 4 d/wk) and severity (baseline severity $\geq$ 5/10) for 75.8% and 87.3% of patients, respectively. Over the same time period, constipation frequency (baseline frequency $\geq$ 3 to 4 d/wk) and severity (baseline severity $\geq$ 5/10) improved in 73.6% and 80.4% of patients, respectively. Most patients reported improvements at day 30 in frequency and severity of straining, urgency, abdominal pain/discomfort, bloating, and distention. Improvements reported at day 30 were generally observable at day 14. No safety signals were identified.

Conclusion: A novel 5-strain probiotic blend improved functional GI symptoms and was safe.

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Functional gastrointestinal (GI) disorders (FGIDs) are characterized by chronic abdominal symptoms arising from disordered gut-brain interactions, dysmotility, and visceral hypersensitivity.[1,2] Common symptoms of FGIDs include abdominal pain, dyspepsia, bloating, constipation, and diarrhea, and patients may present with > 1 FGID.[1,3,4] The symptom-based Rome IV diagnostic criteria, together with absence of identifiable physical or structural GI abnormalities, can be used to confidently diagnose FGIDs.[1,5] More than 40% of people worldwide are estimated to have FGIDs, and functional dyspepsia and irritable bowel syndrome (IBS) are the most common.[2,6,7]

FGIDs may be associated with comorbidities, including psychiatric conditions, chronic fatigue, and chronic somatic and visceral pain disorders, which, when combined with chronic GI symptoms, are associated with substantial social, psychological, and direct and indirect health care costs.[2,8] Patients with IBS-diarrhea report significantly greater reductions in health-related quality of life, greater impairments in work productivity, and higher rates of absenteeism and presenteeism.[9] This translates into a significant burden to employers in terms of indirect costs, of which a large portion are attributable to presenteeism.

Over the past 2 decades, the definition of FGIDs has evolved from a negative definition (absence of demonstrable organic disease) to a positive definition, reflecting a greater awareness of disease pathophysiology.[1] Current understanding is that multiple pathophysiological processes, including motility disturbances, visceral hypersensitivity, altered mucosal and immune function, altered central nervous system processing, and altered gut microbiota, are inherent factors in determining the prevalent symptoms of various FGIDs.[1]

The human body is inhabited by a complex microbe community, called the microbiota. Most of these microbes are found in the GI tract.[10] Gut microbiota can be categorized into 3 broad categories: beneficial, harmful, and intermediary.[11] Beneficial bacteria, including *Lactobacilli* and *Bifidobacteria*, suppress harmful bacteria from growing in and colonizing the gut. Beneficial bacteria also modulate dysregulated immune responses, among other positive physiological effects.[11] The gut microbiota is thought to ferment nondigestible carbohydrates, yielding short-chain fatty acids (acetate, propionate, and butyrate), which promote gut health.[12] Conversely, harmful bacteria such as *Clostridium*, *Veillonella*, and *Enterobacteria* demonstrate

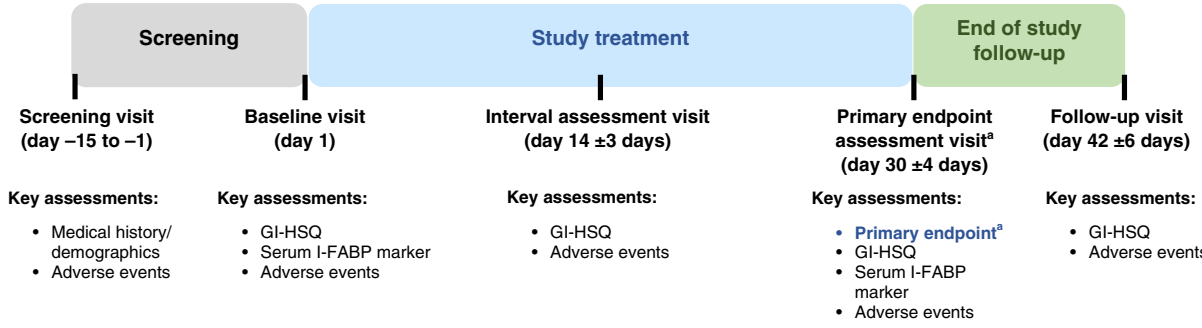

FIGURE 1. Study design. [a]The percentage of subjects with a positive response to the question, "Compared to the way you felt before beginning the supplement, how strongly do you feel you had an improvement of your overall GI well-being?" GI indicates gastrointestinal; GI-HSQ, Gastrointestinal Health Symptom Questionnaire; I-FABP, intestinal fatty-acid binding protein. full color online

characteristic pathogenicity and/or are capable of transforming food components into noxious substances.[11]

In healthy people, an equipoise exists among various communities of intestinal microbiota.[11] This balance can be altered by endogenous (nutrient availability, diet, brain-gut interactions, immune regulation, etc.) and exogenous (antibiotic therapy, excessive hygiene, stress, aging, etc.) factors.[11,13] For example, IBS can develop after either a GI infection or antibiotic therapy, both of which can disrupt normal enteric microbiota homeostasis.[14] In addition, alterations in gut microbiota are linked with depression and anxiety.[15] Despite advancements in knowledge, the regulation and specific effects of the gut microbiota on the host remain poorly understood. It is difficult to distinguish if alterations in microbiota composition represent a cause or effect of disease (or health) states or simply an epiphenomenon.[4,16]

Probiotics are defined by the World Health Organization as live microorganisms that, when administered in adequate amounts, confer a health benefit.[17] It is thought that probiotics compete metabolically with pathogens, thereby improving the intestinal mucosal barrier and/or quiescing the intestinal inflammatory mileu.[14] Administration of probiotics can be effective in restoring intestinal microbial balance and gut homeostasis, but convincing evidence of improvement in chronic GI symptoms with probiotics remains elusive.[18,19] Additional clinical trials are needed to determine the exact combination of species and strains of probiotics with desired treatment effects in functional GI disorders.[18,20]

A novel probiotic blend comprised of 3 strains of *Bifidobacterium lactis* (Bl-04, Bi-07, HN019) and 2 strains of lactobacillus [*Lactobacillus acidophilus* (NCFM) and *Lactobacillus paracasei* (Lpc-37)] was developed for symptomatic treatment of FGIDs. In clinical trials, treatment with these bacteria that was administered individually, in multistrain blends, or in combination with other probiotics and/or prebiotics improved diarrhea, abdominal pain, bloating, and constipation in FGIDs.[21–24] This specific blend of strains administered together has not previously been investigated. The objective of this open-label clinical trial (NCT04155801) was to evaluate the efficacy and safety of this novel 5-strain probiotic blend in patients with functional GI symptoms.

MATERIALS AND METHODS

Study Design and Treatment

This was a single-arm, open-label, multicenter study conducted according to globally accepted standards of Good Clinical Practice (GCP; as defined in the ICH E6 Guideline for GCP [November 9, 2016]), in agreement with the latest locally applicable revision of the Declaration of Helsinki (2013), and in accordance with local regulations. Planned enrollment was 150 patients across 10 centers in the United States. The study comprised the following 5 assessment visits: screening (days –15 to –1), baseline (day 1), interval assessment (day 14), primary endpoint assessment (day 30), and the end of study follow-up visit (day 42). Patients were assessed for efficacy and safety of the probiotic blend at each study visit after the screening visit (Fig. 1).

Patients received probiotic blend supplement capsules (gluten and lactose free) consisting of Bl-04 [2.5 billion (B) colony-forming units (CFU)], Bi-07 (2.5B CFU), HN019 (2.0B CFU), NCFM (2.5B CFU), and Lpc-37 (2.5B CFU), administered orally once daily for 30 days (Table 1). Compliance to study treatment was measured either at the primary assessment visit (day 30) for patients who completed the study, or at the end of study visit for patients who withdrew prematurely. All original containers, either empty or containing remaining probiotic capsules, were returned to the study site, and subsequently counted to determine compliance.

Study Population

Adults (18 to 75 y of age) were eligible for inclusion in the study if they experienced the following clinical symptoms of FGIDs based on the Rome IV diagnostic criteria: recurrent abdominal pain, and/or discomfort, and/or bloating, and/or abdominal distention associated with a change in the frequency of stool, and/or a change in the form (appearance) of stool.

Patients presenting with 1 or more of the following criteria were excluded from participation in the study: active

TABLE 1. Active Ingredients in the Novel 5-Strain Probiotic Blend

Active Ingredient	Strain Number	Label Claim
Bifidobacterium lactis Bl-04	ATCC SD5219	2.5 billion CFU
Bifidobacterium lactis Bi-07	ATCC SD5220	2.5B CFU
Bifidobacterium lactis HN019	AGAL NM97/ 09513	2.0B CFU
Lactobacillus acidophilus NCFM	ATCC 700396	2.5B CFU
Lactobacillus paracasei Lpc-37	ATCC SD5275	2.5B CFU

AGAL indicates Australian Government Analytical Laboratories; ATCC, American Type Culture Collection; CFU, colony-forming units.

treatment with prescription medication for IBS within 6 weeks before screening; active or a history of inflammatory bowel disease; diagnosis of significant systemic disease such as active/ongoing infection, uncontrolled diabetes mellitus, chronic renal failure, cirrhosis, congestive heart failure, and severe chronic obstructive pulmonary disease; diagnosed lactose or fructose intolerance; immunocompromised or immunodeficiency syndrome of any kind; pregnancy or breastfeeding; diagnosis of infectious gastroenteritis within 1 month before screening; diagnosis of gastroparesis; use of antipsychotic medications within 3 months before screening; systemic steroids within the month before screening; active treatment with antibiotics; treatment with probiotics within 6 weeks before screening; history of any abdominal surgery (except for hernia repair or appendectomy); active adherence to a low fermentable oligosaccharides, disaccharides, monosaccharides and polyols diet.

Study Endpoints

The primary efficacy endpoint was global assessment of response to the probiotic blend, defined as the percentage of patients at the primary endpoint assessment visit (day 30) with a positive response (slightly agree, agree, or strongly agree) to the question, "Compared to the way you felt before beginning the supplement, how strongly do you feel you had an improvement of your overall GI well-being?"

Several secondary efficacy endpoints were also assessed using the Gastrointestinal Health Symptom Questionnaire (GI-HSQ). These included frequency and degree of improvement of the symptoms of diarrhea, constipation, incomplete evacuation, mucus and gas, straining, urgency, abdominal pain and discomfort, bloating, distention, and bowel habit satisfaction. The GI-HSQ uses a 5-point scale to assess frequency of GI symptoms (frequency of symptoms ranging from never to 7 d/wk), an 11-point scale to assess severity of GI symptoms (0 represents none and 10 represents severe), and an 11-point scale to assess bowel habit satisfaction (0 indicates not satisfied and 10 indicates very satisfied). Improvement in severity or frequency of symptoms was defined as at least a 1-point improvement on the GI-HSQ from baseline. Only patients with diarrhea or constipation at baseline experiencing ≥ 3 to 4 days per week for frequency endpoints or scoring $\geq 5/10$ for severity endpoints were evaluated in a post hoc analysis for improvement of these symptoms. This helped to avoid including patients who were predominantly constipated when assessing improvement in diarrhea symptoms and vice versa. In addition, baseline values and changes in intestinal fatty-acid binding protein (I-FABP), were assessed. I-FABP is a cytosolic enzyme of the enterocytes that is expressed in epithelial cells of the mucosal layer of intestinal tissue, and I-FABP is released into circulation when intestinal mucosal damage occurs.[25–27] Safety endpoints assessed included incidence of all treatment-emergent adverse events (TEAEs) and changes from baseline in vital sign measurements.

Sample Size and Statistical Methods

No formal sample size calculations were performed for the study. However, it was estimated that 150 patients would be sufficient to assess the safety and to assess the efficacy of the probiotic blend. Descriptive statistics were calculated for all outcomes using the intention-to-treat (ITT) patient population.

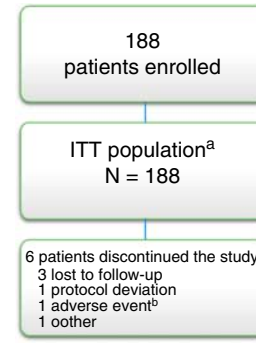

FIGURE 2. Participant flow. [a]The ITT population includes all patients enrolled in the study. [b]Worsening flatulence. ITT indicates intention to treat. full color online

RESULTS

Participants

A total of 188 patients met eligibility criteria and were enrolled in the study. Findings were reported for the ITT population, which consisted of all enrolled patients (Fig. 2). Six patients discontinued the study due to: an adverse event (n = 1), protocol deviation (n = 1), loss to follow-up (n = 3), or other cause (n = 1). The mean (SD) age of patients was 44.1 (13.4) years, and 72.3% of patients were female. Patient demographics and baseline characteristics are described in Table 2.

Primary Outcome

At day 30, 85.1% of participants achieved the primary endpoint, which was a positive response when asked about improvement in overall GI well-being (Fig. 3). Of those with a positive response, 62.2% had a very positive response (agreed or strongly agreed), and 22.3% had an excellent response (strongly agreed).

Secondary Outcomes

Diarrhea

At baseline, 62 patients experienced diarrhea with a frequency of at least 3 to 4 days per week, and 79 patients rated diarrhea severity $\geq 5/10$ on the GI-HSQ. At day 14,

TABLE 2. Demographics and Baseline Patient Characteristics

Demographic	Overall (N = 188) [n (%)]
Age (mean) (y)	44.1
Age group (y)	
18-24	16 (8.5)
25-34	39 (20.7)
35-44	36 (19.1)
45-54	53 (28.2)
55-64	31 (16.5)
≥ 65	13 (6.9)
Gender	
Male	52 (27.7)
Female	136 (72.3)
Race	
White	136 (72.3)
African American	43 (22.9)
Asian	5 (2.7)
Ethnicity	
Hispanic or Latino	60 (31.9)
Not Hispanic or Latino	128 (68.1)

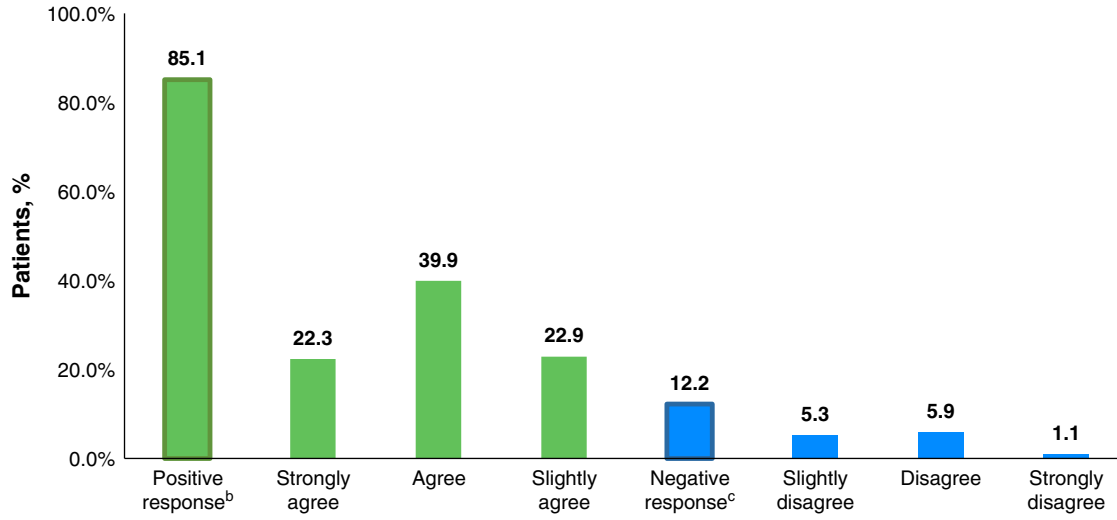

FIGURE 3. Patient Response to the Primary Endpoint Assessment Question at Day 30[a]. [a]Patients were asked, "Compared to the way you felt before beginning the supplement, how strongly do you feel you had an improvement of your overall gastrointestinal well-being?" [b]A "positive response" comprises strongly agree, agree, and slightly agree. [c]A "negative response" comprises slightly disagree, disagree, and strongly disagree. Responses were not available for 5 patients and percentages are based on the total number of patients in the intention-to-treat population (n = 188). full color online

71.0% (44/62) of these patients reported improvements from baseline in diarrhea frequency and 78% (62/79) of patients with diarrhea severity ≥ 5/10 reported an improvement in diarrhea severity (Fig. 4). At day 30, improvements were sustained in these subgroups and increased to 75.8% (47/62) of patients reporting improvement in diarrhea frequency and 87.3% (69/79) reporting improvements in severity. More than half of the patients enrolled in the study with a baseline diarrhea severity ≥ 5/10 (n = 79) had a ≥ 3 point improvement on the GI-HSQ and an improvement in diarrhea severity at day 14 (58.2%) with sustained improvement to day 30 (72.2%).

Constipation

Constipation with a frequency of at least 3 to 4 days per week was reported in 106 patients, and 112 patients rated constipation severity ≥ 5/10 on the GI-HSQ at baseline. At day 14, 68.9% (73/106) of patients reported improvements from baseline in constipation frequency and 77.7% (87/112) of patients reported improvement in severity (Fig. 4). At day 30, sustained and further improvements from baseline were observed with 73.6% (78/106) of patients reporting improvement for constipation frequency and 80.4% (90/112) of patients experiencing improvements in severity. More than half the enrolled patients with a baseline constipation severity ≥ 5/10 (n = 112) had a ≥ 3 point improvement on the GI-HSQ and an improvement in constipation severity at day 14 (53.6%), with sustained improvement to day 30 (67.0%).

Other GI Symptoms

At day 14, 66.0% patients in the overall study population reported an improvement in bowel habit satisfaction and in frequency/severity of GI symptomology, including straining (46.3%/63.3%), urgency (41.5%/64.4%), incomplete evacuation (28.7%/54.8%), abdominal pain/discomfort (56.4%/72.9%), mucus and gas (43.1%/52.7%), bloating (51.6%/69.7%), and distention (44.1%/64.9%) (Fig. 4). At day 30, improvements from day 14 were sustained and a larger percentage of patients reported an improvement in bowel habit satisfaction (73.4%) and frequency/severity of GI symptoms, including straining (54.8%/64.9%), urgency (45.2%/65.4%), incomplete evacuation (36.2%/60.6%), abdominal pain/discomfort (60.1%/79.8%), mucus and gas (46.8%/55.3%), bloating (59.0%/77.7%), and distention (54.8%/70.2%). In addition, a ≥ 3 point improvement on the GI-HSQ and improvement in severity of GI symptoms was seen in a number of patients from the overall study population at day 14 and sustained to day 30 for straining (36.2% and 47.3%, respectively), urgency (35.6% and 39.9%, respectively), abdominal pain/discomfort (42.6% and 51.6%, respectively) bloating (43.1% and 54.3%, respectively), distention (33.0% and 45.2%, respectively), bowel habit satisfaction (43.1% and 48.4%, respectively), and incomplete evacuation (33.0% and 42.6%, respectively).

Patterns in Frequency and Severity of GI Symptoms

In general, patients reported improvements in both the frequency and severity of GI symptoms at day 14 and continued improvement at day 30, as demonstrated by a mean decrease on the GI-HSQ score compared with baseline (Fig. 5). Importantly, although the probiotic blend was discontinued at day 30, many patients reported a sustained improvement over baseline on the GI-HSQ at the study follow-up visit (day 42), especially for severity of GI symptoms, including, straining (64.4%), urgency (61.2%), bloating (75.5), and distention (67.6%). In addition, many patients reported an improvement in both the frequency and severity of mucus and gas symptoms at the study follow-up visit (day 42) (54.8% and 64.9%, respectively).

I-FABP

At baseline, the mean serum I-FABP level among all study participants was 1121.1 pg/mL (SD, 704.7 pg/mL). At day 30, a nonstatistically significant change in I-FABP by a mean of −44.6 pg/mL (SD, 837.7 pg/mL) was observed in patients taking the probiotic blend. In addition, at day 30 a

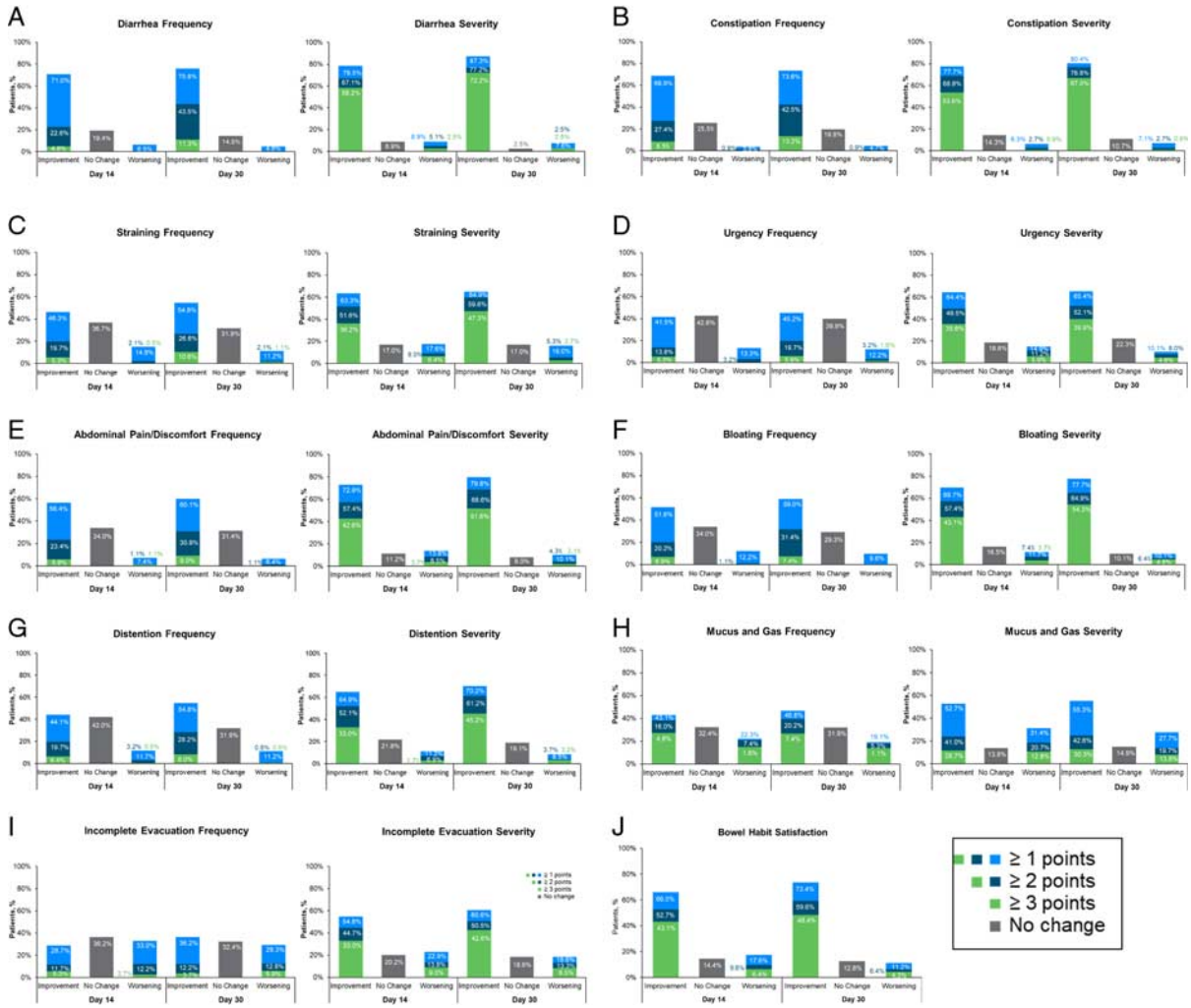

FIGURE 4. Patient Response to the GI-HSQ[a]. A–I, Depict improvements in frequency and severity of GI symptoms. J, Portrays improvements in bowel habit satisfaction. [a]For symptoms of diarrhea and constipation, frequency is shown for patients with a baseline frequency of ≥3 to 4 days/week (diarrhea, n = 62 and constipation n = 106) and severity is shown for patients with a baseline severity score of ≥5 (diarrhea, n = 79 and constipation n = 112); for all other GI symptoms, frequency and severity are shown in the total patient population (n = 188). GI indicates gastrointestinal; GI-HSQ, Gastrointestinal Health Symptom Questionnaire.

mean (SD) change in I-FABP levels of −32.7% (42.7) was seen in patients with the highest quartile of baseline I-FABP levels (n = 42; range, 1385.0 to 3875.0 pg/mL).

Safety

Total and drug-related TEAEs were reported in a small number of patients (18.6% and 8.0%, respectively) (Table 3). Common TEAEs included flatulence (3.2%) and cough (2.7%). No deaths, serious TEAEs, or discontinuations due to a TEAE occurred in any patient taking the probiotic blend. However, 1 patient experienced worsening flatulence, resulting in the probiotic blend being withdrawn, and study discontinuation was documented due to an AE.

DISCUSSION

This open-label, multicenter study demonstrated that treatment with a novel 5-strain probiotic blend (Bl-04, Bi-07, HN019, NCFM, and Lpc-37) taken once daily for 30 days improved common symptoms of FGIDs. Over 80% of patients reported improvement in GI well-being after 1 month of therapy, which was consistent with findings at 2 weeks. Many patients reported rapid improvements in GI symptom frequency and severity at day 14, and sustained improvements to day 30, for frequency and severity of GI symptoms, including, diarrhea, constipation, straining, urgency, abdominal pain, gas, bloating, and distention. Early improvements in GI symptoms persisted to the study follow-up visit (day 42), even though the probiotic was discontinued at day 30. In addition, patient preference questionnaire results of this study show that many patients were satisfied with the probiotic blend and indicated that they would recommend it to others. Furthermore, the probiotic blend displays a favorable safety profile, as evidenced by no discontinuations due to a TEAE, serious TEAEs, or deaths due to the probiotic blend occurring in any patient during the study.

Pharmacological treatments for FGIDs can be a burden to some patients. When surveyed, patients with FGIDs commented on the challenges of pharmacological treatment

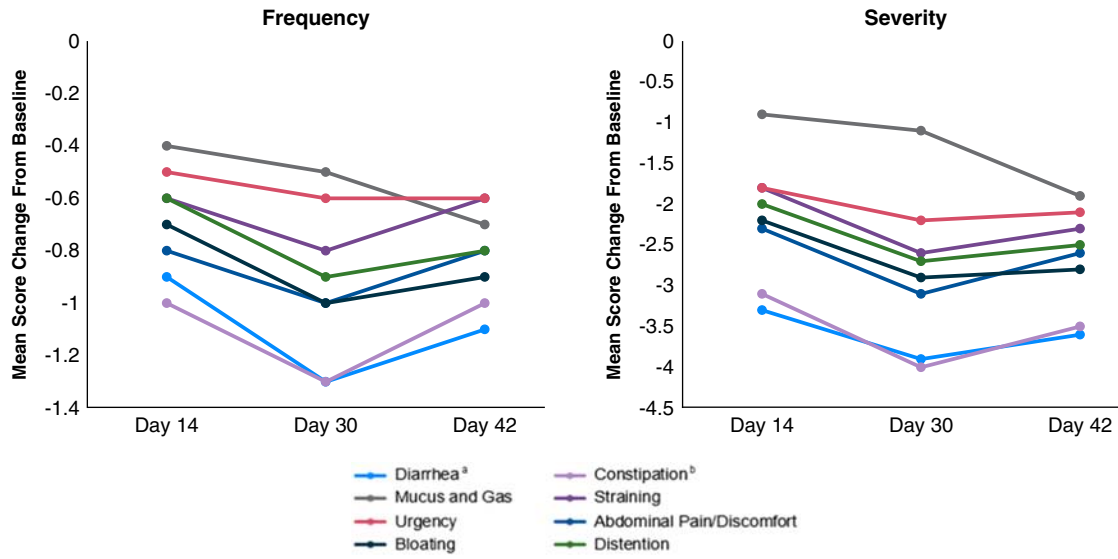

FIGURE 5. Change in Response to GI-HSQ Components Over Time. [a]For symptoms of diarrhea, frequency is shown for patients with a baseline frequency of ≥3 to 4 days/week (n = 62), and severity is shown for patients with a baseline severity score of ≥5 (n = 79). [b]For symptoms of constipation, frequency is shown for patients with a baseline frequency of ≥3 to 4 days/week (n = 106), and severity is shown for patients with a baseline severity score of ≥5 (n = 112). For symptoms other than diarrhea and constipation, frequency and severity are shown in the total patient population (n = 188). GI indicates gastrointestinal; GI-HSQ, Gastrointestinal Health Symptom Questionnaire.

including undesirable side effects of medications and out-of-pocket costs not covered by insurance.[28] Many patients with FGIDs seek lifestyle, dietary, and alternative approaches for symptom relief with variable results.[29,30] Although guidelines recommend lifestyle and dietary approaches as treatment options, the quality of evidence has been described as weak and very low, and the recommended diets can be restrictive and difficult for patients to follow.[19,30] While probiotics are positioned as a patient directed treatment option for functional GI symptoms and are purported to influence the gut ecosystem, the exact mechanism of how probiotics confer benefit to individuals with FGIDs remains unclear and there is a need for evidence-based communications to health care providers and consumers regarding the clinical use of probiotics.

Results of this study build on existing evidence that probiotic strains, Bl-04, Bi-07, HN019, NCFM, and Lpc-37 alone or in combination yield beneficial outcomes in patients with FGIDs[21–24] and are safe for consumption.[31,32] In accordance with previous research, our findings suggest that the intestinal microbiota is an important foundation of healthy GI function and an altered microbiota can lead to functional GI symptoms.[33]

It is thought that dysbiosis promotes enterocyte necrosis and release of I-FABP into circulation, and that gut barrier integrity can be indirectly measured using serum I-FABP.[27] Therefore, I-FABP has emerged as a biomarker of intestinal barrier dysfunction and gut integrity.[25] However, more evidence is necessary to delineate the clinical significance of I-FABP in relation to symptoms of FGIDs.

There are strengths to this open-label study assessing the efficacy and safety of a novel 5-strain probiotic blend in patients with FGIDs. Originally, it was anticipated that 150 patients would enroll, yet 188 patients were enrolled in the study. The ITT population was used to evaluate study outcomes, minimizing bias prone conclusions due to protocol deviations and dropouts. Furthermore, using the ITT population allows for greater generalizability of study results to other patients with FGIDs.[34]

However, inherent in the utilized study design are limitations, which can complicate interpretation of the results. This study enrolled patients with symptoms of FGIDs but not a diagnosis of FGIDs. No formal sample size calculation was performed. Since there were no comparison groups, it could be argued that the responses observed are due to the placebo effect and not the active ingredients in the probiotic blend. The study design also hinders the ability to differentiate if improvements in GI symptoms reported by patients were due to efficacy of the probiotic blend, a placebo effect, or to spontaneous or natural disease improvement.[35] Patients took the probiotic blend for 30 days, which may not be a sufficient duration to capture complete treatment benefit. In addition, the primary endpoint was a global subjective assessment of GI

TABLE 3. TEAEs Reported in ≥2 Patients

TEAE	Total [n (%)]
Any TEAE	35 (18.6)
Gastrointestinal disorders	
Flatulence	6 (3.2)
Constipation	2 (1.1)
Diarrhea	2 (1.1)
Dyspepsia	2 (1.1)
Infections	
Bronchitis	2 (1.1)
Laryngitis	2 (1.1)
Pharyngitis	2 (1.1)
Urinary tract infection	2 (1.1)
Respiratory disorders	
Cough	5 (2.7)
Upper respiratory tract congestion	2 (1.1)

TEAE indicates treatment-emergent adverse event.

well-being which may not be the perfect tool to observe improvements in GI symptoms as opposed to a multi-component endpoint using a validated instrument. However, use of a subjective questionnaire was necessary given the broad array of symptoms of FGIDs exhibited by patients in the trial. There are no data for the length of time patients displayed symptoms before study inclusion, and therefore this study may not describe the efficacy of the novel 5-strain probiotic blend in patients with more chronic symptoms. There was also no collection of stool culture to evaluate for colonization of bacteria contained in the probiotic blend in the colon. Results of this study are not generalizable to pediatric patients because they were excluded from the study.

In conclusion, a novel 5-strain (Bl-04, Bi-07, HN019, NCFM, and Lpc-37) probiotic blend was demonstrated to improve functional GI symptoms as early as day 14 with sustained improvements to day 30. Treatment with the novel probiotic blend was safe and well-tolerated, with few adverse events resulting in discontinuation. These findings support previous studies, which demonstrated a treatment benefit using beneficial strains of probiotics, alone or in combination, in patients with functional GI symptoms. Results of this study are encouraging but further studies are likely needed to support the blend's efficacy, safety, and durability of effect.

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