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Efficacy and Safety of Probiotic *Bacillus coagulans*-SNZ 1969 in Gastrointestinal Discomfort: A Randomized, Placebo-Controlled Study

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ABSTRACT

Purpose: *Bacillus coagulans*-based probiotics restore gut microbiota and alleviate symptoms of gastrointestinal (GI) discomfort. This study evaluated the efficacy and safety of SNZ 1969 in individuals with GI discomfort.
Methods: This was a single-center, randomized, placebo-controlled, parallel-arm, double-blind study. Participants with GI discomfort (n=30 in each arm) without a specific pathology were randomized to receive *B. coagulans*-SNZ 1969, TriBac, or placebo, once daily after a major meal, for 30 days. Symptoms were assessed using the Severity of Dyspepsia Assessment (SODA) scale, Gastrointestinal Symptom Rating Scale (GSRS), and Short Form 36 (SF-36) at baseline, day 15, day 30, and 7 days after the end of treatment.
Results: A total of 29 participants from SNZ 1969 and 28 from the placebo group completed the study. Treatment with SNZ 1969 significantly improved the total SODA score (18.34 ± 5.35 vs. 12.60 ± 4.79; $p < 0.001$), SODA subscores for pain intensity (15.41 ± 4.98 vs. 10.71 ± 3.68; $p < 0.001$), nonpain symptoms (7.28 ± 2.23 vs. 4.89 ± 2.94; $p < 0.001$), satisfaction (-4.43 ± 1.81 vs. -3.00 ± 1.22; $p = 0.002$), and symptom of sour taste (1.52 ± 0.78 vs. 0.75 ± 0.89; $p = 0.001$) compared with placebo and were consistent after 7 days of treatment discontinuation ($p < 0.05$). No significant score reduction was observed for GSRS compared with placebo. Two adverse events, fever and cold, were unrelated to SNZ 1969.
Conclusion: SNZ 1969 was found to be safe and effective in reducing GI discomfort, especially dyspepsia.

Keywords: *Bacillus coagulans*, Gastrointestinal discomfort, Gastrointestinal Symptom Rating Scale, Probiotic, SNZ 1969, Severity of Dyspepsia Assessment scale

INTRODUCTION

Gastrointestinal (GI) disorders affect more than one-third of the global population (40.3%), making them common morbidity of concern. Gastrointestinal disorders manifest as functional disorders such as constipation, bloating, reflux, nausea, vomiting, diarrhea, abdominal pain, and cramping.[1] In India, over 7 million individuals had reported GI diseases such as gastritis and duodenitis in 2016.[2] Gastrointestinal discomfort not only affects the general well-being and the quality of life (QoL) but also imposes a significant economic burden.[3–5] Thus, early and effective management is essential and plays a crucial role. Imbalance in symbiotic intestinal microbiota is one of the several pathophysiological factors predisposing an individual to GI discomfort.[6]

The human microbiota is seeded with maternal microbiota and various perinatal factors such as mode of delivery, diet, genetics, and intestinal mucin glycosylation contributing to its diversity.[5] The microbial diversity grows until 3 to 5 years of age, forming an individual's adult microbiota that usually remains stable throughout life. However, bacterial infections, antibiotic treatments, lifestyle changes can alter this symbiotic microbial system, leading to several GI ailments.[7] Therefore, interventions that restore adequate healthy gut microbiota are imperative for treating GI discomfort. There is strong evidence reporting the beneficial effects of probiotics in treating several gastric disorders, including antibiotic-associated diarrhea, acute infectious diarrhea, *Clostridium difficile*-associated diarrhea, ulcerative colitis, hepatic encephalopathy, functional GI disorders, irritable bowel syndrome (IBS), and necrotizing enterocolitis.[8–12]

Probiotics are live organisms that maintain immunologic equilibrium and exert health benefits to the host when ingested in adequate amounts. Proposed mechanisms of action include competitive exclusion of pathogenic microorganisms, inhibition of pathogen adhesion, production of antimicrobial substances, and modulation of the immune system.[13–15] Several species of microorganisms such as *Lactobacillus, Bifidobacterium, Enterococcus, Streptococcus, Bacillus, Saccharomyces, Propionibacterium, Peptostreptococcus, Pediococcus, Bacteroides, Akkermansia*, and *Bacillus coagulans* are used in the manufacturing of probiotics.[16] *Bacillus coagulans* is known to generate endospores, making them tolerant to harsh GI environments. *Bacillus coagulans*, initially described as *Lactobacillus sporogenes*, was first isolated in 1915 by B.W. Hammer. The strain exhibits characteristics typical of both the *Lactobacillus* and the *Bacillus* genera. It was designated as *Bacillus coagulans*-SNZ 1969 when the formulation and fermentation technologies were transferred from Sankyo Ltd. to Sanzyme Ltd. *Bacillus coagulans*-SNZ 1969 is a rod-shaped, slightly acidophilic, gram-positive, catalase-positive, spore-forming, thermos-tolerant, aerophilic to microaerophilic, highly resilient bacteria, Generally Recognized As Safe (GRAS) by the United States Food and Drug Administration.[17] Sporlac, a registered brand of the strain, is extensively used to restore the normal balance of intestinal microbiota and has shown an antagonistic effect toward pathogenic bacteria. Administration of *Bacillus coagulans* was beneficial in improving the intestinal environment, thereby alleviating diarrhea and acute gastroenteritis in infants and adults.[18–22] However, few systematic reviews and meta-analyses (SRMAs) have shown inconclusive results, [10,23] highlighting the need for robust evidence regarding the benefit of *Bacillus coagulans*-based probiotics in alleviating GI discomfort. Therefore, we conducted a randomized controlled trial (RCT) to evaluate the efficacy of *Bacillus*-based probiotics, SNZ 1969 and TriBac, in individuals with undiagnosed GI discomfort. Results of the efficacy of TriBac have been reported earlier.[24] We report the efficacy and safety of *Bacillus coagulans*-based probiotic, SNZ 1969, in the management of GI discomfort.

MATERIAL AND METHODS

Study design

This was a single-center, prospective, randomized, double-blinded, placebo-controlled, parallel-group study comprising of 3 arms: (a) arm 1: multistrain probiotic TriBac (*Bacillus coagulans* [SNZ 1969], *Bacillus clausii* [SNZ 1971], and *Bacillus subtilis* [SNZ 1972]); (b) arm 2: *Bacillus coagulans*-SNZ 1969; and (c) arm 3: the placebo. The results of the efficacy of TriBac have been reported earlier. [24] The study was conducted at Jehangir hospital, Pune, Maharashtra, India (CTRI registration number:

CTRI/2018/05/014071; registered on: 23/05/2018) from July 19, 2018, to November 16, 2018, in compliance with the International Conference on Harmonization "Guidance on Good Clinical Practice," the Indian Good Clinical Practices Guideline, the National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Indian Council of Medical Research 2017, and the Declaration of Helsinki. The institutional ethics committee of JCDC, Pune, Maharashtra, India, approved this study.

Study population

The study included participants aged 18 to 60 years, presenting with complaints of abdominal distress, such as gas, pain, and abdominal distension (pain and discomfort scores ≥ 1 per the Severity of Dyspepsia Assessment [SODA] and Gastrointestinal Symptom Rating Scale [GSRS] scale), otherwise healthy as confirmed by physical examination, vital signs, hemogram, liver function tests (alanine aminotransferase, aspartate aminotransferase, and total bilirubin), and renal function tests (blood urea nitrogen, serum creatinine). Participants who agreed to exercise and follow dietary restrictions such as no fiber supplements, other probiotics, and unpasteurized bacterial fermented products such as cheese and yogurt during the entire study duration were enrolled. Patients with a history of food intolerance, short gut syndrome, Crohn's disease, inborn errors of metabolism, ulcerative colitis, short bowel, constipation, irritable bowel syndrome (IBS), lactose intolerance, and those participants using GI medications (prokinetic agents, antispasmodics, laxatives, or anti-motility medications) were excluded.

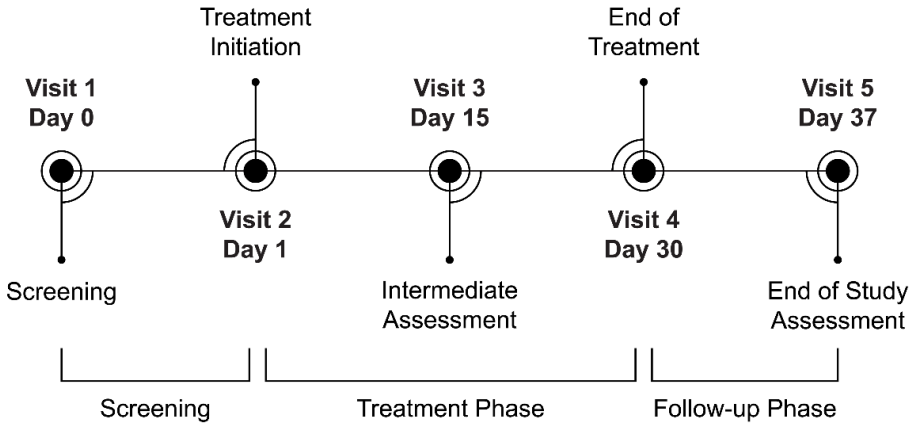

Figure 1 Study design.

Note: This was a three-arm, randomized, parallel-group study. In this manuscript we report on 2 arms, 'SNZ1969' versus 'placebo'. The results of efficacy of the third arm, 'TriBac' have been reported earlier.[24]

The study involved five visits during the three phases of the study: the screening phase: visit 1 (day 0- 7days), the treatment phase: visit 2 (day 1 [randomization]), visit 3 (day 15 ± 2 days), and visit 4: (day 30 ± 2 days), and the follow-up phase: visit 5 (day 37, end of study ± 7 days) (Figure 1). At screening, participants were evaluated for eligibility after obtaining their written informed consent; data on demography and clinical history were collected. In the treatment phase, on day 1 (i.e., treatment initiation), eligible participants were randomized in 1:1:1 proportion to arms 1, 2, and 3 as described earlier. An independent statistician generated a random allocation sequence using a fixed randomization table, and a

designated study coordinator assigned the random allocation sequence to the participants. The participants self-administered probiotic supplements or a matching placebo once daily after the main meal, approximately at the same time for 30 days (Figure 2). Each probiotic capsule contained not less than two billion colony-forming units of *Bacillus coagulans*-SNZ 1969, a safe and well-tolerated dosage in earlier evaluations,[25,26] and color-, shape, and size-matched placebo capsule contained calcium carbonate. Compliance with treatment was assessed based on the number of units per container used by the participants. Participants with compliance of < 80% were not included in the analysis.

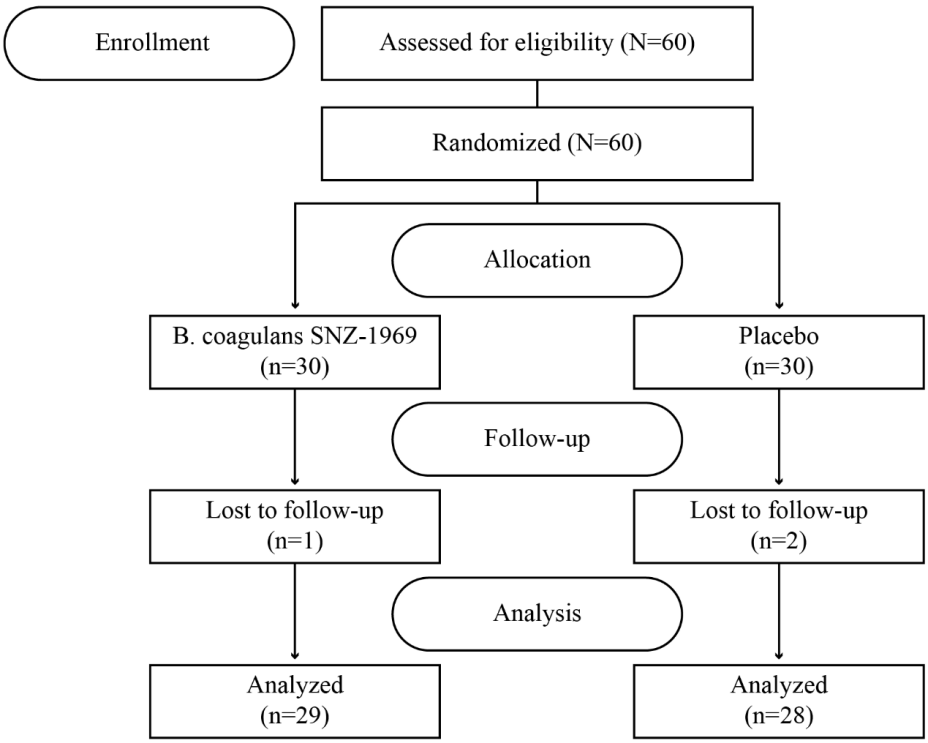

Figure 2 Patient disposition.

The following patient-reported outcomes (PROs) were used to assess the severity of GI discomfort symptoms:

SODA: a multidimensional reliable and validated self-administered health scale with 17 questions divided into three subscales: the extent of pain intensity (6 questions); nonpain symptoms of belching, heartburn, bloating, passing gas, sour taste, nausea, and bad breath (7 questions); and satisfaction level concerning abdominal discomfort (4 questions).[27]

GSRS: a 15-item, structured, and validated questionnaire was used to assess the severity of current GI symptoms.[28]

SF-36 v2: the scale consisted of eight scales yielding physical and mental health measures. The physical health measure included four scales of physical functioning (10 items), role-physical (4 items), bodily pain (2 items), and general health (5 items). The mental health measure is composed of vitality (4 items), social functioning (2 items), role-emotional (3 items), and mental health (5 items). A final item, termed self-reported health transition, is answered by the participant but is not included in the scoring process.[29]

Adverse events (AEs) were monitored throughout the study based on clinically significant changes in vital signs, physical examination findings, and laboratory tests. The severity of the AEs and their relationship with the study intervention were also assessed.

STATISTICAL METHODS

Considering the sigma effect size of 0.8 and a study power of 80%, 25 participants were required to be randomized in each treatment group. Assuming a dropout rate of 15% at the chosen site, 30 participants were recruited in each group. The primary endpoints were assessed at the end of the treatment and follow-up phases (visit 4 and 5, respectively). Data were presented as mean ± standard deviation for numerical data and number (%) for categorical data. The Student unpaired t-test was applied to compare the mean change in scores between SNZ 1969 and placebo. The Fisher-exact probability test or Chi-square test was performed, as applicable, to compare categorical data. To measure the magnitude of the difference, 95% confidence intervals (CIs) of the differences were calculated. Analysis of covariance (ANCOVA) was applied to GSRS subscores for abdominal pain, distension, and flatulence and 2 SODA subscores for bloating and gas by taking the base values (visit 1 value) as a covariate. All statistical tests were two-tailed. The level of significance (α) was set at $p \leq 0.05$. Data were analyzed using SPSS v 15.0 (IBM Corp., NY, USA).

RESULT

Table 1 Demographic and clinical characteristics of participants

Characteristics n (%)	***Bacillus coagulans* SNZ 1969 N = 29**	**Placebo N = 28**
Age, years*	33.72 ± 7.98	34.89 ± 9.95
Body mass index, kg/m^2 *	24.23 ± 3.54	24.97 ± 4.88
Men	10 (37.9)	12 (42.9)
Vegetarian diet	2 (6.9)	4 (14.3)
Never smoked	29 (100)	28 (100)
No alcohol consumption	29 (100)	28 (100)
Nonvegetarian diet	27 (93.1)	24 (85.7)
Normal SBP	29 (100)	28 (100)
Normal DBP	29 (100)	28 (100)
Normal pulse	29 (100)	28 (100)
Normal respiratory rate	29 (100)	28 (100)
Normal temperature	29 (100)	28 (100)

**Data are presented as mean ± SD.*
DBP, diastolic blood pressure; SBP, systolic blood pressure.

A total of 30 participants were enrolled in the SNZ 1969 and placebo arms, respectively; 1 participant from the SNZ 1969 arm and 2 from the placebo arm were lost to follow-up (Figure 2). The mean age of participants in SNZ 1969 and placebo arm was 33.72 ± 7.98 and 34.89 ± 9.95 years. No significant differences between the arms were noted for baseline and demographic characteristics (Table 1).

The reduction in total SODA score from baseline at day 30 was significantly higher for SNZ 1969 compared with placebo (18.34 ± 5.35 vs. 12.60 ± 4.79; $p < 0.001$) (Table 2). The mean baseline and day 30 SODA pain intensity subscores for SNZ 1969 were 29.34 ± 1.57 and 13.93 ± 4.42, respectively. The SODA pain intensity subscore reduction from baseline at day 30 was significantly higher for SNZ 1969 arm than in the placebo arm (15.41 ± 4.98 vs. 10.71 ± 3.68; $p < 0.001$). The SODA nonpain symptom subscore reduction reflected relief from burping/belching, heartburn, bloating, passing of gas, sour taste, nausea, and bad breath. The reduction from baseline was significantly more in participants treated with SNZ 1969 compared with placebo at day 30 (7.28 ± 2.23 vs. 4.89 ± 2.94; $p < 0.001$). Additionally, among the nonpain symptoms, a significantly greater reduction in sour taste was seen after treatment with SNZ 1969 than placebo 1.52 ± 0.78 vs. 0.75 ± 0.89; $p = 0.001$). The SODA satisfaction subscore with abdominal discomfort significantly improved with SNZ 1969 treatment than placebo (−4.34 ± 1.81 vs. −3.00 ± 1.22; $p = 0.002$). Significant improvement in SODA scale scores at day 30 compared with placebo was sustained after 7 days of discontinuing the SNZ 1969 treatment ($p < 0.05$). These included total SODA score (15.57 ± 3.76 vs. 12.18 ± 4.61; $p = 0.003$), SODA pain intensity subscore (15.86 ± 4.20 vs. 10.43 ± 3.97;$p < 0.001$), SODA nonpain subscore (8.76 ± 1.99 vs. 5.00 ± 3.01; $p < 0.001$), SODA satisfaction score (−5.31 ± 2.49 vs. −3.25 ± 2.37; $p = 0.002$), and SODA sour taste (1.52 ± 0.78 vs. 0.71 ± 0.90; $p < 0.001$).

Table 2 Change from baseline to 30 days and day 37 in SODA and GSRS symptoms scores.

Characteristics	Day 30		Day 37	
	***Bacillus coagulans* (SNZ 1969) N = 29**	**Placebo N = 28**	***Bacillus coagulans* (SNZ 1969) N = 29**	**Placebo N = 28**
SODA scale				
SODA total scores	18.34 ± 5.35*	12.60 ± 4.79	15.57 ± 3.76****	12.18 ± 4.61
SODA pain subscore	15.41 ± 4.98*	10.71 ± 3.68	15.86 ± 4.20*	10.43 ± 3.97
SODA nonpain subscore	7.28 ± 2.23*	4.89 ± 2.94	8.76 ± 1.99*	5.00 ± 3.01
SODA satisfaction subscore	−4.34 ± 1.81***	−3.00 ± 1.22	−5.31 ± 2.49***	−3.25 ± 2.37
Burping/Belching	1.28 ± 0.75	1.04 ± 0.96	0.34 ± 0.81	−0.04 ± 0.96
Heartburn	1.41 ± 0.78	0.96 ± 1.20	1.55 ± 0.69	1.07 ± 1.12
Bloating	0.86 ± 0.88	0.82 ± 0.86	1.03 ± 0.87	0.82 ± 0.98
Passing gas	1.00 ± 0.93	0.86 ± 0.80	1.10 ± 0.86	0.86 ± 0.93
Sour taste	1.52 ± 0.78**	0.75 ± 0.89	1.52 ± 0.78**	0.71 ± 0.90
Nausea	0.93 ± 0.75	0.92 ± 0.98	0.97 ± 0.82	0.86 ± 0.97
Bad breath	0.48 ± 0.83	0.36 ± 0.62	0.59 ± 0.82	0.36 ± 0.62
GSRS scale				
GSRS total scores	6.31 ± 4.56	7.18 ± 4.98	7.10 ± 5.11	5.36 ± 6.77
Dyspeptic syndrome subscore	2.86 ± 2.25	3.21 ± 2.47	3.65 ± 2.16	3.18 ± 2.44
Indigestion syndrome subscore	2.41 ± 1.61	2.32 ± 2.07	2.97 ± 1.59	2.29 ± 2.14
Bowel dysfunction syndrome subscore	1.03 ± 2.16	1.64 ± 2.39	1.28 ± 1.93	1.54 ± 2.57

**p < 0.001 vs. placebo; **p = 0.001; ***p = 0.002; ****p = 0.003 (calculated using student unpaired t-test)*
Note: SODA total score, SODA pain subscale, and SODA nonpain subscale: higher score represents worst symptoms
SODA satisfaction subscale: higher score represents better satisfaction
GSRS score: higher score represents sever symptoms.
GSRS, Gastrointestinal Symptom Rating Scale; SODA, Severity of Dyspepsia Assessment

ANCOVA scores of SODA bloating symptoms (coefficient ± standard error: 0.29 ± 0.10; p = 0.008) and SODA passing gas symptom (0.29 ± 0.12; p = 0.015) significantly improved after treatment with SNZ 1969 compared with placebo at day 30. (data not shown).

The changes in GSRS total score from baseline at day 30 (6.31 ± 4.56 vs. 7.18 ± 4.98), dyspeptic syndrome subscore (2.86 ± 2.25 vs. 3.21 ± 2.47), indigestion syndrome subscore (2.41 ± 1.61 vs. 2.32 ± 2.07), and bowel dysfunction syndrome subscore (1.03 ± 2.16 vs. 1.64 ± 2.39) were similar in participants receiving SNZ 1969 vs. placebo (p > 0.05 for all comparisons). Moreover, no significant differences were noted between SNZ 1969 and placebo in terms of changes in QoL scores over 30 and 37 days of treatment.

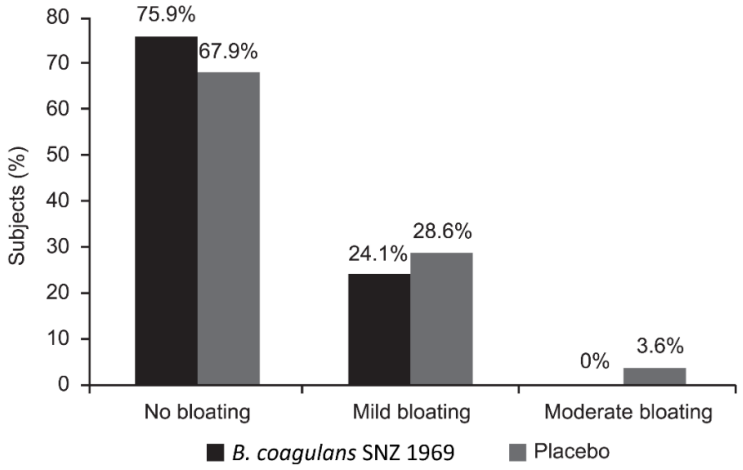

Figure 3(a) Frequency of participants experiencing bloating symptom cluster in SODA scale at day 30.

On comparing participants who had experienced specific symptoms in SODA scales (bloating: Figure 3[a], burping: Figure 3[b], heartburn: Figure 3[c], passing of gas: Figure 3[d]), a greater proportion of SNZ 1969-treated participants experienced no symptoms at day 30. Two AEs (fever and cold) reported in SNZ 1969 arm during

the study, assessed as unrelated to SNZ 1969, were resolved.

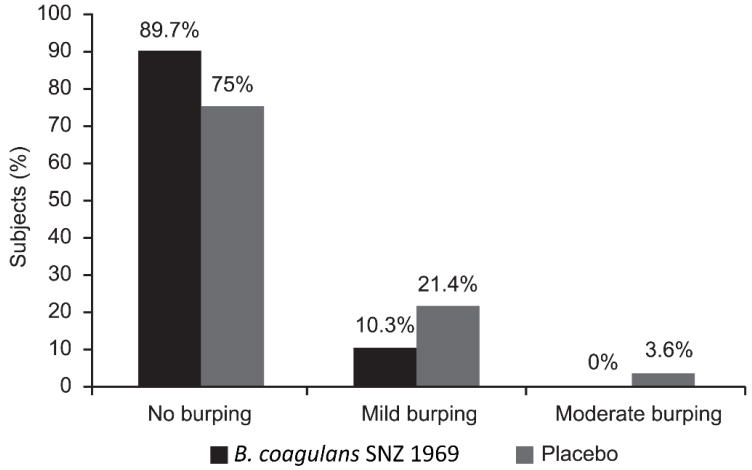

Figure 3(b) Frequency of participants experiencing burping symptom cluster in SODA scale at day 30.

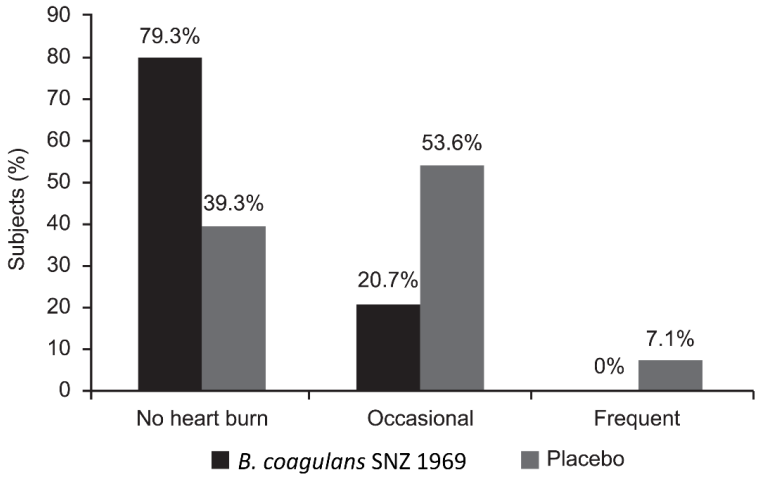

Figure 3(c) Frequency of participants experiencing heart burn symptom cluster in SODA scale at day 30.

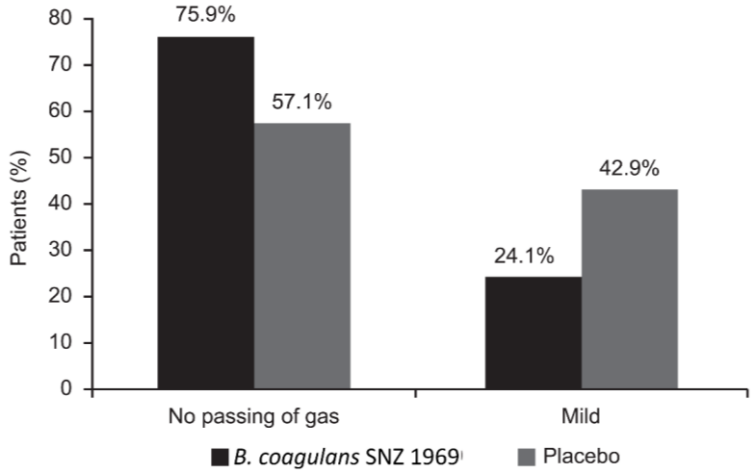

Figure 3(d) Frequency of participants experiencing passing of gas symptom cluster in SODA scale at day 30.

DISCUSSION

Gastrointestinal discomfort is a functional disorder for which diagnosis is often achieved based on functional symptoms.[30] In this study, we found *Bacillus coagulans*-based probiotic (SNZ 1969) effectively reduced the functional symptoms of GI discomfort such as pain, burping/belching, heartburn, bloating, sour taste, nausea, and bad breath

compared with placebo after 30 days of treatment as assessed by PROs. There was a significant reduction in total SODA score, pain score, SODA nonpain score, and improvement in SODA satisfaction score in participants treated with SNZ 1969 for 30 days compared with the placebo arm. Similar to our results, Maity *et al.* reported a reduction in severe abdominal pain by 70% in the probiotic treated group (*Bacillus coagulans* strain LBSC) (absolute relative risk: 0.70, 95% CI: 0.46 to 0.82).[20] Another recent clinical trial conducted by Kang *et al.* demonstrated that *Bacillus coagulans* supplement significantly improved bowel discomfort symptoms at three weeks ($p = 0.019$).[31] Several earlier studies have also reported improvement in abdominal pain and discomfort with probiotic supplements.[10,20,21,31,32] *Bacillus*-based probiotics, specifically, have also been shown to relieve symptoms of general abdominal discomfort, bloating, flatulence, indigestion, nausea, and irregular bowel patterns.[33,34] The improvement in SODA scores, and most participants treated with SNZ1969 not reporting bloating (75,9% vs. 67.9%), burping (89.7% vs. 75%), heartburn (79.3% vs. 39.3%) and flatulence (75.9% vs. 57.1%) at the end of treatment in this study are consistent with earlier reports.

Moreover, improvement in all subscale scores, such as pain and nonpain, satisfaction of SODA, and a reduction in sour taste over placebo with 30 days of treatment with SNZ 1969, indicates that this probiotic may help alleviate dyspepsia for the long-term even after cessation of treatment. No significant reduction in GSRS score indicates minimal effect of SNZ 1969 on bowel dysfunction and indigestion. As these could be chronic symptoms, SNZ 1969 should be evaluated further in long-term studies to assess the impact on these long-standing symptoms.

Probiotics have been shown to be safe in an SRMA, which included 387 studies (of which 121 were RCTs) with 24,615 participants with no significant increase in the relative risk of the number of AEs in individuals treated with short-term probiotics.[35] Furthermore, *Bacillus coagulans*-based probiotics were also found to be safe in earlier reports.[20,21] In the current study SNZ 1969 was safe, with minimal AEs unrelated to SNZ 1969.

The use of probiotics has been endorsed by several evidence-based clinical practice guidelines with a common consensus in lowering GI issues, preventing diarrhea associated with antibiotics, and eradicating *Helicobacter pylori* infection with considerable safety.[12,36,37] Gut microbiota plays a critical role in the overall well-being of an individual, and disruption of its balance is associated with various disorders.[7] The underlying mechanisms of action for beneficial effects of probiotics comprise inhibition of growth of pathogenic microorganisms by interrupting pathogen adhesion, production of antimicrobial substances, modulation of the immune system, maintenance of normal levels of short-chain fatty acids, repairing intestinal permeability, and upregulation of intestinal electrolyte absorption.[12]

Among the available probiotics, *Bacillus*-based probiotics fulfill all characteristics of an ideal probiotic owing to their ability to produce vitamins and enzymes that degrade extracellular carbohydrates and proteins,[33] acid resistance, and thermos-tolerant spore-forming ability. Furthermore, due to their multi-antibiotic resistance, *bacillus*-based probiotics can also help replenish microbiota during antibiotic treatment and can be effective in treating antibiotic-associated diarrhea.[38–40] The significant reduction in dyspepsia symptoms as assessed by SODA in this study and improved satisfaction with SNZ 1969 over placebo shows that SNZ 1969 effectively replenishes gut microbiota.

The current study demonstrated improvement in GI discomfort and treatment satisfaction from a patient perspective as the outcomes were based on PROs. Regulators have often highlighted the importance of PROs in determining the

efficacy and assessing the study endpoints.[41] Participants in our study had high compliance with the treatment. This also suggests that compliance may have a significant role in achieving symptomatic relief.

Being a single-center study may limit the applicability of these results as gut microbiota in various ethnic groups of patients across different geographies of the world may vary.[42]

The difference in GSRS scores remained non-significant between the probiotic and placebo groups. This non-significance could be attributed to a strong placebo effect. Several GI trials have reported a high placebo effect, with studies reporting placebo effects varying from 6% to 72% for functional dyspepsia and 3% to 84% for IBS.[43] The current study findings may need to be substantiated with long-term, extensive, multicenter clinical trials with larger sample size.

To conclude, *Bacillus. coagulans-based* probiotics SNZ 1969 could be an effective and safe option for relieving symptoms of abdominal discomfort, especially dyspepsia, in otherwise healthy individuals. It showed an improvement in total SODA scores, including specific symptoms such as burping/belching, bloating, heartburn, passing gas, nausea, bad breath, and sour taste compared with placebo. Moreover, relief from these symptoms lasted for one week after the final dose. These promising therapeutic implications will need to be better defined in more extensive clinical studies. Nevertheless, the plausible benefits of this probiotic supplement may be considered for the management of functional GI disorders without any other established etiology.

Disclosures

Authors' contributions

All authors made equal contributions to study conception, acquisition of data, and preparation of this manuscript. All authors read and approved the final version of this manuscript.

Conflicts of Interest

R J Soman and M V Swamy are employees of Sanzyme Biologics Pvt. Ltd. Authors do not have other conflicts of interest to declare with respect to this authored publication.

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Compliance with Ethical Standards

Before participation in the study, all subjects provided written informed consent. This study was performed in compliance with International Conference on Harmonisation (ICH E6[R2]) "Guidance on Good Clinical Practice," Declaration of Helsinki; Indian Good Clinical Practices Guideline; National Ethical Guidelines for Biomedical and Health Research involving human participants, Indian Council of Medical Research 2017; and, relevant standard operating protocols of Jehangir Clinical Development Centre, Pune, Maharashtra, India. This study was approved by the institutional review board of Jehangir

Clinical Development Centre, Pune, Maharashtra, India, and was registered in the Clinical Trials Registry of India (CTRI/2018/05/014071).

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