The Probiotic Preparation, VSL#3 Induces Remission in Patients With Mild-to-Moderately Active Ulcerative Colitis

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BACKGROUND & AIMS: Probiotics can maintain ulcerative colitis (UC) in remission effectively, but little is known of their ability to induce remission. We conducted a multicenter, randomized, double-blind, placebo-controlled trial of a high-potency probiotic, VSL#3, for the treatment of mild-to-moderately active UC. METHODS: Adult patients with mild-to-moderate UC were assigned randomly to groups that were given 3.6 X 10^11 CFU VSL#3 (n = 77) or placebo (n = 70), twice daily for 12 weeks. The primary end point was a 50% decrease in the Ulcerative Colitis Disease Activity Index (UCDAI) at 6 weeks. The secondary end points included remission by 12 weeks and reduction in total individual UCDAI parameters from baseline at 12 weeks. Intention-to-treat analysis was performed. RESULTS: At week 6, the percentage of patients with an improvement in UCDAI score that was greater than 50% was significantly higher in the group given VSL#3 (25; 32.5%) than the group given placebo (7; 10%) (P = .001). At week 12, there were 33 patients given VSL#3 (42.9%) who achieved remission, compared with 11 patients given placebo (15.7%) (P < .001). Furthermore, significantly more patients given VSL#3 (40; 51.9%) achieved a decrease in their UCDAI that was greater than 3 points, compared with those given placebo (13; 18.6%) (P < .001). The VSL#3 group had significantly greater decreases in UCDAI scores and individual symptoms at weeks 6 and 12, compared with the placebo group. CONCLUSIONS: VSL#3 is safe and effective in achieving clinical responses and remissions in patients with mild-to-moderately active UC.

The exact pathogenesis of ulcerative colitis (UC) is not known. However, an interaction between genetic susceptibility, environmental factors, and immune dysregulation is implicated in the causation of UC. Intestinal microflora have been implicated both in the initiation and maintenance of the inflammatory process in patients with UC.1–4 Swidinski et al5 showed that patients with IBD have a greater number of mucosa-associated bacteria, particularly Bacteroides species and Escherichia coli. In general, larger numbers of Bacteroides species and Enterobacteriaceae and lower numbers of presumably beneficial bacteria, such as Bifidobacteria and Lactobacilli, have been reported in patients with UC.3,6 The mainstay of treatment of UC centers around suppression or modulation of the host’s immune response and limited attention has been given to the pathogenic contribution of the intestinal microenvironment. Current medical management consists of aminosalicylates, steroids, and immunosuppressants and biologics. A significant proportion of patients do not tolerate existing treatments because of their adverse effects and about 20% to 30% of patients fail to respond to the drugs given for induction of remission.7 Consequently, new alternatives for the treatment of UC constantly are being sought.3,6–9

Probiotics are defined as living microorganisms that, when consumed in adequate amounts, confer a health benefit to the host.10 There are many probiotic preparations; the efficacy of the preparation depends on the bacterial or fungal strains it contains. Unlike most probiotic products that are composed of either single microbes or a combination of a few microbes, VSL#3 is a high-concentration probiotic preparation of 8 live, freeze-dried bacterial strains, including 4 strains of Lactobacilli (L. paracasei, L. plantarum, L. acidophilus, and L. delbrueckii subspecies bulgaricus), 3 strains of Bifidobacteria (B. longum, B. breve, and B. infantis), and Streptococcus thermophilus.11

Probiotics have been used for induction of remission, maintenance of remission of UC, and maintenance of remission of pouchitis.12–26 Probiotic preparations such as E. coli Nissle 1917 and bifidobacterium-fermented milk have been found to be effective in maintenance of remission of UC.12 In 2 randomized controlled trials, VSL#3 has been shown to be highly effective in maintenance of remission of pouchitis.13,14 In a number of open-label and randomized studies, E. coli Nissle 1917, bifidobacterium-fermented milk, and VSL#3 also have shown efficacy in induction of remission of UC.18–22 However, Cochrane review of the 4 available studies did not find a significant effect of probiotics in the induction of remission of UC.23 In 2 small recent studies, VSL#3 has been reported to achieve remission/response in children with mild to moderate UC.24,25 Although there is growing data on the efficacy of VSL#3, there is a lack of a large randomized, placebo-controlled trial in the management of mild-to-moderately active UC. Hence, the objective of this study was to study the efficacy and safety of VSL#3 in mild-to-moderately active UC in achieving clinical response at week 6 and clinical remission at week 12.

Patients and Methods

Design
This was a multicenter, double-blind, placebo-controlled, randomized trial. The study was conducted at 3 tertiary care centers in North India between June 2005 and August 2007.

Abbreviations used in this paper: IL, interleukin; UC, ulcerative colitis; UCDAI, Ulcerative Colitis Disease Activity Index.
Participants

Adult patients (>18 y) who had mild-to-moderately active UC (Ulcerative Colitis Disease Activity Index [UCDAI] score, 3-9; with minimum sigmoidoscopic score of 2) extending for more than 15 cm from the anal verge with at least one previously documented attack of active disease were included in this study. None of the participants had enteral infection. Patients were excluded if they had disease limited to the rectum, evidence of severe disease (UCDAI, >10), concurrent enteric infection, use of oral steroids within the past 4 weeks, use of antibiotics within the past 2 weeks, change in dose of oral mesalamine within the past 4 weeks, and use of rectal mesalamine or steroids within 7 days before entry into the study. Patients requiring hospitalization and imminent need for surgery, lactating and pregnant women, and those who received any investigational medicines within 3 months were excluded. Patients with significant hepatic, renal, endocrine, respiratory, neurologic, or cardiovascular diseases also were excluded.

Randomization

Sequence generation. The random numbers were generated by computerized random number. The randomization list and numbered packing of the intervention was prepared by a person not involved in the study. Randomization was performed using permuted blocks of 10. There was a separate randomization list for each study center. Patients were randomized separately at all 3 study centers.

Randomization-allocation concealment. All the randomization numbers were concealed in separate envelopes and marked by patient number on the outer envelope.

Randomization implementation. The randomization was performed by staff not involved with the study. The intervention was provided at each center. Patients were assigned the next serial number (corresponding to the randomization code) of the intervention.

Blinding

The individual sealed envelope method was used to maintain blinding of the investigators and study participants.

Activity of Ulcerative Colitis

The activity of UC was assessed using the UCDAI. The UCDAI was calculated by the investigator by adding the individual scores of the 4 parameters: bowel frequency, rectal bleeding, endoscopic score, and physician’s rating of severity26 (Table 1). Rectal bleeding and stool frequency score was assessed by asking the patient about his/her symptoms over the past 3 days. The score for these parameters was calculated individually by mixing the contents of the sachet in a glass of cold water or yogurt.

Assessment

At entry to the study (screening visit), each patient’s demographic characteristics, medical history, and current medications were recorded. At this point, baseline clinical laboratory tests were conducted. All the laboratory tests were performed at the local laboratories. Individual disease activity was assessed at the baseline visit and after 6, 9, and 12 weeks. At each visit, a detailed physical examination and history was performed. All the patients underwent sigmoidoscopic examination at the baseline and then at weeks 6 and 12.

All adverse events were documented, classified, and graded. Daily disease activity records were written up by the study participants, who were provided with diary cards to assess and record their symptoms (stool frequency, bleeding, and abdominal pain) on a daily basis. Participants’ compliance in taking the study medications (VSL#3 and placebo) was assessed by the investigators, who counted the used and the unused sachets that the patients were required to bring with them on post-screening visits (weeks 6, 9, and 12).

If the condition of the patients deteriorated clinically, they were withdrawn from the study and put on standard medical treatment. In these cases, assessment of disease activity (including sigmoidoscopy), adverse events, and compliance (sachet count) were performed. All the patients were given a symptom diary card. The diary cards were reviewed and symptoms were

<table>
<thead>
<tr>
<th>Table 1. Ulcerative Colitis Disease Activity Index</th>
<th>Score</th>
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<tbody>
<tr>
<td>Stool frequency</td>
<td>Score</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>1–2 stools/d &gt; normal</td>
<td>1</td>
</tr>
<tr>
<td>3–4 stools/d &gt; normal</td>
<td>2</td>
</tr>
<tr>
<td>&gt;4 stools/d &gt; normal</td>
<td>3</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>None</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Streaks of blood</td>
<td>1</td>
</tr>
<tr>
<td>Obvious blood</td>
<td>2</td>
</tr>
<tr>
<td>Mostly blood</td>
<td>3</td>
</tr>
<tr>
<td>Mucosal appearance</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Mild friability</td>
<td>1</td>
</tr>
<tr>
<td>Moderate friability</td>
<td>2</td>
</tr>
<tr>
<td>Exudation, spontaneous bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Physician’s rating of disease activity</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
</tr>
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</table>

longum, B breve, and B infantis), and 1 strain of Streptococcus thermophilus. Four sachets of VSL#3 were given daily equating to a dose of 3600 billion viable lyophilized bacteria. The study drugs were supplied by VSL Pharmaceuticals, Inc (Gaithersburg, MD). However, they were imported in India by CD Pharma India Pvt Ltd (Sister company of VSL Pharmaceuticals, Inc) and distributed to trial sites. Placebo was supplied in identical sachets containing maize powder. Patients were asked to take the contents of the sachets morning and evening by mixing the contents of the sachet in a glass of cold water or yogurt.
assessed on a scale of 0 to 3. The individual scores for the last available 3 days before the visit were recorded.

**Concomitant Medicines**

Patients currently taking maintenance oral mesalamine therapy (stable for 4 weeks before study entry) were continued on the drug at a stable dose. Patients were off rectal medications at least 7 days before inclusion in the study. Rectally administered mesalamine or steroids, systemic corticosteroids, antibiotics, nonsteroidal anti-inflammatory drugs, and antidiarrheal drugs were not allowed during the course of the study. Patients taking azathioprine or 6-mercaptopurine were maintained on a stable dose for at least 3 months before entry and throughout the study. All concomitant medications taken during the study period were recorded in the case record form.

**Outcome Measures**

**Primary outcome measure.** The primary outcome measure was improvement in activity of UC. This was defined as a decrease in the UCDAI by 50% or more from baseline to week 6.

**Secondary outcome measures.** Secondary outcome measures were as follows. First, the proportion of patients achieving remission (defined by UCDAI score of 0–2) at week 12 of treatment (clinical and endoscopic remissions were defined as a score of 0 in the rectal bleeding and stool frequency parts of the UCDAI together with a score of 0 or 1 in the sigmoidoscopy activity subscore of the UCDAI). Second, improvement in activity of UC. This was defined as a decrease in the UCDAI of 3 or more points from baseline to week 12. Third, change in subjective symptoms (rectal bleeding and stool frequency) score from baseline to weeks 6 and 12 of treatment. Fourth, mucosal healing (mucosal appearance score 0) at week 12. Fifth, treatment failure. Lack of improvement at the end of 6 weeks was considered a treatment failure (failure to decrease UCDAI score by 3 points or at least 50% of baseline UCDAI score at week 6).

**Ethics Committee Approval and Patient Consent**

The protocol was approved by the investigational review board of all 3 respective centers. Written informed consent was obtained from all the participants. Patients were allowed to withdraw at any time point during the study, either because of lack of efficacy or for any other reasons.

**Safety Assessments**

A safety assessment was performed on the following protocol: eliciting of a detailed medical history; conduct of a detailed physical examination at each visit, including vital signs; and documentation of any adverse events that occurred during the study period.

**Sample Size**

The sample size was based on a power of 80% and a statistical significance (alpha) of 95% (P = .05). This assumed that a response to treatment at 12 weeks, such as with oral mesalamine preparations, was expected to occur in 65% of patients treated with VSL#3 compared with 40% treated with placebo (ie, an expected difference of 25%). This assumed that the probiotic is as effective as oral mesalamine. Hence, 70 patients were required in each group with an additional 10% for drop-outs, therefore we planned to have a total of 154 patients included in the trial.

**Statistical Analysis**

Data were presented in terms of minimum/maximum, mean/median, standard deviation/standard error of mean in place for quantitative variables, and proportion/counts and percentage in case of categoric variables. Comparisons between VSL#3 and placebo group for various parameters were performed by using the unpaired t tests. In cases in which the data did not follow normal distribution, the comparison was performed by using a nonparametric Wilcoxon Mann–Whitney test. Similarly for comparing various parameters over a period of time within each group (VSL#3 or placebo), we performed a paired t test/nonparametric Wilcoxon signed rank-sum test in cases in which data did not follow normal distribution. The comparison for different categoric variables between 2 groups (VSL#3/placebo) was performed by the chi-square test/Fisher exact test in case of expected cell counts less than 5. The analysis was subjected further to intention-to-treat analysis. Analysis was performed for all the primary and secondary end points. For the purpose of analysis, for patients who dropped out before the 12-week time point their data were carried forward from their last assessment to be included in the final analysis. A P value of .05 or less was considered statistically significant and a P value of .01 or less was considered highly statistically significant. The data were analyzed by using SPSS statistical software version 12.0 (SPSS Inc, Chicago, IL).

**Results**

**Participant Flow**

Of 187 patients screened for inclusion in the study, 40 could not be included (18 did not meet inclusion criteria, 12 were excluded, and 10 refused to participate). A total of 147 patients were randomized; 77 received VSL#3 and 70 received placebo (Supplementary Figure 1). Fifty-five patients in the VSL#3 group and 29 patients in the placebo group completed the entire study. Among the 22 patients who withdrew from the VSL#3 group, 17 had worsening of symptoms and 5 were lost to follow-up evaluation. In the placebo group, 13 were lost to follow-up evaluation and 28 patients discontinued therapy (disease worsening in 18 patients, noncompliance in 3 patients, and other reasons in 7 patients).

**Demographic and Clinical Characteristics**

The demographic and clinical characteristics such as age, sex, number of previous relapses, extent of disease, and the use of steroids or immunosuppressive drugs in both groups were comparable (Table 2). The median baseline UCDAI in the VSL#3 and placebo groups were 6 (range, 4–8) and 6 (range, 3–9), respectively. Seventy-four (96%) and 62 (88.5%) patients were receiving mesalamine compounds either alone or in combination with azathioprine in the VSL#3 and placebo groups, respectively. Although 69 (89.6%) patients were receiving only mesalamine compound (median dose, 2400 mg) in the VSL#3 group, 27 (67.1%) in the placebo group were on mesalamine compound (median dose, 2400 mg) alone. A significantly higher number of patients (15 [21.4%] vs 5 [6.4%]) were receiving a combination of mesalamine and azathioprine in the placebo as com-
pared with the VSL#3 group (P = .01). Twenty-two patients in the VSL#3 group and 24 patients in the placebo group had been exposed to corticosteroids earlier (P = NS) (Table 2).

**Clinical Response/Remission**

**Number of patients with a decrease in UCDAI score of 50% or more from baseline to week 6.** A significantly higher number of patients on VSL#3 experienced an improvement in UCDAI score of at least 50% at week 6 than those who received placebo (25 [32.5%] in the VSL#3 group versus 7 [10%] in the placebo group; P = .001) (Figure 1A). The median improvement in the UCDAI at 6 weeks in the VSL#3 and placebo groups was 25% (range, 20%-100%) and 0% (range, 75%-80%), respectively (P = .001). The absolute risk reduction in the UCDAI at week 6 in the VSL#3 and placebo groups was 1.87 and 0.34 (P < .001).

**Number of patients with a decrease in UCDAI score of 3 points or more from baseline to week 12.** Similarly, a significantly higher number of patients in the VSL#3 group had a decrease in UCDAI score of 3 or more points from week 0 to week 12 (40 [51.9%] in VSL#3 vs 13 [18.6%] in placebo; P < .001) (Figure 1B). The mean (±standard deviation) decrease in UCDAI from baseline to week 12 also was significantly higher in the VSL#3 group compared with placebo (2.7 ± 2.2 vs 0.67 ± 2.08; P < .001) (Figure 2E).

**Number of patients who attained remission (UCDAI subscore of 0 to 2) at week 12.** Thirty-three (42.9%) patients in the VSL#3 group and 11 (15.7%) patients in the placebo group experienced remission by the end of 12 weeks (P < .001) (Figure 1C).

**Decrease in individual symptom score.** The improvement in stool frequency score, blood in the stool score, mucosal appearance, and physician’s global assessment were significantly higher in the VSL#3 group than in the placebo group both at week 6 and week 12 (Figure 2).

**Mucosal Healing**

The mucosal healing rate (mucosal appearance score, 0) at week 12 was significantly higher in patients in the VSL#3 group as compared with the placebo group (24 [32%] vs 10 [14.7%]; P < .028) (Figure 1D).

**Treatment failure (number of patients who failed to decrease UCDAI by at least 50% of baseline or by at least 3 points from baseline to 6 weeks).** A significantly higher number (88.6%) of patients in the placebo arm were treatment failures as defined as failure to decrease total UCDAI by at least 50% or by at least 3 points from baseline to week 6 (88.6% vs 62.3%; P = .001).

**Effect of VSL#3 on patients with proctosigmoiditis and left-sided colitis/pancolitis.** We performed a subgroup analysis and compared the primary and secondary outcome measures in the VSL#3 group with only proctosigmoiditis or left-sided colitis/pancolitis. There was no difference in the response/remission rate in these 2 groups (Table 3).

**Safety and Tolerability**

No major adverse event was reported in either of the 2 groups. Fourteen (18.2%) patients on VSL#3 reported abdominal bloating and discomfort for the initial few days and 7 of these patients also felt an unpleasant taste in their mouth during study drug administration.

**Discussion**

This was a multicenter, randomized, double-blind, placebo-controlled trial evaluating the role of the probiotic cock-
The addition of VSL#3 to conventional treatment resulted in significantly higher clinical response and remission rates. Moreover, VSL#3 therapy significantly decreased the frequency of stools and rectal bleeding, resulting in overall improvement in participant well-being.

There are a few studies that have shown the effectiveness of probiotics in the induction of remission in patients with mild-to-moderately active UC. Rembacken et al., in a study including 116 patients with active UC randomized to E. coli Nissle 1917 or mesalamine, after a 1-week course of oral gentamicin to suppress native flora, reported inductions of remission in 68% and 75% receiving E. coli Nissle 1917 and mesalamine, respectively. Kato et al., in another double-blind, placebo-controlled randomized trial, showed a significant reduction in clinical activity index at 3 months using Bifidobacterium fermented milk as compared with placebo. Similarly, in an open-label trial, Guslandi et al. showed a remission rate of 68% at week 4 using Saccharomyces boulardii in patients with active UC who failed to respond to mesalamine. In an open-label study including patients with mild-to-moderately active UC who failed to respond to mesalamine or corticosteroids, Bibiloni et al. reported induction of remission in 63% at 6 weeks using VSL#3. These results were higher than ours, but the difference perhaps can be attributed to the study’s inclusion of concomitant medication use, such as corticosteroids and rectal therapies, both of which were excluded from our study. The lack of placebo control also may have contributed to the disparity in the 2 studies. In addition, another study reported similar results to ours, with a combination of low-dose balsalazide and VSL#3 resulting in improvements in treatment of mild-to-moderate UC when compared with balsalazide alone or mesalamine alone. However, these studies had methodologic limitations such as small size; inadequate power to detect a statistically significant difference; problems in concealment of allocation, generation of random allocation, and double-blinding procedures; and use of concomitant therapies. In the recent Cochrane review, investigators concluded that there was not sufficient evidence to support the use of probiotics in patients with active UC. Our study builds on this earlier work while paying particular attention to methodologic standards, and clearly indicates that there is a promising role for therapeutic use of VSL#3 in the treatment of mild-to-moderate UC. In the placebo group, about 20% of the patients were lost to follow-up evaluation, which is rather high for a randomized trial. This was a limitation of this study.

Treatment with mesalamine-containing drugs is the gold standard for treatment of mild-to-moderate UC, but the results found with this treatment are far from satisfactory. However, our study results show that the probiotic cocktail VSL#3, in conjunction with mesalamine, improves symptoms for patients who have not responded to mesalamine alone. It is possible that VSL#3 may act in synergy with, or perhaps augment, the antiinflammatory action of mesalamine compounds. Mesalamine compounds are potent inhibitors of several inflammatory mediators, such as leukotrienes, prostaglandins, and platelet-activating factor, which all play a role in the pathogenesis of UC.

Probiotics ameliorate inflammation via a number of mechanisms, including alteration of the mucosal immune system,
competitive exclusion of proinflammatory pathogens, and production of antimicrobial factors such as bacteriocins and other metabolites. One type (eg, VSL#3) might be more effective than another because strain-specific properties might influence the efficacy in different cases and situations. Although the precise mechanism of action of VSL#3 is not known, in vivo and in vitro studies have shown that VSL#3 modulates the host-immune response, improves epithelial barrier function, and increases mucus production. After ingestion, VSL#3 strains are able to survive gastric acidity and bile salt barrier and to colonize the bowel. VSL#3 has been shown to modify MUC gene expression and mucus secretion by enhancing MUC2, MUC3, and MUC5 gene and protein expression in intestinal epithelial cells in culture. VSL#3 has been shown to increase anti-inflammatory cytokine interleukin (IL)-10, and inhibit secretion of proinflammatory cytokines including tumor necrosis factor-α, interferon-γ, and IL-1β. Lammers et al showed that bacterial genomic DNA induced a remarkable strain-specific immune response. DNA isolated from feces before VSL#3 ingestion induced higher levels of IL-1 than IL-10, whereas DNA from feces after VSL#3 treatment enhanced the IL-10 secretion but reduced the IL-1 secretion. VSL#3 also has been shown to inhibit experimentally induced colitis in mice. Madsen et al showed a decrease in the severity of colitis in IL-10 mice, as evidenced by decreasing tumor necrosis factor-α and interferon-γ production, and improvement in histologic scores and barrier integrity by VSL#3. In the indocetamide model of colitis, pretreatment either with Lactobacillus GG or VSL#3 significantly decreased the severity of colonic damage, as indicated by decreased myeloperoxidase activity and nitric oxide synthase activity. Rachmilewitz et al showed that VSL#3 significantly decreased colonic disease activity score, myeloperoxidase activity, and histologic scores in chronic dextran sulfate sodium–induced colitis.

Probiotics have a good safety profile. Cases of infection as a result of Lactobacilli and Bifidobacteria are extremely rare, occurring at a rate of approximately 0.05% to 0.4% of all cases of bacteremia. Indeed, when bacteremia with probiotics has been described, it has been associated with the extremes of age and/or with concomitant immunosuppression therapy. The main side effects in this study were minor and included alteration in taste and bloating.

In conclusion, VSL#3 led to a 50% decrease in UCDAI at week 6 and clinical remission at week 12 in significantly more patients with mild-to-moderately active UC than placebo.

Table 3. Effect of VSL#3 on Patients With Proctosigmoiditis and Left-Sided Colitis/Pancolitis

<table>
<thead>
<tr>
<th>End points</th>
<th>Proctosigmoiditis, n = 38 (49.3%)</th>
<th>Left-sided colitis and pancolitis, n = 39 (50.5%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with decrease in UCDAI score of ≥50% from baseline to week 6</td>
<td>12 (31.6%)</td>
<td>13 (33.3%)</td>
<td>.08</td>
</tr>
<tr>
<td>No. of patients with decrease in UCDAI score of ≥3 points from baseline to week 12</td>
<td>22 (57.9%)</td>
<td>18 (46.2%)</td>
<td>.3</td>
</tr>
<tr>
<td>No. of patients who attained remission (UCDAI 0–2) at week 12</td>
<td>17 (44.7%)</td>
<td>16 (41%)</td>
<td>.7</td>
</tr>
<tr>
<td>Mucosal healing at week 12</td>
<td>13 (34.2%)</td>
<td>11 (28.2%)</td>
<td>.5</td>
</tr>
</tbody>
</table>

Figure 2. Line diagrams showing the decrease in (A) stool frequency score, (B) rectal bleeding score, (C) mucosal appearance score, (D) physician’s global assessment score, and (E) UC disease activity score at baseline, week 6, and week 12 in the VSL#3 and placebo groups.
Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org.

References


Reprint requests

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The clinical trial is registered with Clinical Trial Registry India, UTRN no. UTRN 082813953-29052008152129, CTRI no. CTRI/2008/091/000076, dated June 6, 2008.

Conflicts of interest
The authors disclose no conflicts.

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Supplementary Figure 1. Flow of patients in the VSL#3 and placebo groups.