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Budesonide Is More Effective Than Mesalamine or Placebo in Short-term Treatment of Collagenous Colitis

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See Covering the Cover synopsis on page 1139.

BACKGROUND & AIMS: Studies reporting that budesonide is effective for the treatment of collagenous colitis have been small and differed in efficacy measures. Mesalamine has been proposed as a treatment option for collagenous colitis, although its efficacy has never been investigated in placebo-controlled trials. We performed a phase 3, placebo-controlled, multicenter study to evaluate budesonide and mesalamine as short-term treatments for collagenous colitis. **METHODS:** Patients with active collagenous colitis were randomly assigned to groups given pH-modified release oral budesonide capsules (9 mg budesonide once daily, Budenofalk, n = 30), mesalamine granules (3 g mesalamine once daily, Salofalk, n = 25), or placebo for 8 weeks (n = 37) in a double-blind, double-dummy fashion. The study was conducted in 31 centers (hospital clinics and private practices) in Germany, Denmark, Lithuania, Spain, and the United Kingdom. The primary end point was clinical remission at 8 weeks defined as ≤3 stools per day. Secondary end points included clinical remission at 8 weeks, according to the Hjortswang-Criteria of disease activity, taking stool consistency into account. **RESULTS:** A greater percentage of patients in the budesonide group were in clinical remission at week 8 than the placebo group (intention-to-treat analysis, 80.0% vs 59.5%; $P = .072$; per-protocol analysis, 84.8% vs 60.6%; $P = .046$). Based on the Hjortswang-Criteria, 80.0% of patients given budesonide achieved clinical remission compared with 37.8% of patients given placebo ($P = .0006$); 44.0% of patients given mesalamine achieved clinical remission, but budesonide was superior to mesalamine ($P = .0035$). Budesonide significantly improved stool consistency and mucosal histology, and alleviated abdominal pain. The rate of adverse events did not differ among groups. **CONCLUSIONS:** Oral budesonide (9 mg once daily) is effective and safe for short-term treatment of collagenous colitis. Short-term treatment with oral mesalamine (3 g once daily) appears to be ineffective. ClinicalTrials.gov number, NCT00450086.

Keywords: Therapy; Clinical Trial; Drug; Microscopic Colitis.

Collagenous colitis, a subgroup of microscopic colitis, is a chronic inflammatory bowel disease characterized by chronic watery diarrhea and few or no endoscopic abnormalities. A considerable number of patients suffer from additional symptoms, such as abdominal pain, nocturnal diarrhea, fecal incontinence, and weight loss.[1,2] Due to the symptom burden, collagenous colitis impairs the patient's quality of life significantly, in a manner similar to other inflammatory bowel diseases.[3,4] Epidemiological studies from Europe and North America suggest that microscopic colitis is being increasingly diagnosed, with its incidence and prevalence rates similar to those of other inflammatory bowel diseases.[5–8] Because of the significant symptom overlap between microscopic colitis and irritable bowel syndrome/functional diarrhea, the true prevalence of microscopic colitis might be underestimated.[9,10]

The strongest evidence of success in treating collagenous colitis is currently available for budesonide, a locally active corticosteroid with extensive first-pass metabolism in the liver and low systemic exposure. Three randomized, placebo-controlled trials have shown that oral budesonide at a dosage of 9 mg/d is effective for short-term treatment in collagenous colitis.[11–13] However, those trials were relatively small and their study designs differed, as did their definitions of treatment response.

Although oral mesalamine at various doses is frequently used to treat microscopic colitis, its efficacy has never been formally evaluated in randomized placebo-controlled trials. A prospective uncontrolled study reported high response rates of long-term treatment with mesalamine alone or in combination with cholestyramine.[14] However, several large retrospective

Abbreviations used in this paper: **AE, adverse event; CR, clinical remission; ITT, intention-to-treat; PP, per-protocol.**

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case series suggest that mesalamine might be beneficial in less than half of patients with microscopic colitis.[15–17]

The aim of our study was to evaluate and compare the efficacy and tolerability of short-term treatment of pH-modified release oral budesonide capsules (9 mg budesonide once daily) and mesalamine granules (3 g mesalamine once daily) in collagenous colitis in a randomized, placebo-controlled fashion.

Methods

All authors had access to the study data and reviewed and approved the final manuscript.

Study Design and Setting

This was a double-blind, double-dummy, randomized placebo-controlled, comparative phase-3 clinical trial conducted in 31 centers (hospital clinics and private practices) in Germany, Denmark, Lithuania, Spain, and the United Kingdom. The study protocol was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and was approved by the Ethics Committee of the University of Hamburg, Germany, as well as by the national ethics committees in the participating countries. The study protocol was registered at www.clinicaltrials.gov (NCT00450086) and at www.clinicaltrialsregister.eu (EudraCT 2006-004159-39).

Study Population

Men or women between 18 and 80 years of age were eligible for randomization if they met all of the following inclusion criteria: >4 watery/soft stools on at least 4 days in the week before baseline; >3 stools per day on average within the last 7 days before baseline (anti-diarrheals had to have been discontinued 2 weeks before baseline); chronic diarrhea for at least 3 months before baseline; complete colonoscopy within the last 12 weeks (originally 4 weeks; amended because restriction of time frame hindered recruitment and, in some cases, clinical symptoms were reduced after colonoscopy and did not reappear in due time) before baseline; histologically confirmed collagenous colitis (thickness of collagen band >10 μm, degeneration of surface epithelium). Women of childbearing potential had to use appropriate contraceptive methods. All participants provided written informed consent.

Exclusion criteria for participation included other significant colonic diseases (ie, polyps >2 cm, tumors, Crohn's disease, ulcerative colitis, ischemic colitis), partial colonic resection, infectious diarrhea, celiac disease (blood tests and/or duodenal histology required), diarrhea caused by other organic diseases of the gastrointestinal tract, treatment with budesonide, *Boswellia serrata* extract, salicylates, steroids, antibiotics, cholestyramine, nonsteroidal anti-inflammatory, or other immunosuppressant drugs within the last 4 weeks before baseline, malignant disease, severe comorbidity, abnormal hepatic function or liver cirrhosis, renal insufficiency, active peptic ulcer disease, known intolerance or resistance to study drugs, pregnancy, or breast-feeding.

Treatment Allocation and Open Label

For allocation of the participants, a computer-generated list of random numbers was used, which had been prepared by contract research organization with no clinical involvement in the trial. Eligible patients were randomly assigned to 1 of 3 treatment groups at a 1:1:1 ratio. The study medication was packed in boxes, and consecutively numbered for each patient according to the randomization schedule. The investigators at the centers enrolled the patients and dispensed the study medication as per randomization schedule. Patients received either budesonide 9 mg once daily (3 × 3 mg pH-modified release capsules, Budenofalk) 30 minutes before breakfast or mesalamine 3 g once daily (2 sachets each containing 1.5 g mesalamine presented as a granule formulation, Salofalk) in the morning or placebo for 8 weeks in a double-blind, double-dummy fashion. Interim visits were made at weeks 2, 4, and 6. Patients nonresponsive after 4 weeks were allowed to discontinue the double-blind treatment and begin open-label treatment with budesonide (Budenofalk) 9 mg once daily for 4 weeks. Patients in clinical remission at the end of double-blind treatment entered a 16-week treatment-free follow-up phase, which included clinical visits after 8 and 16 weeks and in case of symptom relapse, ie, >4 watery/soft stools on at least 4 days in the week before the visit and >3 stools per day within the last 7 days before the visit. Patients with symptom relapse underwent open-label treatment with budesonide (Budenofalk) 9 mg once daily for 4 weeks. Adherence to the study treatment was monitored by pill count at each study visit and patient diaries. During the entire study period, the use of other anti-inflammatory drugs, immunosuppressants, cholestyramine, anti-diarrheals, other drugs causing constipation, and nonsteroidal anti-inflammatory drugs (for more than 2 weeks; except acetylsalicylic acid up to 100 mg/d and paracetamol for analgesic use) was not permitted.

Endoscopy and Histology

A complete colonoscopy was performed at baseline (within 12 weeks before randomization) and, if possible, at the end of the 8-week double-blind treatment. For patients who refused the follow-up colonoscopy, we suggested sigmoidoscopy. At each colonoscopy, biopsies were obtained from the terminal ileum, cecum, the ascending, transverse, descending, and sigmoid colon, and the rectum. In case of sigmoidoscopy, biopsies were obtained from the sigmoid colon and rectum.

Biopsy specimens were fixed in 10% formalin and embedded in paraffin. Sections (5 μm) were stained with H&E. Van Gieson staining was used to assess the collagen band. On well-oriented sections in which at least 3 adjacent crypts were cut in their vertical plane, we measured the thickness of the collagen band (μm) and inflammation of the lamina propria (semi-quantitative score 0−3). Histologic remission was defined as a collagen band thickness ≤10 μm and no inflammation of the lamina propria with neutrophilic and eosinophilic granulocytes. All biopsies were analyzed in blinded fashion by a single pathologist (M.V.).

Clinical Outcomes Evaluation

Our primary end point was clinical remission (CR) at 8 weeks, defined as a mean of ≤3 stools per day in the week before the visit. Patients who stopped double-blind treatment and switched to open-label treatment before the study end point of 8 weeks were considered as nonresponders. Secondary end points included CR at 8 weeks, according to the

Hjortswang-Criteria of disease activity (mean <3 stools per day, with <1 watery stool per day),[18] prespecified in the statistical analysis plan. We added this new remission criterion because the authors could show that the parameters stool frequency and frequency of watery stools correlate best with health-related quality of life in patients with collagenous colitis. Additional end points were time to remission, number of watery and solid stools per week, abdominal pain, histopathology, tolerability and safety, symptom relapse during treatment-free follow-up, and response to open-label budesonide. An interim analysis was planned with 50% of total sample size and conducted by an independent data monitoring committee.

Safety Evaluation

At each clinic visit of the 8-week double-blind treatment as well as open-label and follow-up phase, patients underwent physical examination (at baseline and final visit), vital signs, previous (at baseline) and concomitant medications, and adverse events were recorded, and general laboratory tests and urinalysis were performed.

Statistical Analyses

This study was conducted using an adaptive 2-stage group sequential test design with possible sample-size adaptation after the interim analysis. Assuming rates of clinical remission of 65% in the verum group (budesonide or mesalamine) and of 30% in the placebo group, the statistical power of the test procedure was 80% with 16 patients per group in each of the 2 stages. Consequently, with a proposed sample size of 96 patients (3×32 patients) in the intention-to-treat (ITT) analysis, the study had 80% power to yield a statistically significant result. For hypothesis testing of the primary end point, the overall (experiment-wise) type I error rate was 2-sided $\alpha = .05$. All other statistical tests (Wald test for risk difference, Wilcoxon signed rank test, log-rank test, Fisher's exact test, t test) were performed 2-sided with a significance level of $\alpha = .05$ on an exploratory basis.

Efficacy was analyzed for the ITT population with a sensitivity analysis for the per-protocol (PP) population. Patients with lack of compliance, intake of forbidden concomitant medication, violation of eligibility criteria, or early discontinuation due to adverse event without causal relationship with study drug, were excluded from PP population. Safety analysis was performed descriptively for the safety population. Statistical testing of the primary end point was done via the ADDPLAN system. All other analyses were conducted using the SAS statistical package for Windows (SAS Institute, Cary, NC).

Results

Patient Population

We randomized a total of 92 patients (budesonide 30, mesalamine 25, placebo 37) eligible for ITT analysis. The first patient was enrolled on May 22, 2007. The last patient left the study on June 21, 2011. Fifty-three patients were considered for the interim analysis (budesonide 16, mesalamine 22, placebo 15). Recruitment continued during analysis. The interim analysis revealed that mesalamine was less effective than placebo and the conditional power to gain a positive final result was near zero (stopping by futility) and, consequently, the independent data review board recommended closure of this study arm. A total of 15 patients were considered as major protocol violators, leaving 77 patients for the PP analysis (Supplementary Figure 1). The baseline demographic and clinical characteristics of the ITT population were similar across the treatment groups without any statistical differences among the 3 treatment groups (Table 1, Supplementary Table 1). The patients' drug histories revealed the use of nonsteroidal anti-inflammatory drugs or aspirin in 19 and 15 cases, respectively, with no relevant differences among treatment groups. Only 3 patients were exposed to lansoprazole and none were exposed to sertraline, ticlopidine, or acarbose. Thirty-one patients were treated for the current acute episode before randomization. Eighteen of which (58.1%) received anti-diarrheals, but only in 1 patient was efficacy judged to be good or very good.

Clinical Efficacy

According to the primary end point, the proportion of patients in CR at week 8 was higher with budesonide than with placebo. The difference was statistically significant in the PP analysis, but did not quite reach significance in the ITT analysis (Figure 1*A*). The rate of CR with mesalamine was lower than that with placebo at the interim analysis. Budesonide was significantly superior to mesalamine in the ITT and PP analyses. According to the secondary end point (CR by Hjortswang-Criteria), budesonide was significantly superior to both placebo and mesalamine in ITT and PP analyses (Figure 1*B*).

The Kaplan-Meier analysis revealed that the time to CR was significantly shorter with budesonide (median 7 days) compared with placebo (median 21 days; $P = .0144$) or mesalamine (median 24 days; $P = .0071$) (Figure 2).

Budesonide significantly reduced the mean number of watery stools per week from 29.7 to 2.4 ($P < .0001$), and increased the mean number of solid stools per week from 0.3 to 6.7 ($P < .0001$). Budesonide reduced the number of days with watery stools per week substantially within the first 2 weeks of treatment (Figure 3). This effect was mirrored by a significant increase in the number of days with solid stools per week within the first 2 weeks of budesonide treatment (Supplementary Figure 2).

On ITT analysis, the number of days with moderate-to-severe abdominal pain within the week before assessment was significantly reduced from 1.8 to 0.8 ($P = .047$) in patients receiving budesonide, and the placebo recipients displayed no significant change.

Histologic Features at Baseline and Histologic Remission

The 3 treatment groups' mean collagenous band thickness and degree of chronic lamina propria inflammation were similar at baseline. To examine the topographical distribution of histologic features of collagenous colitis, we analyzed a subgroup of patients who had had biopsies

Table 1. Baseline Demographic and Clinical Characteristics for Each Group

Characteristics	Budesonide (n = 30)	Mesalamine (n = 25)	Placebo (n = 37)	Total (n = 92)
Sex, n (%)				
Male	5 (16.7)	7 (28.0)	4 (10.8)	16 (17.4)
Female	25 (83.3)	18 (72.0)	33 (89.2)	76 (82.6)
Age, *y*, mean (SD)	62.0 (13.1)	56.4 (13.3)	57.8 (12.3)	58.8 (12.9)
BMI, mean (SD)	25.2 (4.4)	25.1 (5.0)	24.2 (4.1)	24.8 (4.4)
Smoking habit, n (%)				
Current	8 (26.7)	11 (44.0)	12 (32.4)	31 (33.7)
Former	7 (23.3)	4 (16.0)	10 (27.0)	21 (22.8)
Never	15 (50.0)	10 (40.0)	15 (40.5)	40 (43.5)
Caffeine intake, n (%)	28 (93.3)	24 (96.0)	32 (86.5)	84 (91.3)
Duration of symptoms, *y*, mean (SD)	2.7 (3.9)	4.7 (7.5)	3.7 (4.8)	3.6 (5.4)
New diagnosis, n (%)	21 (70.0)	19 (76.0)	25 (67.6)	65 (70.7)
Time since diagnosis, *y*, mean (SD)	0.6 (1.4)	1.4 (3.0)	1.9 (3.5)	1.3 (2.9)
Time since diagnosis, n (%)				
<1 mo	20 (66.7)	14 (56.0)	20 (54.1)	54 (58.7)
1 to <12 mos	4 (13.3)	6 (24.0)	6 (16.2)	16 (17.4)
1 to <5 y	5 (16.7)	1 (4.0)	4 (10.8)	10 (10.9)
5 to <10 y	1 (3.3)	3 (12.0)	6 (16.2)	10 (10.9)
≥10 y	0	1 (4.0)	1 (2.7)	2 (2.2)
No. of previous episodes, mean (SD)	0.7 (2.0)	0.3 (0.7)	7.5 (30.3)	3.4 (19.8)
Previous episodes, n (%)				
0	22 (73.3)	16 (64.0)	25 (67.6)	63 (68.5)
1	5 (16.7)	4 (16.0)	1 (2.7)	10 (10.9)
2	0	0	2 (5.4)	2 (2.2)
>2	2 (6.6)	1 (4.0)	8 (21.6)	11 (12.0)
Missing	1 (3.3)	4 (16.0)	1 (2.7)	6 (6.5)

BMI, body mass index.

taken from all 5 colonic segments (n = 42). A collagenous band thickness >10 μm in all 5 colonic segments was present in 71.4% of patients, in 4 segments only in 11.9%, in 3 segments only in 9.5%, and in only 1 or 2 segments in 4.8% of patients. Virtually all patients had an at least mild lymphoplasmacellular inflammation in 4 or 5 colonic segments.

Follow-up biopsies were available from 63 patients (budesonide 23, mesalamine 18, placebo 22), which allowed paired analysis of pre- and post-treatment histology. Follow-up biopsies were obtained from 46 patients from the right and left colon, although left-side only biopsies were available from 17 patients (sigmoid, descending colon). Histologic post-treatment remission was observed in 87% of the budesonide patients, in 50% of the placebo recipients ($P = .0106$), and in 45% of the mesalamine patients. In the budesonide group, 78% of patients in clinical remission also presented histologic remission. We observed no correlation between clinical and histologic remission in patients taking mesalamine or placebo (data not shown).

Safety

The rates of adverse events (AE) were similar among the 3 treatment groups (budesonide 47%, mesalamine 68%, placebo 54%; Table 2). None of the AE in the budesonide patients were considered drug related, and 5 AEs with mesalamine and 2 AEs with placebo were considered drug related. None of the budesonide patients experienced a serious AE, and 3 patients in the mesalamine group and 1 patient in the placebo group experienced a serious AE. None of the serious AEs were considered drug related. The most frequent AEs were headache (budesonide 13%, mesalamine 16%, placebo 11%), nasopharyngitis (budesonide 13%, mesalamine 12%, placebo 14%), and dyspepsia (budesonide 10%, mesalamine 12%, placebo 3%). All other AEs were reported in 5 or fewer patients (all treatment groups combined).

Follow-up and Open-Label Treatment

A total of 54 patients (Supplementary Figure 3) entered the treatment-free follow-up phase. During follow-up, 19 patients (35%) experienced a symptom relapse, with a mean of 24.4 watery/soft stools per week and a mean time to relapse of 58 days. After 4 weeks of open-label budesonide treatment, the mean frequency of watery stools decreased to 0.9 per week, with 14 patients achieving CR as defined by Hjortswang (ITT 74%). Another 26 patients (Supplementary Figure 3) started open-label budesonide treatment after premature discontinuation of the double-blind treatment phase (n = 10) or immediately after the final visit during the double-blind phase (n = 16), of which 8 (ITT 80%) and 11 (ITT 69%) patients achieved CR, respectively.

Discussion

Our study confirms the high efficacy of budesonide for the treatment of collagenous colitis in a multinational

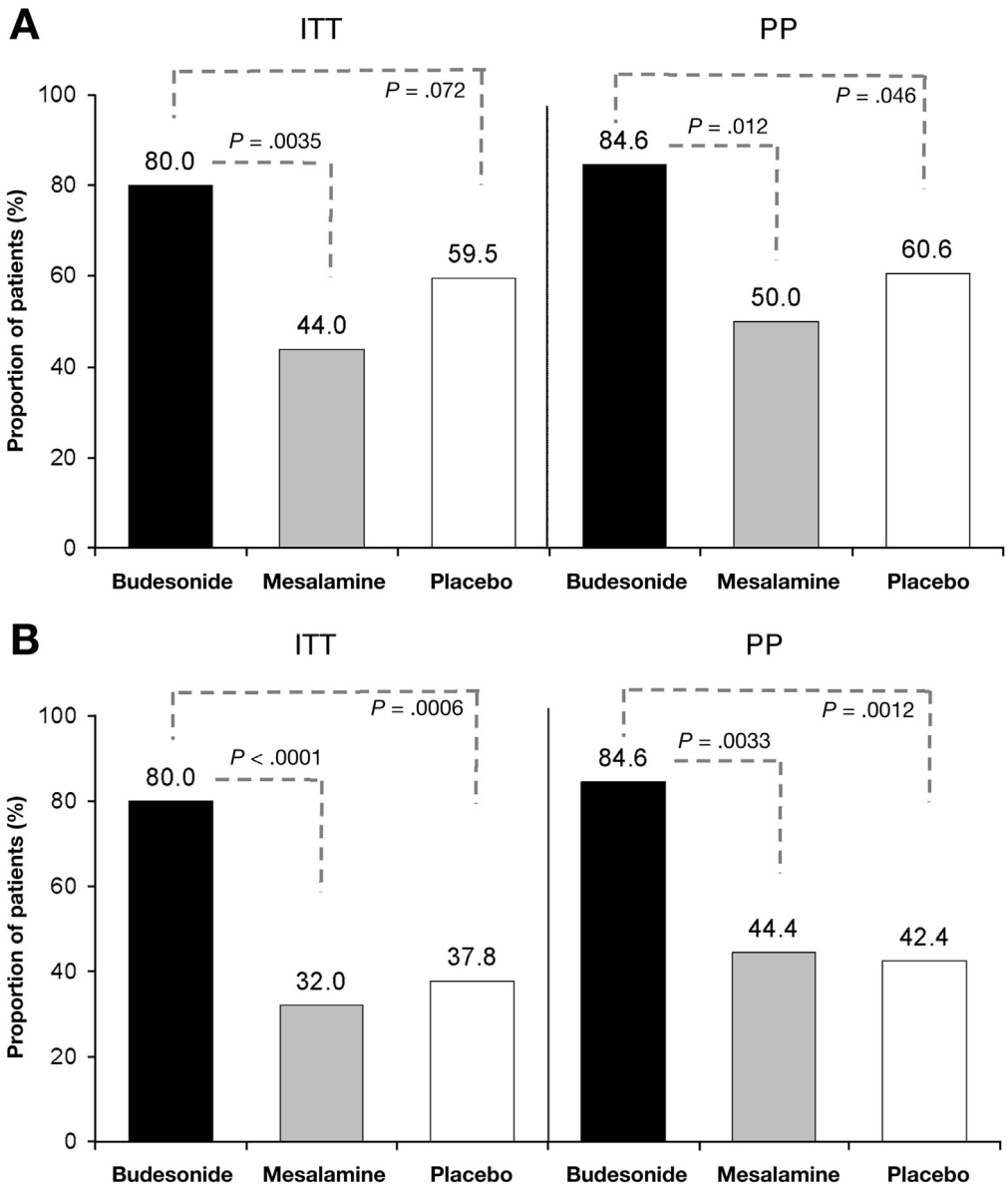

Figure 1. (*A*) Clinical remission (%) according to the primary end point definition (mean $\leq$3 stools per day). (*B*) Clinical remission (%) according to the secondary end point definition (mean $<$3 stools per day, $<$1 of which was watery stool).

setting. Budesonide was significantly superior to placebo and, as demonstrated for the first time for this indication, to mesalamine as well for the primary end point in the PP population and the vast majority of other secondary efficacy criteria in both ITT and PP populations. The primary end point remission rate of budesonide observed in the ITT population is similar to that reported from meta-analyses.[19–21] However, we failed to note a statistically significant difference due to an unexpectedly high placebo response rate. One major reason for this high placebo response rate might be due to our having defined clinical remission by stool frequency only. This end-point definition was chosen arbitrarily when the study was initiated in 2007. Based on intensive quality-of-life analyses, Hjortswang et al demonstrated in 2009 that both stool frequency and stool consistency are important when differentiating between disease activity and remission in collagenous colitis.[18] When the Hjortswang-Criteria for remission were applied to our study, we detected a highly significant difference between budesonide and placebo in both the ITT and PP populations. Our findings support the notion that both stool frequency and consistency are key when determining disease activity and remission; they are probably more accurate than stool frequency alone to differentiate between active intervention and placebo in collagenous colitis.

There might be several reasons behind the high efficacy of budesonide in collagenous colitis. First, it exerts a well-documented and potent anti-inflammatory effect in the terminal ileum and right colon, as clearly shown in Crohn's disease.[22] In microscopic colitis, there are data to suggest that the histopathology might be more severe in the right colon,[23–25] and that some inflammatory changes can also occur in the ileum.[26,27] These observations might be relevant to the local anti-inflammatory action of budesonide.

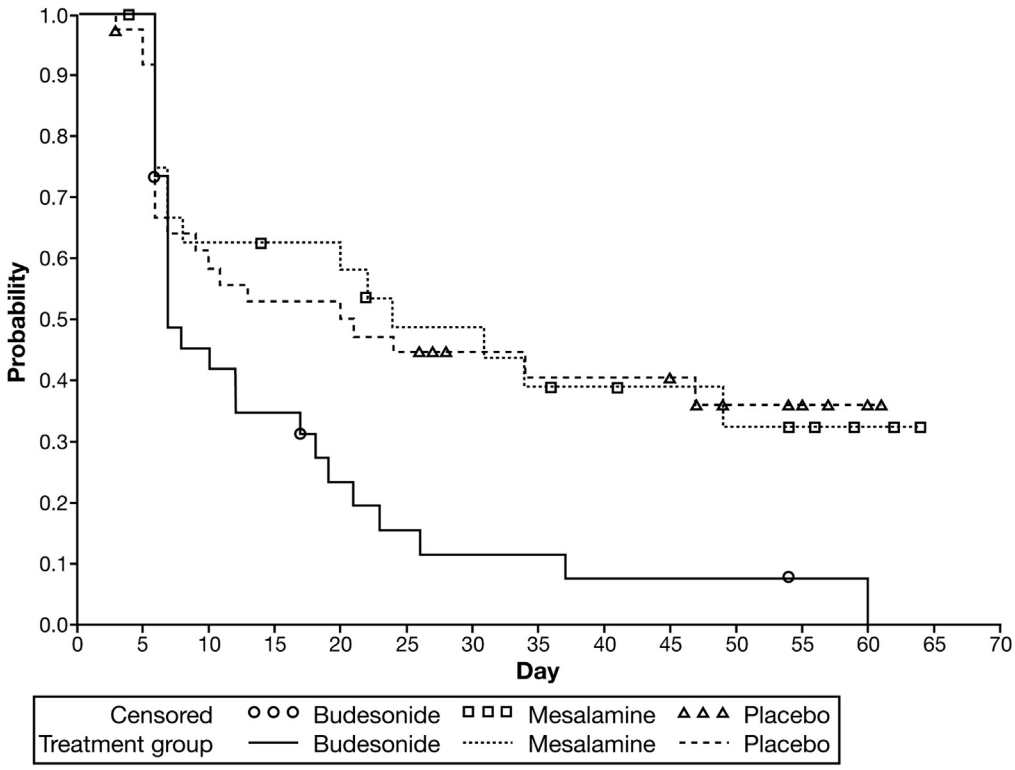

Figure 2. Time to clinical remission.

In addition, an anti-inflammatory property of budesonide can also extend to the left colon, as suggested by clinical studies in ulcerative colitis and collagenous colitis.[12,28] In addition, budesonide improves bile acid malabsorption, which might occur in a substantial number of patients with microscopic colitis, by up-regulating the bile acid transporter gene expression in the small bowel.[29,30] Finally, there is evidence that budesonide improves the small intestine's water-absorption capacity, lowering the ileostomy output in quiescent Crohn's disease,[31,32] as well as alleviating chemotherapy-induced diarrhea refractory to loperamide.[33] Budesonide appears to exhibit an array of pharmacological mechanisms likely to contribute to its consistent clinical efficacy in microscopic colitis.

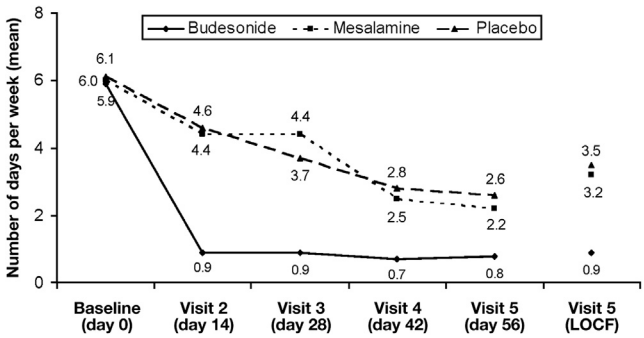

Figure 3. Number of days with watery stools in the week before visit (ITT).

Our study also confirms the safety of short-term budesonide treatment by revealing no significant difference between the adverse-event rates of budesonide and placebo. Budesonide's favorable safety profile has also been documented in placebo-controlled studies on short-term treatment in collagenous and lymphocytic colitis,[11–13,34,35] as well as in studies addressing long-term treatment with budesonide in collagenous colitis.[36,37] A meta-analysis of steroids in microscopic colitis confirmed that in terms of adverse events, budesonide was similar to placebo, and the incidence of adverse events with prednisolone was about 5 times that with placebo.[21] In addition, a recent population-based US cohort study of 315 patients with microscopic colitis demonstrated a higher response rate to budesonide compared with prednisone and a lower relapse rate after budesonide therapy compared with prednisone therapy.[38]

Based on this body of data, the European Microscopic Colitis Group recently recommended budesonide as the treatment of choice for active microscopic colitis.[39] The results of this study support the therapeutic value for this indication.

Our study is the first to compare mesalamine with placebo in collagenous colitis. The clinical remission rate we observed with mesalamine resembles the experience from large retrospective series.[15–17] However, there were no statistically significant differences from placebo in any of the efficacy criteria applied in our study, suggesting that mesalamine is ineffective in collagenous colitis. In contrast, a prospective single-center study reported a clinical response in 8 of 9 patients with collagenous colitis taking

Table 2. Patients with Adverse Events by System Organ Class and Preferred Term Occurring in at Least 2 Patients in the Double-Blind Phase

Adverse events	Budesonide (n = 30), n (%)	Mesalamine (n = 25), n (%)	Placebo (n = 37), n (%)
Total	14 (47)	17 (68)	20 (54)
Infections and infestations	6 (20)	6 (24)	9 (24)
Bronchitis	1 (3)	1 (4)	—
Nasopharyngitis	4 (13)	3 (12)	5 (14)
Gastrointestinal disorders	5 (17)	7 (28)	7 (19)
Abdominal pain	—	—	2 (5)
Abdominal pain upper	—	1 (4)	1 (3)
Constipation	—	1 (4)	1 (3)
Diarrhea	—	—	2 (5)
Dyspepsia	3 (10)	3 (12)	1 (3)
Flatulence	—	1 (4)	1 (3)
Vomiting	—	2 (8)	2 (5)
Nervous system disorders	5 (17)	5 (20)	5 (14)
Dizziness	1 (3)	2 (8)	—
Headache	4 (13)	4 (16)	4 (11)
Investigations	1 (3)	6 (24)	2 (5)
C-reactive protein increased	—	3 (12)	2 (5)
Musculoskeletal and connective tissue disorders	4 (13)	1 (4)	4 (11)
Muscle spasms	2 (7)	—	—
Neck pain	1 (3)	—	1 (3)
General disorders and administration site conditions	2 (7)	2 (8)	—
Pyrexia	—	2 (8)	—
Respiratory, thoracic and mediastinal disorders	2 (7)	2 (8)	—
Cough	—	2 (8)	—
Oropharyngeal pain	2 (7)	—	—
Psychiatric disorders	1 (3)	1 (4)	1 (3)
Ear and labyrinth disorders	1 (3)	1 (4)	—
Vertigo	1 (3)	1 (4)	—
Metabolism and nutrition disorders	—	2 (8)	—
Dehydration	—	2 (8)	—

2.4 g mesalamine per day for 6 months.[14] However, that finding remains difficult to appraise due to the lack of a placebo-control group. To shed more light on the value of mesalamine in microscopic colitis, our group is now conducting a randomized placebo-controlled, multicenter study to investigate mesalamine in lymphocytic colitis (ClinicalTrials.gov number, NCT01209208).

The pharmacokinetic profile of the test medication budesonide (Budenofalk)[40,41] differs from those of other commercially available budesonide preparations (eg, Entocort, Uceris).[42,43] Budenofalk pellets release the active ingredient budesonide only at a pH of 6.4 or higher,[44] which is reached in the terminal ileum. In contrast, Entocort starts to release budesonide earlier than Budenofalk, and Uceris targets primarily the colon.[43] The release profile of the mesalamine formulation used in this study (Salofalk granules) is comparable with that of Apriso,[45,46] but reveals marked differences from other commercially available mesalamine formulations (eg, Asacol, Pentasa).[47,48] Given the colonic topography of the disease and the topical action of the test medication, it remains speculative whether the efficacy data achieved in our study can be extrapolated to other budesonide or mesalamine formulations.

In summary, our study confirms that budesonide is effective and safe for short-term treatment of collagenous colitis. However, our study has failed to provide evidence of the efficacy of mesalamine in short-term therapy of collagenous colitis. Additional studies might be necessary to elucidate the role of mesalamine in microscopic colitis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.01.019.

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Members of the independent data monitoring committee: Professor Walter Lehmacher (statistician), Professor Volker Groß (gastroenterologist), Professor Wolfgang Kruis (gastroenterologist).

Conflicts of interest
These authors disclose the following: Ole K. Bonderup, Ahmed Madisch, Stephan Miehlke, and Michael Vieth have received honoraria from Dr Falk Pharma GmbH; Roland Greinwald and Ralf Mohrbacher are employees of Dr Falk Pharma GmbH. All remaining authors disclose no conflicts.

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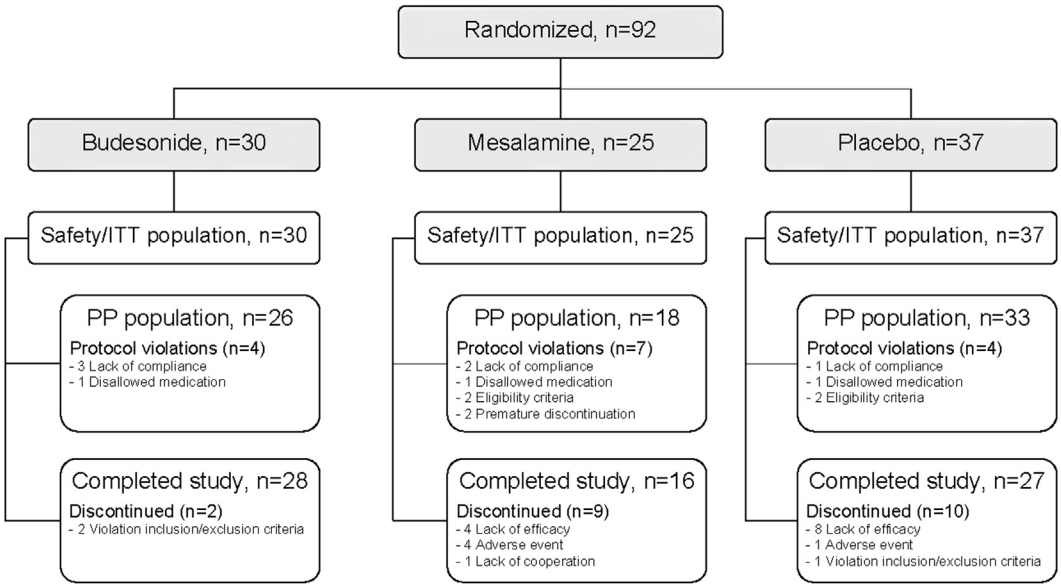
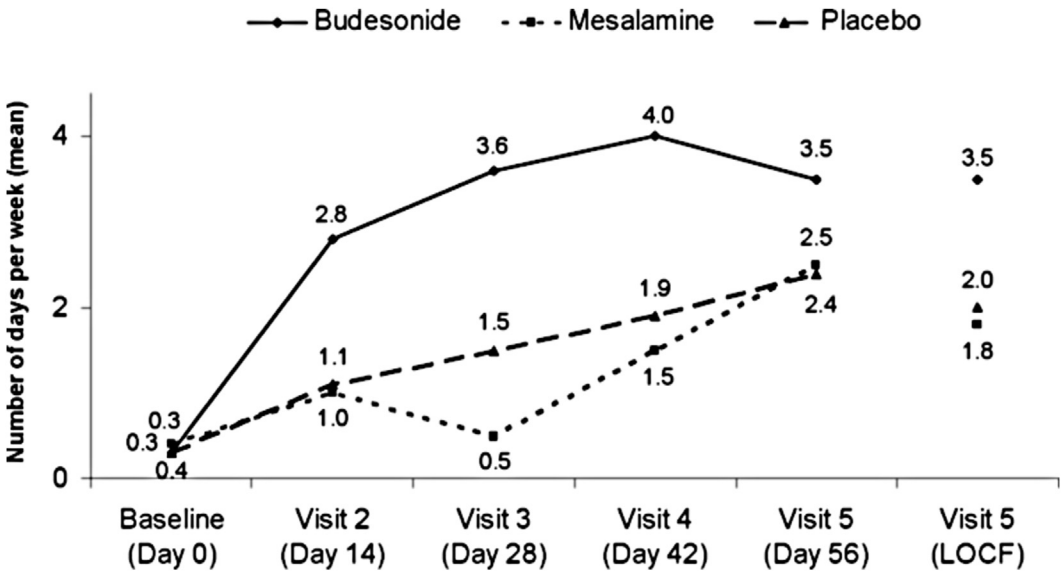
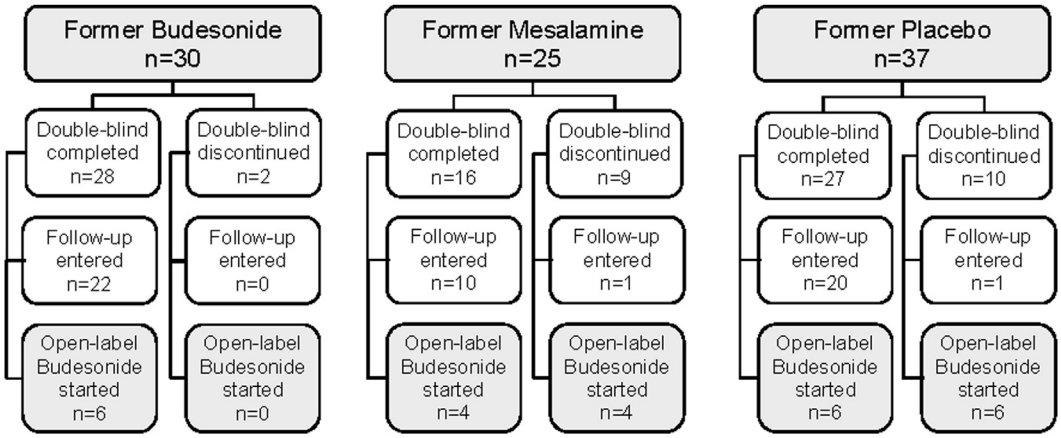


Supplementary Figure 1. Study flow of randomized patients.



Supplementary Figure 2. Number of days with solid stools in the week before visit (ITT).



Supplementary Figure 3. Study flow in follow-up and open-label phase.

Supplementary Table 1. Baseline Demographic and Clinical Characteristics, *P* Values

	Budesonide vs placebo, *P* value	Mesalamine vs placebo, *P* value	Overall *P* value
Sex	.4999[a]	.1007[a]	.2057[a]
Age	.1521[d]	.6511[d]	.1980[b]
BMI	.2971[d]	.6893[d]	.6217[b]
Smoking habit	.7770[c]	.5702[c]	.6679[c]
Caffeine intake	.4468[a]	.3870[a]	.4674[a]
Duration of symptoms	.7240[d]	.8746[d]	.8725[b]
New diagnosis	1.0000[a]	.5740[a]	.8056[a]
Time since diagnosis	.4194[d]	.6877[d]	.5479[b]
No. of previous episodes	.3441[d]	.3313[d]	.5017[b]

BMI, body mass index.
[a]Fisher's exact test.
[b]Kruskal-Wallis test.
[c]Fisher's exact test for smoking (current, former, never).
[d]Wilcoxon Mann-Whitney test.