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Efficacy and Safety of Budesonide, vs Mesalazine or Placebo, as Induction Therapy for Lymphocytic Colitis

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BACKGROUND & AIMS: Lymphocytic colitis is a common cause of chronic, nonbloody diarrhea. However, the effects of treatment are unclear and randomized placebo-controlled trials were requested in a Cochrane review. We performed a randomized, placebo-controlled, multicenter study to evaluate budesonide and mesalazine as induction therapy for lymphocytic colitis. **METHODS:** Patients with active lymphocytic colitis were randomly assigned to groups given budesonide 9 mg once daily (Budenofalk granules), mesalazine 3 g once daily (Salofalk granules), or placebo for 8 weeks in a double-blind, double-dummy design. The primary endpoint was clinical remission, defined as ≤21 stools (including ≤6 watery stools), in the 7 days before week 8. **RESULTS:** The final analysis included 57 patients (19 per group). Most patients were female (72%) and the mean age was 59 years. The proportion of patients in clinical remission at week 8 was significantly higher in the budesonide group than in the placebo group (intention-to-treat analysis, 79% vs 42%; $P = .01$). The difference in proportions of patients in clinical remission at week 8 between the mesalazine (63%) and placebo groups was not significant ($P = .09$). The proportion of patients with histologic remission at week 8 was significantly higher in the budesonide group (68%) vs the mesalazine (26%; $P = .02$) or placebo (21%; $P = .008$) groups. The incidence of adverse events was 47.4% in the budesonide group, 68.4% in the mesalazine group, and 42.1% in the placebo group. **CONCLUSIONS:** In a randomized multicenter study, we found oral budesonide 9 mg once daily to be effective and safe for induction of clinical and histologic remission in patients with lymphocytic colitis, compared with placebo. Oral mesalazine 3 g once daily was not significantly better than placebo. ClinicalTrials.gov no: NCT01209208.

Keywords: Corticosteroid; 5-Aminosalicylic Acid; Microscopic Colitis; Intraepithelial Lymphocytes.

Lymphocytic colitis, a subtype of microscopic colitis, is characterized by microscopic abnormalities in the colonic mucosa and an increased number of intraepithelial lymphocytes (IELs).[1] The leading symptom is chronic or recurrent nonbloody diarrhea, with some patients experiencing additional symptoms such as abdominal pain and fecal incontinence. The disease is socially disabling and inflicts a substantial decrease in quality of life.[2] Epidemiological studies have estimated the annual incidence to be 2.6 to 10.0 per 100,000 population,[3–6] with evidence for an increased incidence over time.[7,8] However, because endoscopic findings are usually normal, and symptoms overlap with diarrhea-predominant irritable bowel syndrome,[9,10] the true incidence may be higher. The clinical presentation of lymphocytic colitis is also indistinguishable from collagenous colitis, the more frequent subtype of microscopic colitis,[3–5] and misdiagnosis is possible in the absence of histological examination.[11]

Expert guidelines recommend budesonide as first-line treatment for active microscopic colitis.[1,12,13] Budesonide, a locally active corticosteroid with extensive first-pass metabolism in the liver and low systemic exposure, is widely used in this context. Robust evidence for its use in lymphocytic colitis, however, has been limited. One fully published randomized trial with budesonide (9 mg/d) in 42 patients showed significantly higher rates of clinical remission (86%) and histological (73%) remission vs placebo after 6 weeks of treatment.[14] One further randomized trial, published in abstract form only, recruited only 15 patients but found a significant reduction in the primary endpoint of

Abbreviations used in this paper: CI, confidence interval; IEL, intraepithelial lymphocyte; ITT, intention-to-treat; LOCF, last observation carried forward; PP, per-protocol.

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CLINICAL AT

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

There is no established treatment for active lymphocytic colitis. Expert guidelines recommend budesonide as first-line therapy for induction of remission in microscopic colitis but data in lymphocytic colitis are limited.

NEW FINDINGS

In a well-designed study, budesonide achieved clinical remission in lymphocytic colitis significantly more frequently than placebo; adverse event rates were similar. Mesalazine therapy did not significantly improve clinical remission versus placebo.

LIMITATIONS

The study used pH-modified release oral budesonide granules, and the findings may not apply to other budesonide formulations. Patients with suspected drug-induced lymphocytic colitis were excluded.

IMPACT

Budesonide (9 mg once daily) for 8 weeks can be considered the treatment of choice for patients with active lymphocytic colitis.

improvement in diarrhea under budesonide compared with placebo (91% vs 25%, $P = .03$), accompanied by superior histological improvement.[15] Mesalazine is currently considered to be a second-line treatment option for microscopic colitis[1,12,13]; however, only 1 randomized trial compared mesalazine vs mesalazine plus cholestyramine in 41 patients with lymphocytic colitis.[16] Clinical and histological remission was achieved in 85% of patients, with no difference in remission rates between treatment groups. No placebo-controlled trial of mesalazine has been performed in lymphocytic colitis. Consequently, a recent Cochrane review concluded that budesonide may be an effective therapy for treatment of lymphocytic colitis, but that the evidence to support this statement is of low quality and further randomized, placebo-controlled trials studying interventions for lymphocytic colitis are warranted.[17]

The objective of this randomized trial was to demonstrate superiority for short-term treatment with pH-modified release oral budesonide granules (9 mg budesonide once daily) or mesalazine granules (3 g mesalazine once daily) vs placebo in terms of achieving clinical remission in patients with active lymphocytic colitis.

Methods

Study Design and Conduct

This was a double-blind, double-dummy, randomized, placebo-controlled, phase 3 study comparing the efficacy and tolerability of 8 weeks' treatment with budesonide (9 mg once daily) or mesalazine (3 g once daily) vs placebo in patients with active lymphocytic colitis. Patients in clinical remission at the end of the 8-week double-blind phase entered a 16-week treatment-free follow-up phase. Patients who were not in remission or who experienced a clinical relapse during the follow-up phase were offered open-label once-daily budesonide therapy (1 sachet of Budenofalk 9-mg granules) for 4 weeks, as were patients who were withdrawn from treatment during the double-blind phase due to lack of efficacy. The double-blind phase was undertaken from May 2010 to November 2016. The follow-up phase was completed in January 2017. The study was performed at 30 gastroenterology centers in Germany, Sweden, Denmark, Hungary, Spain, the Netherlands, Czech Republic, and Lithuania.

The study protocol was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice and was approved by the national ethics committees in all participating countries. All patients provided written informed consent. The study protocol was registered at www.clinicaltrials.gov (NCT01209208) and at www.clinicaltrialsregister.eu (EudraCT 2008-005994-36). All authors had access to the study data and reviewed and approved the final manuscript.

Patients

Key inclusion criteria were a history of nonbloody, watery diarrhea for $\geq$12 weeks before randomization in patients with newly diagnosed lymphocytic colitis, or a history of clinical relapse for $\geq$1 week before randomization in patients with previously established lymphocytic colitis; $\geq$28 stools within the 7 days before randomization, of which $\geq$20 were watery/soft stools; complete colonoscopy (or proctosigmoidoscopy) within the 12 weeks before randomization; a histologically confirmed diagnosis of lymphocytic colitis, defined as >20 IELs per 100 surface epithelium cells (as confirmed by one central pathologist [DA]); signs of inflammation of the lamina propria; and normal (ie, <10 μm) subepithelial collagen layer on well-oriented sections. The key exclusion criteria were evidence of infectious diarrhea, diarrhea due to other organic diseases of the gastrointestinal tract (ie, collagenous colitis, ulcerative colitis, ischemic colitis, radiation colitis, Crohn's disease, tumors, or polyps >2 cm); celiac disease (blood tests and/or duodenal histology required); suspicion of drug-induced lymphocytic colitis; abnormal hepatic function or renal function; severe comorbidity; active peptic ulcer disease; treatment with antidiarrheals (eg, loperamide), *Boswellia serrata* extract, cholestyramine or bulking agents within the 14 days before randomization; treatment with immunomodulators (eg, azathioprine, 6-mercaptopurine, thioguanine, or methotrexate) within 3 months before randomization; and treatment with budesonide, mesalazine, steroids, or oral antibiotics within 4 weeks before randomization.

Randomization and Interventions

After a 2-week screening phase, eligible patients were randomized at the baseline visit to 1 of the 3 treatment groups at a 1:1:1 ratio. For allocation of the patients, a computer-generated list of random numbers was prepared using a block size of 3. Randomization was concealed by packaging the study medication using the double-dummy technique to guarantee blinding for all patients and investigators as well as all other persons involved in the conduct of the study. The study medication was consecutively numbered for each patient according to the randomization schedule, and investigators

dispensed the study medication to enrolled patients as per the randomization schedule.

Patients received either budesonide 9 mg once daily (1 sachet of Budenofalk 9-mg granules and 2 sachets of placebo Salofalk 1.5-g granules), or mesalazine 3 g once daily (2 sachets of Salofalk 1.5-g granules and 1 sachet of placebo Budenofalk 9-mg granules), or placebo (1 sachet of placebo Budenofalk 9-mg granules and 2 sachets of placebo Salofalk 1.5-g granules), in the morning for 8 weeks. Adherence to the study treatment was monitored by sachet count at each study visit.

During the entire study period, the use of other anti-inflammatory drugs, *Boswellia serrata* extract, immunosuppressants, antidiarrheals, spasmolytics (except butylscopolamine for the treatment of abdominal pain), and oral antibiotics (except for up to a 7-day course for conditions unrelated to lymphocytic colitis) was not permitted.

Sample Size

Assuming rates of clinical remission of 80% in the verum group (budesonide or mesalazine) and of 40% in the placebo group, the statistical power of the test procedure was 82.1% with 18 patients per group in the first stage and an additional 7 patients per group in the second stage, resulting in a total sample size of 75 patients (3×25 patients) in the intention-to-treat (ITT) analysis. For hypothesis testing of the primary endpoint, the overall (experiment-wise) type I error rate was $\alpha = 0.025$ (1-sided). All other statistical tests were performed 2-sided with a significance level of $\alpha = 0.05$ on an exploratory basis.

The study protocol prespecified a 2-stage group-sequential adaptive design with possible sample size adjustment or early stopping of the study for efficacy, futility, or safety after the interim analysis. The interim analysis was planned when 54 ITT patients were evaluable (approximately 18 patients per group), conducted by an independent data monitoring committee established by the sponsor before the interim analysis.

Evaluation Schedule and Study Endpoints

Postrandomization study visits took place at weeks 2, 4, 6, and 8 during the double-blind treatment phase, at weeks 8 and 16 after entry to the follow-up phase, and at the start and end of the 4-week open-label treatment phase, as applicable.

The primary endpoint was clinical remission at the week 8 visit (applying the last observation carried forward [LOCF] method). Clinical remission was defined according to the Hjortswang criteria,[18] that is, $\leq$21 stools (including $\leq$6 watery stools) in the preceding 7 days. Patients withdrawn from the double-blind treatment phase due to lack of efficacy were considered to be nonresponders. Secondary efficacy endpoints included time to clinical remission, mean number of watery stools per week, mean number of days with watery or solid stools per week (LOCF); abdominal pain; quality of life; histopathology; safety and tolerability; clinical relapse during the follow-up phase; and response to open-label budesonide. A full list of study endpoints is shown in Supplementary Table 1.

Endoscopy and Histology

A complete colonoscopy was performed at the screening visit (within 12 weeks before randomization) and, if possible, at the end of the 8-week double-blind treatment. At each colonoscopy, 2 biopsy samples were obtained from each of the following colon segments: rectum, sigmoid, descending, transverse, ascending/cecum, and terminal ileum. Where proctosigmoidoscopy was performed, biopsies were obtained from the sigmoid colon and rectum.

Biopsy specimens were fixed in 4% formalin and embedded in paraffin. Sections ($2-4$ μm) were stained with hematoxylin and eosin, with CD3 immunohistochemistry used when the number of IELs could not otherwise be determined. Goldner staining was used to assess the subepithelial collagen layer. Well-oriented sections in which at least 3 adjacent crypts were present, were cut in their vertical plane and evaluated for each colon section for (1) the total number of IELs per 100 surface epithelium cells, (2) the thickness of the collagen band (μm), (3) inflammation of the lamina propria with lymphocytes and plasma cells (semiquantitative score, 0–3), (4) inflammation of the lamina propria with neutrophilic and eosinophilic granulocytes (semiquantitative score, 0–3), and (5) degeneration of the surface epithelium (present/absent). All biopsies were analyzed in blinded fashion by a central pathologist (Gustavo Baretton/Daniela Aust, Dresden, Germany). Histological remission was defined as $\leq$20 IELs per 100 surface epithelium cells.

Safety and Tolerability

At each study visit, patients underwent physical examination (at the randomization and final visits), vital signs, previous (at the randomization visit) and concomitant medications, and adverse events were recorded, and general laboratory tests and urinalysis were performed.

Statistical Analyses

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 events without causal relationship with study drug, were excluded from the PP population. Safety analyses were performed for the safety population. Statistical testing of the primary endpoint was done via the ADDPLAN system (Icon plc, Dublin, Ireland). All other analyses were conducted using the SAS statistical package for Windows (SAS Institute, Cary, NC).

Results

Study Population

A total of 105 patients were screened for enrollment. The interim analysis of 54 ITT patients showed superiority of budesonide vs placebo. Consequently, the independent data monitoring committee recommended that patient recruitment be stopped. Recruitment continued during the interim analysis and a further 3 randomized patients (2 in the mesalazine group and 1 in the placebo group) completed the study. Thus, 57 patients were included in the ITT and safety population (19 in each treatment group). Thirteen patients discontinued the study prematurely (4 budesonide, 4 mesalazine, 5 placebo). Patients discontinued due to adverse events only in the budesonide and mesalazine

groups (2/4 and 3/4 patients, respectively) and discontinued due to lack of efficacy only in the placebo group (5/5 patients) (Supplementary Figure 1). Ten patients were excluded from the PP population, including 2 patients in whom the diagnostic criteria for lymphocytic colitis were not met. The PP population thus comprised 47 patients (Supplementary Figure 1).

Baseline demographic and clinical characteristics were similar among the 3 treatment groups other than a higher proportion of current smokers and longer duration of current symptoms in the placebo group (Table 1). Twelve patients had received treatment for the previous episode in the form of budesonide (n = 7; budesonide group 1, mesalazine group 1, placebo group 5), mesalazine (1 patient in the budesonide group), and/or other interventions (n = 6; budesonide group 3, mesalazine group 2, placebo group 1). Treatment for the current episode had been given to 13 patients, most frequently antidiarrheals (n = 10; budesonide group 3, mesalazine group 4, placebo group 3); no patient had been given budesonide or mesalazine.

Clinical Efficacy

The primary endpoint of clinical remission at week 8 occurred significantly more frequently in the budesonide group than in the placebo group based on the ITT population (78.9% [15/19] vs 42.1% [8/19], $P = .010$) (Figure 1*A*). The difference in clinical remission at week 8 between mesalazine (63.2% [12/19]) and placebo failed statistical significance ($P = .097$). Similar results were observed in the PP population (budesonide 93.3% [14/15; $P = .002$ vs placebo], mesalazine 68.8% [11/16; $P = .077$ vs placebo], placebo 43.8% [7/16]) (Figure 1*B*).

The Kaplan-Meier analysis revealed that the median time to clinical remission was significantly shorter in the budesonide group compared with the placebo group (ITT: 3 days vs 21 days, $P = .044$), whereas median time to remission in the mesalazine group was not significantly different from the placebo group (ITT: 12 days vs 21 days, $P = .337$) (Figure 2).

Consequently, the mean number of watery stools per day in the budesonide group decreased from 4.0 (95% CI 2.6–5.5) at baseline to 0.4 (95% CI 0.0–0.9) in the first 2 weeks of treatment. From baseline to week 8, the mean reduction in the number of watery stools per week in the budesonide group was 3.7 (95% CI 2.5–4.8), but was only 2.2 (95% CI 1.3–3.1) and 1.7 (95% CI 0.8–2.5) in the mesalazine and placebo group, respectively. A rapid and marked reduction in the mean number of days with watery stools per week in the budesonide group (Figure 3*A*) was mirrored by an increase in the number of days with solid stools (Figure 3*B*).

The mean number of stools per day with severe abdominal pain or cramps decreased by 1.0 (95% CI 0.3–2.2) from baseline to week 8 (LOCF) in the budesonide group but decreased by only 0.1 (95% CI 0.0–0.3) in the mesalazine group and by 0.1 (95% CI 0.1–0.2) in the placebo group.

The mean Short Health Scale (SHS) value for symptom burden improved from baseline to week 8 by 42 mm (95% CI 23–61), 36 (95% CI 22–49), and 21 (95% CI 3–38) in the budesonide, mesalazine, and placebo groups, respectively, representing a significant improvement within each group. Similarly, the other 3 SHS health dimensions (social function, disease-related worry, and general well-being) also showed a numerically greater improvement in the budesonide group vs the other

Table 1. Baseline Demographic and Clinical Characteristics (ITT Population)

	Budesonide (n = 19)	Mesalazine (n = 19)	Placebo (n = 19)
Female gender, n (%)	15 (78.9)	14 (73.7)	12 (63.2)
Age (*y*), mean (SD)	60.8 (11.5)	57.4 (18.5)	59.0 (12.7)
Body mass index (kg/m^2), mean (SD)	25.4 (3.7)	25.1 (3.7)	23.2 (2.5)
Smoking habit, n (%)			
Current	5 (26.3)	3 (15.8)	10 (52.6)
Former	3 (15.8)	7 (36.8)	4 (21.1)
Never	11 (57.9)	9 (47.4)	5 (26.3)
Caffeine intake, n (%)	16 (84.2)	17 (89.5)	16 (84.2)
Duration of current symptoms (*mo*), median (IQR)	4.4 (2.2, 10.3)	4.3 (2.4, 6.3)	6.6 (3.9, 10.7)
New diagnosis, n (%)	7 (36.8)	7 (36.8)	8 (42.1)
Time since first symptoms (*y*), median (IQR)	0.8 (0.3, 3.5)	0.6 (0.4, 2.3)	1.0 (0.4, 4.1)
Number of previous episodes[a]			
1 to <3	11 (91.7)	11 (91.7)	9 (81.8)
3 to <5	–	–	1 (9.1)
≥5	1 (8.3)	1 (8.3)	–
Missing	–	–	1 (9.1)
Number of stools/day in the past 7 days, mean (SD)	5.7 (2.3)	5.1 (1.1)	5.1 (1.5)
Number of watery stools/day in the past 7 days, mean (SD)	4.0 (3.0)	2.7 (1.7)	3.8 (2.0)

IQR, interquartile range.
[a]In patients with established diagnosis.

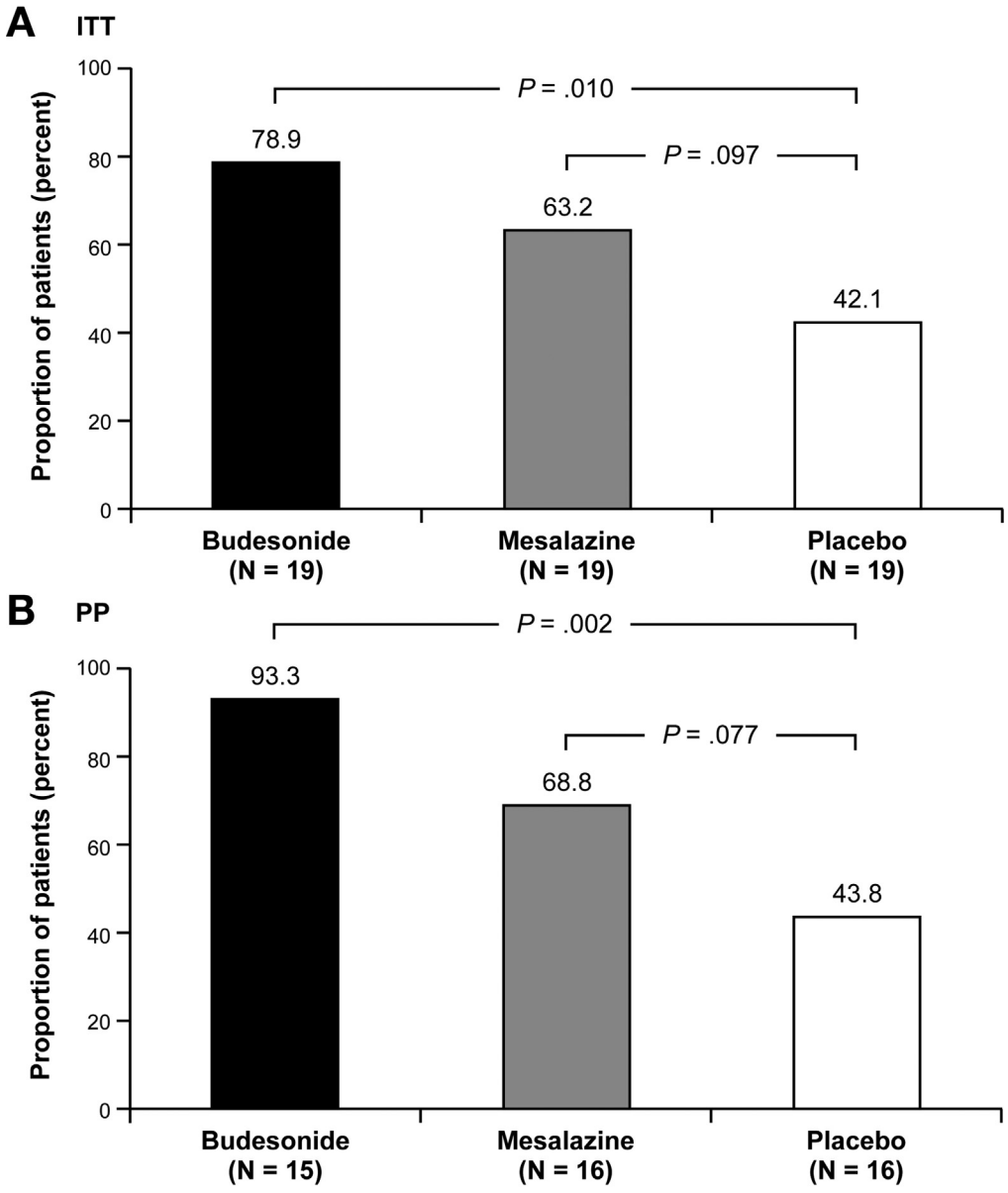

Figure 1. Clinical remission in (*A*) ITT population, and (*B*) PP population during the double-blind phase of the study. Clinical remission was defined as ≤21 stools including ≤6 watery stools in the 7 days before week 8 or withdrawal visit (LOCF method).

treatment arms, but no between-group differences were statistically significant.

Histology

Histological examination at baseline confirmed the diagnosis of lymphocytic colitis in all patients except for 2 patients in the budesonide group. There was a mean of 34.0, 42.1, and 43.3 IELs per 100 surface epithelium cells in the budesonide, mesalazine, and placebo groups, respectively. The mean thickness of the collagen band was 5.0 μm, 4.1 μm, and 3.8 μm in the budesonide, mesalazine, and placebo groups at baseline, respectively. The degree of lamina propria inflammation showed no marked differences among the 3 treatment groups at baseline.

Biopsies were available at week 8 in 42 patients, allowing a comparison between pre- and posttreatment histology. Histological remission was achieved in 13 of 15, 5 of 14, and 4 of 13 patients in the budesonide, mesalazine, and placebo groups, respectively, representing remission rates of 68.4% with budesonide ($P = .008$ vs placebo), 26.3% with mesalazine ($P = 1.000$ vs placebo), and 21.1% with placebo. At week 8, the mean (SD) number of IELs in surface epithelium over all colon segments in this subpopulation was 16 (7) in the budesonide group, 31 (19) in the mesalazine group, and 38 (21) in the placebo group.

Safety

The incidence of adverse events was comparable between budesonide (47.4%) and placebo (42.1%) but higher with mesalazine (68.4%) (Supplementary Table 2). Adverse events with a suspected relation to study drug were reported in 3 patients in the budesonide group (increased

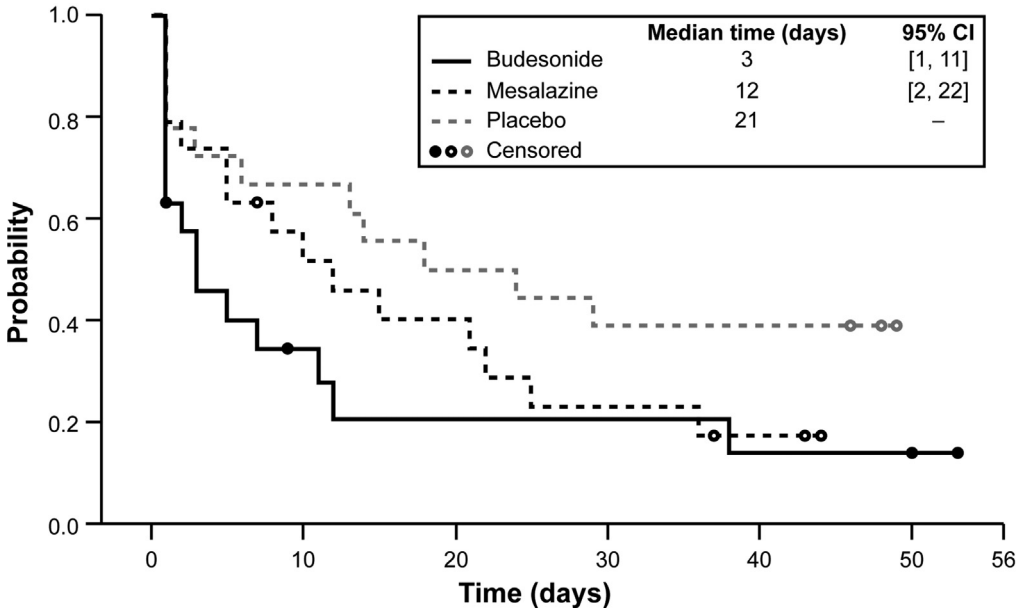

Figure 2. Time to clinical remission, defined as the time to first of ≥7 days each with, on average, ≤3 stools per day, including <1 watery stool per day (ITT population). The upper limit of the 95% CI values could not be calculated for the placebo group.

weight, transient ischemic attack, affective disturbance, and sleep disorder), 3 patients in the mesalazine group (acute pancreatitis, increased hepatic enzymes, and dizziness), and 4 patients in the placebo group (nausea [2], upper abdominal pain, abdominal pain, dizziness, hyperhidrosis, and night sweats). Serious adverse events occurred in 2 patients in the budesonide group (urinary tract infection and transient ischemic attack), 2 patients in the mesalazine group (acute pancreatitis and metatarsalgia), and 1 patient in the placebo group (alcohol abuse). The mean cortisol level at baseline compared with week 8 was 12.9 vs 11.8 μg/dL in the budesonide group, 16.8 vs 15.6 μg/dL in the mesalazine group, and 12.1 vs 12.9 μg/dL in the placebo group. No patient in any group had a clinically significant shift in cortisol level between baseline and week 8 that was considered related to study drug. Other changes in laboratory parameters were not considered clinically relevant in any treatment group.

Follow-up and Open-label Treatment

Thirty-one patients entered the treatment-free follow-up phase (Supplementary Figure 2), of whom 27 were in clinical remission at the end of the double-blind phase. During the follow-up phase, 7 (25.9%) of these 27 patients experienced a clinical relapse, defined as at least 28 stools within 7 days including 20 watery/soft stools. Relapse occurred in 2 (16.7%) of 12, 3 (37.5%) of 8, and 2 (28.6%) of 7 patients formerly in the budesonide, mesalazine, and placebo groups, respectively. Two adverse events (hemorrhoids, worsening of femoral head avascular necrosis) in 2 patients (former mesalazine and placebo group) occurred during the follow-up phase. Both adverse events were serious and considered unrelated to the former study medication.

Nineteen patients entered the open-label treatment phase, including 6 patients due to a relapse during the previous follow-up phase (Supplementary Figure 2). One patient was in remission and 1 patient did have a relapse during the follow-up phase when they entered the open-label treatment phase, contravening the inclusion criteria, so were excluded from analysis. Clinical remission was achieved by the end of the 4-week open-label phase in 15 (88.2%) of 17 patients, including 2 (66%) of 3, 4 (100%) of 4, and 9 (90%) of 10 patients formerly in the budesonide, mesalazine, and placebo groups. Five adverse events in 5 patients occurred during open-label treatment phase. None was serious or severe in intensity.

Discussion

This study confirms that budesonide is effective for the induction of remission in active lymphocytic colitis. Clinical remission was achieved in 79% of patients, with histological remission in 68% of patients, after an 8-week course of oral budesonide at a dosage of 9 mg/d. These response rates were significantly better than those seen in the placebo group. Strikingly, a substantial improvement in symptoms, including a profound reduction in the number of watery stools, was seen within a median of 3 days after starting budesonide therapy. These changes were accompanied by a marked increase in patients' quality of life as assessed by the SHS score. In contrast, neither clinical nor histological remission was significantly more frequent with mesalazine than placebo.

This trial addressed the need for well-designed trials to assess the efficacy of budesonide in treating active lymphocytic colitis.[17] The outcomes observed are very similar to those in the previous randomized trial of budesonide vs placebo in this setting published by Miehlke et al.[14] Six weeks' budesonide therapy in that study was associated with clinical remission in 86% of patients (defined as ≤3 stools per day on average and a

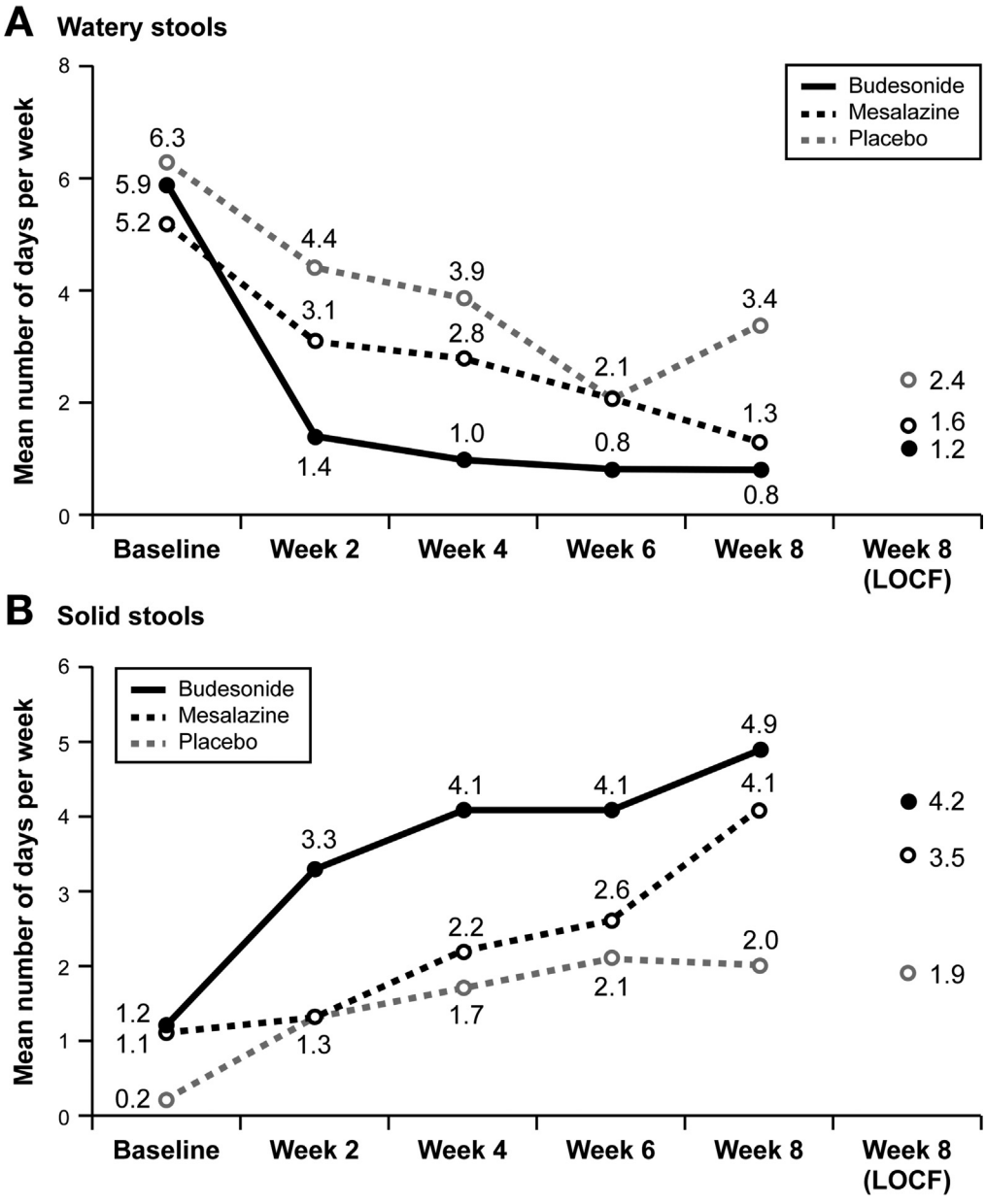

Figure 3. Mean number of days with (*A*) watery stools and (*B*) solid stools in the week before visit (ITT population). BL, baseline (day 0).

reduction of ≥1 stool per day compared with baseline in the previous week), and histological remission in 73% of cases. Retrospective data have also shown favorable results, with one such study reporting an 88% response rate using budesonide in 168 patients with histologically confirmed lymphocytic colitis.[5]

In our study, the relatively small number of patients entering the follow-up phase did not allow firm conclusions to be drawn, but the observation that only 1 in 4 patients relapsed over 16 weeks' follow-up is encouraging. One population-based study of microscopic colitis observed a significantly lower rate of recurrence after budesonide treatment compared with prednisone in a cohort of 74 patients followed for a median follow-up of 4 years (hazard ratio 0.38; $P = .02$).[19]

Similar to the current study, a recent trial by our group that followed a similar protocol in a population in patients with collagenous colitis found a clinical remission rate of 80% with budesonide but no significant benefit for mesalazine vs placebo.[20] The only other randomized trial of mesalazine in microscopic colitis, in which patients were randomized to mesalazine treatment with or without cholestyramine, reported 83% remission in the 41 patients with lymphocytic colitis at a median of 9.7 days.[16] However, the clinical criteria for diagnosis were less strict than in the present study and the definition of remission was simply "complete resolution of diarrhea." Moreover, the study was not blinded or placebo-controlled.

The effectiveness of budesonide in microscopic colitis reflects the pathology of the disease. Morphological

abnormalities in microscopic colitis can be diffuse throughout the colon, with histological findings in the left, right, and transverse colon as well as the terminal ileum,[5,21] or can be restricted to the right colon.[22] In the present study, we found that inflammation of the lamina propria was distributed throughout the entire colon. Budesonide is known to exert a potent anti-inflammatory effect in the proximal colon and ileum in the treatment of Crohn's disease,[23] whereas mesalazine is less effective.[24] Bile acid diarrhea is a frequent feature of lymphocytic colitis,[11] and the symptomatic effect of budesonide may be partly due to enhanced ileal bile acid resorption and a decreased bile acid load on the colon.[25] In addition, a budesonide-induced improvement in the water-absorption capacity of the small bowel has been reported,[26] an effect that would alleviate watery diarrhea.

Based on the available data in lymphocytic colitis, and randomized trials in collagenous colitis,[27–29] the American Gastroenterological Association[12,13] and the European Microscopic Colitis Group[1] both recommend budesonide 9 mg/d for 8 weeks[12,13] or 6 to 8 weeks[1] as first-line therapy for active microscopic colitis.[12,13] In patients who experience relapse after withdrawal of budesonide, low-dose maintenance therapy is recommended, starting at no more than 6 mg/d, then tapered to the lowest effective dose and continued for 6 to 12 months if relapse occurs following remission.[1,12,13] Recommendations for long-term therapy are based on studies of budesonide in collagenous colitis[29–31] because no long-term randomized trials of budesonide have been performed in lymphocytic colitis.

In terms of safety, the overall rate of adverse events was higher in the mesalazine group than with budesonide or placebo, but rates of adverse events with a suspected relation to study drug were comparable in all 3 arms. Serious adverse events were infrequent in all 3 groups. The previous randomized trial of budesonide in lymphocytic colitis also observed a similar rate of adverse events and serious adverse events with budesonide or placebo.[14] More generally, a meta-analysis that included 7 randomized trials of budesonide for the short- or long-term treatment of microscopic colitis concluded that withdrawal due to adverse events was similar for budesonide- or placebo-treated patients.[32]

The study benefited from a randomized, double-blind, double-dummy, multicenter design. The study population was not large, but the trial was adequately powered. Patients were required to have histological confirmation of the diagnosis, although against protocol 2 patients were randomized to budesonide despite not meeting the diagnostic criteria for lymphocytic colitis and were consequently excluded from the PP population. There was an imbalance among treatment groups in the proportion of current smokers, with a substantially higher rate of smokers in the placebo arm than in either active treatment arm, and a somewhat longer duration of current symptoms in the placebo group, which potentially biased the results. Certain categories of patients were excluded, for example, those with suspected drug-induced disease, and the results cannot necessarily be extrapolated to all individuals with lymphocytic colitis. Patients with only mild symptoms, or with symptoms lasting for <12 weeks, were not enrolled and it has been suggested that antidiarrheals or cholestyramine may be considered in such cases,[1] although this is not evidence-based. Last, the study used pH-modified release oral budesonide granules (Budenofalk) which release the active ingredient only at pH 6.4 or higher[33] (ie, not before the terminal ileum). The gastro-resistant controlled-ileal release formulation (Entocort) starts to release drug from the proximal jejunum onward (pH 5.5),[34] whereas the multimatrix formulation (Cortiment) releases drug throughout the colon (pH 7.0)[33] and as a result is licensed only for ulcerative colitis and not for collagenous colitis or Crohn's disease. These variations in the site of release mean that the current findings may not necessarily apply to budesonide formulations other than the pH-modified formulation used here.

In conclusion, short-term budesonide is effective and safe for induction of clinical and histological remission in lymphocytic colitis. Approximately 80% of patients achieved clinical remission with a profound improvement seen within 2 weeks. Mesalazine did not show a significant benefit for either clinical or histological remission vs placebo. These results confirm the efficacy of budesonide for the induction of remission in active lymphocytic colitis and are consistent with expert recommendations[1,12,13] for its use as first-line therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.08.042.

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Author contributions: Stephan Miehlke, Andreas Münch, and Roland Greinwald contributed to the study design. Stephan Miehlke, Daniela Aust, Emese Mihaly, Peter Armerding, Günther Böhm, Ole Bonderup, Fernando Fernández-Bañares, Juozas Kupcinskas, Lars Kristian Munck, Kai-Uwe Rehbehn, and Andreas Münch recruited and managed patients and collected data. Stephan Miehlke, Tanju Nacak, and Roland Greinwald analyzed the data and contributed to writing the manuscript, which was critically reviewed and approved for publication by all authors.

Conflicts of interest
These authors disclose the following: Stephan Miehlke has received speaker's fees from Dr Falk Pharma and consultancy fees from Tillots. Daniela Aust has received speaker's fees from Dr Falk Pharma. Ole Bonderup has received speaker fees from Tillotts and Dr Falk Pharma, is a member of an advisory board for Tillotts, and has received grants from Tillotts. Fernando Fernández-Bañares has received consultancy fees from Tillots. Tanju Nacak and Roland Greinwald are employees of Dr Falk Pharma GmbH. Andreas Münch is a member of an advisory board for Tillotts, has received grants/honoraria from Ferring, research funding from Dr Falk Pharma, and has received speaker/consulting fees from Tillotts, Vifor, and Dr Falk Pharma. The remaining authors disclose no conflicts.

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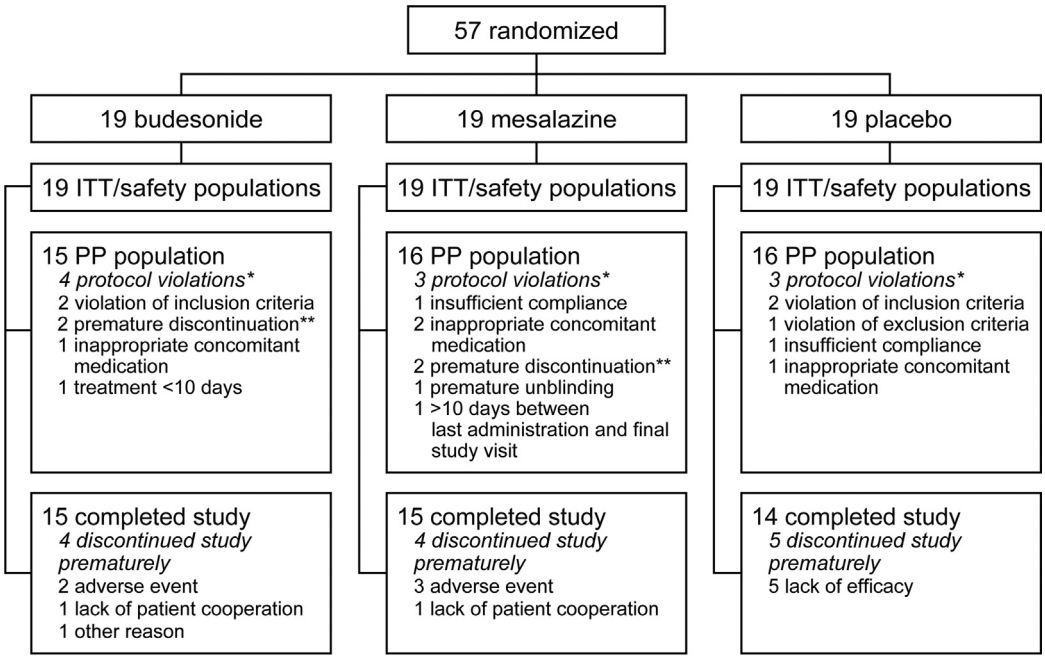
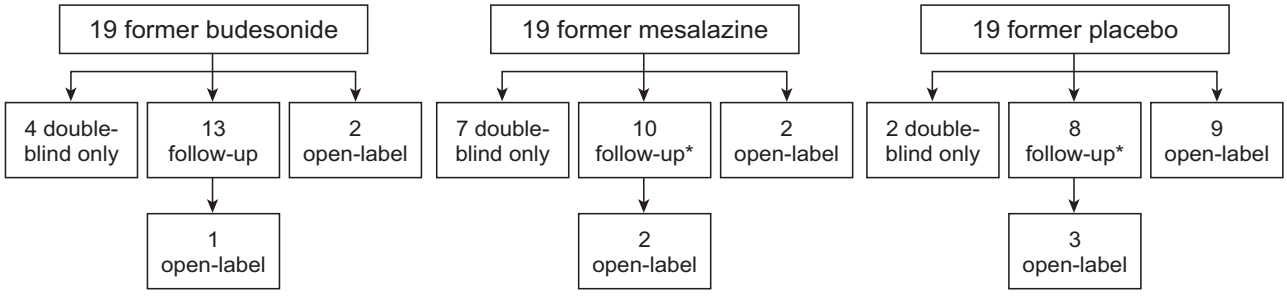


* Exclusion from the PP population was due to more than one protocol violation in some patients
** For reason other than lack of efficacy, adverse event with suspected causal relationship to study drug, or intolerable adverse event that was deterioration of study disease

Supplementary Figure 1. Patient disposition during the double-blind phase of the study.



* Including 1 patient who started open-label treatment then entered the follow-up phase

Supplementary Figure 2. Patient disposition during the follow-up phase of the study.

Supplementary Table 1. Study Endpoints

Primary efficacy variable	– Clinical remission, defined as ≤21 stools (including ≤6 watery stools) in the 7 days before the week 8 visit (LOCF)
Secondary efficacy variables: double-blind phase	*Clinical* – Number (%) of patients with ≤21 stools (including ≤6 watery stools) in the 7 days before the visit at weeks 2, 4, 6, and 8 – Number (%) of patients with ≤21 stools in the 7 days before the visit at weeks 2, 4, 6, 8, and 8 (LOCF) – Number (%) of patients with ≤6 watery stools in the 7 days before the visit at weeks 2, 4, 6, 8, and 8 (LOCF) – Number (%) of patients with baseline mean of >3 stools per day who have a mean of ≤3 stools per day and a reduction of ≥1 stool from baseline in the 7 days before the visit at weeks 2, 4, 6, 6 (LOCF), 8, and 8 (LOCF) – Time to resolution of symptoms, defined as the first of 7 consecutive days with: – ≤3 stools per day on average, *or* – <1 watery stool/day on average, *or* – ≤3 stools per day on average, including <1 watery stool/day on average – Time to resolution of symptoms, defined as the first of 3 consecutive days with: – ≤3 stools per day on average, *or* – <1 watery stool per day on average, *or* – ≤3 stools per day on average, including <1 watery stool per day on average – Impact on stool consistency (watery/soft/solid) – Impact on abdominal pain – Impact on patient's general well-being – Severity of diarrhea – Number of days with diarrhea (>3 stools per day) in each week – Number of days in each week with watery, soft, soft or solid, or solid stool consistency, respectively – Average frequency of stools per day in each week – Disease activity at week 8 and change of disease activity from baseline to week 8 (LOCF) – Quality of life (by GIQLI, SHS) – Physician's Global Assessment (PGA) *Histology* – Histological remission at week 8 (LOCF), defined as ≤20 IELs per 100 epithelial cells – Histological remission at week 8 (LOCF), defined as ≤20 IELs per 100 epithelial cells and a reduction in lamina propria inflammation – Histological improvement at week 8 (LOCF), defined as a reduction of ≥50% in the number of IELs per 100 epithelial cells compared with baseline and/or a reduction in lamina propria inflammation – Histological nonresponse at week 8 (LOCF), defined as no significant change in IEL numbers and no change in lamina propria inflammation, at week 8
Secondary efficacy variables: open-label phase	– Clinical remission, defined as a maximum of 21 stools, including ≤6 watery stools in the last 7 days before the visit at week 4 (LOCF) of the open-label phase – Change of disease activity from start of open-label phase to week 4 (LOCF) – Change of quality of life (by GIQLI, SHS) from start of open-label phase to week 4 (LOCF) – Physician Global Assessment
Secondary efficacy variables: follow-up phase	– Number (%) of patients maintaining clinical remission at weeks 16, 24, and 24 (LOCF), with remission defined as ≤21 stools, including ≤6 watery stools in the 7 days before the visit – Number (%) of patients who experienced a relapse at weeks 16, 24, and 24 (LOCF), defined as ≥28 stools within the 7 days before the visit, including ≥20 watery/soft stools – Time to relapse – Time to failure (relapse, not any more in remission, or withdrawal due to lack of efficacy or adverse drug reaction) – Time to withdrawal – Time in study
Safety variables	– Adverse events – Vital signs (blood pressure, heart rate) and body weight – Standard hematology, blood chemistry, urine analysis – Serum cortisol – Assessment of tolerability by investigator and patient

GIQLI, Gastrointestinal Quality of Life Index; SHS, Short Health Scale.

Supplementary Table 2. Adverse Events During the Double-Blind Phase, n (%)

	Budesonide (n = 19)	Mesalazine (n = 19)	Placebo (n = 19)
Any adverse event	9 (47.4)	13 (68.4)	8 (42.1)
Adverse events with suspected relation to study drug	3 (15.8)	3 (15.8)	4 (21.1)
Serious adverse event	2 (10.5)	2 (10.5)	1 (5.3)
Adverse events leading to discontinuation of study drug	2 (10.5)	3 (15.8)	–
Adverse events occurring in >2 patients			
Gastrointestinal disorders	2 (10.5)	3 (15.8)	3 (15.8)
Abdominal pain	–	1 (5.3)	1 (5.3)
Abdominal pain upper	1 (5.3)	–	1 (5.3)
Dyspepsia	1 (5.3)	–	1 (5.3)
Nausea	–	1 (5.3)	2 (10.5)
General disorders and administrative site conditions	–	2 (10.5)	–
Fatigue	–	2 (10.5)	–
Infections and infestations	2 (10.5)	6 (31.6)	4 (21.1)
Influenza	–	2 (10.5)	1 (5.3)
Nasopharyngitis	1 (5.3)	–	2 (10.5)
Sinusitis	–	2 (10.5)	–
Upper respiratory tract infection	–	2 (10.5)	–
Urinary tract infection	1 (5.3)	–	1 (5.3)
Nervous system disorders	2 (10.5)	3 (15.8)	1 (5.3)
Headache	1 (5.3)	2 (10.5)	–
Investigations	3 (15.8)	1 (5.3)	–
Musculoskeletal and connective tissue disorders	–	4 (21.1)	1 (5.3)
Back pain	–	1 (5.3)	1 (5.3)
Nervous system disorders	2 (10.5)	3 (15.8)	1 (5.3)
Dizziness	–	1 (5.3)	1 (5.3)
Headache	1 (5.3)	2 (10.5)	–
Psychiatric disorders	2 (10.5)	–	1 (5.3)
Sleep disorder	2 (10.5)	–	–
Renal and urinary disorders	–	2 (10.5)	1 (5.3)
Hematuria	–	2 (10.5)	–
Skin and subcutaneous tissue disorders	–	2 (10.5)	2 (10.5)