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Journal:

Gastroenterology 2012

GASTROENTEROLOGY 2012;143:1218–1226

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Once-Daily Budesonide MMX® Extended-Release Tablets Induce Remission in Patients With Mild to Moderate Ulcerative Colitis: Results From the CORE I Study

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BACKGROUND & AIMS: Budesonide is a corticosteroid with minimal systemic corticosteroid activity due to first-pass hepatic metabolism. Budesonide MMX® is a once-daily oral formulation of budesonide that extends budesonide release throughout the colon using multi-matrix system (MMX) technology. **METHODS:** We performed a randomized, double-blind, double-dummy, placebo-controlled trial to evaluate the efficacy of budesonide MMX for induction of remission in 509 patients with active, mild to moderate ulcerative colitis (UC). Patients were randomly assigned to groups that were given budesonide MMX (9 mg or 6 mg), mesalamine (2.4 g, as reference), or placebo for 8 weeks. The primary end point was remission at week 8. **RESULTS:** The rates of remission at week 8 among subjects given 9 mg or 6 mg budesonide MMX or mesalamine were 17.9%, 13.2%, and 12.1%, respectively, compared with 7.4% for placebo ($P = .0143$, $P = .1393$, and $P = .2200$). The rates of clinical improvement at week 8 among patients given 9 mg or 6 mg budesonide MMX or mesalamine were 33.3%, 30.6%, and 33.9%, respectively, compared with 24.8% for placebo ($P = .1420$, $P = .3146$, and $P = .1189$). The rates of endoscopic improvement at week 8 among subjects given 9 mg or 6 mg budesonide MMX or mesalamine were 41.5%, 35.5%, and 33.1%, respectively, compared with 33.1% for placebo. The rates of symptom resolution at week 8 among subjects given 9 mg or 6 mg budesonide MMX or mesalamine were 28.5%, 28.9%, and 25.0%, respectively, compared with 16.5% for placebo ($P = .0258$, $P = .0214$, and $P = .1025$). Adverse events occurred at similar frequencies among groups. **CONCLUSIONS: Budesonide MMX (9 mg) was safe and more effective than placebo in inducing remission in patients with active, mild to moderate UC. ClinicalTrials.gov, Number: NCT00679432.**

Keywords: Inflammatory Bowel Disease; Clinical Trial Result; Inflammation; Colon.

Ulcerative colitis (UC) is a chronic, idiopathic, immune-mediated inflammatory disease of the colon.[1] Systemic corticosteroids are effective for the treatment of patients with active UC.[2–4] However, serious adverse events (AEs) associated with systemic corticosteroid therapy preclude their use as first-line therapy, and corticosteroid therapy is typically reserved for patients who have failed to respond to mesalamine and those who have severe disease.[5,6] Corticosteroids can be administered topically as rectal enemas to reduce systemic exposure and toxicity, but these enema formulations are primarily used in patients with distal UC or ulcerative proctitis, and patient acceptance is limited.[7,8] An orally administered topical corticosteroid formulation with reduced systemic exposure would be of value for the management of active, mild to moderate UC.

Budesonide is a potent corticosteroid that can be administered topically with minimal systemic corticosteroid activity due to nearly 90% first-pass metabolism in the liver to metabolites with minimal or no corticosteroid activity.[9–11] Controlled ileal release budesonide formulations (Entocort; AstraZeneca, Wilmington, DE), Budenofalk (Dr Falk Pharma, Freiburg, Germany) release in the distal ileum and right colon and are effective at a 9-mg dose for induction of remission[12–16] and at a 6-mg dose for prolongation of time to relapse in patients with mild to moderate Crohn's disease involving the terminal ileum and right colon.[17–20] These formulations do not deliver budesonide to the left colon and therefore are not optimally designed for the treatment of patients with UC. An investigational formulation of oral budesonide designed for the treatment of patients with UC suggested possible efficacy but was not further developed.[21] Budesonide MMX® (Cosmo Pharmaceuticals SpA, Lainate, Italy) is a novel, once-daily oral formulation of budesonide that uses a multi-matrix system (MMX) technology to extend the release of budesonide throughout the colon.[22,23] A randomized pilot study showed that budesonide MMX delivered budesonide throughout the colon and might be effective for the treatment of active UC.[24]

We designed an 8-week, placebo-controlled, dose-finding induction trial of budesonide MMX in patients with active, mild to moderate UC.

Materials and Methods

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

Abbreviations used in this paper: AE, adverse event; CI, confidence interval; ITT, intention-to-treat; MMX, multi-matrix system; OR, odds ratio; UCDAI, Ulcerative Colitis Disease Activity Index.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2012.08.003

Patients

This phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled trial was conducted at 108 centers in North America and India between August 2008 and May 2010. The protocol was approved by the institutional review board for each center. All patients gave written consent.

Eligible patients were adults up to 75 years of age with active, mild to moderate UC for at least 6 months, with an Ulcerative Colitis Disease Activity Index (UCDAI) score of 4–10 points.[25,26] The UCDAI is a composite score of 4 items (stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease activity). For the baseline scoring of the rectal bleeding and stool frequency items, the worst score from the previous 7 days of diary data before day 1 was used. The diagnosis of UC was histologically confirmed from a biopsy specimen obtained at the baseline colonoscopy and read by a blinded central reader. Because the turnaround time for the histologic central reading was several weeks, the presence of active UC by histology was not an eligibility criterion, but rather was used to define the modified intention-to-treat (ITT) population (see the following text). Concurrent therapy for UC was not permitted during the study. Patients receiving oral mesalamine or other oral 5-aminosalicylic acid medications at the screening visit were required to wash out of their medication at least 2 days before randomization.

Patients were excluded from study entry if they had any of the following: use of oral or rectal corticosteroids within 4 weeks of screening, use of immunosuppressive agents within 8 weeks of screening, use of anti–tumor necrosis factor α agents (infliximab, adalimumab) within 3 months of screening, or participation in experimental therapeutic studies in the past 3 months. Patients were also excluded for the following: diagnosis of severe UC (UCDAI $>$10 points); evidence or history of toxic megacolon; disease limited to the rectum (proctitis extending from the anal verge up to 15 cm); presence of infectious colitis; presence of severe anemia, leukopenia, or granulocytopenia; verified, presumed, or expected pregnancy or ongoing lactation; presence of cirrhosis or evident hepatic or renal disease or insufficiency; presence of severe diseases in other organs and systems; local or systemic complications or other pathological states requiring therapy with corticosteroids and/or immunosuppressive agents; type 1 diabetes; glaucoma; or known infection with hepatitis B or C or with human immunodeficiency virus.

Study Design

This was a multicenter, randomized, double-blind, double-dummy, parallel group, 8-week study comparing budesonide MMX® 9 mg or 6 mg tablets with placebo in patients with active mild to moderate UC. The choice of the 9-mg dose strength for budesonide MMX was based on a pilot phase 2 budesonide MMX study that showed numerically favorable efficacy results in the 9-mg dose strength versus placebo.[24] In addition, the 9-mg dose strength has been established as the optimal dose for controlled ileal release budesonide (Entocort EC) in Crohn's disease (based on both efficacy and safety data), and dosages greater than 9 mg/day did not result in incremental efficacy but did increase the potential risk for corticosteroid-related side effects.[12] The 6-mg dose strength was included as an additional treatment arm, at the request of regulatory authorities, to establish the lowest effective dose for budesonide MMX in inducing remission in active mild to moderate UC. A nonpowered reference arm using Asacol 2.4 g (Warner Chilcott plc, Dublin, Ireland) was also included as active control and internal reference. Patients were randomly assigned to receive one of 4 treatments: placebo, oral budesonide MMX 9 mg once daily, oral budesonide MMX 6 mg once daily, or oral Asacol 2.4 g/day (administered as two 400-mg tablets 3 times daily [US formulation, Procter & Gamble Pharmaceuticals, Cincinnati, OH]) for 8 weeks. Randomization for this study was developed by an external contractor and administered centrally (not within site) via an interactive voice response system. Patients were randomized to one of 4 treatments at a 1:1:1:1 ratio using a block size of 4. As each new patient was randomized via the interactive voice response system, he or she was given the next available randomization number that was associated with a study drug. Patients were followed up through week 10. A follow-up safety visit was to be conducted 2 weeks after the final visit (week 8 or early withdrawal). The interactive voice response system was used to centrally randomize patients to study drug. A double-dummy procedure was used to maintain blinding, with patients in each treatment group receiving their blinded study drug 3 times daily.

Efficacy Evaluations

Patients were evaluated at screening; at weeks 0 (baseline), 2, 4, and 8; and at early termination. The UCDAI score was determined at screening and week 8 and included the use of colonoscopy at both visits to evaluate disease severity and treatment efficacy.[25,26] Remission was defined as combined clinical and endoscopic remission with a UCDAI score $\leq$1 point, with subscores of 0 for both rectal bleeding and stool frequency (based on the 3 days closest to the week 8 visit with nonmissing diary data within a 5-day window closest to the visit [the 5 days did not include any days on which a colonoscopy or the preparation for colonoscopy occurred]), no mucosal friability on colonoscopy, and a $\geq$1-point reduction from baseline in the endoscopic index score.[27] This definition is very similar to the definition of remission used to show the efficacy of MMX mesalamine.[28,29] Clinical improvement was defined as a $\geq$3-point reduction in the UCDAI score. Endoscopic improvement was defined as a $\geq$1-point reduction in the UCDAI mucosal appearance subscore. This definition or a very similar definition has been used in multiple previous clinical trials.[25,26,28–31] Symptom resolution was defined as a score of 0 for both rectal bleeding and stool frequency subscores from the UCDAI.[25,26] Histologic healing was defined as a histologic score of $\leq$1 (corresponding to a histologic activity grade of 0) according to the Saverymuttu scale.[32]

Safety Evaluations

At each clinic visit from screening to week 10 or early termination, patients underwent physical examination, measurement of vital signs, review of previous (at baseline) and concomitant medications, and assessment for AEs. General laboratory tests, morning plasma cortisol levels, and urinalyses were performed at screening, weeks 2 and 4, and final visit (defined as week 8 or early withdrawal). Potential glucocorticoid effects were assessed at screening, week 4, and final visit.

Statistical Methods

The primary efficacy end point was combined clinical and endoscopic remission at week 8. Secondary and other efficacy end points included clinical improvement, endoscopic improvement, symptom resolution, and histologic healing. Demographics and baseline characteristics were summarized using descriptive statistics. Efficacy analyses were performed in the modified ITT population, which included all randomized pa-

tients who received at least one dose of a study drug and excluded patients with major good clinical practice or entry criteria violations (enteric infection during screening) and those with normal histology at baseline (defined as a histology score of 0 or 1) as determined by central histopathology review. A sensitivity analysis was also performed for the primary efficacy analysis in which these excluded patients were included in the analysis and considered to be treatment failures. The percentages of patients achieving combined clinical and endoscopic remission in both the 9-mg and 6-mg budesonide MMX® groups were compared with the percentage of patients receiving placebo achieving combined clinical and endoscopic remission, using the χ^2 test at the $\alpha = .025$ level of significance to adjust for multiple comparisons. A hierarchical testing procedure was used for the analysis of both secondary end points at the $\alpha = 0.025$ level of significance. If at least one primary end point comparison was statistically significant, then both dosage strengths were compared with placebo with respect to the first secondary end point (clinical improvement). If at least one secondary end point comparison for clinical improvement was statistically significant, then both dosage strengths were compared with placebo with respect to the second secondary end point (endoscopic improvement). If at least one primary end point comparison was statistically significant, remission rates between budesonide MMX and placebo were compared, adjusting for region (Canada, United States [and Mexico], and India), age (median age at randomization or younger, older than median age at randomization), and sex using the Cochran–Mantel–Haenszel test.

An analysis of all other end points was conducted using the modified ITT population at the $\alpha = .05$ level of significance for the statistically significant dosage strength(s) for the primary end point comparison without adjustment for multiple comparisons. Therefore, the reported *P* values are nominal *P* values, and these analyses should be considered exploratory. Treatment-emergent adverse events were summarized using descriptive statistics for the safety population, which included all patients who received at least one dose of study drug during the study. Patients with missing or incomplete data at week 8 were considered not to be in remission or to have clinical improvement, endoscopic improvement, symptom resolution, or histologic healing.

Sample Size

Assuming a difference of 20 percentage points between at least one budesonide MMX treatment group (estimated remission rate of 47%) and placebo (estimated remission rate of 27%) at week 8, 110 patients per group provided 80% power to detect a statistically significant difference between at least one budesonide MMX treatment group and placebo at the 2-sided $\alpha = .025$ level of significance. Assuming a dropout rate of approximately 10%, 123 patients per group or 492 patients total were to be randomized in this study. The study was not powered to detect a statistically significant difference between the budesonide MMX and Asacol groups.

Results

Patients

Supplementary Figure 1 shows the disposition of patients. A total of 489 patients were included in the modified ITT population. Twenty randomized patients were excluded from the modified ITT analysis because of normal histology at baseline (17 patients) or major entry criteria violations (3 patients with confirmed infectious colitis at study entry). The baseline characteristics were similar across the treatment groups, except that the percentage of male patients in the budesonide MMX 9 mg group was somewhat higher (62.6%) than that of the other groups (48.8%–56.2%) (Table 1).

Efficacy

Primary end point. The percentage of patients achieving combined clinical and endoscopic remission in the budesonide MMX 9 mg group was significantly greater than the percentage of patients in the placebo group (17.9% vs. 7.4%, $P = .0143$ [95% confidence interval {CI}, 2.2–18.7]; odds ratio [OR], 2.71 [95% CI, 1.19–6.16]) (Figure 1*A*). The combined clinical and endoscopic remission rates for budesonide MMX 6 mg (13.2% vs 7.4%, $P = .1393$ [95% CI, −1.8 to 13.4]; OR, 1.90 [95% CI, 0.80–4.48]) and Asacol (12.1% vs 7.4%, $P = .2200$ [95% CI, −2.7 to 12.1]; OR, 1.71 [95% CI, 0.72–4.08]) were numerically greater than placebo, but the differences did not reach statistical significance (Table 2). An analysis of clinical and endoscopic remission using the Cochran–Mantel–Haenszel test indicated that the difference between budesonide MMX 9 mg and placebo remained statistically significant after adjusting for age, sex, and geographic region. In North American centers, the combined clinical and endoscopic remission rates in the placebo, budesonide MMX 9 mg, budesonide MMX 6 mg, and Asacol groups were 4.9%, 14.5%, 11.3%, and 9.8%, respectively. In the Indian centers, the clinical and endoscopic remission rates in the placebo, budesonide MMX 9 mg, budesonide MMX 6 mg, and Asacol groups were 12.8%, 25.0%, 17.1%, and 16.7%, respectively. Subgroup analyses were performed for the mutually exclusive categories of proctosigmoiditis, left-sided disease (up to the splenic flexure), and extensive disease (beyond the splenic flexure). In patients with proctosigmoiditis, the clinical and endoscopic remission rate for budesonide MMX 9 mg was numerically greater than placebo (23.5% vs. 12.2%, $P = .1967$). For left-sided disease, the clinical and endoscopic remission rate for budesonide MMX 9 mg was significantly higher than for placebo (31.3% vs 5.9%, $P = .0076$). For extensive disease, no significant differences in clinical and endoscopic remission rates were observed between budesonide MMX 9 mg and placebo (7.1% vs 5.0%, $P = 1.000$). A sensitivity analysis in which all patients excluded in the modified ITT population were included and considered to be treatment failures showed results that were similar to analysis in the modified ITT population (Supplementary Table 1).

Secondary end points. The percentages of patients achieving clinical improvement and endoscopic improvement were both numerically greater in the budesonide MMX 9 mg group than in the placebo group (Table 2). Clinical improvement was achieved by 33.3% ($P = .1420$), 30.6% ($P = .3146$), and 33.9% ($P = .1189$) of patients in the budesonide MMX 9 mg, budesonide MMX

Table 1. Baseline Demographics and Clinical Characteristics

	Placebo (n = 121)	Budesonide MMX 9 mg (n = 123)	Budesonide MMX 6 mg (n = 121)	Asacol 2.4 g (n = 124)	Total (N = 489)
Age (*y*)					
Median	39	42	43	45	42
Minimum, maximum	18, 77	19, 68	18, 75	18, 72	18, 77
Sex, n (%)					
Male	68 (56.2)	77 (62.6)	59 (48.8)	69 (55.6)	273 (55.8)
Female	53 (43.8)	46 (37.4)	62 (51.2)	55 (44.4)	216 (44.2)
Race, n (%)					
White	64 (52.9)	60 (48.8)	60 (49.6)	61 (49.2)	245 (50.1)
Black	7 (5.8)	9 (7.3)	11 (9.1)	8 (6.5)	35 (7.2)
Hispanic or Latino	9 (7.4)	8 (6.5)	7 (5.8)	12 (9.7)	36 (7.4)
Asian	39 (32.2)	44 (35.8)	42 (34.7)	43 (34.7)	168 (34.4)
Other	2 (1.7)	2 (1.6)	1 (0.8)	0	5 (1.0)
Disease extent, n (%)					
Proctosigmoiditis	41 (33.9)	34 (27.6)	28 (23.1)	37 (29.8)	140 (28.6)
Left-sided colitis	34 (28.1)	32 (26.0)	41 (33.9)	35 (28.2)	142 (29.0)
Extensive/pancolitis	40 (33.1)	56 (45.5)	50 (41.3)	52 (41.9)	198 (40.5)
Missing	6	1	2	0	9
Number of flares in past 2 years					
Median	2.0	2.0	3.0	2.0	2.0
Minimum, maximum	0, 24	0, 90	0, 30	0, 80	0, 90
Severity of last flare, n (%)					
Mild	30 (24.8)	31 (25.2)	29 (24.0)	25 (20.2)	115 (23.5)
Moderate	79 (65.3)	82 (66.7)	80 (66.1)	81 (65.3)	322 (65.8)
Missing	12	10	12	18	52
Baseline UCDAI score[a]					
Median	7.0	7.0	6.0	7.0	7.0
Minimum, maximum	1, 11	2, 10	2, 11	2, 11	1, 11
Missing	13	9	6	10	38
Baseline endoscopic index score[b]					
Median	7.0	7.0	7.0	8.0	7.0
Minimum, maximum	0, 12	3, 12	1, 12	1, 12	0, 12
Prior mesalamine use	74 (61.2)	58 (47.2)	76 (62.8)	72 (58.1)	280 (57.3)
Prior any 5-ASA use[c]	82 (67.8)	69 (56.1)	89 (73.6)	79 (63.7)	319 (65.2)

[a]For study entry, patients were required to have a UCDAI score between 4 and 10, inclusive. However, a number of patients were enrolled in the study with scores outside of the range (<4 [n = 32] or >10 [n = 3]). Additionally, there were 38 patients for whom the UCDAI score at baseline could not be calculated. In the spirit of the ITT principal, all of these subjects were enrolled in the study and were included in the modified ITT population analysis as long as they did not have normal histology or infectious colitis (ie, if the patient was found to have active UC, which was the disease under study, then they were included in the primary analysis).

[b]Five patients had a baseline endoscopic index score of 0 or 1 (2 in the placebo group, 0 in the 9 mg budesonide MMX group, 1 in the 6 mg budesonide MMX group, and 2 in the Asacol group).

[c]Includes mesalamine, balsalazide, balsalazide sodium, and sulfasalazine.

6 mg, and Asacol groups, respectively, versus 24.8% of patients in the placebo group. Subgroup analyses were performed for clinical improvement in patients with mild and moderate disease. In patients with mild disease (UCDAI score 4–5 points), the clinical improvement rates in the placebo, budesonide MMX® 9 mg, budesonide MMX 6 mg, and Asacol groups were 25.0%, 44.4%, 32.3%, and 32.3%, respectively. In patients with moderate disease (UCDAI score 6–10 points), the clinical improvement rates in the placebo, budesonide MMX 9 mg, budesonide MMX 6 mg, and Asacol groups were 30.1%, 39.7%, 34.2%, and 40.3%, respectively. Endoscopic improvement was achieved by 41.5%, 35.5%, and 33.1% of patients in the budesonide MMX 9 mg, budesonide MMX 6 mg, and Asacol groups, respectively, versus 33.1% of patients in the placebo group ($P = .1746$, $P = .6846$, and $P = .9991$, respectively) and should be considered nominal because statistical testing was not prespecified due to the hierarchical testing procedures. Subgroup analyses for the exploratory end point of mucosal healing (defined as UCDAI mucosal appearance sub-score of 0) were performed for the categories of proctosigmoiditis, left-sided disease, and extensive disease. In patients with proctosigmoiditis, the mucosal healing rate for budesonide MMX 9 mg was numerically greater than that for placebo (32.4% vs 19.5%; $P = .2031$). For left-sided disease, the mucosal healing rate for budesonide MMX 9 mg was numerically greater than that for placebo (40.6% vs 26.5%; $P = .2228$). For extensive disease, the mucosal healing rate for budesonide MMX 9 mg was numerically greater than that for placebo (16.1% vs 10.0%; $P = .3914$). For other prespecified end points, the percentages of patients achieving symptom resolution were significantly higher for the budesonide MMX 9 mg (28.5%) and 6 mg (28.9%) groups when compared with the placebo group (16.5%) ($P = .0258$ and $P = .0214$ for budesonide MMX 9 mg and 6 mg versus placebo, respec-

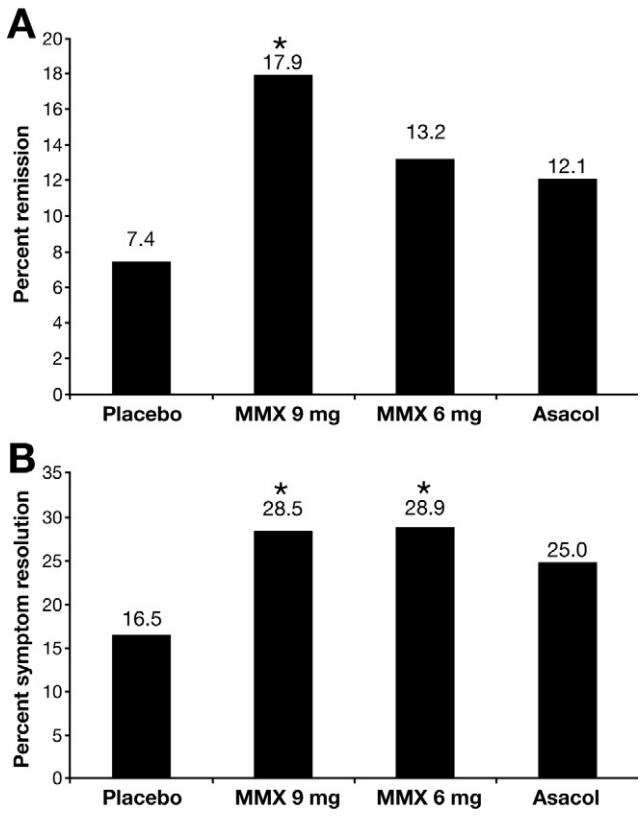

Figure 1. (*A*) Combined clinical and endoscopic remission at week 8. Modified ITT population, N = 489. *Statically significant ($P < .025$). (*B*) Symptom resolution at week 8. Modified ITT population, N = 489. *Statically significant ($P < .05$). This study was not powered to show a statistical difference between budesonide MMX treatment arms and Asacol.

tively). The percentage of patients achieving symptom resolution was numerically higher for the Asacol (25.0%) group when compared with placebo, although it was not statistically significant ($P = .1025$) (Table 2). The percentages of patients with histologic healing were not significantly different between any active treatment group and placebo (Table 2).

Safety

Treatment with budesonide MMX® was generally well tolerated with an overall safety profile comparable to that of placebo. A similar proportion of patients in each study group experienced the most common treatment-emergent AEs (Table 3). Most patients experienced AEs that were mild or moderate in severity and were considered not related to the study drug according to the investigator evaluation. The percentage of patients with severe AEs was highest in the placebo group (12.4%) compared with the budesonide MMX 9 mg group (6.3%), budesonide MMX 6 mg group (9.5%), and Asacol 2.4 g group (5.5%). The rates of treatment-related serious AEs were low and occurred in similar percentages of patients across all treatment groups. There was no evidence of a dose trend for budesonide MMX with respect to the overall percentages of patients with AEs or serious AEs. In addition, the rates of AEs and serious AEs leading to discontinuation were infrequent and similar across all study groups. There were no deaths during the study (Table 4).

With regard to the AEs of special interest, potential glucocorticoid effects occurred in similar percentages of patients across all treatment groups. Potential glucocorticoid effects were defined as the occurrence of one or more of the following symptoms: moon face, striae rubrae, flushing, fluid retention, mood changes, sleep changes, insomnia, acne, and hirsutism. There was no evidence of any increase in the numbers of patients experiencing glucocorticoid effects in the budesonide MMX groups when compared with the placebo group. Potential glucocorticoid effects were observed in 10.1% of patients in the placebo group, 11.8% of patients in the budesonide MMX 9 mg group, 5.6% of patients in the budesonide MMX 6 mg group, and 7.9% of patients in the Asacol group (Figure 2*A*).

Although a decrease in mean morning plasma cortisol levels was observed at week 2 and week 4 for the budesonide MMX groups, the levels gradually increased toward the baseline values by the final visit. The mean percentage change from baseline to the final visit was −17.9% in the budesonide MMX 9 mg group and −9.4% in the budesonide MMX 6 mg group. By comparison, mean percentage changes at the final visit were +0.9% in the Asacol group and +5.3% in the placebo group. Throughout the entire study period, the mean values in all treatment groups (including the budesonide MMX groups) remained within normal limits (5–25 μg/dL) (Figure 2*B*). Furthermore, the observed changes in plasma cortisol were not associated with any increases in glucocorticoid-related effects across the budesonide MMX groups. As noted previously, glucocorticoid effects occurred in a similar percentage of patients in the placebo, budesonide MMX 9 mg, and budesonide MMX 6 mg groups.

Discussion

Treatment with budesonide MMX 9 mg showed a significant benefit over placebo in the rate of combined clinical and endoscopic remission at week 8 among patients with active, mild to moderate UC. Exploratory analyses suggested a possible benefit for symptom resolution, and there were trends toward greater rates of clinical improvement and endoscopic improvement. Incidence rates of treatment-emergent adverse events were similar across treatment groups, and no clinically important safety trends were identified.

Our results confirm the findings of another 8-week induction trial with budesonide MMX in patients with active, mild to moderate UC showing that budesonide MMX 9 mg was effective for inducing combined clinical and endoscopic remission.[33] Similar to the current study, in that study there also were trends toward greater rates of clinical improvement and endoscopic improvement with budesonide MMX, but the differences were not significant. The discrepancy between the primary end point,

Table 2. Primary and Secondary End Points

	Placebo (n = 121)	Budesonide MMX 9 mg (n = 123)	Budesonide MMX 6 mg (n = 121)	Asacol 2.4 g (n = 124)
Combined clinical and endoscopic remission, n (%)	9 (7.4)	22 (17.9)	16 (13.2)	15 (12.1)
95% CI	2.8 to 12.1	11.1 to 24.7	7.2 to 19.3	6.4 to 17.8
Difference between active and placebo (%)	—	10.4	5.8	4.7
95% CI		2.2 to 18.7	−1.8 to 13.4	−2.7 to 12.1
P value	—	.0143[a]	.1393	.2200
OR	—	2.71	1.90	1.71
95% CI	—	1.19 to 6.16	0.80 to 4.48	0.72 to 4.08
Clinical improvement[b]	30 (24.8)	41 (33.3)	37 (30.6)	42 (33.9)
Difference between active and placebo (%)	—	8.5	5.8	9.1
P value	—	.1420	.3146	.1189
Endoscopic improvement[c]	40 (33.1)	51 (41.5)	43 (35.5)	41 (33.1)
Difference between active and placebo (%)	—	8.4	2.5	0
Histologic healing[d]	8 (6.6)	5 (4.1)	9 (7.4)	14 (11.3)
Difference between active and placebo (%)	—	−2.5	0.8	4.7
P value	—	.3759	.8014	.2003
Symptom resolution[e]	20 (16.5)	35 (28.5)	35 (28.9)	31 (25.0)
Difference between active and placebo (%)	—	11.9	12.4	8.5
P value	—	.0258[f]	.0214[f]	.1025

NOTE. This study was not powered to show a statistical difference between budesonide MMX treatment arms and Asacol.
[a]Statistically significant ($P < .025$).
[b]Clinical improvement defined as a ≥3-point reduction in UCDAI from baseline to week 8.
[c]Endoscopic improvement defined as a ≥1-point reduction in the mucosal appearance score of the UCDAI from baseline to week 8; statistical significance for endoscopic improvement was not tested due to prespecified hierarchical testing procedures.
Other prespecified end points: [d]histologic healing defined as total histologic score of 0 or 1 for all biopsy specimens; [e]symptom resolution defined as UCDAI stool frequency and rectal bleeding subscores of 0.
[f]Statistically significant ($P < .05$).

which was positive in both trials, and the secondary end points may be due to the relatively high rates of clinical improvement and endoscopic improvement in patients receiving placebo. The reasons for these high placebo rates are not entirely clear but may relate to not using central reading for endoscopy measures, which can directly affect the mucosal appearance subscore and indirectly affect the physician's rating of disease activity subscore, both of which then impact the overall UCDAI score. Notably, in both studies, exploratory analyses suggested that the rates of symptom resolution, which are based on the patient-reported components of the UCDAI, stool frequency and rectal bleeding, might be greater in patients treated with budesonide MMX® 9 mg as compared with placebo. When these 2 studies were designed and the sample size was calculated, the available preliminary data of remission rates with budesonide MMX were based on a study by D'Haens et al that used the Clinical Activity Index,[27] which does not include an endoscopic component. In the study by D'Haens et al, the clinical remission rate for budesonide MMX 9 mg, as measured by the Clinical Activity Index, was 47%.[24] We based the sample size calculations for the current trial on the assumption of a 20% difference between budesonide MMX and placebo, which yields a placebo remission rate of 27% and an OR of 1.7 between budesonide MMX and placebo. However, in the current 2 trials, the remission end point combined clinical and endoscopic remission and was based on the UCDAI, not the Clinical Activity Index. The actual placebo remission rates in these 2 trials were 7.4% and 4.5%, respectively,

Table 3. Summary of Treatment-Emergent Adverse Events Experienced by ≥5.0% of Patients in Any Treatment Group

MedDRA preferred term	Placebo (n = 129)	Budesonide MMX 9 mg (n = 127)	Budesonide MMX 6 mg (n = 126)	Asacol 2.4 g (n = 127)
Any AE	81 (62.8)	73 (57.5)	74 (58.7)	80 (63.0)
Colitis ulcerative	21 (16.3)	14 (11.0)	15 (11.9)	13 (10.2)
Headache	19 (14.7)	8 (6.3)	17 (13.5)	12 (9.4)
Pyrexia	9 (7.0)	3 (2.4)	5 (4.0)	3 (2.4)
Insomnia	9 (7.0)	5 (3.9)	6 (4.8)	3 (2.4)
Back pain	7 (5.4)	5 (3.9)	4 (3.2)	2 (1.6)
Nausea	8 (6.2)	5 (3.9)	5 (4.0)	10 (7.9)
Abdominal pain	8 (6.2)	6 (4.7)	2 (1.6)	10 (7.9)
Diarrhea	7 (5.4)	2 (1.6)	5 (4.0)	8 (6.3)
Flatulence	2 (1.6)	1 (0.8)	1 (0.8)	7 (5.5)

NOTE. All values are expressed as n (%).
MedDRA, Medical Dictionary for Regulatory Activities (version 11.0).

Table 4. Treatment-Emergent and Treatment-Related AEs

Category	Placebo (n = 129)	Budesonide MMX 9 mg (n = 127)	Budesonide MMX 6 mg (n = 126)	Asacol 2.4 g (n = 127)
Any AE	81 (62.8)	73 (57.5)	74 (58.7)	80 (63.0)
Treatment-related AEs	34 (26.4)	36 (28.3)	35 (27.8)	31 (24.4)
Severity of AEs				
Mild	31 (24.0)	30 (23.6)	33 (26.2)	39 (30.7)
Moderate	34 (26.4)	35 (27.6)	29 (23.0)	34 (26.8)
Severe	16 (12.4)	8 (6.3)	12 (9.5)	7 (5.5)
AEs leading to discontinuation	24 (18.6)	15 (11.8)	18 (14.3)	14 (11.0)
Any serious AEs	3 (2.3)	3 (2.4)	2 (1.6)	4 (3.1)
Treatment-related serious AEs	0	1 (0.8)	1 (0.8)	0
Serious AEs leading to discontinuation	2 (1.6)	2 (1.6)	2 (1.6)	1 (0.8)

NOTE. All values are expressed as n (%).

and the budesonide MMX® remission rates were 17.9% and 17.4%, respectively, yielding ORs of 2.7 and 4.5, respectively.[33] Thus, although the 10% effect observed in the current trial is smaller than the 20% effective size that was used to plan the sample size calculation, the OR for achieving remission is 2.7, which is actually numerically greater than the OR of 1.7 from which the sample size calculations were taken. When taken together, the results of the current trial and the second 8-week induction trial with budesonide MMX clearly show that budesonide MMX 9 mg is an effective regimen for inducing remission in patients with active, mild to moderate UC.

For the comparison of Asacol 2.4 g/day with placebo, there were no significant differences as compared with placebo for the end points of combined clinical and endoscopic remission, clinical improvement, and endoscopic improvement at week 8. The absolute combined clinical and endoscopic remission rate for Asacol was relatively low (12.1%). Previous studies clearly showed that Asacol is effective as an induction agent for UC, using a measure of clinical improvement as the primary end point.[34,35] The outcome measures in these trials were different from those used in the budesonide MMX trials, and thus any comparisons, even indirect comparisons, are very difficult. The fact that a positive control known to be effective for the treatment of UC failed to show efficacy relative to placebo in this trial provides additional support for the idea that the 10% difference in combined clinical and endoscopic remission rates between budesonide MMX 9 mg and placebo observed in this trial was clinically meaningful. The trial was not powered to directly compare budesonide MMX and Asacol.

A

Parameter	Placebo N=129 n (%)	Budesonide MMX 9 mg N=127 n (%)	Budesonide MMX 6 mg N=126 n (%)	Asacol 2.4 gm N=127 n (%)
Any Potential Glucocorticoid Effect	13 (10.1)	15 (11.8)	7 (5.6)	10 (7.9)
Moon face	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Striae rubrae	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Flushing	1 (0.8)	0 (0.0)	0 (0.0)	2 (1.6)
Fluid retention	1 (0.8)	2 (1.6)	2 (1.6)	1 (0.8)
Mood changes	3 (2.3)	5 (4.0)	6 (4.8)	2 (1.6)
Sleep changes	7 (5.4)	4 (3.2)	3 (2.4)	1 (0.8)
Insomnia	6 (4.7)	5 (4.0)	3 (2.4)	2 (1.6)
Acne	3 (2.3)	3 (2.4)	0 (0.0)	4 (3.1)
Hirsutism	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

B

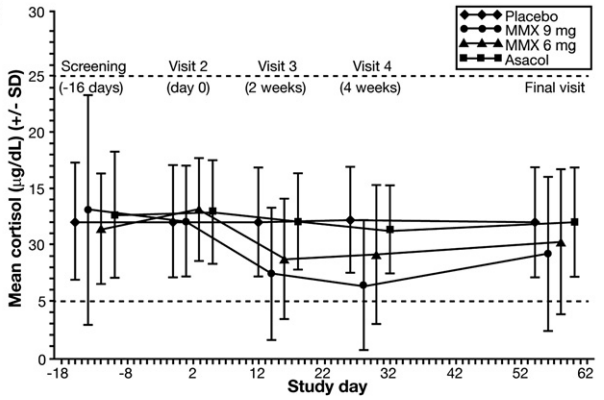

Figure 2. (*A*) Summary of potential glucocorticoid effects. (*B*) Morning cortisol levels (mean ± SD). *Symbols* indicate mean plasma cortisol level for each visit for each treatment. *Error bars* indicate SDs. Treatments are offset for readability. *Dashed lines* indicate normal limits (5–25 µg/dL).

Our study has a number of important limitations. First, we studied budesonide MMX as induction therapy in patients with active, mild to moderate UC who were not receiving any concomitant UC medications. However, we do know that 56.1% and 73.6% of patients treated with budesonide MMX 9 mg and 6 mg, respectively (Table 1), were previously treated with a 5-ASA and 54.5% and 61.2%, respectively, were treated with a 5-ASA within 14 days of randomization (during the screening period). Although we do not know their remission status per se, it is reasonable to assume that some patients were responders, indicating that budesonide MMX is beneficial in a certain percentage of patients who failed to respond to prior treatment. More proactive data directly related to mesalamine failures or combination use of mesalamine and budesonide MMX are needed. Second, we showed efficacy as defined by combined clinical and endoscopic remission (which occurred in 17.9% of patients), but we did not show efficacy for clinical or endoscopic improvement (which occurred in a larger number of patients). Thus, additional information on the clinical benefits of budesonide MMX therapy in patients who do not achieve combined clinical and endoscopic remission is needed. Third, information on the efficacy of budesonide MMX as maintenance therapy in patients with UC in remission is unknown. Additional clinical trials should be performed to

address these limitations to better define how budesonide MMX® should be incorporated in clinical practice.

The incidence rates of AEs, serious AEs, and corticosteroid-related AEs were similar in the 4 treatment groups. The overall safety profile of budesonide MMX in this study was generally similar to that seen in other trials of another budesonide formulation, controlled ileal release budesonide, in patients with Crohn's disease.[12–16] The mean morning cortisol levels were lowest among patients treated with budesonide MMX 9 mg, but the magnitude of decrease from baseline was relatively small and appears to be considerably lower than the magnitude of decrease observed in patients with Crohn's disease treated with prednisolone.[13,14]

In conclusion, budesonide MMX 9 mg tablets represent the first orally administered topical corticosteroid formulation specifically targeting the entire colon for the management of patients with active, mild to moderate UC. Budesonide MMX 9 mg was safe, well tolerated, and more effective than placebo for inducing combined clinical and endoscopic remission in patients with active, mild to moderate UC.

Supplementary Materials

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.2012.08.003.

References

1. Ordas I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet 2012 Aug 17 [Epub ahead of print].
2. Truelove SC, Witts LJ. Cortisone in ulcerative colitis. Final report on a therapeutic trial. BMJ 1955;2:1041–1048.
3. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105:501–523; quiz 524.
4. Travis SPL, Stange EF, Lémann M, et al. European evidence-based consensus on the management of ulcerative colitis: current management. J Crohns Colitis 2008;2:24–62.
5. Lichtenstein GR, Abreu MT, Cohen R, et al. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006;130:940–987.
6. Lewis JD, Gelfand JM, Troxel AB, et al. Immunosuppressant medications and mortality in inflammatory bowel disease. Am J Gastroenterol 2008;103:1428–1435.
7. Truelove SC. Treatment of ulcerative colitis with local hydrocortisone hemisuccinate sodium. A report on a controlled therapeutic trial. BMJ 1958;2:1072–1077.
8. Hanauer SB, Robinson M, Pruitt R, et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. Gastroenterology 1998;115:525–532.
9. Brattsand R. Overview of newer glucocorticosteroid preparations for inflammatory bowel disease. Can J Gastroenterol 1990;4:407–414.
10. Edsbacker S, Larsson P, Wollmer P. Gut delivery of budesonide, a locally active corticosteroid, from plain and controlled-release capsules. Eur J Gastroenterol Hepatol 2002;14:1357–1362.
11. Edsbacker S, Bengtsson B, Larsson P, et al. A pharmacoscintigraphic evaluation of oral budesonide given as controlled-release (Entocort) capsules. Aliment Pharmacol Ther 2003;17:525–536.
12. Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. N Engl J Med 1994;331:836–841.
13. Rutgeerts P, Lofberg R, Malchow H, et al. A comparison of budesonide with prednisolone for active Crohn's disease. N Engl J Med 1994;331:842–845.
14. Campieri M, Ferguson A, Doe W, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. Gut 1997;41:209–214.
15. Tremaine WJ, Hanauer SB, Katz S, et al. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. Am J Gastroenterol 2002;97:1748–1754.
16. Bar-Meir S, Chowers Y, Lavy A, et al. Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. Gastroenterology 1998;115:835–840.
17. Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide as maintenance treatment for Crohn's disease: a placebo- controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. Gastroenterology 1996;110:45–51.
18. Lofberg R, Rutgeerts P, Malchow H, et al. Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo controlled one year study. Gut 1996;39:82–86.
19. Ferguson A, Campieri M, Doe W, et al. Oral budesonide as maintenance therapy in Crohn's disease—results of a 12-month study. Global Budesonide Study Group. Aliment Pharmacol Ther 1998;12:175–183.
20. Hanauer S, Sandborn WJ, Persson A, et al. Budesonide as maintenance treatment in Crohn's disease: a placebo-controlled trial. Aliment Pharmacol Ther 2005;21:363–371.
21. Lofberg R, Danielsson A, Suhr O, et al. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. Gastroenterology 1996;110:1713–1718.
22. Brunner M, Vogelsang H, Greinwald R, et al. Colonic spread and serum pharmacokinetics of budesonide foam in patients with mildly to moderately active ulcerative colitis. Aliment Pharmacol Ther 2005;22:463–470.
23. Brunner M, Ziegler S, Di Stefano AF, et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. Br J Clin Pharmacol 2006;61:31–38.
24. D'Haens GR, Kovacs A, Vergauwe P, et al. Clinical trial: preliminary efficacy and safety study of a new Budesonide-MMX(R) 9 mg extended-release tablets in patients with active left-sided ulcerative colitis. J Crohns Colitis 2010;4:153–160.
25. Sutherland LR, Martin F, Greer S, et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology 1987;92:1894–1898.
26. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy endponts for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology 2007;132:763–786.
27. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ 1989;298:82–86.
28. Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily high concentration MMX mesalamine in active ulcerative colitis. Gastroenterology 2007;132:66–75.
29. Lichtenstein GR, Kamm MA, Boddu P, et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. Clin Gastroenterol Hepatol 2007;5:95–102.
30. Hanauer SB, Sandborn WJ, Dallaire C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: the ASCEND I trial. Can J Gastroenterol 2007;21:827–834.

31. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.
32. Saverymuttu SH, Camilleri M, Rees H, et al. Indium 111-granulocyte scanning in the assessment of disease extent and disease activity in inflammatory bowel disease. A comparison with colonoscopy, histology, and fecal indium 111-granulocyte excretion. Gastroenterology 1986;90:1121–1128.
33. Sandborn WJ, Travis S, Danese S, et al. Budesonide-MMx® 9 mg for induction of remission of mild-to-moderate ulcerative colitis (UC): data from a multicenter, randomized, double-blind placebo-controlled study in Europe, Russia, Israel and Australia. Gastroenterology 2011;140(Suppl 1):S-65.
34. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–1629.
35. Sninsky CA, Cort DH, Shanahan F, et al. Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis. A multicenter study. Ann Intern Med 1991;115:350–355.

Received March 30, 2012. Accepted August 1, 2012.

Reprint requests

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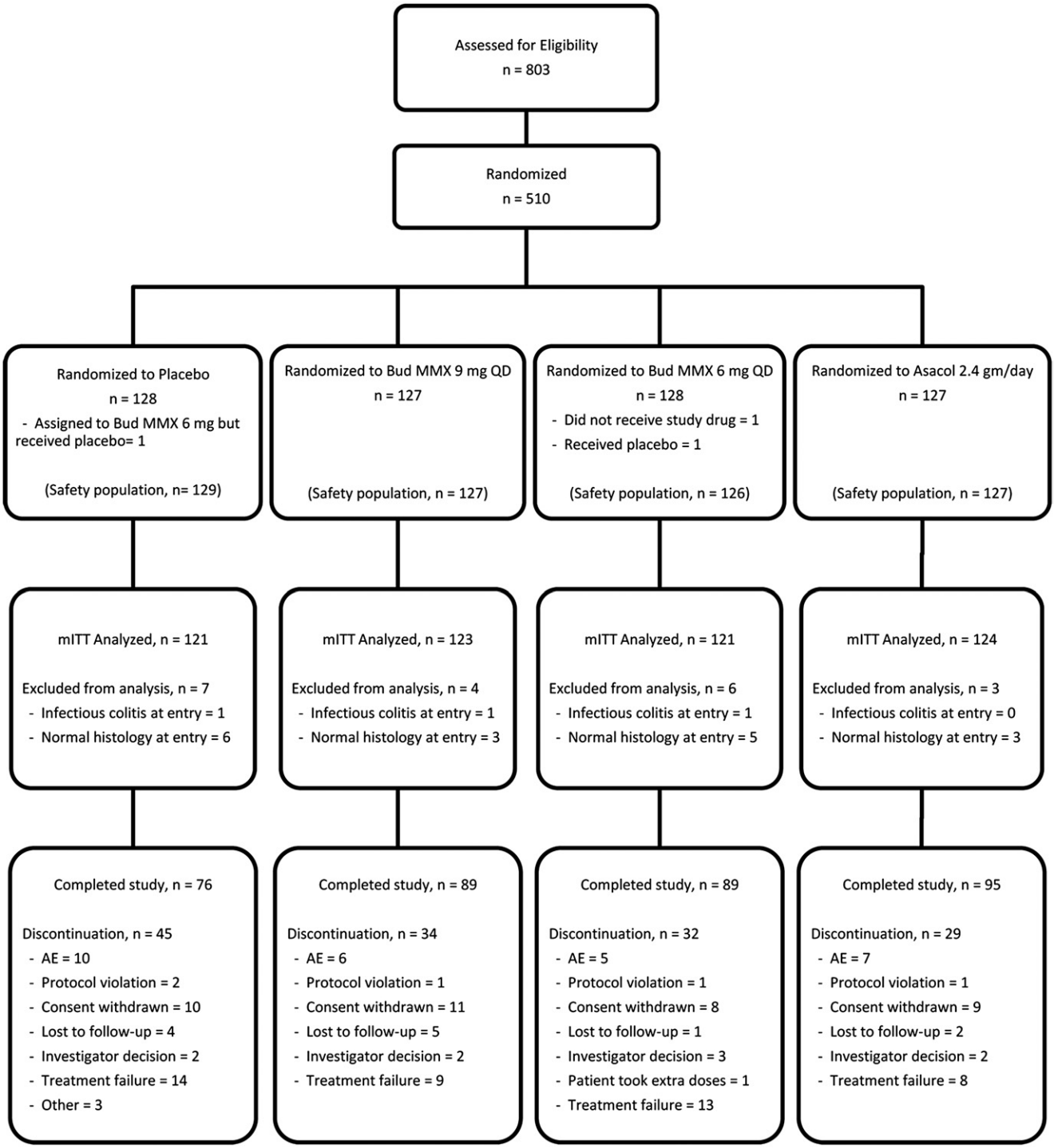
Conflicts of interest

The authors disclose the following: Dr Sandborn has received consulting fees from Abbott Laboratories, ActoGeniX NV, AGI Therapeutics Inc, Alba Therapeutics Corp, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas, Athersys Inc, Atlantic Healthcare Ltd, Aptalis, BioBalance Corp, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corp, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine PharmaSciences Inc, Eagle Pharmaceuticals, enGene Inc, Eli Lilly and Company, EnteroMedics, Exagen Diagnostics Inc, Ferring Pharmaceuticals, Flexion Therapeutics Inc, Funxional Therapeutics Ltd, Genzyme Corp, Gilead Sciences, Given Imaging, GlaxoSmithKline, Human Genome Sciences, Ironwood Pharmaceuticals, KaloBios Pharmaceuticals Inc, Lexicon Pharmaceuticals, Lycera Corp, Meda Pharmaceuticals, Merck Research Laboratories, Merck Serono, Millennium Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics Inc, PDL BioPharma, Pfizer Inc, Procter & Gamble, Prometheus Laboratories, ProtAb Ltd, PurGenesis Technologies Inc, Relypsa Inc, Roche, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus Inc, Schering-Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Sirtris Pharmaceuticals, SLA Pharma UK Ltd, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG, TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics Ltd, Warner Chilcott UK Ltd, and Wyeth; has received research grants from Abbott Laboratories, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen, Millennium Pharmaceuticals, Novartis, Pfizer, Procter & Gamble, Shire Pharmaceuticals, and UCB Pharma; has received payments for lectures/speakers bureau from Abbott Laboratories, Bristol-Myers Squibb, and Janssen; and holds stock/stock options in EnteroMedics. Dr Travis has received consulting fees from Abbott Laboratories, Asahi, Aspreva, Cosmo Technologies, Elan, Ferring Pharmaceuticals, Genzyme Corp, Genentech, Glenmark, GlaxoSmithKline, Lexicon Pharmaceuticals, Merck Research Laboratories, Merck Serono, Millennium Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, PDL BioPharma, Pfizer Inc, Procter & Gamble, Santarus Inc, Schering-Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Tillotts Pharma AG, TxCell SA, UCB Pharma, Vertex, Vifor, Warner Chilcott UK Ltd, and Wyeth; has received research grants from Abbott, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen, Novartis, Pfizer Inc, Procter & Gamble, Shire Pharmaceuticals, and UCB Pharma; has received payments for lectures/speakers bureau from Abbott Laboratories, Ferring Pharmaceuticals, Merck, Shire Pharmaceuticals, Tillotts, Warner Chilcott, and Vertex; and holds no stock/stock options. Dr Moro and Dr Jones are employees of and own stock in Cosmo Pharmaceuticals SpA. Drs Ballard, Bagin, Huang, and Yeung and Ms Gautille are employees of and own stock in Santarus, Inc.

Funding

Supported by Santarus, Inc, and Cosmo Pharmaceuticals SpA.



Supplementary Figure 1. Patient disposition. Safety population, n = 509; modified ITT population, n = 489; completed study, n = 349.

Supplementary Table 1. Sensitivity Analysis of Primary End Point

	Placebo (n = 128)	Budesonide MMX 9 mg (n = 127)	Budesonide MMX 6 mg (n = 127)	Asacol 2.4 g (n = 127)
Combined clinical and endoscopic remission, n (%)	9 (7.0)	22 (17.3)	16 (12.6)	15 (11.8)
95% CI	2.6 to 11.5	10.7 to 23.9	6.8 to 18.4	6.2 to 17.4
Difference between active and placebo (%)	—	10.3	5.6	4.8
95% CI		2.4 to 18.2	−1.7 to 12.8	−2.4 to 11.9
P value	—	.0119[a]	.1350	.1912

NOTE. The sensitivity population includes all patients who received at least one dose of a study drug; patients with enteric infection and normal histology at baseline were included but considered as not meeting the end point. This study was not powered to show a statistical difference between budesonide MMX® treatment arms and Asacol.

[a]Statistically significant ($P < .025$).