

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

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 remission¹²⁻¹⁶ 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.

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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 refer-

ence. 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 ≤ 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 ≥ 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 ≥ 3 -point reduction in the UCDAI score. Endoscopic improvement was defined as a ≥ 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 ≤ 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

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

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 1A). 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

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)

^aFor 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).

^bFive 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).

^cIncludes 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

chical 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

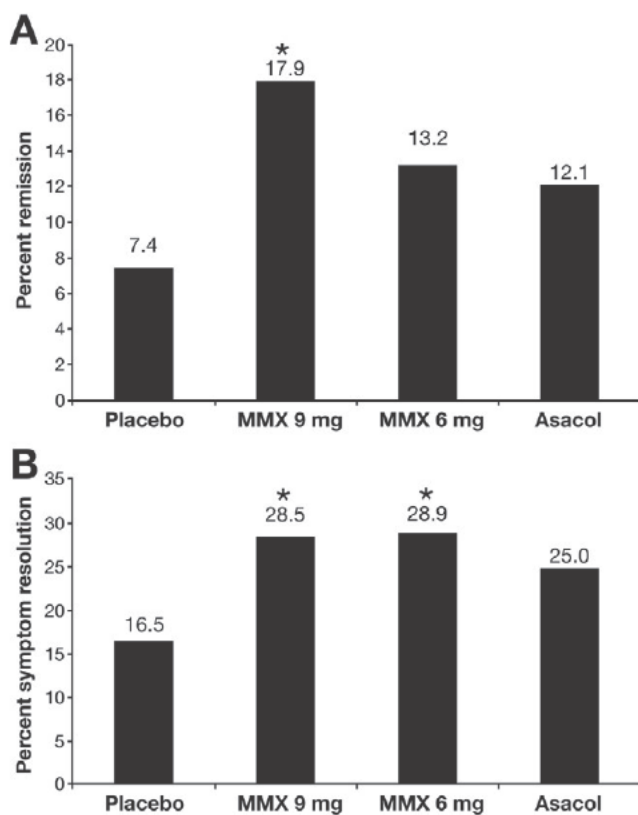


Figure 1. (A) Combined clinical and endoscopic remission at week 8. Modified ITT population, N = 489. *Statically significant ($P < .025$). (B) Symptom resolution at week 8. Modified ITT population, N = 489. *Statically significant ($P < .05$). This study was not powered to show a statistical difference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

tion, 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 2A).

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 ($5\text{--}25 \mu\text{g/dL}$) (Figure 2B). 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 signifi-

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