

Effect of Once- or Twice-Daily MMX Mesalamine (SPD476) for the Induction of Remission of Mild to Moderately Active Ulcerative Colitis

GARY R. LICHTENSTEIN,* MICHAEL A. KAMM,[†] PRABHAKAR BODDU,[§] NATALYA GUBERGRITS,^{||} ANDREW LYNE,[¶] TODD BUTLER,[#] KIRSTIN LEES,[#] RAYMOND E. JOSEPH,[#] and WILLIAM J. SANDBORN**

*Division of Gastroenterology, University of Pennsylvania, Philadelphia, Pennsylvania; [†]Department of Gastroenterology, St Mark's Hospital, London, United Kingdom; [§]Department of Gastroenterology, Osmania General Hospital, Afzalgunj, India; ^{||}Department of Internal Diseases, Donetsk State Medical University, Donetsk, Ukraine; [¶]Shire Pharmaceuticals Inc, Basingstoke, Hampshire, United Kingdom; [#]Shire Pharmaceuticals Inc, Wayne, Pennsylvania; and **IBD Clinic, Mayo Clinic, Rochester, Minnesota

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Background & Aims: SPD476 (MMX mesalamine), a novel, once-daily mesalamine formulation, uses MMX Multi Matrix System (MMX) technology to delay and extend delivery of active drug throughout the colon. We performed a randomized, double-blind, parallel-group, placebo-controlled, multicenter phase III study in patients with mild to moderately active ulcerative colitis. **Methods:** Two hundred eighty patients with mild to moderately active ulcerative colitis received MMX mesalamine 2.4 g/day given twice daily (n = 93), 4.8 g/day given once daily (n = 94), or placebo (n = 93) for 8 weeks. The primary end point was the percentage of patients in clinical and endoscopic remission (modified ulcerative colitis disease activity index score of ≤ 1 , with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction in sigmoidoscopy score) at week 8. Patients with mucosal friability were not considered to have achieved this end point. **Results:** Clinical and endoscopic remission at week 8 was achieved by 34.1% and 29.2% of patients receiving MMX mesalamine 2.4 g/day given twice daily and MMX mesalamine 4.8 g/day given once daily, respectively, versus 12.9% receiving placebo ($P < .01$). MMX mesalamine was generally well-tolerated. **Conclusions:** MMX mesalamine given once or twice daily is well-tolerated and, compared with placebo, demonstrated efficacy for the induction of clinical and endoscopic remission in mild to moderately active ulcerative colitis.

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disorder limited to the colonic mucosa. UC might affect any part of the colon, although left-sided or distal diseases are most common. Patients with UC frequently experience symptoms that include diarrhea containing blood and mucus, fecal urgency, and abdominal pain. These symptoms might often be associated with the presence of anemia, weight loss, and a general feeling of malaise.¹ Consequently, in periods of increased disease activity, patients with UC experience a greatly reduced quality of life.²

Left untreated, UC usually follows a relapsing-remitting course. This course can be altered in patients with mild to moderately active UC with induction and subsequent maintenance therapy with mesalamine therapy.^{3,4} Mesalamine appears to act topically on the colonic mucosa; current mesalamine

delivery systems have been developed to avoid absorption of mesalamine in the small intestine, thereby delivering maximal amounts of mesalamine to colonic tissue. Current delivery systems include delayed-release formulations that use a pH-sensitive outer film such as Eudragit (Rhom Pharma, Darmstadt, Germany) L or S; time-dependent, controlled (sustained)-release formulations; and azo-bonded prodrug formulations (eg, sulfasalazine, olsalazine, and balsalazide). These oral mesalamine formulations are effective but require inconvenient, multiple-daily dosing regimens with 6–12 tablets or capsules daily, which might lead to noncompliance,⁵ increased risk of UC flare, and reduced quality of life.^{2,6}

Compliance rates reported in clinical trials of mesalamine are often high ($>80\%$)⁷⁻⁹; however, these rates might be considered to reflect the supervised environment in which the study was conducted. In contrast, compliance rates in community-based studies of mesalamine treatment regimens are much lower, particularly in patients in symptomatic remission, with as many as 60% of patients failing to adhere to a prescribed dose regimen and taking less than 70% of their prescribed medication.¹⁰⁻¹² Moreover, Kane et al⁵ found that patient noncompliance with mesalamine therapy leads to a 5-fold increase in the risk of UC flare.

Preliminary data suggest that once-daily dosing regimens might offer some advantage over multiple-daily dosing regimens in terms of patient compliance. In a pilot trial to assess compliance rates following a once-daily or conventional mesalamine dosing schedules in patients with quiescent UC, significantly higher compliance rates were demonstrated in the once-daily group compared with more frequent dosing groups (100% vs 70%, respectively; $P = .04$).¹³ However, the study was not designed to evaluate the efficacy of the once-daily mesalamine dose.

MMX mesalamine (SPD476; Shire Pharmaceuticals Inc, Wayne, PA; in partnership with Giuliani SpA, Milan, Italy) is a novel, high-strength formulation of mesalamine (1.2 g per tablet), which uses Multi Matrix System (MMX) technology designed to release mesalamine throughout the colon. This patented delivery system uses hydrophilic and lipophilic matrices

Abbreviations used in this paper: AE, adverse event; CI, confidence interval; GCP, good clinical practices; ITT, intent to treat; MMX, Multi Matrix System; OR, odds ratio; PGA, Physician's Global Assessment; PP, per protocol; SAE, serious adverse event; UC, ulcerative colitis; UC-DAI, ulcerative colitis–disease activity index.

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enclosed within a pH-dependent coating to facilitate prolonged exposure of the colonic mucosa to mesalamine.⁹ The pH-dependent coating covering the multi-matrix core is resistant to gastric juices and delays release of mesalamine until the tablet is exposed to a pH of ≥ 7.0 , normally in the terminal ileum. On exposure to intestinal fluid, the tablet core swells (because of the presence of the hydrophilic matrix) in a manner similar to that of a sponge exposed to water, and a viscous gel mass is formed. The viscous gel mass is expected to slow the diffusion of the active drug from the tablet core. As the tablet core and its surrounding gel mass move through the colon, it is believed that fragments of the gel mass gradually break away from the core, releasing mesalamine in proximity to the colonic mucosa. Literature suggests that the hydrophilic matrix might also adhere to the colonic mucosa.^{14,15} The lipophilic matrix is interspersed within the hydrophilic matrix, creating a partially hydrophobic environment that slows the penetration of aqueous fluids into the tablet core. This is expected to slow dissolution of the drug, further extending its release. It is hypothesized that this extended release might prolong therapeutic activity.

The primary purpose of this study (SPD476-301) was to investigate the efficacy of 2 doses of MMX mesalamine given once or twice daily for the induction of clinical and endoscopic remission in patients with mild to moderately active UC.

Materials and Methods

Participants

Eligible male and female patients aged ≥ 18 years with newly diagnosed or relapsing (relapsed ≤ 6 weeks before baseline) mild to moderately active UC (score of 4–10 on a modified version of the Sutherland UC-disease activity index¹⁶ (UC-DAI) (Table 1), with a sigmoidoscopy score ≥ 1 and a Physician's Global Assessment (PGA) score ≤ 2 with compatible histology, were enrolled in the study.

Patients were excluded from the study if they had: severe UC defined by PGA > 2 ; current relapse lasting > 6 weeks; current relapse while on maintenance therapy with doses of mesalamine > 2.0 g/day or within 2 weeks of dose reduction from > 2.0 g/day to ≤ 2.0 g/day mesalamine; inadequate/failed response to steroids or a mesalamine dose of > 2.0 g/day during relapse; used immunosuppressants within the previous 6 weeks; used systemic or rectal steroids within the previous 4 weeks; used antibiotics within the previous 7 days; received chronic treatment with anti-inflammatory drugs within the 7 days before baseline (with the exception of aspirin at doses of ≤ 325 mg/day for cardioprotection, which was permitted throughout the study); proctitis (extent of inflammation ≤ 15 cm); previous colonic surgery; Crohn's disease; bleeding disorders; active ulcer disease; stools positive for enteric pathogens; or moderate or severe renal impairment.

The study was conducted in accordance with current applicable regulations and the International Conference on Harmonisation and complied with the principles of the World Medical Assemblies, Declaration of Helsinki. Written informed consent was obtained for each patient.

Intervention and Randomization

The study was a phase III, multicenter, double-blind, parallel-group study in patients with mild to moderately active UC. The study was conducted at a total of 52 centers in the following countries: Australia, Costa Rica, the Czech Republic, India, Mexico, New Zealand, Romania, the Ukraine, and the USA. The number of patients recruited in each country is provided in the results section. Patients were randomized to receive placebo, MMX mesalamine 2.4 g/day (1.2 g given twice daily), or MMX mesalamine 4.8 g/day given once daily in a 1:1:1 ratio. To ensure that the study was blinded, allocation of active drug and placebo was concealed.

MMX mesalamine and placebo tablets were identical in appearance, and each MMX mesalamine tablet contained 1.2 g of the active ingredient (mesalamine) and was administered orally. Patients were randomized centrally via an interactive voice response system. Patients in the MMX mesalamine 2.4 g/day group received 1 MMX mesalamine tablet and 3 placebo tablets in the morning and 1 MMX mesalamine tablet in the evening, whereas patients in the MMX mesalamine 4.8 g/day group received 4 MMX mesalamine tablets in the morning and 1 placebo tablet in the evening. Patients in the placebo group received 4 placebo tablets in the morning and 1 placebo tablet in the evening. All tablets and capsules were taken with food.

During the study, patients were required to visit the clinic on 5 different occasions, which were defined as screening visit (week -1); baseline visit (week 0); visit 3 (week 2); visit 4 (week 4); and end of study/withdrawal visit (week 8). During the 3- to 7-day screening period, patients were permitted to continue on a stable dose of mesalamine (≤ 2 g/day) if they were receiving this therapy before screening. This was withdrawn at baseline if the patient was found to be eligible for study inclusion. During the 8-week treatment period, rescue medication was not permitted.

Evaluation of Treatment Efficacy

The UC-DAI scoring system, developed by Sutherland et al,¹⁶ was modified in our study and used to evaluate treatment efficacy. Total UC-DAI score is calculated by the sum of its components (range, 0–12): rectal bleeding, stool frequency, sigmoidoscopy (mucosal appearance) and PGA scores. Individual scores for these parameters are assessed on a scale from 0–3 points, where 0 points represented normal status. In our study, the scoring system used for sigmoidoscopy was modified to be more stringent than the standard UC-DAI system,¹⁶ which

Table 1. Modified UC-DAI Scoring System

	Mild (score = 1)	Moderate (score = 2)	Severe (score = 3)
Rectal bleeding	Streaks of blood	Obvious blood	Mostly blood
Stool frequency	1–2/day $>$ normal	3–4/day $>$ normal	> 4 /day $>$ normal
Mucosal appearance	Erythema; decreased vascular pattern; minimal granularity	Marked erythema; friability; granularity; absent vascular pattern; bleeding minimal trauma; no ulcerations	Ulceration; spontaneous bleeding
PGA	Mild	Moderate	Severe

NOTE. Data from Sutherland et al.¹⁶

allows patients with mild friability to be given a sigmoidoscopy score of 1. In our study, patients found to have any mucosal friability were given a sigmoidoscopy score of ≥ 2 (Table 1). Importantly, this modified sigmoidoscopy scoring system did not allow patients with mucosal friability to be considered as having achieved remission.

Patients reported their UC symptoms (rectal bleeding and stool frequency) on a daily basis via an interactive voice response system throughout the study. Scores for these symptoms were calculated at all visits by averaging the total score during the last available 3 days before the study visit. Data recorded more than 5 days before the study visit were not used. Sigmoidoscopy was performed at the baseline and week 8 visits by the same endoscopist for individual patients, with the same areas examined at both visits, specifically, the worst inflamed area in the rectum or the sigmoid colon, if the rectum was not grossly inflamed. A PGA assessment, which was based on the other modified UC-DAI assessments, was performed at the baseline and week 8 visits by the same investigator for individual patients.

Objectives/Outcomes

The primary end point of this study was to compare the percentage of patients in clinical and endoscopic remission at week 8 for each of the 2 MMX mesalamine dose groups versus placebo. As described above, the UC-DAI scoring system was modified such that patients who presented with mucosal friability were given a sigmoidoscopy score of 2 rather than 1. Therefore, clinical and endoscopic remission was defined as a modified UC-DAI score of ≤ 1 , with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and at least a 1-point reduction from baseline in the more stringently defined sigmoidoscopic score.

Secondary end points were a comparison of: remission rates (clinical and endoscopic combined) at week 8 between the 2 MMX mesalamine dose groups; clinical improvement rates (defined as a decrease of ≥ 3 points from baseline in the overall modified UC-DAI score) at week 8 between each treatment group; clinical remission rates (defined as scores of 0 points for total stool frequency and total rectal bleeding scores) at week 8 between each treatment group; change in the total modified UC-DAI score from baseline to week 8 between each treatment group; change in symptoms (rectal bleeding and stool frequency) from baseline to each study visit between each treatment group; and change in sigmoidoscopic (mucosal) appearance from baseline to week 8 between each treatment group. Comparison of time to withdrawal and treatment failures (defined as unchanged, worsened, or missing modified UC-DAI scores) between the 3 treatment groups was also assessed. Time to initial clinical remission (the first day of 3 consecutive days of complete symptom resolution) was also assessed in each of the study arms. Safety and tolerability of MMX mesalamine were assessed throughout the study via adverse event (AE) reporting, laboratory testing (hematology, biochemistry, and urinalysis), physical examination, and vital signs. Compliance, which was measured throughout the study, was assessed by pill count and patient diary entries.

Statistical Analysis

On the basis of the modified criteria described above, the placebo remission rate in this study was estimated to be 15%. Considering a clinical and endoscopic remission rate of

40% in the MMX mesalamine treatment arm to represent a clinically worthwhile improvement, it was calculated that 255 patients (85 per treatment arm) would provide 90% power to detect this improvement, assuming a two-sided .025 significance level. The intent-to-treat (ITT) and safety populations were defined as all randomized patients who received at least 1 dose of study medication. The per-protocol (PP) population was defined as all patients in the ITT population who were not major protocol violators.

For the primary analysis, the ITT population was used. The proportion of patients in clinical and endoscopic remission at week 8 was compared with placebo for both active treatment groups by using the χ^2 test. The false-positive error rate from performing 2 primary comparisons was controlled by using the Bonferroni-Holm method; the treatment comparison with the smaller P value was evaluated at the .025 significance level. If that comparison was significant, the treatment comparison with the larger P value was evaluated at the .05 significance level. Odds ratio (OR) between active treatment and placebo, together with the associated confidence interval (CI), analogous to the significance level used for each test, were calculated. If the primary analysis yielded a statistically significant result, an exploratory secondary analysis adjusting for the center effect was carried out.

Patients excluded from the ITT population, as a result of study center-associated good clinical practice (GCP) noncompliance, were included in the safety population. To assess the robustness of the results after exclusion of these patients after randomization, sensitivity analyses were performed comparing the safety and ITT populations with respect to demographic and clinical characteristics and the primary efficacy variable (clinical and endoscopic remission rate).

For the secondary prespecified analyses, hypothesis tests and two-sided 95% CIs were used throughout. A prespecified analysis (termed *Endpoint*) was performed with data from the ITT population at week 8 combined with the last observation carried forward for patients who had withdrawn early. Change from baseline in modified UC-DAI score was compared with placebo for both active treatment arms by using an analysis of covariance, with change from baseline as the response variable and baseline modified UC-DAI score, treatment group, and pooled center as explanatory variables. Change from baseline in sigmoidoscopy score was compared with placebo for both active treatment arms by using the Mantel-Haenszel χ^2 test. Kaplan-Meier curves were used to compare time to withdrawal, time to treatment failures, and time to initial and sustained clinical remission between the treatment groups. Descriptive summary statistics are presented for AEs, laboratory safety variables, and vital signs.

Results

The study was conducted between September 2003 and January 2005. Two hundred eighty patients were randomized from 52 centers in Australia ($n = 3$), the Czech Republic ($n = 16$), India ($n = 71$), Mexico ($n = 18$ [this country group also included 1 center in Costa Rica]), New Zealand ($n = 12$), Romania ($n = 11$), the Ukraine ($n = 78$), and the USA ($n = 71$). Ten patients underwent forced randomization (5 in each of the SPD476 2.4 g/day given twice daily and SPD476 4.8 g/day given once daily groups). Three sites were excluded from the results of the study as a result of GCP noncompliance. Issues identified during ongoing monitoring and/or auditing included, among

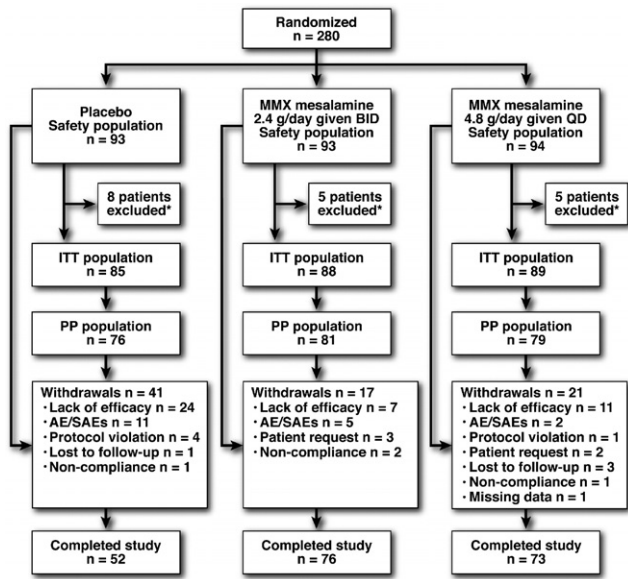


Figure 1. Patient flow. *Patients excluded from ITT population as a result of deviations from the protocol and GCP. QD, once daily; BID, twice daily; ITT, intent to treat; AEs, adverse events; SAEs, serious adverse events; PP, per protocol.

other things, problems with the accuracy and reliability of patient data generated. These sites were discontinued from the study, and the Food and Drug Administration was notified of their termination. Therefore, a total of 18 patients were excluded from the ITT population. To ensure statistical power, additional patients were randomized to compensate for this. However, the 18 patients from non-GCP-compliant sites were included in the safety population, and additional sensitivity

analyses were carried out on this population including summaries of demographic characteristics and UC history data and an analysis of the proportion of patients in clinical and endoscopic remission.

Details of patient flow throughout the study are presented in Figure 1. Patients were balanced between groups with respect to demographic characteristics (Table 2). The majority of concomitant medications were taken by a similar proportion of patients in each treatment group in the safety population. The most frequent concomitant medications taken during the treatment period were anilides (8% overall), aminosalicic acid and similar agents (7% overall), proton pump inhibitors (6% overall), and enemas (5% overall).

Compliance

In this double-blind, double-dummy study, compliance was similar in all the treatment groups. Ninety percent of patients in the safety population took between ≥80% and <120% of the study medication.

Efficacy

Primary end point. For the primary end point, significantly more patients treated with either dose of MMX mesalamine achieved clinical and endoscopic remission at week 8 compared with placebo. At week 8, significantly more patients achieved clinical and endoscopic remission after receiving MMX mesalamine 2.4 g/day given twice a day (OR, 3.48; 97.5% CI, 1.44–8.41; *P* = .001) or MMX mesalamine 4.8 g/day given once daily (OR, 2.78; 95% CI, 1.27–6.06; *P* = .009) compared with placebo (Figure 2). There was no significant difference between the MMX mesalamine groups (*P* = .485; OR, 1.25; 95% CI, 0.66–2.36).

Secondary end points. For all secondary outcome measures, a greater proportion of patients receiving either dose

Table 2. Demographics and Baseline Characteristics (ITT Population)

	Placebo (n = 85)	MMX mesalamine 2.4 g/day given BID (n = 88)	MMX mesalamine 4.8 g/day given QD (n = 89)
Gender; n (%)			
Male	41 (48.2)	46 (52.3)	48 (53.9)
Female	44 (51.8)	42 (47.7)	41 (46.1)
Mean (SD) age (y)	42.6 (11.68)	40.2 (11.97)	41.8 (13.62)
Mean (SD) weight (kg)	69.0 (16.87)	68.1 (17.20)	70.8 (18.03)
Mean (SD) height (cm)	167.7 (9.93)	168.3 (10.91)	167.8 (9.54)
Ethnic origin; n (%)			
White	56 (65.9)	57 (64.8)	54 (60.7)
Black	3 (3.5)	3 (3.34)	3 (3.4)
Hispanic	5 (5.9)	6 (6.8)	6 (6.7)
Asian/Pacific Islander	16 (18.8)	17 (19.3)	22 (24.7)
Other	5 (5.9)	5 (5.7)	4 (4.5)
Mean (SD) time since diagnosis (wk)	226.1 (282.94)	216.1 (298.59)	266.8 (396.84)
Classification of disease, n (%)			
Left-sided	66 (77.6)	78 (88.6)	71 (79.8)
Involvement of transverse colon	4 (4.7)	4 (4.5)	6 (6.7)
Pancolitis	15 (17.6)	6 (6.8)	11 (12.4)
Severity of disease; n (%) ^a			
Mild	29 (34.1)	38 (43.2)	35 (39.3)
Moderate	55 (64.7)	50 (56.8)	53 (59.6)
Patients with ≥1 concurrent illnesses, n (%)	52 (55.9)	37 (39.8)	46 (48.9)

BID, twice daily; QD, once daily; SD, standard deviation.

^aDisease severity was not recorded for 1 patient in the placebo group and 1 patient in the MMX mesalamine 4.8 g/day group because of missing modified UC-DAI scores. Mild disease = UC-DAI score of 4 to <6; moderate disease = UC-DAI score of 6–10.

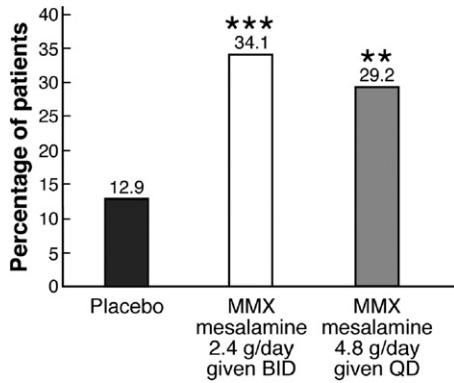


Figure 2. Percentage of patients with UC who achieved clinical and endoscopic remission after 8 weeks' treatment with placebo (n = 85), MMX mesalamine 2.4 g/day given twice daily (BID; n = 88), or 4.8 g/day given once daily (QD; n = 89) (ITT population). ****P* < .001, ***P* = .009 vs placebo.

of MMX mesalamine showed a trend toward improvement compared with placebo at week 8 (Figure 3). Clinical improvement was seen in statistically significantly more patients (*P* < .001) in the MMX mesalamine 2.4 g/day given twice a day (OR, 3.6; 95% CI, 1.89–6.84) and 4.8 g/day given once daily groups (OR, 4.22; 95% CI, 2.21–8.03) compared with placebo at week 8 (Figure 3).

There were statistically significantly fewer treatment failures (*P* < .001) at week 8 in the MMX mesalamine 2.4 g/day given twice a day group (OR, 0.34; 95% CI, 0.18–0.63) and 4.8 g/day given once daily group (OR, 0.28; 95% CI, 0.15–0.53) compared with placebo (Figure 3).

Clinical remission was experienced by statistically more patients (*P* < .05) receiving either MMX mesalamine dose (OR, 2.59; 95% CI, 1.29–5.18 for MMX mesalamine 2.4 g/day given twice a day and OR, 2.08; 95% CI, 1.03–4.20 for MMX me-

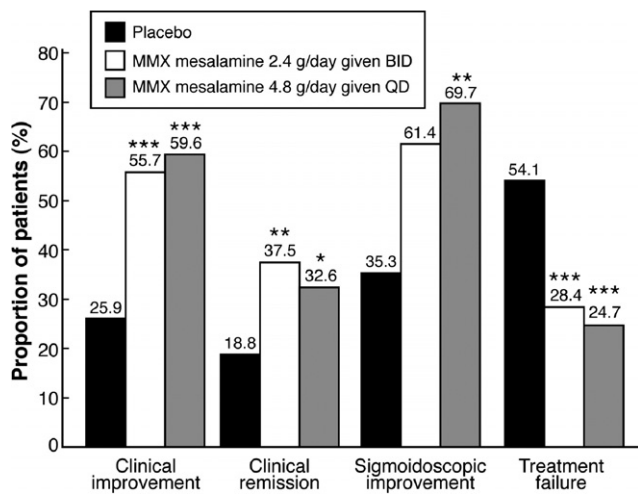


Figure 3. Summary of the proportion of patients with UC (ITT population) achieving clinically relevant secondary outcomes at week 8 after treatment with placebo (n = 85), MMX mesalamine 2.4 g/day given twice daily (n = 88), or 4.8 g/day given once daily (n = 89). Clinical improvement = reduction in modified UC-DAI from baseline of ≥3 points; clinical remission = scores of 0 for stool frequency and rectal bleeding; treatment failure = unchanged, worsened, or missing modified UC-DAI scores. ****P* < .001; ***P* < .01; **P* < .05 vs placebo.

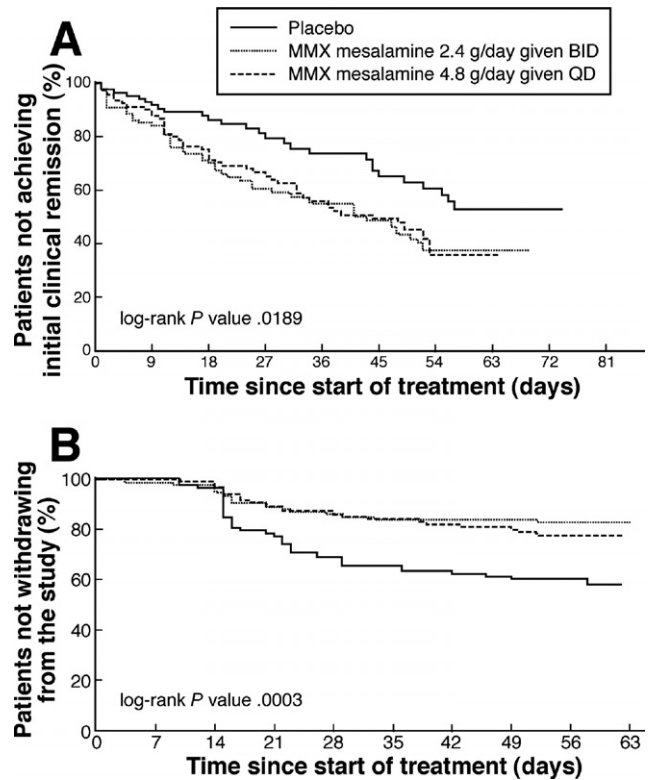


Figure 4. Kaplan–Meier curves showing time to (A) initial clinical remission (*P* = .0189 between the 3 treatment groups; log-rank test; ITT population); (B) withdrawal (*P* = .0003 between the 3 treatment groups; log-rank test; safety population) in patients with UC after 8 weeks' treatment with MMX mesalamine 2.4 g/day given twice daily (BID; n = 88) or 4.8 g/day given once daily (QD; n = 89) or placebo (n = 85). Time to initial clinical remission = the time between the first study dose and the first of 3 consecutive days of complete symptom resolution. (Because some patients returned to the investigator site after the 8-week scheduled visit, censored observations have been recorded in excess of 56 days.)

salamine 4.8 g/day given once daily) at week 8 than placebo (Figure 3).

Kaplan-Meier analysis (and a log-rank test) of time to initial clinical remission revealed a statistical difference (*P* = .0189) between the 3 treatment groups (Figure 4A). Median time to initial clinical remission was 43 days (95% CI, 25–52) in the MMX mesalamine 2.4 g/day given twice daily group and 44 days (95% CI, 32–53) in the 4.8 g/day given once daily group. A median value was not achieved in the placebo group; thus an estimated survivor function (*S*[^] = 0.53; 95% CI, 0.39–0.67) at the last non-censored day was calculated for the purpose of statistical analysis.

Patients treated with either dose of MMX mesalamine experienced statistically significantly greater improvements in their overall modified UC-DAI scores from baseline to week 8 (*P* < .05) and from baseline to Endpoint (with last observation carried forward data; *P* < .001) compared with placebo (Table 3).

In the MMX mesalamine 4.8 g/day given once daily dose group, a larger proportion of patients achieved symptom scores of <1 at week 8 compared with the lower dose of MMX mesalamine and placebo (59.6% vs 51.1% vs 30.6%, respectively, for stool frequency and 70.8% vs 63.6% vs 37.6%, respectively, for rectal bleeding). Similarly, the proportion of patients with

Table 3. Change in Total Modified UC-DAI Score From Baseline to Week 8 and Endpoint

	Mean (SD) UC-DAI score at baseline	Week 8 data			Endpoint ^a data		
		LSM change from baseline (n ^b)	<i>P</i> value vs placebo	<i>P</i> value vs MMX mesalamine 4.8 g/day given QD	LSM change from baseline (n ^c)	<i>P</i> value vs placebo	<i>P</i> value vs MMX mesalamine 4.8 g/day given QD
Placebo, n = 85	6.68 (1.77)	-2.25 (48)			-0.79 (80)		
MMX mesalamine 2.4 g/day given BID, n = 88	6.13 (1.53)	-3.15 (72)	.036	.033	-2.71 (85)	<.001	.085
MMX mesalamine 4.8 g/day given QD, n = 89	6.44 (1.63)	-3.98 (70)	<.001		-3.46 (81)	<.001	

LSM, least square mean; SD, standard deviation.

^aEndpoint includes last observation carried forward data for patients who withdrew before week 8.

^bNo. of patients with a modified UC-DAI score at week 8.

^cNo. of patients with a modified UC-DAI score at Endpoint.

symptom scores of <1 at Endpoint was greater in the MMX mesalamine groups than in the placebo group (61.8% vs 55.7% vs 31.8%, respectively, for stool frequency and 75.3% vs 72.7% vs 43.5%, respectively, for rectal bleeding). Overall, improvements in rectal bleeding and stool frequency scores were greater in the MMX mesalamine groups compared with the placebo group. Improvement in rectal bleeding scores from baseline was observed as early as week 2 in the MMX mesalamine groups.

The percentage of patients achieving sigmoidoscopic improvement was statistically significantly greater ($P = .002$) in the MMX mesalamine 4.8 g/day given once daily group (69.7%) and compared with the placebo group (35.3%) at week 8 (Figure 3). The percentage of patients achieving sigmoidoscopic improvement in the MMX mesalamine 2.4 g/day group (61.4%) was not significantly greater than placebo ($P = .300$). However, the percentage of patients with an improved sigmoidoscopy score at Endpoint was statistically significantly greater in both the MMX mesalamine 2.4 g/day given twice daily group (64.8%; $P = .002$) and the MMX mesalamine 4.8 g/day given once daily group (71.9%; $P < .001$) compared with placebo (36.5%).

An additional sensitivity analysis of the primary efficacy variable, comparing the ITT population with the safety population (which included the 18 patients excluded from the ITT population), demonstrated no notable differences between these 2 populations (33.3%, $P = .001$ and 28.7%, $P = .008$ vs 12.9% of patients in clinical and endoscopic remission at week 8 in the MMX mesalamine 2.4 g/day given twice daily, MMX mesalamine 4.8 g/day given once daily, and placebo groups, respectively). Furthermore, there were no notable differences between the ITT and safety populations with regard to the demographic characteristics, UC disease history, or the extent of treatment exposure. Thus, the sensitivity analysis demonstrated that the exclusion of these patients did not affect the overall study results.

Safety

Treatment with either dose of MMX mesalamine was generally well tolerated in this study. No clinically significant differences in safety were observed between placebo and MMX mesalamine at either dose. There was no evidence to suggest a dose-response relationship for any safety parameter.

There was a statistically significant difference between treatment groups in time to withdrawal ($P = .0003$; Figure 4B).

Patients who received placebo were more likely to withdraw from the study early (44.1% vs 18.3% for MMX mesalamine 2.4 g/day given twice daily vs 22.3% for MMX mesalamine 4.8 g/day given once daily), with the majority of withdrawals occurring during the first 4 weeks of the study.

A total of 233 treatment-emergent AEs, the majority of which were mild or moderate in intensity, were experienced by 129 patients in the safety population (Table 4). The most frequently reported treatment-emergent AEs were gastrointestinal disorders including worsening UC, flatulence, nausea, diarrhea (not otherwise specified), and dyspepsia (Table 4). Gastrointestinal disorders were also the most frequent AEs that led to study discontinuation, accounting for all but one of the discontinuations as a result of AEs. Discontinuation as a result of AEs occurred more frequently in the placebo group than in either of the MMX mesalamine groups (Table 4).

Only a small number of patients experienced serious AEs (SAEs); 7 patients experienced a total of 8 SAEs (Table 4). All SAEs were considered to be unrelated to study medication, with the exception of 2 cases of pancreatitis, caused by mesalamine hypersensitivity, experienced by 1 patient in each of the MMX mesalamine dose groups, both of whom had not received mesalamine for at least 6 weeks before entering the trial. Both cases of pancreatitis followed a benign course before completely resolving without sequelae after discontinuation from the study.

The most frequent AEs thought to be related to treatment before unblinding were gastrointestinal in nature (experienced by 26 of the 46 patients with treatment-related AEs) and occurred in a greater proportion of patients in the placebo group (13 patients [14.0%]) than in the MMX mesalamine groups (8 patients [8.6%] in the 2.4 g/day given twice daily group and 5 patients [5.3%] in the 4.8 g/day given once daily group).

Discussion

This study demonstrates that MMX mesalamine, given once or twice daily, was efficacious for the induction of clinical and endoscopic remission of mild to moderately active UC. Significantly more patients receiving either dose of MMX mesalamine achieved clinical and endoscopic remission than those receiving placebo ($P < .01$). Approximately 1 in 3 patients in both MMX mesalamine groups achieved clinical and endoscopic remission compared with 1 in 8 in the placebo group (a

Table 4. Treatment-Emergent AEs (Safety Population)

	Placebo (n = 93)		MMX mesalamine 2.4 g/day given BID (n = 93)		MMX mesalamine 4.8 g/day given QD (n = 94)	
	n	%	n	%	n	%
Any AE	47	50.5	44	47.3	38	40.4
Any treatment-related AE	17	18.3	15	16.1	14	14.9
Any SAE	3	3.2	2	2.2	2	2.1
AE that led to withdrawal	11	11.8	5	5.4	2	2.1
Most frequent treatment-emergent AEs						
Worsening UC	9	9.7	6	6.5	1	1.1
Flatulence	4	4.3	3	3.2	2	2.1
Headache	1	1.1	5	5.4	2	2.1
Nausea	2	2.2	3	3.2	3	3.2
Diarrhea (nos)	2	2.2	4	4.3	0	0.0
Dyspepsia	3	3.2	2	2.2	1	1.1

nos, not otherwise specified.

2.3-fold to 2.6-fold increase in the clinical and endoscopic remission rate). It must be noted that the remission rates (clinical and endoscopic combined) reported in our study were achieved in patients with mild to moderately active UC, with criteria that assess both symptoms and mucosal appearance rather than the symptoms alone. We believe that the use of such an end point, in which remission is defined as both symptomatic resolution and complete mucosal healing, should be included in all trials of UC therapies. This is particularly pertinent in the light of mounting evidence that suggests an association between UC, damage to the colonic mucosa, and the development of colorectal cancer.¹⁷⁻²⁰

Both MMX mesalamine dose groups consistently demonstrated better values for secondary efficacy measures (clinical improvement, change from baseline in modified UC-DAI and its components, treatment failure, clinical remission, and sigmoidoscopy score) than placebo, the majority of which were statistically significant.

Once-daily dosing encourages long-term compliance in clinical practice.¹³ This study, like similar trials with other mesalamine formulations,^{7,8} demonstrated that all trial patients exhibited a high degree of compliance. In contrast, patient compliance in clinical practice can be as low as 40%-60%,^{10,21} particularly among patients in symptomatic remission.^{5,10-12} Once-daily MMX mesalamine has the potential to maximize treatment compliance and thus minimize the risk of UC flare in clinical practice. Clearly, further trials in an outpatient setting are required to demonstrate whether once-daily dosing is non-inferior to multiple-daily dosing.

The results of our study highlight how the use of MMX technology allows treatment of UC with mesalamine. MMX technology might also have advantages for delivery of other drugs to the colonic mucosa, particularly those for which prolonged release throughout the colon would be beneficial. Clinical studies are required to test the extent to which MMX technology might improve treatment with other therapeutic agents.

Much of the study design reported here has been driven by considering the "real world" use of MMX mesalamine in clinical practice. For example, in this study we examined the time to initial clinical remission (absence of rectal bleeding and normalization of stool frequency) by using strict criteria to reflect the predicted needs of an outpatient. Indeed, whereas other

studies have defined initial clinical remission as the "first day of complete symptom resolution,"²² whereby a patient could relapse on the day after an initial report of symptom resolution, we have stipulated that symptom resolution must last at least 3 consecutive days, a time period that might be considered to be both more clinically relevant and beneficial to the patient.

In addition to the efficacy benefits shown by MMX mesalamine, both doses (2.4 g/day given twice daily and 4.8 g/day given once daily) were well tolerated in this study, with a safety profile similar to other mesalamine formulations. Furthermore, there was no evidence of a dose-response relationship for any safety parameter, and no clinically significant differences in safety were observed between placebo and either dose of MMX mesalamine. In general, patients who received placebo withdrew from the study earlier than those who received MMX mesalamine, with a statistically significant difference between the 3 groups observed for time to withdrawal. As a consequence of the withdrawals, the number of patients exposed to less than 4 weeks of treatment was greater in the placebo group than in either MMX mesalamine group. Most AEs were mild or moderate in intensity and were considered not related to the study medication. Adverse events that were considered related to study medication were predominantly gastrointestinal events (most commonly, aggravated UC) and were more common in the placebo group than in either of the MMX mesalamine groups.

Two cases of pancreatitis were reported in this study, one in each of the MMX mesalamine study arms. Mesalamine-associated acute pancreatitis is a well-recognized AE believed to be a hypersensitivity reaction.²³⁻²⁶ Moreover, no other events of pancreatitis were reported during 2 other trials (1 phase II²⁷ and 1 phase III²⁸) of MMX mesalamine for the induction of remission in patients with active mild to moderate UC.

Overall, the AE profile was consistent with the known safety profile of currently available mesalamine products,^{29,30} and in the current study, both the once-daily and twice-daily dosing regimens of MMX mesalamine were at least as well tolerated as placebo in patients with mild to moderate UC.

The sensitivity analysis demonstrated that the exclusion of 18 patients from the primary analysis (remission in the ITT population), as a result of deviations from protocol and GCP guidelines, did not affect the overall conclusions.

In conclusion, this study has shown MMX mesalamine (4.8 g/day given once daily or 2.4 g/day given twice daily) to be efficacious for the induction of clinical and endoscopic remission of mild to moderately active UC with a safety profile that is comparable to other mesalamine formulations. A larger patient population will be required to address whether there are differences in the relative efficacy between the 2 dose regimens.

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Address requests for reprints to: Gary R. Lichtenstein, MD, Division of Gastroenterology, Department of Medicine, University of Pennsylvania School of Medicine, Hospital of the University of Pennsylvania, 3rd Floor Ravidin Pavilion, 3400 Spruce St, Philadelphia, PA 19104-4283.

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