

# MMX Mesalamine for Induction and Maintenance Therapy in Mild-to-Moderate Ulcerative Colitis

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**Abstract:** Two 8-week, randomized, placebo-controlled parent studies, SPD476-301 (by Lichtenstein and associates) and SPD476-302 (by Kamm and colleagues), of MMX Multi Matrix System (MMX) mesalamine have evaluated the induction of remission in ulcerative colitis patients, and a third study has evaluated the maintenance of remission in patients from these parent studies. Here, we examine data only from patients who received MMX mesalamine 2.4 g or 4.8 g daily in these trials. In total, 63.6% of patients (220/346) achieved remission following 8–16 weeks of MMX mesalamine therapy. Among these 220 eligible patients, 218 entered the 12-month maintenance phase, and of this group, 89.9% (196/218) were relapse-free at study end. Overall, 56.6% (196/346) of patients who started MMX mesalamine therapy both achieved and maintained remission for 12 months. The adverse-event profile of MMX mesalamine was similar to the profile of the parent studies' placebo arms at all doses and frequencies. Therefore, the majority of patients with active, mild-to-moderate ulcerative colitis can achieve remission, including complete symptom resolution and mucosal healing, and remain relapse-free for at least 1 year with MMX mesalamine.

**5**-aminosalicylic acid (5-ASA) is the mainstay of first-line therapy for the induction of remission of active, mild-to-moderate ulcerative colitis (UC) and the subsequent maintenance of remission. Although 5-ASAs are available in a variety of oral and rectal formulations, clinical experience shows that physicians and patients may be more likely to continue with the same formulation of mesalamine for both induction and maintenance therapy.

Mesalamine with MMX Multi Matrix System<sup>®</sup> (MMX<sup>™</sup>) technology (Lialda, Shire) is a novel, high-strength (1.2 g per tablet) formulation of 5-ASA designed to be administered once daily (QD). MMX mesalamine is currently approved for the induction of remission of UC in the United States and the induction and maintenance

## Keywords

MMX mesalamine, 5-aminosalicylic acid, ulcerative colitis

of clinical and endoscopic remission of mild-to-moderate UC in Europe.

MMX technology comprises lipophilic and hydrophilic excipients enclosed within a gastro-resistant, pH-dependent coating.<sup>1,2</sup> The suggested mechanism of 5-ASA release from MMX mesalamine tablets has been described elsewhere.<sup>3</sup> The combination of the high dose of 5-ASA per tablet coupled with the MMX drug delivery technology allows a dose of 5-ASA to be delivered throughout the colon in a single daily dose.

MMX mesalamine has been shown to be efficacious for the induction of clinical and endoscopic remission of active, mild-to-moderate UC in two phase III, placebo-controlled, double-blind, randomized studies published by Lichtenstein and associates (SPD476-301)<sup>4</sup> and Kamm and colleagues (SPD476-302).<sup>5</sup> Analyses of subpopulations of patients in these studies have shown that MMX mesalamine was effective, irrespective of disease extent, disease severity, gender, and previous low-dose 5-ASA experience.<sup>6</sup> MMX mesalamine was subsequently shown to be effective for the maintenance of remission in a follow-on study (SPD476-303).<sup>7</sup> As patients who received MMX mesalamine maintenance therapy had participated in the studies for induction of remission, it is possible to determine the efficacy of this formulation for both the induction and maintenance of remission in the same patient population.

Here, we explore the entire course of UC treatment with MMX mesalamine by examining patients with active disease through induction therapy in the Lichtenstein and Kamm studies and following them through an extension of their induction therapy (where required) and/or maintenance therapy in the follow-on extension study. This particular analysis focuses exclusively on the patients who initially received MMX mesalamine in the Lichtenstein and Kamm studies and subsequently received further treatment with MMX mesalamine in the follow-on study. We can, therefore, consider whether patients will be able to achieve and maintain remission using this strategy if they were to be treated with MMX mesalamine over 14–16 months.

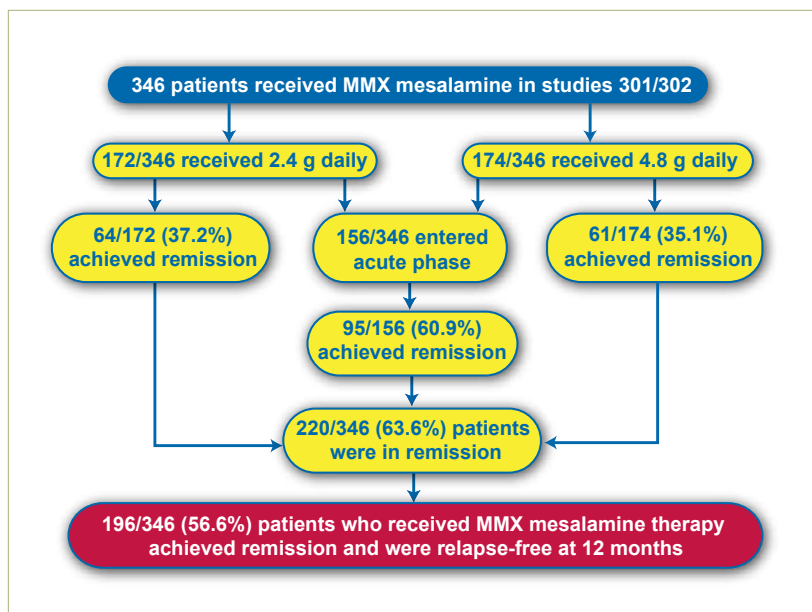
## Materials and Methods

### *Participants and Design of the Original Studies*

**Inclusion and Exclusion Criteria** The two initial studies (Lichtenstein and coworkers<sup>4</sup> and Kamm and associates<sup>5</sup>) enrolled men and women 18 years of age or older who had newly diagnosed or relapsing (relapsed  $\leq 6$  weeks prior to baseline), active, mild-to-moderate UC (defined as a score of 4–10 on a modified UC Disease Activity Index [UC-DAI], with a sigmoidoscopy score of  $\geq 1$  and a Physician's Global Assessment [PGA] score of  $\leq 2$ )

with compatible histology. Exclusion criteria included patients who had: previously experienced an inadequate or failed response to steroids or a mesalamine dose of more than 2.0 g daily; relapsed while on maintenance therapy with doses of 5-ASA of more than 2.0 g daily; and relapsed within 2 weeks of dose reduction from over 2.0 g daily to no more than 2.0 g daily 5-ASA. Patients were also excluded if they had received: systemic or rectal steroids within the 4 weeks prior to baseline; immunosuppressants within the previous 6 weeks; antibiotics within the previous 7 days; and repeated treatment with anti-inflammatory drugs ( $>3$  days of use at doses that exceed those available without prescription) within 7 days prior to baseline (with the exception of prophylactic aspirin at doses of  $\leq 325$  mg daily for cardiac disease). Patient consent and ethical approval have been described previously for these studies.<sup>4,5</sup>

**Phase III Program Study Design** Both initial studies utilized a similar design. In one of the studies (Lichtenstein and colleagues<sup>4</sup>), patients were randomized to receive placebo, MMX mesalamine 2.4 g daily given as 1.2 g twice daily (BID), or MMX mesalamine 4.8 g daily given QD for 8 weeks. In the other initial study (Kamm and coworkers<sup>5</sup>), patients were randomized to placebo, MMX mesalamine 2.4 g daily given QD, MMX mesalamine 4.8 g daily QD, or delayed-release mesalamine (Asacol, Proctor & Gamble) 400 mg tablets 2.4 g daily given as 0.8 g three times daily (TID; as an internal reference) for 8 weeks. Analysis of remission was performed at the end of each study. Patients not in remission at the end of the two initial studies could enter an 8-week acute-treatment phase of an open-label follow-on study (SPD476-303), in which they received MMX mesalamine 4.8 g daily (2.4 g BID) for 8 weeks (Kamm and associates<sup>7</sup>). Analysis of remission was performed at the end of the 8 weeks of therapy. In all three studies, remission was defined as a modified UC-DAI score of no more than 1, calculated as: scores of 0 for rectal bleeding and for stool frequency; a combined PGA and sigmoidoscopy score of no more than 1; and no mucosal friability. In addition, for increased stringency, patients had to achieve a reduction in sigmoidoscopy score of at least 1 point from initial study baseline. Patients who were in remission at the end of the initial studies or after the 8-week extension phase of the follow-on study could enter the maintenance phase of the follow-on study (303, Kamm and colleagues<sup>8</sup>). In the maintenance phase, patients were randomized to receive MMX mesalamine 2.4 g daily given either QD or as 1.2 g BID for up to 12 months. As previously described, in all three studies, patients were randomized via an interactive voice recognition system.



**Figure 1.** Participant flow for patients receiving Multi Matrix (MMX) mesalamine in the parent studies and study 303. Numbers represent patients in the intent-to-treat/efficacy population.

Data reproduced from Lichtenstein GR, et al<sup>4</sup> and Kamm MA, et al.<sup>5</sup>

### Current Analysis

In this post-hoc analysis, we aimed to determine the efficacy of MMX mesalamine as the sole agent for the induction and maintenance of remission.

Data were used from the two 8-week, randomized, placebo-controlled studies and the follow-on study of MMX mesalamine in the treatment of patients with mild-to-moderate UC, including the induction and maintenance of remission. Patients not in remission at the end of the two initial studies could continue into the 8-week extension phase of the follow-on study. Patients not in remission at the end of the 8-week extension phase of the follow-on study were not eligible to enter the maintenance phase. In this analysis, data were excluded for those patients who received placebo or delayed-release mesalamine in either of the two initial 8-week induction studies.

In the current analysis, remission rates were calculated at Week 8 of the initial studies and Week 8 of the extension phase of the follow-on study. Relapse was assessed throughout the 12-month maintenance phase and was defined as the need for alternative medication or surgery for UC exacerbation.

**Endpoints** The following main endpoints were defined: remission rates following 8–16 weeks of therapy (initial treatment  $\pm$  8 additional weeks of treatment); relapse rates throughout 12 months of maintenance therapy; 12-month relapse rates in patients who required an additional 8 weeks of induction therapy; and overall efficacy

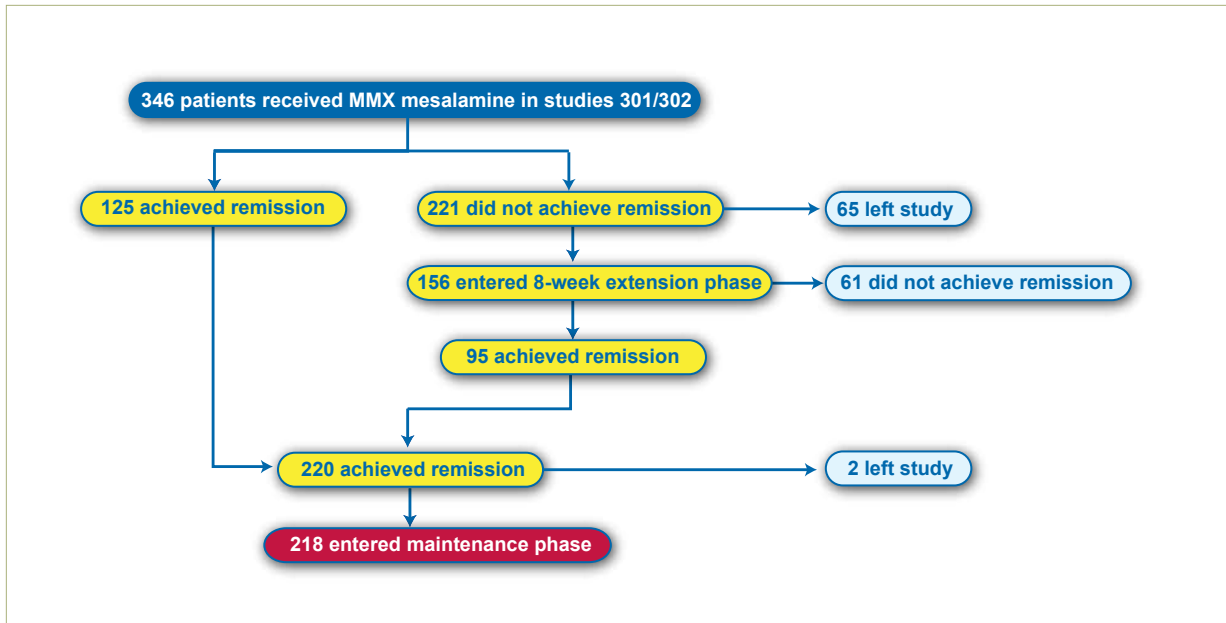
(ie, the percentage of patients who started MMX mesalamine therapy, achieved remission, and were relapse-free during 12 months of maintenance therapy).

**Statistical Analyses** In this post-hoc analysis, variables were expressed descriptively. Continuous variables were summarized using summary statistics (number of observations, mean, standard deviation, median, minimum, and maximum). Categorical values were summarized using frequencies and percentages.

## Results

### Participant Flow

The participant flow is outlined in Figure 1.<sup>4,5</sup> A total of 346 patients received MMX mesalamine therapy for up to 8 weeks in the initial studies. One hundred and seventy-two patients received a dose of 2.4 g daily, and 174 received a dose of 4.8 g daily. Demographics for patients included in the two initial studies and the follow-on study have been described previously.<sup>9</sup> In summary, 172 of the enrolled patients were men and the mean age was 42 years. Approximately 81% of patients were white. The ratio of patients with mild disease to those with moderate disease was 40%:60%, and approximately 16% of patients had newly diagnosed UC. Overall, 60% had experienced two relapses or fewer (as described by patient self-report) in the previous two years. Approximately 80% had a medical history of left-sided disease (upper limit in the sigmoid or descending colon).



**Figure 2.** Overall efficacy of Multi Matrix (MMX) mesalamine for the treatment of ulcerative colitis.

### **Induction of Remission**

A total of 36.1% (125/346) of patients were in remission following 8 weeks of MMX mesalamine therapy in the initial studies. The remission rate was similar for the two dosages. Overall, 37.2% (64/172) of patients who received 2.4 g daily and 35.1% (61/174) of patients who received 4.8 g daily achieved strictly defined remission (Figure 2).

Among the 221 patients who failed to achieve remission in the initial studies (ie, after up to 8 weeks of therapy), 156 entered the 8-week, open-label, extension phase. Of these 156 patients, 60.9% (95/156) achieved remission with an additional 8 weeks of MMX mesalamine at a dose of 4.8 g daily. The remission rate was similar for patients who had received 2.4 g or 4.8 g daily in the initial studies: 61.5% (48/78) of patients who received 2.4 g daily and 60.3% (47/78) of patients who received 4.8 g daily achieved remission.

Using an intent-to-treat approach, in which patients not receiving an additional 8 weeks of therapy are included in the overall population, a total of 63.6% (220/346) of patients achieved remission after 8–16 weeks of MMX mesalamine therapy.

### **Prevention of Relapse**

Among the 220 patients who achieved remission following 8–16 weeks of acute therapy, 218 entered the maintenance phase. At the end of this 12-month maintenance phase, 89.9% (196/218) of patients who had achieved

remission during 8–16 weeks of acute therapy were relapse-free.

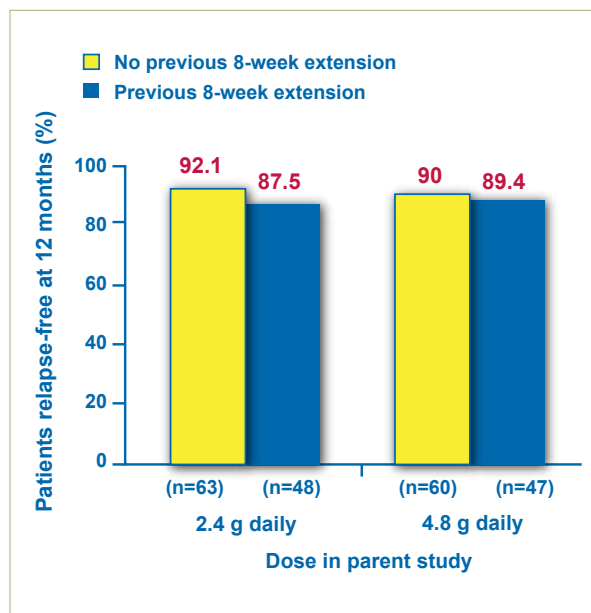
### **Overall Efficacy**

Combining data from all three studies, 56.6% (196/346) of the patients who started MMX mesalamine therapy achieved remission and were maintained relapse-free for over 14–16 months of therapy. This percentage was similar, regardless of whether patients were started on MMX mesalamine 2.4 g daily (58.1%; 100/172) or 4.8 g daily (55.2%; 96/174).

### **The Effect of Requiring an Additional 8 Weeks of Induction Therapy**

Among the patients who achieved remission with MMX mesalamine 2.4 g daily and entered the maintenance phase directly, 92.1% (58/63) were relapse-free throughout 12 months of therapy with MMX mesalamine 2.4 g daily (Figure 3). Of those patients requiring an additional 8 weeks of therapy with MMX mesalamine 4.8 g daily to achieve remission, 87.5% (42/48) were relapse-free at 12 months.

Of the patients who achieved remission with MMX mesalamine 4.8 g daily and entered the maintenance phase directly, 90.0% (54/60) remained relapse-free throughout 12 months of further therapy with MMX mesalamine 2.4 g daily. In those patients requiring an additional 8 weeks of therapy with MMX mesalamine



**Figure 3.** Percentage of patients in clinical and endoscopic remission after 12 months of Multi Matrix mesalamine maintenance treatment, by parent study dose and requirement for treatment extension.

4.8 g daily to achieve remission, 12-month relapse-free rates were 89.4% (42/47).

**Safety** Safety data have previously been published for MMX mesalamine for both the induction<sup>4,5</sup> and maintenance (Kamm and coworkers<sup>9</sup>) of remission. In these studies, the adverse-event profile of MMX mesalamine, regardless of dose strength or frequency, was shown to be similar to that reported for placebo in the induction studies.<sup>4,5</sup> The most frequently reported adverse events were gastrointestinal disorders, including aggravated UC, abdominal pain, nausea, and flatulence.

## Discussion

This is the first analysis performed to examine the overall efficacy of 5-ASA for the induction of remission and prevention of relapse of mild-to-moderate UC. Moreover, this is also the first analysis to examine the effect of prolonged 5-ASA therapy in patients with an incomplete response, following the recommended 4–8 weeks of therapy.<sup>10</sup>

In this analysis, we have demonstrated that more than 60% of patients who start MMX mesalamine therapy can achieve remission following 8–16 weeks of therapy. Specifically, over one third of patients achieved remission with up to 8 weeks of MMX mesalamine therapy (2.4 g or 4.8 g daily). Of those patients who did not achieve remis-

sion but continued on MMX mesalamine therapy for up to an additional 8 weeks, greater than 60% subsequently achieved strictly defined remission. For some patients, this may be attributed to a dose escalation from 2.4 g daily in the parent studies to 4.8 g daily in the 8-week extension period. Although a dose response for 5-ASA in mild-to-moderate UC has yet to be unequivocally proven, most studies describing a dose response, or lack thereof, have been conducted over 6–8 weeks.<sup>11,12</sup> It is possible that the patients in the current study would have subsequently achieved remission with prolonged therapy at a dose of 2.4 g daily.

For other patients, a total of up to 16 weeks of high-dose (4.8 g daily) MMX mesalamine therapy was required to achieve remission. Using current guidelines, these patients would possibly have been considered 5-ASA-refractory after 8 weeks of high-dose therapy and would have been scheduled to receive step-up treatment to corticosteroids, immunosuppressives, or biologic agents that are associated with undesirable side effects, including an increased risk of opportunistic infections. Further responses with prolonged 5-ASA therapy have been suggested in a small number of 12-week studies<sup>13–17</sup> and the results of a 34-week study of prolonged rectal mesalamine demonstrated a substantial increase in cumulative rates of response and remission.<sup>18</sup> Our data further challenge the current treatment algorithm, suggesting that high-dose 5-ASA therapy using MMX mesalamine can be continued beyond 8 weeks to avoid therapeutic escalation in many patients who do not completely respond to an initial 8 weeks of 5-ASA treatment.

It must be noted that many patients who did not achieve strictly defined clinical and endoscopic remission in the first 8 weeks did have improved clinical symptoms prior to subsequently achieving remission following 8 additional weeks of therapy. Although in clinical practice, symptom resolution might be considered disease remission, our studies required patients to achieve substantial mucosal healing. If patients in our studies had not demonstrated an improvement in mucosal appearance, even though they had shown complete resolution of all clinical symptoms, they were not deemed to be in remission. This is important, as it has been demonstrated that those patients who do achieve mucosal healing are less likely to relapse during maintenance therapy than those who do not.<sup>19,20</sup> This is adequately reflected by the extremely low relapse rate observed in our analysis. Indeed, over 85% of patients who initially achieved remission had not relapsed during 1 year of maintenance therapy, and relapse-free rates were similar, irrespective of acute treatment dose and duration. Furthermore, mucosal healing in UC patients provides additional benefit, including a potential reduction in the risk of developing colorectal cancer.<sup>21</sup>

Long-term (>6 months) remission rates reported from previous studies vary considerably. For example, in a 1-year follow-up study of 156 patients with quiescent UC receiving oral mesalamine, less than 30% of patients were in remission at the end of the study.<sup>22</sup> By contrast, a double-blind, randomized study comparing balsalazide (3.0 g or 6.0 g daily given BID) with mesalamine (1.5 g daily given TID) demonstrated 6-month clinical remission rates (defined as a Rachmilewitz clinical activity index of <6) of 43.8%, 77.5%, and 56.8% of patients, respectively.<sup>23</sup> This phenomenon is due to the variety of clinical and endoscopic indices utilized by the investigators in such studies. These differences make it difficult to make comparisons among different studies.

Long-term remission is, at least partly, associated with treatment compliance.<sup>24</sup> It is well known that many patients are not compliant with their prescribed 5-ASA dosing schedules, particularly when their disease is in remission.<sup>25-27</sup> Noncompliance results in reduced drug efficacy, disease flare, and, thus, reduced quality of life.<sup>24,28</sup> Many factors contribute to noncompliance; however, pill burden and frequent daily dosing contribute significantly to this phenomenon.<sup>28</sup> Hence, compliance with a convenient, oral, once-daily formulation of 5-ASA such as MMX mesalamine may enable patients to derive the most benefit from their medication throughout the induction and maintenance of remission. In clinical trial settings, compliance with MMX mesalamine regimens has been high.<sup>9</sup> Compliance in the extension study may have benefited from the open-label nature of this part of the study; however, compliance in clinical trials is generally considered not to be a true reflection of clinical practice. Further studies will be required to investigate patient compliance with MMX mesalamine therapy outside of the strict clinical trial setting.

## Conclusion

Based upon our studies, the majority of patients with active, mild-to-moderate UC may be able to achieve remission, including complete symptom resolution and mucosal healing, and remain relapse-free for at least 1 year with MMX mesalamine therapy. These results demonstrate the efficacy of MMX mesalamine therapy for the induction of UC remission and prevention of relapse. Furthermore, prolonged or increasing doses of MMX mesalamine therapy for the induction of remission may prevent the use of step-up therapy to steroids or other immunosuppressive therapies. The convenience of MMX mesalamine given once daily may improve overall treatment success through improved patient compliance.

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