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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.
SYNOPSIS

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**Title of Study:** Strategies in Maintenance for Patients Receiving Long-term Therapy™ (S.I.M.P.L.E.): A Phase IV, Multi-center, Open-label Study to Assess Clinical Recurrence Related to Compliance With Treatment With MMX® Mesalamine 2.4g/day Given Once Daily for the Maintenance of Quiescent Ulcerative Colitis (UC)

**Investigator:** [Redacted], MD (USA)

**Study Centers:** 51 centers in the USA

**Publications (reference):** None

**Studied period:**
- First subject screened: 01 May 2007
- First subject dosed: 08 May 2007
- Last subject dosed: 23 Jul 2009
- Last subject/last observation: 17 Aug 2009

**Phase of development:** 4

**Objectives:**
The primary objective of this study was to evaluate the percentage of subjects with clinical recurrence (defined as 4 or more bowel movements per day above the subject’s normal frequency and associated with any of the following: urgency, abdominal pain, or rectal bleeding) at 6 months.

The secondary objectives were as follows:
- To evaluate the percentage of subjects with clinical recurrence (defined as 4 or more bowel movements per day above the subject’s normal frequency and associated with any of the following: urgency, abdominal pain, or rectal bleeding) at 12 months.
- To assess the time to clinical recurrence (defined as 4 or more bowel movements per day above the subject’s normal frequency and associated with any of the following: urgency, abdominal pain or rectal bleeding).
- To assess clinical recurrence related to subject compliance with Multi Matrix System® (MMX) mesalamine at doses of 2.4g/day dosed once daily (QD) at 6 months and 12 months.
- To evaluate the percentage of subjects with quiescent UC (scores of 0 for both rectal bleeding and bowel movements) at 12 months.
- To assess endoscopic remission (endoscopy score of ≤1) at 12 months.
- To assess the safety and tolerability of MMX mesalamine 2.4–4.8g/day dosed QD.
### The tertiary objectives were as follows:

- To assess scores of individual symptoms (frequency of bowel movements above normal per day, urgency, abdominal pain, rectal bleeding) at 6 and 12 months.
- To compare the percentage of subjects with clinical recurrence with published data from Sunanda Kane.
- To assess quality of life (QoL) by the Medical Outcomes Study 12-Item Short Form Health Survey (SF-12 v2), the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem v2.0 (WPAI:SHP) at baseline, 6 months, and 12 months.
- To assess demographic and baseline disease predictors of compliance at 6 months and 12 months.
- To assess demographic and baseline disease predictors of QoL at 6 months and 12 months.
- To assess predictors of treatment response based on demographic and baseline characteristics of patient populations.
- To compare the change in histology scores from maintenance baseline at 12 months.

### Methodology:

This was a Phase 4, multicenter, open-label, 12-14 month compliance and dosing study consisting of an acute phase and a maintenance phase. Subjects whose UC was in flare at screening were enrolled in the 2-month acute phase, while those whose UC was quiescent at screening were enrolled directly into the 12-month maintenance phase. Subjects who were treated in the acute phase and attained quiescence were continued into the maintenance phase.

This study was designed to evaluate compliance in a clinical practice type setting; that is, to determine if once daily dosing would lead to fewer symptomatic recurrences of the disease (quiescence of UC). In addition, tracking of filled prescriptions was conducted to determine if once daily dosing increased compliance. With fewer pills and a true once-a-day dosing regimen, it was anticipated that patient compliance would be enhanced with the MMX mesalamine delivery system. The levels of compliance and disease recurrence assessed in this study were compared to historical data with current 5-aminosalicylate (5-ASA) oral formulations.

### Number of subjects (planned and analyzed):

Approximately 360 subjects were expected to enter the study: 288 were expected to enter the acute phase, and of these, approximately 115 were expected to enter the maintenance phase. Additionally, approximately 72 subjects were expected to enter the maintenance phase directly. A total of 290 subjects were enrolled into this study. Of the 290 subjects, 138 (47.6%) subjects were enrolled into the acute phase, and of these, 56 subjects continued into the maintenance phase. A total of 208 (71.7%) subjects entered the maintenance phase either directly or after completion of the acute phase.

### Diagnosis and main criteria for inclusion:

Male and female adult subjects (≥18 years) with mild to moderate UC in flare or quiescent, with a previous diagnosis of UC confirmed by histology and endoscopy or histology and radiology.

### Test product, dose and mode of administration, batch number:

In the acute phase, subjects received 2.4-4.8g/day QD (two to four 1.2g tablets, respectively), of MMX mesalamine to be taken orally. In the maintenance phase, subjects received 2.4g/day QD (two 1.2g tablets) of MMX mesalamine to be taken orally. MMX mesalamine was supplied through local pharmacies; lot numbers were not recorded.

### Duration of treatment:

Subjects who qualified for the maintenance phase following successful completion of the acute phase were in the study for approximately 14 months. Subjects who entered the maintenance phase directly were in the study for approximately 12 months.

### Reference therapy, dose and mode of administration, batch number:

None
### Criteria for Evaluation:

**Efficacy:** Efficacy was evaluated through sigmoidoscopy and mucosal appearance, Physician’s Global Assessment (PGA), UC symptoms assessment (rectal bleeding, bowel movements, urgency, and abdominal pain), and histology.

**Quality of Life:** Quality of life assessments included the SF-12 v2, the SIBDQ, and the WPAI:SHP. In addition, subjects completed a Health Economics Outcomes Research (HEOR) survey at the baseline visit.

**Safety and Tolerability:** Safety was evaluated by collecting spontaneously reported adverse events (AEs) at regular intervals throughout the study and assessment of clinical laboratory parameters, vital signs, and physical examination findings.

### Statistical Methods:

No formal hypothesis testing was performed on the demographic, baseline characteristic, and safety data for this study.

Categorical variables were summarized using frequencies and percentages. Percentage calculations were based on the number of subjects for whom there were non-missing data. Continuous variables were summarized using descriptive statistics (number of subjects with an observation [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]).

### Primary Efficacy

The acute phase efficacy population included all subjects who, during the acute phase, took at least 1 dose of study medication and had at least 1 post-dose efficacy assessment. The maintenance phase efficacy population included all subjects who, during the maintenance phase, took at least 1 dose of study medication and had at least 1 post-dose efficacy assessment. All efficacy and medical outcome (QoL and productivity) endpoints during each study phase were analyzed using the respective efficacy population.

The proportion of subjects with clinical recurrence (defined as 4 or more bowel movements per day above the subject’s normal frequency and associated with any of the following: urgency, abdominal pain or rectal bleeding) at Visit M3 (Month 6) of the maintenance phase was presented together with the 95% CIs. If a subject had >21 consecutive days of symptom data missing, then clinical recurrence was not determined and was set to missing unless the subject had previously been determined to have clinical recurrence. A sensitivity analysis was performed where subjects who withdrew due to reasons other than lack of efficacy were also set to missing.

### Key Secondary Efficacy

The proportion of subjects with clinical recurrence at Month 12 of the maintenance phase, together with associated 95% CIs, was presented. Time to clinical recurrence was defined as the time in days from the first dose of study medication in the maintenance phase to the time of clinical recurrence, defined as the first day of the clinical recurrence window. The proportion of subjects with clinical recurrence during the maintenance phase was presented by compliance defined as <80% compliant, 80-120% compliant, and >120% compliant. The proportion of subjects with quiescent UC (scores of 0 for both rectal bleeding and bowel movements for each of the last available 3 days immediately prior to a study visit) at each visit during the maintenance phase was tabulated. A summary of subjects with quiescent UC at the end of the acute phase (Visit A3) was also presented. Endoscopic remission (normal or mild mucosal appearance as assessed by an endoscopy score ≤1) at Visit M1 (Month 0) and Visit M5 (Month 12) of the maintenance phase were summarized. The mucosal appearance (endoscopy score) was summarized at each timepoint during the maintenance phase using frequencies and percentages.
Safety

The acute phase safety population included all subjects who, during the acute phase, took at least 1 dose of study medication. The maintenance phase safety population included all subjects who, during the maintenance phase, took at least 1 dose of study medication. All safety endpoints during each study phase were summarized using the respective safety population.

Adverse Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 11. Each AE was classified as either a treatment-emergent AE (TEAE) during the acute phase or the maintenance phase or a post-treatment AE. All AEs were collected from the time the informed consent was signed until 7 days following the last dose of MMX mesalamine. Treatment-emergent adverse events were also summarized by MedDRA system organ class and preferred term for each of the acute and maintenance phases of the study, as well as by maximum severity. All laboratory values were summarized and listed. Summary statistics were presented for the vital signs parameters by study timepoint within each phase of the study, and changes from baseline were also summarized at each post-baseline timepoint during the acute and maintenance phases. Physical examination data were listed by subject.

SUMMARY – CONCLUSIONS

Study Population

A total of 290 subjects were enrolled in this study; 138 subjects were enrolled into the acute phase, and of these, 56 subjects continued into the maintenance phase. A total of 208 subjects entered the maintenance phase either directly or after completion of the acute phase. Approximately 41% of subjects who entered the acute phase completed it (56/138 subjects), and two-thirds of subjects who were enrolled into the maintenance phase completed it (138/208 subjects). Of the subjects who prematurely withdrew from either study phase, the most common reason for withdrawal was lack of efficacy/relapse. In this population of subjects with mild to moderate or quiescent UC, the median age was 43.0 years in the acute phase and 46.0 years in the maintenance phase. Slightly over half of all subjects were female, and the majority of subjects in both treatment phases were Caucasian.

Efficacy Results

The primary efficacy analysis was the proportion of subjects with clinical recurrence at Month 6 of the maintenance phase. In the maintenance phase efficacy population, 23.5% of subjects had clinical recurrence at Month 6. Thus, >75% of subjects did not have disease recurrence after 6 months of maintenance treatment with MMX mesalamine. Results were similar between subjects who were previously treated in the acute phase and those who entered directly into the maintenance phase. As an ad hoc analysis, clinical recurrence at Month 6 of the maintenance phase was also calculated by subject’s quiescent UC status; that is, by whether subjects had quiescent UC per protocol at Month 0 of the maintenance phase. The results were similar to those of the primary analysis, as 23.6% of subjects with quiescent UC at Month 0 had clinical recurrence at Month 6. A sensitivity analysis was performed in which subjects who withdrew due to reasons other than lack of efficacy were also set to missing. Results of the sensitivity analysis show that only 17.1% of subjects had clinical recurrence at Month 6 of the maintenance phase.

In the maintenance phase efficacy population, 35.6% of subjects had clinical recurrence at Month 12. As an ad hoc analysis, clinical recurrence at Month 12 of the maintenance phase was also calculated by subject’s quiescent UC status. The results were similar to those of the secondary analysis, as 36.2% of subjects with quiescent UC at Month 0 had clinical recurrence at Month 12. Results of the sensitivity analysis show that 24.2% of subjects had clinical recurrence at Month 12 of the maintenance phase.
Efficacy Results (cont)

The proportion of subjects with clinical recurrence at Month 6 during the maintenance phase was summarized by compliance. Among the subjects who were 80-120% compliant, only 20.9% had clinical recurrence at Month 6. In comparison, 36.1% of subjects who were <80% compliant with treatment had clinical recurrence at Month 6. The majority of subjects in the maintenance phase efficacy population were compliant (160/207, 77.3%). Among the subjects who were 80-120% compliant, 31.2% had clinical recurrence at Month 12. In comparison, over half (52.5%) of subjects who were <80% compliant with treatment had clinical recurrence at Month 12.

All subjects entering the maintenance phase, either directly at study entry or after completion of the 2-month acute phase, were to have quiescent UC. However, over 25% of subjects who entered the maintenance phase did not have quiescent UC at Month 0 according to the definition used in this study. The proportion of subjects with quiescent UC during the maintenance phase was highest at Month 9, at 83.3%. At the end of the 12-month maintenance phase, 80.2% of subjects had quiescent UC. At Month 12, 93.9% of subjects were in endoscopic remission and 65.2% of subjects had a normal mucosal appearance.

At baseline of the acute phase, 30.0% had a score of 0 for bowel movement (defined as 0-1 more than normal per day), 29.2% had a score of 0 for rectal bleeding (defined as no rectal bleeding), 19.2% had a score of 0 for urgency (defined as no sense of urgency), and 41.5% had a score of 0 for abdominal pain (defined as no abdominal pain). At Month 2 of the acute phase, the proportions of subjects with scores of 0, reflective of no UC symptoms, increased substantially, as scores of 0 were reported by 57.5% for bowel movement, 69.8% for rectal bleeding, 50.0% for urgency, and 71.7% for abdominal pain. The proportions of subjects with scores of 0 at baseline of the maintenance phase were much higher than those in the acute phase because subjects in the maintenance phase were to have quiescent disease. At baseline, scores of 0 were reported by 76.8% of subjects for bowel movement, 95.1% for rectal bleeding, 67.8% for urgency, and 79.7% for abdominal pain. After 6 months of maintenance treatment with MMX mesalamine, greater proportions of subjects had scores of 0 for 3 of the UC symptoms (84.7% for bowel movement, 80.7% for urgency, and 85.3% for abdominal pain). After 12 months of maintenance treatment, the proportions of subjects with UC symptoms scores of 0 remained high (83.3% for bowel movement, 92.9% for rectal bleeding, 78.6% for urgency, 87.3% for abdominal pain), demonstrating the efficacy of MMX mesalamine during long-term treatment.

A tertiary objective in this study was to compare the percentage of subjects with clinical recurrence with published data from Sunanda Kane (2003). Due to the different population used in the Kane study (subjects had been in UC remission for more than 6 months, had a shorter disease duration, and were based at 1 clinical site that was closely monitored), no statistical comparisons were made; the data were compared descriptively only. Kane et al. 2003 reported that by 6 months, 12/99 subjects (12%) in her study had clinical recurrence of their disease. The proportion of subjects with clinical recurrence at Month 6 in this study was 23.5%. A sensitivity analysis, in which subjects who withdrew due to reasons other than lack of efficacy were also set to missing, showed that 17.1% of subjects had clinical recurrence at Month 6 of the maintenance phase.

Quality of Life Results

Non-quiescent UC subjects who received MMX mesalamine treatment during the acute phase showed statistically and clinically significant improvement on almost all measured aspects of health-related QoL using the SF-12, SIBDQ, and WPAI:SHP. Furthermore, quiescent patients who received MMX mesalamine treatment during the maintenance phase showed no declines in any aspect of health-related QoL. When subjects were stratified based upon their clinical outcomes, such as bowel movement frequency and rectal bleeding severity, health-related QoL varied directly, such that those with poor clinical outcomes had worse health-related QoL than those with better clinical outcomes. Improvement in these clinical outcomes was accompanied by improvement in health-related QoL.
Safety Results

The median duration of treatment was 57.0 days during the acute phase and 358.5 days during the maintenance phase.

Of the 137 subjects in the acute phase safety population, 57 (41.6%) had at least 1 TEAE. The most frequently reported TEAEs during the acute phase were abdominal pain and headache (each reported by 3.6% of subjects). Treatment-related TEAEs occurred infrequently during the acute phase as 12 (8.8%) subjects in the acute phase safety population had at least 1 treatment-related TEAE. The most frequently reported treatment-related TEAEs by system organ class were gastrointestinal disorders (4 subjects, 2.9%). Only 1 treatment-related TEAE occurred in more than 1 subject, abdominal pain (2 subjects, 1.5%). All other treatment-related TEAEs during the acute phase occurred in only 1 subject each.

Of the 208 subjects in the maintenance phase safety population, 123 (59.1%) had at least 1 TEAE. The most frequently reported TEAE during the maintenance phase was sinusitis (5.8% of subjects). Treatment-related TEAEs also occurred infrequently during the maintenance phase as 24 (11.5%) subjects in the maintenance phase safety population had at least 1 treatment-related TEAE. As with the acute phase, the most frequently reported treatment-related TEAEs by system organ class were gastrointestinal disorders (14 subjects, 6.7%). The most frequently reported treatment-related TEAE was abdominal distension, occurring in 3 (1.4%) subjects during the maintenance phase.

No subject died during the study. Three subjects had TEAEs that were serious during the acute phase; none of these was considered related to study drug. During the maintenance phase, 9 subjects had TEAEs that were serious; 1 subject had a treatment-emergent serious adverse event (SAE) considered by the investigator to be related to study drug (pancreatitis). During the acute phase, 2 subjects (1.5%) had TEAEs that led to withdrawal from the study. Neither of these events (abdominal pain and anemia) was considered serious. During the maintenance phase, 15 subjects (7.2%) had TEAEs that led to withdrawal from the study. Each TEAE that led to withdrawal was reported by 1 subject each except for exacerbation of UC (coded as colitis ulcerative; 6 subjects, 2.8%) and abdominal pain (2 subjects, 1.0%).

There was 1 pregnancy during the study. The subject, who had no difficulties during the pregnancy or delivery, gave birth to a healthy baby girl.

There were no notable median changes from baseline in any of the laboratory parameters studied. Additionally, there were no notable trends or changes from baseline in blood pressure or pulse measurements during either treatment phase.
**Name of Sponsor/Company:** Shire  
**Name of Finished Product:** LIALDA®  
**Name of Active Ingredient:** MMX® Mesalazine (Mesalamine)

| Individual Study Table Referring to Part of the Dossier | Volume: <Insert volume number> | Page: <Insert page number> | (for National Authority Use only) |

**Conclusions**

Once daily MMX mesalamine was efficacious in maintaining quiescence of UC as evidenced by the following:

- Over 75% of subjects did not have clinical recurrence at 6 months and nearly 65% did not have clinical recurrence at 12 months. No clinically meaningful difference was observed in the incidence of clinical recurrence between subjects who were previously treated in the acute phase and those who directly entered the maintenance phase.
- Treatment compliance was correlated with better outcomes.
- The majority of subjects had quiescent UC at 12 months of maintenance treatment.
- The vast majority of subjects were still in endoscopic remission at 12 months and 65% of subjects had a normal mucosal appearance at 12 months of maintenance treatment.
- The proportions of subjects with UC symptoms scores of 0 remained high at 12 months of maintenance treatment.
- Subjects’ QoL improved during the acute phase, and the improvements were sustained during the maintenance phase.

The safety data from adult subjects with UC treated with MMX mesalamine 2.4–4.8g/day dosed QD in this study suggests that the study medication was well tolerated. There were no signals of specific long-term safety concerns. Additionally, the long-term safety profile of MMX mesalamine was considered comparable to that of other 5-ASA treatments. There were no unexpected related AEs observed in this study.

**Date of the Report:** 21 Jan 2010