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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.

STUDY SYNOPSIS

Name of Sponsor/Company: Shire Development, LLC **Name of Finished Product:** LIALDA®/MEZAVANT® **Name of Active Ingredient:** MMX® mesalazine	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	(for National Authority Use only)

Title of Study: A Phase 3b/4, Open-label, Multicenter, Prospective Study to Evaluate the Effect of Remission Status on the Ability to Maintain or Achieve Clinical and Endoscopic Remission During a 12-Month, Long-term Maintenance Phase With 2.4g/day MMX® Mesalamine/mesalazine Once Daily in Adult Subjects With Ulcerative Colitis

Investigators: This was a multicenter study with 2 coordinating principal investigators:

[redacted] MD, PhD, [redacted], The Netherlands

[redacted] MD, [redacted], USA

Study Centers: The study was conducted at 83 sites in 14 countries (Belgium, Canada, Colombia, Czech Republic, France, Hungary, India, Ireland, Poland, Romania, South Africa, Spain, United Kingdom, United States).

Publications (References): None

Study Period: 22 Jun 2010 (First Subject Consented) to 14 Dec 2012 (Last Patient Last Visit)	**Phase of Development:** 3b/4

Objectives: The primary objective of this study was to compare the percentage of subjects in complete (clinical and endoscopic) remission after 12 months of maintenance treatment with 2.4g/day MMX mesalamine/mesalazine given QD between subjects who were in complete remission and subjects who were in partial remission at the end of 8 weeks acute treatment with 4.8g/day MMX mesalamine/mesalazine given QD.

Secondary objectives were:

- To compare the percentage of subjects in clinical remission at 12 months between subjects who were in complete remission and subjects who were in partial remission at the end of 8 weeks acute treatment.
- To compare the time to relapse between subjects who were in complete remission and subjects who were in partial remission at the end of 8 weeks acute treatment.
- To compare the percentage of subjects who achieved or maintained mucosal healing (endoscopy score ≤1) at 12 months between subjects who were in complete remission and subjects who were in partial remission at the end of 8 weeks acute treatment.
- To assess the improvement in symptoms at 3 and 8 weeks of acute treatment.
- To assess the percentage of subjects who achieved complete remission at the end of 8 weeks acute treatment.
- To assess the safety and tolerability of MMX mesalamine/mesalazine.

Name of Sponsor/Company: Shire Development, LLC	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	(for National Authority Use only)
Name of Finished Product: LIALDA®/MEZAVANT®		
Name of Active Ingredient: MMX® mesalazine		

Tertiary objectives were:

- To assess improvement in quality of life by showing an improvement in subjects' ability to perform daily activities over time from Baseline (Visit 0) to 3 weeks, 8 weeks, and 12 months.
- To assess improvement in pain and discomfort from Baseline (Visit 0) to 3 weeks, 8 weeks, and 12 months.
- To assess improvement in mental health (feeling less discouraged and depressed) associated with worry about the disruption of an acute ulcerative colitis (UC) flare from Baseline Visit (Visit 0) to 3 weeks, 8 weeks, and 12 months.
- To assess reduction in work loss and activity impairment and increase in productivity at work from Baseline (Visit 0) to 3 weeks, 8 weeks, and 12 months.
- To examine the changes in histology score over time.

Methodology: This was a Phase 3b/4, open-label, multicenter, prospective study with an 8-week single-arm, open-label acute phase with MMX mesalamine/mesalazine 4.8g/day given QD and a 12-month single-arm, open-label Maintenance Phase with MMX mesalamine/mesalazine 2.4g/day given QD. Subjects who were suspected to have an acute flare of mild to moderate UC, with a known diagnosis established by sigmoidoscopy or colonoscopy with compatible histology, were screened. Subjects with a suspected, but not confirmed diagnosis of mild to moderate UC, were also screened; however, the diagnosis of UC must have been confirmed by sigmoidoscopy or colonoscopy with compatible histology prior to the Baseline Visit. For the purpose of this study, the standard ulcerative colitis disease activity index (UC-DAI) scale was modified so that an endoscopy score of mild disease did not include friability; instead friability was scored as 2: moderate disease. Disease activity at screening was confirmed by the modified UC-DAI score calculation at baseline. The modified UC-DAI score consisted of 4 parameters: rectal bleeding, stool frequency, endoscopy, and Physician's Global Assessment (PGA). Each parameter was scored on a scale from 0-3 and, therefore, the maximum total modified UC-DAI score was 12. Study visits occurred during the Screening Period, at baseline, Week 3, Week 8/Month 0, Month 3, Month 6, Month 9, and Month 12 (Final/Withdrawal).

Number of Subjects (Planned and Analyzed): It was anticipated that approximately 875 subjects would be screened in order to enroll the required 695 subjects into the study. It was expected that 306 subjects would complete through Month 12 of the Maintenance Phase. A total of 894 subjects were screened and 722 subjects were enrolled into the study. Of the 639 subjects who completed the Acute Phase, 167 subjects did not achieve a CR or PR and were discontinued at the end of the Acute Phase. A total of 373 subjects completed the study and 349 subjects were prematurely withdrawn from the study.

Diagnosis and Main Criteria for Inclusion: Male and female adult subjects who were suspected to have an acute flare of mild to moderate UC, or subjects who were suspected to have a new diagnosis of UC, were screened. If the subject was on a maintenance therapy of 5-aminosalicylic acid (5-ASA; excluding MMX mesalamine/mesalazine), the dose needed to be stable and ≤3.2g/day. Stable maintenance therapy was defined as no change in dose, or no initiation of 5-ASA, from the onset of the acute flare through the Baseline Visit. Acute flare of mild to moderate UC was defined by a modified UC-DAI score of 4-10 inclusive with an endoscopy score of ≥1 and a PGA of ≤2.

Name of Sponsor/Company: Shire Development, LLC	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	(for National Authority Use only)
Name of Finished Product: LIALDA®/MEZAVANT®		
Name of Active Ingredient: MMX® mesalazine		

Investigational Product, Dose, Mode of Administration, and Lot/Batch Number(s): The investigational product was MMX mesalamine/mesalazine (MMX® mesalazine) 1.2g tablets for oral administration at doses of 4.8g/day QD (Acute Phase) and 2.4g/day QD (Maintenance Phase). Bulk batch numbers used in this study were as follows: [redacted] (Belgium, Canada, Czech Republic, France, Germany, Hungary, Ireland, Romania, South Africa, Spain, United Kingdom, United States), [redacted] (Canada, Colombia, India, United States), [redacted] (Belgium, Columbia, Czech Republic, France, Hungary, India, Ireland, Romania, South Africa, Spain, Great Britain), and [redacted] (Belgium, Canada, Columbia, Czech Republic, France, Hungary, India, Ireland, Poland, Romania, South Africa, Spain, United Kingdom, United States).

Duration of Treatment: Up to 14 months (including a 3-10 day screening period, an 8-week Acute Phase, a 12-month Maintenance Phase, and a 7-day follow-up period).

Reference therapy, dose and mode of administration, batch number: Not applicable, as this was a single arm, open-label study.

Criteria for Evaluation:

Primary Efficacy Endpoint: The primary efficacy endpoint (complete remission) was evaluated through the modified UC-DAI score, which included endoscopy, PGA, and symptom assessments (rectal bleeding and stool frequency).

- **Complete remission** was defined as a modified UC-DAI score ≤1 with a score of 0 for both rectal bleeding and stool frequency and at least a 1-point reduction in endoscopy score from baseline.
- **Partial remission** was defined as a modified UC-DAI score ≤3 with a combined stool frequency and rectal bleeding score of ≤1 and not in complete remission.
- **Clinical remission** was defined as stool frequency and rectal bleeding scores equal to 0.
- **Endoscopic remission** was defined as an endoscopy score of ≤1.
- **Modified UC-DAI score**: For the purpose of this study, the standard UC-DAI scale was modified so that an endoscopy score of mild disease did not include friability; instead friability was scored as 2: moderate disease. Disease activity at screening was confirmed by the modified UC-DAI score calculation at baseline. The modified UC-DAI score consisted of 4 parameters: rectal bleeding, stool frequency, endoscopy, and PGA. Each parameter was scored on a scale from 0-3 and, therefore, the maximum total modified UC-DAI score was 12.

Secondary Efficacy Endpoints: Secondary efficacy endpoints were evaluated by clinical remission, relapse, mucosal healing, symptom improvement, and complete remission at Week 8.

- **Relapse** was defined as the need for alternative treatment for UC (including surgery).
- **Mucosal healing** was defined as an endoscopy score ≤1 on the UC-DAI.
- **Improvement in UC symptoms** was measured by assessing improvement in rectal bleeding and stool frequency from baseline to Weeks 3 and 8 of acute treatment. Improvement was defined as at least a 1-point reduction in the symptom score from baseline to each assessment point.

Name of Sponsor/Company: Shire Development, LLC	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	(for National Authority Use only)
Name of Finished Product: LIALDA®/MEZAVANT®		
Name of Active Ingredient: MMX® mesalazine		

Tertiary Endpoints: Tertiary endpoints were evaluated through Health Economics and Outcomes Research (HEOR) using the following questionnaires: The Short Form 12v2 (SF-12v2), the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), and the Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis (WPAI:UC). Tertiary endpoint evaluations also included changes in histology assessments over time.

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

Statistical Methods: Continuous variables were summarized using number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized using number of observations and percentages. For the Acute Phase, summaries were presented overall only. For the Maintenance Phase, summaries were presented by remission group and overall. Remission group (complete remission or partial remission) was defined according to remission status at Month 0 of the Maintenance Phase. The Acute Phase endpoint was defined as data from the Week 8, or early withdrawal visit if the subject withdrew prior to Week 8. The Maintenance Phase endpoint was defined as data from the Month 12, or early withdrawal visit if the subject withdrew during the Maintenance Phase prior to Month 12.

Primary Efficacy Analysis: The primary efficacy endpoint was the proportion of subjects in complete (clinical and endoscopic) remission after 12 months of maintenance treatment with 2.4g/day MMX mesalamine/mesalazine given QD. The primary analysis compared the proportion of subjects in complete (clinical and endoscopic) remission after 12 months of maintenance treatment between subjects who were in complete remission and subjects who were in partial remission at the end of 8 weeks acute treatment with 4.8g/day MMX mesalamine/mesalazine given QD (i.e., at Month 0 of the Maintenance Phase).

The primary analysis was performed on the Maintenance Phase Efficacy Population which included all subjects who, during the Maintenance Phase, took at least 1 dose of investigational product and had at least 1 post-dose efficacy assessment (at least 1 valid diary or eCRF efficacy entry).

The null hypothesis tested was that the proportion of subjects who were in complete remission at Month 12 was equal between the group of subjects who were in complete remission at Month 0 and the group who were in partial remission at Month 0. The proportion of subjects in complete remission was compared between remission groups using a logistic regression model with a term for remission group only. The odds ratio comparing the 2 groups, together with the 95% confidence interval (2-sided) and associated p-value, was presented.

Health Economics and Outcomes Research Analysis: All Health-related Quality of Life (HRQL) data and Work-Related Outcomes (WRO) were listed. Results from the SF-12v2, SIBDQ, and WPAI:UC assessments were summarized.

Safety: Adverse events were coded using MedDRA Version 15.0. Coding included system organ class and preferred term. All verbatim descriptions and coded terms were listed for all adverse events (AEs). One listing was produced for all AEs (serious and not serious) and a separate listing was also produced for serious AEs only. Adverse events were classified as either pre-treatment AEs, treatment-emergent AEs

Name of Sponsor/Company: Shire Development, LLC	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	(for National Authority Use only)
Name of Finished Product: LIALDA®/MEZAVANT®		
Name of Active Ingredient: MMX® mesalazine		

(TEAEs); during the Acute Phase or the Maintenance Phase), or post-treatment AEs. Summaries of AEs were presented separately for the acute and Maintenance Phases for the Acute Phase Safety Population (overall only) and for the Maintenance Phase Safety Population (overall and by remission group) respectively:

- The Acute Phase Safety Population included all subjects who, during the Acute Phase, took at least 1 dose of investigational product.
- The Maintenance Phase Safety Population included all subjects who, during the Maintenance Phase, took at least 1 dose of investigational product.

Clinical laboratory data (hematology, clinical chemistry, and fecal calprotectin from the stool assessments) and vital signs data were presented using summary statistics (number of observations [N], mean, standard deviation [SD], median, minimum, and maximum).

Results:

Study Population:
A total of 722 subjects were enrolled into the study. Of these, 717 (99.3%) subjects were treated in the Acute Phase (Acute Phase Safety Population) and 461 (63.9%) subjects were treated in the Maintenance Phase (Maintenance Phase Safety Population). A total of 373 (51.7%) subjects completed the study. Among the 349 (48.3%) subjects who did not complete the study, the most common primary reason for withdrawal was lack of efficacy in 17 (2.4) subjects in the Acute Phase and 40 (8.5%) subjects in the Maintenance Phase. Of the 461 subjects in the Maintenance Phase Safety Population, 183 subjects were in complete remission at the end of the Acute Phase and 278 subjects were in partial remission at the end of the Acute Phase. Overall demographic characteristics for the Maintenance Phase were similar to those for the Acute Phase and were well-balanced between the 2 groups. Subjects in the Acute Phase had a median age of 42.0 years; 56.4% were male and the majority of subjects (85.9%) were not Hispanic or Latino. Approximately half (55.5%) of the subjects were white and 31.0% of non-white subjects were Asian. For the Acute Phase Safety Population, the median time since diagnosis was 37.7 months and most subjects' UC was diagnosed through a colonoscopy (78.9%) and 99.4% of all subjects had compatible histology. The classification of disease in the Acute Phase Safety Population was most commonly left-sided (77.7%); 15.3% of subjects had pancolitis.

Efficacy Results:
The primary efficacy endpoint was the proportion of subjects in complete remission at 12 months. Complete remission was defined as a modified UC-DAI score ≤1 with a score of 0 for both rectal bleeding and stool frequency and at least a 1 point reduction in endoscopy score from the Baseline Visit.

- For the Maintenance Phase Efficacy Population, 87 (47.8%) subjects who were in complete remission at Month 0 were in complete remission at Month 12, compared to 72 (26.0%) subjects who were in partial remission at Month 0. The odds ratio of complete to partial remission was 2.61 (95% confidence interval: 1.76, 3.87) and the difference between the 2 groups was statistically significant ($p<0.001$); thus the primary endpoint was met.
- Results for the sensitivity analyses (Maintenance Phase Positive Baseline Biopsy Population and Maintenance Phase Final on Treatment Assessment [FoTA]) supported the primary endpoint results.

Name of Sponsor/Company: Shire Development, LLC	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	(for National Authority Use only)
Name of Finished Product: LIALDA®/MEZAVANT®		
Name of Active Ingredient: MMX® mesalazine		

Overall, results for secondary efficacy endpoints supported the primary endpoint results:

- Clinical Remission at Month 12: At the end of the Maintenance Phase, 107 (58.8%) subjects who were in complete remission at Month 0 were in clinical remission at Month 12, compared to 112 (40.4%) subjects who were in partial remission at Month 0. The difference between the 2 groups was statistically significant ($p<0.001$).
- Time to Relapse at Month 12: At the end of the Maintenance Phase, relapse rates were low in both the complete and partial remission groups (6.0% and 10.5%).
- Mucosal Healing at Month 12: The proportion of subjects with mucosal healing at Month 12 was higher in the complete remission group (76.4%) than in the partial remission group (63.5%).

Acute Phase endpoints:

- Symptom Improvement During the Acute Phase: Rectal bleeding and stool frequency symptoms improved over time. By Week 8, approximately 60% of subjects had improvement in both rectal bleeding and stool frequency symptoms.
- Remission at the end of the Acute Phase 186 (25.9%) subjects were in complete remission and 282 (39.3%) subjects were in partial remission.
- Supportive Assessments: At the end of the Acute Phase, improvements were observed for the following individual assessments: total modified UC-DAI score, rectal bleeding and stool frequency scores, PGA score, and endoscopy score. During the Maintenance Phase, these improvements were maintained at all time points and the Month 12 outcomes were better for the complete remission group compared to the partial remission group.

Results for tertiary efficacy endpoints also supported the primary endpoint results:

- Health Economics and Outcomes Research: The results of the HEOR analyses provided evidence for improvements in all measured aspects of HRQL and WRO during the Acute Phase; these improvements were sustained during the Maintenance Phase of the study.
- Histology: Compared to baseline, median histology scores were lower at the end of the Acute Phase and remained lower during the Maintenance Phase and histology scores were better for subjects who had been in complete remission at the end of the Acute Phase compared to those who had been in partial remission at the end of the Acute Phase.

Safety Results

Treatment-emergent AEs were more frequent in the partial remission group (139 of 278 subjects, 50%) than in the complete remission group (68 of 183 subjects, 37.2%). The frequency of treatment-related TEAEs was generally low (Acute Phase: 43 of 717 subjects, 6.0%; Maintenance Phase complete remission 7 of 183 subjects, 3.8%; Maintenance Phase partial remission 24 of 278 subjects, 8.6%) and most TEAEs were mild to moderate in severity.

During the Acute Phase, TEAEs were most frequently reported in the gastrointestinal disorders, general disorders and administration site conditions system organ classes and the most frequently reported individual TEAEs were drug ineffective in 50 (7.0%) subjects and headache in 15 (2.1%) subjects. During the Maintenance Phase, TEAEs were most frequently reported in the gastrointestinal disorders, infections

Name of Sponsor/Company: Shire Development, LLC	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	(for National Authority Use only)
Name of Finished Product: LIALDA®/MEZAVANT®		
Name of Active Ingredient: MMX® mesalazine		

and infestations, and general disorders and administration site conditions system organ classes and the most frequently reported individual TEAEs were UC (complete remission in 14, 7.7% of subjects; partial remission in 29, 10.4% of subjects) and drug ineffective (complete remission in 2, 1.1% of subjects; partial remission in 20, 7.2% of subjects). The frequency of TEAEs was higher in the partial remission group (246 events) compared to the complete remission group (126 events) and the most notable difference between the 2 groups was for drug ineffective (complete remission 2 subjects; partial remission 20 subjects).

Treatment-related TEAEs occurred infrequently during both the Acute Phase and Maintenance Phase and those most frequently reported were headache in 7, 1.0% of subjects during the Acute Phase, and UC (complete remission in 2, 1.1% of subjects; partial remission in 7, 2.5% of subjects and drug ineffective (complete remission in 0 subjects; partial remission in 7, 2.5% of subjects) during the Maintenance Phase.

There were no unexpected safety concerns in this study. One subject died during the Maintenance Phase of the study due to a cerebrovascular accident complicated by subsequent aspiration. The subject died after being withdrawn from the study and none of the events that led to his death were considered to be related to investigational product. The frequency of non-fatal, serious TEAEs was low (13, 1.8% of subjects during the Acute Phase, and 4, 2.2% and 10, 3.6% of subjects respectively for the Maintenance Phase complete remission and partial remission groups). The frequencies of treatment-related serious TEAEs were also low: during the Acute Phase 3 subjects each experienced 1 treatment related serious TEAE (exacerbation of UC, acute pancreatitis, and lung infection), and during the Maintenance Phase 1 subject had worsening diarrhea that was reported as a serious TEAE and was considered treatment-related.

Similarly, the frequency of TEAEs that led to withdrawal was low (47, 6.6% subjects during the Acute Phase and 15, 8.2% and 42, 15.1% subjects respectively for the Maintenance Phase complete and partial remission groups). During the Acute Phase the most frequently reported TEAEs that led to withdrawal were drug ineffective (24, 3.3% subjects), UC (9, 1.3% subjects), and diarrhea (3, 0.4% subjects). During the Maintenance Phase the most frequently reported TEAEs that led to withdrawal were UC (complete remission in 10, 5.5% subjects; partial remission in 17, 6.1% subjects) and drug ineffective (complete remission in 2, 1.1% subjects; partial remission in 18, 6.5% subjects). The most notable difference between the 2 groups was for drug ineffective.

One subject had a serious TEAE of acute pancreatitis during the Acute Phase of the study that was considered to be related to investigational product. The pancreatitis was initially reported as moderate, and the subject was withdrawn from the study due to this event. The subject continued to experience acute pancreatitis, but the severity and seriousness were reduced to mild and non-serious and the event resolved on Day 97.

In summary, there were no unexpected safety signals and these data are consistent with other studies of MMX mesalamine and 5-ASAs in general.

Conclusions:
The overall conclusions for this Phase 3b/4, multicenter, open-label study are as follows:

- The primary endpoint was met, showing that there was a statistically significant ($p<0.001$) difference in the proportion of subjects in complete remission at Month 12 between subjects who were in complete remission at Month 0 compared to subjects who were in partial remission at Month 0. The primary endpoint results were supported by the sensitivity analyses.

Name of Sponsor/Company: Shire Development, LLC	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	(for National Authority Use only)
Name of Finished Product: LIALDA®/MEZAVANT®		
Name of Active Ingredient: MMX® mesalazine		

- The primary endpoint result was supported by analyses of the following secondary endpoints: clinical remission, mucosal healing, and relapse at Month 12. Subjects who were in complete remission at Month 0 generally had better outcomes than subjects who had been in partial remission at Month 0.
- The results of the HEOR analyses provided evidence for improvements in all measured aspects of HRQL and WRO during the Acute Phase. These improvements were sustained during the Maintenance Phase of the study.
- Histology results supported the primary and secondary endpoints showing that subjects who were in complete remission at the end of the Acute Phase generally showed histological improvement at the end of the Maintenance Phase compared to subjects who were in partial remission at the end of the Acute Phase.
- The safety data from adult subjects who had been experiencing an acute flare of mild to moderate UC, or who had been diagnosed with UC at the time of entry into the study, showed that MMX mesalamine/mesalazine administered QD at 4.8g/day during the Acute Phase of the study and at 2.4g/day during the Maintenance Phase of the study was well tolerated. There were no new signals of specific acute or long term safety concerns. Additionally, the safety profile of MMX mesalamine/mesalazine was comparable between subjects who had been in complete remission at the end of the Acute Phase compared to subjects who had been in partial remission at the end of the Acute Phase. There were no unexpected related AEs observed in this study.

Date of Report: 17 May 2013