

10.2 STUDY PROTOCOL MPUC3004

10.2.1 Protocol Summary

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Use of Mesalamine Pellet Formulation 1.5 g QD to Maintain Remission from Mild to Moderate Ulcerative Colitis.

Study Centers

A total of 257 patients from 37 centers participated in this study. There were 29 study sites in the US and eight in Russia. The US sites had an average of 3.6 patients per site for a total of 103 randomized patients. The Russian sites had an average of 19.3 patients per sit for a total of 154 randomized patients.

See Appendix 10.4.2 for a chart of study centers and investigators participating in Study MPUC3004.

Study Period

24 December 2004 to 08 August 2007

Objectives

The primary study objective was to assess the ability of encapsulated mesalmine granules (eMG) at 1.5 g once daily to maintain remission of mild to moderate ulcerative colitis (UC) as measured by rectal bleeding and endoscopic mucosal appearance as compared with placebo after six months of treatment.

The secondary objective was to compare the safety and tolerability of long-term dosing with eMG at 1.5 g once daily compared with placebo in the maintenance of remission from mild to moderate UC.

Study Design

This was a randomized, multi-center, double-blind, placebo-controlled Phase 3 study to compare the maintenance of remission in patients with demonstrated mild to moderate ulcerative colitis using eMG 1.5 g once daily as compared to placebo. Maintenance was measured by rectal bleeding and endoscopic mucosal appearance after six months of treatment. For patients who discontinued the study prior to Month 6, an end of study visit was conducted including sigmoidoscopy and the rectal bleeding and mucosal appearance scores from that visit were used to determine treatment failure or success.

MO Comment: The study design appears adequate to achieve the study objective.

10.2.2 Inclusion Criteria

1. Age older than 18
2. Males or non-pregnant, non-lactating females of non-child-bearing potential or agreeing to an acceptable form of birth control as outlined in the protocol.
3. Historically confirmed diagnosis of mild to moderate UC in remission at least one month, but not more than 12 months with a history of at least one flare within the past 12 months
4. Confirmed current remission defined as a rectal bleeding score on revised Sutherland DAI of 0 (none) *and* sigmoidoscopy score of 0 to 1 for mucosal appearance (0=intact mucosa; 1=erythema, decreased vascular pattern, granularity, no mucosal hemorrhage).

10.2.3 Exclusion Criteria

1. History of receiving immunosuppressive therapy (e.g., azathioprine, 6-mercaptopurine) or corticosteroids (oral, intravenous, or topical rectal) within 30 days prior to screening.
2. History of infectious, ischemic, or immunologic disease involving the GI tract.
3. History of a significant medical condition, including, but not limited to, psychiatric conditions, impaired immune function, HIV, in-born errors of metabolism, hepatitis B or C, unstable cardiovascular disease, unstable renal disease, coagulopathy, or unstable pulmonary disease.
4. History of current or malignancy or same within the last five years, except basal cell carcinoma of the skin, or if female, cervical carcinoma in situ that has been surgically excised.
5. History of any prior bowel surgery, except appendectomy.
6. Any of the following laboratory abnormalities: Serum Cr or BUN >1.5 ULN, CrCl <60 mL/min, twice the ULN for ALT, AST, or total bilirubin.
7. Current excessive alcohol use or drug dependence.
8. History of allergy or intolerance to aspirin, mesalamine, or other salicylates.
9. Personal history of phenylketonuria or history of parent's having the same.

MO comment: Inclusion and exclusion criteria are appropriate for the study.

10.2.4 Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of patients who remained relapse-free after six months of treatment. The endpoint was calculated using the results of all randomized patients who received at least one dose of study drug. Relapse or treatment failure was defined as a rectal bleeding score of 1 or more **and** mucosal appearance score of 2 or more, both as described in the

revised Sutherland Disease Activity Index (DAI). Patients who experienced an UC flare or initiated medication used previously to treat UC were also considered a treatment failure. Early study termination was not considered to be a relapse unless the reason for early termination was lack of efficacy or discontinuation due to a UC-related AE.

This primary endpoint represents a change from the definition of treatment failure presented in the original study protocol. Originally, the Applicant planned to count all premature withdrawals as having relapsed regardless of the reason for premature study discontinuation. The protocol amendment which changed this definition was made August 9, 2007, after completion of Study MPUC3004, but before unblinding of the data. Efficacy results using both this original definition and the revised definition are presented in the Efficacy Results section 10.2.12.2 below.

The Sutherland DAI is comprised of four indices of disease: stool frequency, rectal bleeding, mucosal appearance, and a physician's rating of disease severity. Each index is evaluated on a scale of 0 to 3, with a maximum total score of 12. To improve the clarity of the DAI, the term friability was removed from the mucosal appearance definitions resulting in the *revised* DAI used for studies MPUC3003 and MPUC3004. The change was requested by the Agency at the 06 October 2004 End of Phase 2 Meeting. The term "mild friability" was removed from the mucosal appearance score of 1 and replaced with "erythema, decreased vascular pattern, granularity, no mucosal hemorrhage." The term "moderate friability" was removed from the mucosal appearance score of 2 and replaced with "mucosal hemorrhage without blood in the lumen or gross ulceration, marked erythema, absent vascular pattern, and small ulcers." To calculate the DAI, sigmoidoscopy was performed at screening and at Month6/EOS. Unscheduled sigmoidoscopies were also performed if a patient experienced a flare in disease activity. Efforts were made to have the same clinician perform all sigmoidoscopies for a given patient. Study patients self-reported rectal bleeding and stool frequency symptoms for scoring.

The number and proportion of relapse-free patients after 6 months of treatment/EOS was summarized by treatment group using the ITT population. For all endpoints, comparisons between treatment groups were based on a Cochrane-Mantel Haenszel test, stratifying by country. As a sensitivity analysis to assess the effect of protocol compliance on drug efficacy, the primary efficacy analysis was also done using the per protocol population, those patients without a major protocol violation. Only the primary result obtained from the ITT population was considered to be inferential.

10.2.5 Secondary Efficacy Endpoints

Secondary efficacy analyses were performed using all randomized patients who received at least one dose of study drug. Statistical tests on secondary endpoints were performed in a hierarchical fashion. Once a non-significant p-value (>0.05) was encountered, all subsequent significance tests were considered exploratory in nature. The hierarchy of the secondary endpoints was as follows:

1. The number and proportion of patients in each level of change from baseline in rectal bleeding score at Months 1, 3, and 6/EOS.
2. The number and proportion of patients in each level of change from baseline in mucosal appearance score at Month 6/EOS.
3. The number and proportion of patients in each level of change from baseline in physician's rating of disease activity at Months 1, 3, and 6/EOS.
4. The number and proportion of patients maintaining the revised Sutherland DAI ≤ 2 with no individual component > 1 and rectal bleeding score of 0 at Month 6/EOS.
5. Mean change from baseline in the revised Sutherland DAI at Month 6/EOS.
6. Relapse-free duration, defined as the number of days between the start of study drug and the date that relapse is first detected or early termination from the study, plus 1 day.
7. The number and proportion of patients in each level of change from baseline in stool frequency score at Months 1, 3, and 6/EOS.

Clinical Reviewer's Comment: Currently, there is no validated disease activity index used for ulcerative colitis. Instead, a host of indices, many involving endoscopy, are used to measure disease activity. The Sutherland Disease Activity Index is a commonly used disease activity index.

10.2.6 Treatment

Upon enrollment in the study, patients were randomly assigned to a treatment group in a 2:1 (active:placebo) ratio. Patients received 0.375g eMG capsules or matched placebo product at each study visit in an adequate amount to allow proper dosing until the next scheduled visit. Patients self-administered four capsules once daily, in the morning, for not more than 24 weeks. All study site personnel were blinded to the patient treatment assignment.

10.2.7 Monitoring

Once patients were enrolled in the study, they underwent screening within seven days prior to randomization and beginning of product administration (Day 1). Screening included informed consent, assessment of concomitant medications, medical history, physical examination, laboratory measurements, and sigmoidoscopy. The Laboratory measurements included serum chemistry and hematology panels, serum β HCG, serum HIV, Hepatitis A and B, and urinalysis for calculation of creatinine clearance. Each patient's initial revised Sutherland DAI score was also calculated.

On study Day 1, eligible patients were seen in the office to have Study Visit 1. During this visit, patients underwent physical examination and repeat serum hematology, blood chemistry, and urinalysis testing. In addition, each patient's DAI score was calculated using the sigmoidoscopy score obtained during screening. Patients received a one month supply of the appropriate study drug along with daily diary cards to monitor compliance, concomitant medications, and AEs. Adverse events and concomitant medications were also recorded at this visit and during each subsequent telephone contact and in-office visit.

Visit 2 (Month 1±7 days) occurred in –office and was identical to Visit 1 with two exceptions. First, a *modified* DAI was calculated for each patient, which did not include a sub-score for mucosal appearance because no sigmoidoscopy was performed. Second, a two month supply of study treatment was dispensed at this visit.

Visit 3 (Month 3±14 days) was also identical to the previous in-office visits except patients received a three month supply of study drug.

Visit 4 (Month 6±21 days) served as the end of study (EOS) visit. During this visit, patients underwent all of the physical examination and laboratory testing that occurred during screening, including sigmoidoscopy. Patients who discontinued the study for any reason prior to study completion had all of the EOS visit assessments done at the time of study withdrawal.

On Week 2, Month 2, Month 4, and Month 5, patients were contacted by telephone to have concomitant medications and adverse events recorded.

A follow-up visit occurred Week 2 Post EOS ± 3 days. For this visit, patients returned to the office for physical examination Concomitant medications and adverse events were also recorded at this visit. This was each patient’s final study-related visit.

Unscheduled visits were to occur during the study if a patient experienced symptoms of relapse. Assessments performed at this visit were symptom directed at the investigator’s discretion. If patient assessment was positive for rectal bleeding, a stool specimen was obtained for *Clostridium difficile* and ova and parasites. If the results were negative, a sigmoidoscopy was scheduled to occur within 7 days to determine whether or not the patient had experienced relapse. Oral antibiotic treatment with metronidazole and ciprofloxacin for *C. difficile* and ova and parasite infections for a 7 to 10 day course was allowed during the course of the study.

Scheduled In-Person Study Assessments and Evaluations

Study Assessment	Screening Visit (within 7 days prior to randomization)	Visit 1 (Day 1)	Visit 2 (Month 1)	Visit 3 (Month 3 ±14 days)	Visit 4/EOS (Month 6±21 days)	Follow-up Visit (2 weeks post- EOS ± 3 days)
Informed consent	X					
Medical History	X					
Physical Examination	X	X ^a	X ^a	X ^a	X	X ^a
Serum Pregnancy test	X				X	
Record concomitant meds	X	X	X	X	X	X
Serum sample for HIV, Hepatitis B,C	X					
Clinical laboratory tests ^b	X	X	X	X	X	X
Calculated Creatinine Clearance	X				X	
Sigmoidoscopy	X				X	
Calculate DAI	X	X ^c	X ^d	X ^d	X	
Dispense Study Drug		X	X	X		
Assess and record AEs		X	X		X	X
Dispenses AE and concomitant medication diary		X	X	X		
Retrieve AE and concomitant medication diary			X	X	X	
Collect study drug and determine compliance			X	X	X	

^a symptom-directed physical exam only to be performed if necessary

^b includes hematology, blood chemistry, and urinalysis

^c Sigmoidoscopy component of Sutherland DAI will be scored utilizing the screening sigmoidoscopy score

^d DAI score will only include 3 of the 4 individual components, i.e., stool frequency, rectal bleeding, and physician's rating of disease activity.

10.2.8 Control Procedures

Randomization

Patients who met eligibility criteria were identified by a consecutively assigned, unique Patient ID number. Just prior to study drug dispensation, patients who continued to be eligible were assigned a unique Treatment ID number via a randomization schedule. Study treatments were randomly assigned to consecutive treatment numbers using an allocation ratio of 2:1 (eMG:placebo).

Placebo control

Each placebo consisted of color-matched granules over-encapsulated in matching hard gelatin capsules. Both the active study drug and the placebo were manufactured by Cardinal Health in Winchester, Kentucky and packaged identically.

Blinding

In this double-blind study, all study site personnel were blinded to the patient treatment assignment. In the case that a blind needed to be broken, a concealed section of the study drug label could be removed revealing the patient's treatment assignment. A concealed section of the study drug label, attached to a detachable portion of the label contained the product

identification. This detachable portion was affixed to the label page in the CRF. Any broken blind was to be recorded on the appropriate page of the CRF with an explanation. If a blind was broken for any reason, the investigator was to notify immediately the appropriate Salix representative.

Patients were dispensed blinded study drug at each study visit in an adequate amount to allow proper dosing until the next scheduled study visit.

Prior and Concomitant Therapy

The dose, duration, and indication of all concomitant medications were recorded in each patient's file and CRF. Existing, permitted, concomitant treatments were not to be changed during the course of the study. Patients who experienced relapse could have been offered, at investigator discretion the option of receiving standard treatment or enrolling in an open-label extension study (MPUC3005).

Prohibited concomitant medications were as follows:

- Immunosuppressants including azathioprine, 6-mercaptopurine, and glucocorticoids
- TNF blockers, methotrexate, cyclosporine
- Alternative or complimentary therapies for UC or any other experimental drugs.
- Oral, rectal, or IV corticosteroids, glucocorticoids.
- Chronic NSAIDS , >6weeks (exception acetylsalicylic acid \leq 150 mg/day).
- Oral antibiotics, Rifampin (metronidazole and ciprofloxacin were allowed for a seven to ten day course, if necessary).
- Psyllium-containing intestinal regulators, anticholinergics, sucralfate.
- Loperamide, opioids, opiates, and Lactulose or similar preparations used for diarrhea.
- Warfarin.
- Probenecid/sulphinpyrazone.
- Spironolactone/furosemide.
- Sulphonylureas.
- 5-ASA medications

Compliance

Treatment compliance was assessed at Months 1, 3, and 6 during scheduled in-office visits. Site coordinators determined compliance by counting the capsules remaining in the bottles and directly questioning patients. Patients were instructed to record compliance in a daily diary. The study monitor confirmed capsule counts during monitoring visits. Upon study completion, all unused, partially used, and fully used (empty) bottles and cartons along with a packing slip were returned to Cardinal Health Clinical Services for final drug reconciliation.

Patient compliance was calculated during each study interval and at the end of the study using the following formula: $100 * (\text{number of capsules dispensed} - \text{number of capsules returned}) / (4 *$

number of days of exposure). A patient was considered compliant if he or she took at least 70% of the study drug.

10.2.9 Safety evaluation

The primary measure of safety was the incidence of treatment-emergent adverse events (TEAEs). The safety and tolerability of the study medication was also assessed by monitoring laboratory test results (hematology, chemistry, calculated creatinine clearance, and urinalysis), physical examination, reported concomitant medications, and vital signs.

An adverse event was defined as any untoward medical occurrence in a patient which did not necessarily have to have a causal relationship with this treatment.

10.2.10 Protocol Amendments

Protocol Amendment 1 was finalized April 19, 2005. This date is after the study began, but before study completion. The Amendment was introduced for the following main reasons:

1. To increase the geographic scope of the study to include international sites.
2. To introduce less restrictive inclusion criteria such that patients could be in remission ≤ 12 months, instead of ≤ 6 months.
3. To outline procedures for patients who are believed to be experiencing a flare in disease activity
4. To reduce the minimum washout period for immunosuppressants from 90 days to 30 days
5. To allow the concomitant use of PPIs

Protocol Amendment 2 was finalized 09 August 2007. This date is after study completion. The Amendment was introduced for the following main reasons:

1. To change the number of randomized patient for the study from 300 to 250.
2. To change the definition of relapse to no longer include patients terminating early for reasons other than lack of efficacy or a UC-related AE.
3. To enumerate secondary endpoints allowing hierarchical testing.
4. To change the ITT population definition from all randomized patients to all randomized patients who received at least one dose of study drug.
5. To add a sensitivity analysis to the primary efficacy analysis using the PP population
6. To specify the major protocol deviations excluded from the PP population
7. To add a modified last observation carried forward (LOCF) procedure for imputing missing values of primary and secondary efficacy endpoint for patients who terminated the study early.
8. To designate the 6 month/EOS time point as the single time point for secondary analyses to reduce the likelihood of a type 1 error resulting from multiple secondary efficacy variable collected at numerous time points.

10.2.11 Statistical Methods

Data Set Analyzed

The intent-to-treat (ITT) population was defined as all randomized patients who received at least one dose of study drug. The per protocol (PP) population included all patients in the ITT population without a major protocol deviation. Major protocol deviations were defined prior to un-blinding of the data and included deviations from specific inclusion criteria, use of prohibited medications that would interfere with study results; and wrongful dispensation of study drug. The safety population included all randomized patients who received at least one dose of study drug and provided at least one post-baseline safety assessment.

10.2.12 Study Results

10.2.12.1 *Demographics and Baseline Disease Characteristics*

In a late stage protocol amendment, the Applicant changed the number of planned patients from 300 to 250. Therefore, Study MPUC3004 is smaller than study MPUC3003 by about 50 patients.

Overall, the eMG and placebo groups did not vary significantly with regard to demographic characteristics. There were slightly more females in the eMG group (56.0%). In the placebo group, there were slightly more males (52%). In both treatment groups, the majority of patients were younger than 65 years of age (91% eMG, 88% placebo) and White (95% eMG, 97% placebo). Likewise, the number of patients from Russia and the US were similar and nearly evenly distributed across treatment groups.

Demographics by Treatment Group

MPUC3004 ITT Population			
Demographic Subgroup	eMG N=164	Placebo N=93	All Patients N=257
Sex (n,%)			
Male	74 (45.1)	48 (51.6)	122 (47.5)
Female	90 (54.9)	45 (48.4)	135 (52.5)
Age (years) (n,%)			
<65	149 (90.9)	82 (88.2)	231 (89.9)
≥65	15 (9.1)	11 (11.8)	26 (10.1)
Mean (SD)	45.7 (14.0)	45.6 (14.1)	45.6 (14.0)
Median (min,max)	46 (18, 82)	46 (18, 76)	46 (18, 82)
Race[^] (n,%)			
AI/AN [*]	1 (0.6)	0	1 (0.4)
Asian	2 (1.2)	2 (2.2)	4 (1.6)
Black/AA ^{**}	5 (3.0)	1 (1.1)	6 (2.3)
White	156 (95.1)	90 (96.8)	246 (95.7)
Missing	1 (0.6)	0	1 (0.4)
Ethnicity (n,%)			
Hispanic or Latino	4 (2.4)	5 (5.4)	9 (3.5)
Not Hispanic or Latino	160 (97.6)	88 (94.6)	248 (96.5)
Country (n,%)			
Russia	102 (62.2)	52 (55.9)	154 (59.9)
United States	62 (37.8)	41 (44.1)	103 (40.1)
Weight (lbs) (n,%)			
N	164	93	257
Mean (SD)	66.5 (4.0)	66.8 (3.7)	66.6 (3.9)
Median (min,max)	66.4 (57.0, 75.7)	67.0 (56.3, 75.0)	66.9 (56.3, 75.7)
Height (inches) (n,%)			
N	164	93	257
Mean (SD)	66.5 (4.0)	66.8 (3.7)	66.6 (3.9)
Median (min,max)	66.4 (57.0, 75.7)	67.0 (56.3, 75.0)	66.9 (56.3, 75.7)
Body Mass Index (kg/m²)			
N	164	93	257
Mean (SD)	26.0 (4.6)	25.8 (4.4)	25.9 (4.5)
Median (min, max)	25.1 (16.9, 41.3)	25.2 (17.5, 38.4)	25.1 (16.9, 41.3)

Source: Summary Table 14.1.4, Table 10, MPUC3004 Study Report

[^]Patients were allowed to check more than one race and so percentages may be greater than 100%

^{*}American Indian/Alaskan Native

^{**}African-American

In general, the patients in each treatment group did not differ greatly in baseline disease characteristics. In both treatment groups, patients had a mean duration of disease of about 290 weeks.

Baseline Disease Characteristics

Study MPUC3004			
Category	eMC N=164	Placebo N=93	All Patients N=257
Duration of disease (weeks)			
Mean (SD)	275.3 (317.0)	306.9 (415.5)	286.8 (355.4)
Median (min,max)	159.0 (13.0, 2049.0)	149.0 (9.0, 2151.0)	156.0 (9.0, 2151.0)
Time since most recent flare (weeks)			
Mean (SD)	23.0 (14.0)	25.7 (16.7)	24.0 (15.0)
Median (min,max)	20.0 (5.0, 91.0)	21.0 (5.0, 93.0)	20.0 (5.0, 93.0)
Duration of current remission (weeks)			
Mean (SD)	16.4 (12.0)	17.1 (11.4)	16.7 (11.8)
Median (min,max)	12.0 (3.0, 59.0)	15.0 (2.0, 52.0)	13.0 (2.0, 59.0)
Disease severity			
0	71 (43.3)	39 (41.9)	110 (42.8)
≥1	93 (56.7)	54 (58.1)	147 (57.2)
Normal Number of Stools Daily			
Mean (SD)	1.5 (1.1)	1.6 (1.0)	1.5 (1.1)
Median (min,max)	1 (1,9)	1 (1,8)	1 (1,9)
Revised Sutherland DAI total score			
Mean (SD)	0.9 (0.9)	1.0 (1.1)	0.9 (1.0)
Median (min, max)	1 (0, 4)	1 (0, 5)	1 (0, 5)
Revised Sutherland DAI Component Scores			
Mean (SD)			
Stool Frequency	0.1 (0.4)	0.2 (0.4)	0.1 (0.4)
Rectal Bleeding	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
Mucosal Appearance	0.4 (0.5)	0.5 (0.5)	0.4 (0.5)
Physician's rating of disease severity	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)
Baseline Renal Function (n,%)			
(Cockcroft-Gault formula)			
Normal (≥90 mL/min)	104 (63.4)	65 (69.9)	169 (65.8)
Mild (60-<90 mL/min)	52 (31.7)	25 (26.9)	77 (30.0)
Moderate (30-<60 mL/min)	5 (3.0)	2 (2.2)	7 (2.7)
Severe (<30 mL/min)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Summary Table 14.1.6, Sponsor Table 11, MPUC3004 Clinical Study Report

A larger percentage of eMG patients completed the study (72.6%) as compared with placebo (61.3%). Reasons for study discontinuation are presented in the Patient Disposition Table below.

Patient Disposition, Study MPUC3004

	RCT Population		
	eMG N=164 (%)	Placebo N=93 (%)	Total N=257 (%)
Safety population	161	91	252
Completed Study	119 (72.6)	57 (61.3)	176 (68.5)
Discontinued Study	45 (27.4)	36 (38.7)	81 (31.5)
AE	9 (5.5)	6 (6.5)	15 (5.8)
Lost to follow-up	2 (1.2)	3 (3.2)	5 (1.9)
Lack of efficacy	25 (15.2)	22 (23.7)	47 (18.3)
Patient request	2 (1.2)	1 (1.1)	3 (1.2)
Did not meet entry criteria	5 (3.0)	2 (2.1)	7 (2.7)
Use of excluded medications	0	1 (1.1)	1 (0.4)
Noncompliance	1 (0.6)	0	1 (0.4)
Sponsor's request	1 (0.6)	1 (1.1)	2 (0.8)
Continued into MPUC3005			

Source: Summary Table 14.1.1, 14.1.2, Data Listing 16.2.1, Appendix 16.2, MPUC3004 Clinical Study Report

Compliance

Treatment compliance was comparable between treatment groups. The mean calculated study compliance was 97.2% in the eMG group and 97.5% in the placebo group.

10.2.12.2 Efficacy Analyses

All randomized patients who received at least one dose of study drug were included in the efficacy analyses. The last-observation-carried forward (LOCF) method was used for imputing missing values of primary and secondary efficacy endpoints for patients who terminated early. Patients who terminated the study early due to lack of efficacy or UC-related AEs (abdominal pain, abdominal tenderness, ulcerative colitis, diarrhea, frequent bowel movements, hematochezia, loose stools, proctitis, rectal hemorrhage, rectal tenesmus, stomach discomfort, and watery stools) were classified as treatment failures. Patients who terminated the study early for other reasons were not considered treatment failures. In addition, patients who experienced a UC flare or initiated medication that had previously been used to treat UC were also considered treatment failures. For patients who withdrew prematurely for other reasons, the last observation carried for ward (LOCF) method was used to impute their EOS remission status.

This primary endpoint represents a change from the definition of treatment failure presented in the original study protocol. Originally, the Applicant planned to count all premature withdrawals as having relapsed regardless of the reason for premature study discontinuation. The protocol amendment which changed this definition was made August 9, 2007 after study completion, but before un-blinding of the data.

Clinical Reviewer's comment: The Applicant changed the definition of relapse after study completion, but before un-blinding. It is important to re-calculate the primary efficacy endpoint results using the original definition of relapse. See the Primary Endpoint Efficacy Results Table below. These results show that the magnitude of the difference in efficacy between the eMG and placebo group is smaller; however, remains statistically significant.

Primary Endpoint

Statistical analysis for the primary endpoint, proportion of patients using eMG 1.5g/day who remained in remission at Month 6 versus placebo, utilized a CMH test controlling for country. At Month6/EOS, 79.9% of patients in the eMG group and 67.7% of patients in the placebo group remained relapse-free ($p < 0.001$) when using the revised definition of relapse which did not count all early terminations as treatment failures. When the data are analyzed using the original definition of the primary endpoint which counted all early withdrawals as relapses, the results become only marginally statistically significant, $p = 0.046$.

Primary Efficacy Endpoint

Relapse-free at Month 6/EOS					
Study Population	Definition of Relapse	eMG	Placebo	95% CI for Difference	p-value
MPUC3004	Original	117/164= 71.3%	55/93=59.1%	12% (0%, 24.5%)	0.046
ITT	Revised	131/164=79.9%	63/93=67.7%	12 % (1.1%, 24%)	0.029
PP	Revised	129/161=80.1%	58/86=67.4%		0.027

Source of Data: Statistical Reviewer's Calculations

Clinical Reviewer's comment: The Applicant changed the definition of relapse after study completion, but before un-blinding. The Applicant also decreased the planned study size from 300 to 250 in a late stage protocol amendment. Overall, using both definitions of relapse, Study MPUC3003 showed a greater difference in efficacy between eMG and placebo groups than did Study MPUC3004. Studies MPUC3003 and MPUC3004 used identical study designs and the only substantial difference is the number of patients randomized suggesting that Study MPUC3004 may not have been adequately powered.

Secondary Endpoints

The statistical analyses of the secondary endpoints were performed in a hierarchical fashion. According to the Applicant's statistical analysis plan, if statistical significance was not achieved for any secondary end point, all subsequent endpoints would be considered exploratory (and not inferential) in nature. In study MPUC3004, the difference between eMG and placebo did not reach the level of statistical significance for any of the secondary end points. Therefore, all secondary end points are to be considered exploratory in nature.

Secondary endpoint six, Month 6 Cumulative relapse-free probability has the smallest nominal p-value. This endpoint is basically a re-statement of the primary endpoint. It is important that

this endpoint is highly statistically significant and further corroborates the primary endpoint's statistical significance. However, it was also expected that the first two secondary endpoints, difference in rectal bleeding and mucosal appearance scores, would have reached the level of statistical significance given that they are directly related to the definition of relapse used in the study's primary endpoint.

Clinical Reviewer's Comment: The fact that the first two secondary endpoints did not reach statistical significance does not corroborate the study's primary endpoint and further suggests that the study may have been underpowered given the highly statistically significant results of Study MPUC3003, an identically designed study with 50 more randomized patients.

Study MPUC3004 Secondary Efficacy Endpoints

Study 3004	Mesalamine N= 164	Placebo N= 93	P-Value
Change from Baseline in Rectal Bleeding			
-1	1 (0.6)	1 (1.1)	0.119
0	138 (84.1)	69 (74.2)	
1	12 (7.3)	13 (14.0)	
2	12 (7.3)	9 (9.7)	
3	1 (0.6)	1 (1.1)	
Change from Baseline in Mucosal Appearance			
-1	26 (15.9)	13 (14.0)	0.496
0	104 (63.4)	56 (60.2)	
1	18 (11.0)	14 (15.1)	
2	16 (9.8)	10 (10.8)	
3	0 (0.0)	0 (0.0)	
Change from Baseline in Physician's Rating of Disease Severity			
-2	1 (0.6)	0 (0.0)	0.254
-1	16 (9.8)	10 (10.8)	
0	122 (74.4)	60 (64.5)	
1	16 (9.8)	16 (17.2)	
2	8 (4.9)	7 (7.5)	
3	1 (0.6)	0 (0.0)	
Patients maintaining the Sutherland DAI ≤2 with no individual component of the Sutherland DAI >1 and rectal bleeding =0 at Month 6 Successes: n (%) Failures: n (%)	118(72.0) 46 (28.0)	54 (58.1) 39 (41.9)	0.039
Mean change from baseline in the Sutherland DAI at Month 6/EOS Mean (SD)	0.7 (2.4)	1.2 (2.7)	0.167
Relapse-free duration Month 6 Cumulative relapse-free probability (SE)	0.8 (0.0)	1.2 (2.7)	0.024
Stool Frequency at Month 6/EOS Patients in each level of change from baseline Change from Baseline in Mucosal Appearance			
-1	12 (7.3)	4 (4.3)	0.142
0	124 (75.6)	67 (72.0)	
1	11 (6.7)	8 (8.6)	
2	14 (8.5)	0 (9.7)	
3	3 (1.8)	5 (5.4)	

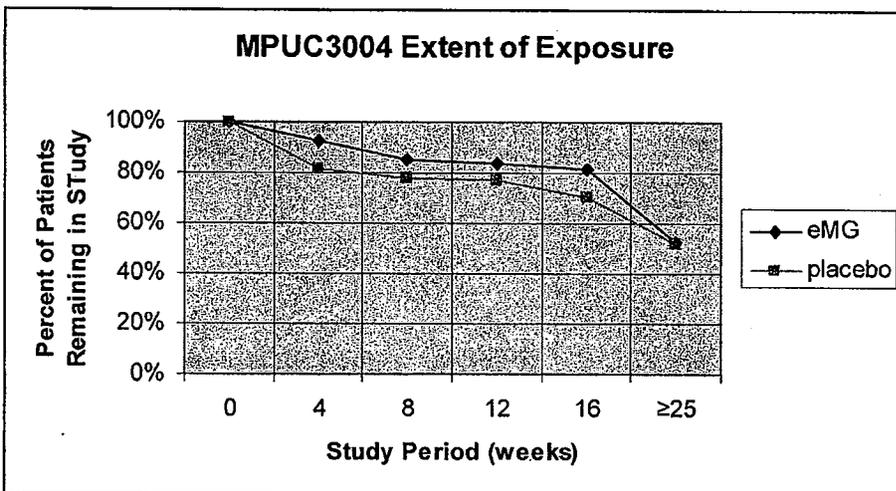
Source: Summary Table 14.2.1, Appendix 16.2.6, MPUC3004 Clinical Study Report

10.2.12.3 Safety Analyses

The safety population was defined as all randomized patients who received at least one dose of study drug and had at least one post-baseline safety assessment. The safety population for Study MPUC3004 included 252 patients (161 eMG, 91 placebo).

Extent of exposure

As expected, study attrition occurred in both treatment groups. Approximately half (53% eMG, 52% placebo) of study participants remained in the study for greater than 25 weeks.



Concomitant Medications

Overall, 54.0% of eMG patients, and 50.5% of placebo patients used concomitant medications during Study MPUC3004. The alimentary tract and metabolism medication groups were combined. A review of the medications in this group reveals that the reason for grouping these medications together was likely that the intended use of the medications could have been for GI or metabolic issues. For example, calcium carbonate is both a calcium supplement and an antacid. There were many concomitant medications used by study participants, but other than those listed in the Table below, most medications were used by only 1 or 2 patients.

Concomitant Medications Reported by ≥2% of Patients

Study MPUC3004		
Medication Class Medication Name	eMG N=161 (%)	Placebo N=91 (%)
Alimentary Tract & Metabolism	59 (36.6)	33 (36.3)
Fortrans	23 (14.3)	9 (9.9)
Macrogol 4000	17 (10.6)	9 (9.9)
Bismuth subsalicylate	1 (0.6)	4 (4.4)
Balsalazide sodium	0	3 (3.3)
Magnesium citrate	1 (0.6)	2 (2.2)
Omeprazole	1 (0.6)	2 (2.2)
Magnesium hydroxide	0	2 (2.2)
Anti-infectives for Systemic Use	34 (16.5)	10 (10.6)
Azithromycin	4 (2.5)	4 (4.4)
Amoxicillin	4 (2.5)	2 (2.2)
Ciprofloxacin	5 (3.1)	1 (1.1)
Cefalexin	1 (0.6)	2 (2.2)
Blood and Blood Forming Organs	2 (1.0)	4 (4.3)
Heparin	0	2 (2.2)
Cardiovascular System	12 (7.5)	2 (2.2)
Preparation H	0	2 (2.2)
Musculoskeletal System	12 (7.5)	2 (2.2)
Ibuprofen	6 (3.7)	1 (1.1)
Nervous System	27 (16.8)	8 (8.8)
Paracetamol	10 (6.2)	5 (5.5)
Vicodin	4 (2.5)	1 (1.1)
Respiratory Medications	11 (6.8)	8 (8.8)
Loratadine	1 (0.6)	2 (2.2)

Source: Summary Table 14.3.6.3, MPUC3004 Clinical Study Report

The medications with the highest rate of use by eMG and placebo patients were Fortrans and Macrogol 4000 (both laxatives). Paracetamol, a common pain medication, was the next most frequently used medication in both the eMG and placebo groups. It is possible that the use of paracetamol is linked to the incidence of headache, a common adverse reaction associated with the use of eMG. However, the incidence of paracetamol use was only slightly higher in the eMG group (6.2%) versus the placebo group (5.5%).

Adverse Reactions

In study MPUC3004, 64.1% of eMG patients and 63.8% of placebo patients reported experiencing an adverse event. Most of the adverse events were mild (23.3%) or moderate (33.7%) in intensity. Four patients (two in each treatment group) experienced a serious adverse event. There were no deaths reported during this study.

Patients Reporting Adverse Events By Treatment Group

MPUC3004			
Category	eMG N=161 (%)	Placebo N=91 (%)	Total N=252
Patients Experiencing any TEAE	86 (53.4)	58 (63.7)	144 (57.1)
Patients Experiencing Serious TEAEs	2 (1.2)	2 (2.2)	4 (1.6)
TEAEs by Severity			
Mild	40 (24.8)	36 (39.6)	76 (30.2)
Moderate	41 (25.5)	17 (18.7)	58 (23.0)
Severe	5 (3.1)	5 (5.5)	10 (4.0)
Patients Experiencing any TEAE possibly related to study drug, per Investigator	11 (6.8)	10 (11.0)	21 (8.3)
TEAEs Resulting in Study Discontinuation	9 (5.6)	6 (6.6)	15 (6.0)
Deaths	0	0	0

Source: Table 14.3.1.1., Section 14.3.1, MPUC3004 Clinical Study Report

Serious Adverse Events

Serious adverse events occurred in 1% of eMG patients and 2% of placebo patients.

eMG Patient 419-04

The patient, a 33 year old African-American female, was in remission for three months before entry into the study and had a baseline DAI score of 1. The patient was using acetaminophen to treat pain, and dietary supplements (calcium and Dexatrim) before and during the study. The patient received study drug for 14 days before being withdrawn due to the TEAE of UC flare. At the time of the UC flare, the total DAI score was 11 (SF=2, RB=3, MA=3, PRDA=3). For the flare, the patient was started on oral mesalamine, mesalamine suppositories, rectal mesalamine, and azathioprine. Approximately two weeks later, the patient was admitted to the hospital with abdominal cramps, pain, and multiple bloody bowel movements per day. The patient was diagnosed with pancreatitis and received IV methylprednisolone, ferrous sulfate, morphine, mesalamine 1.2 g TID, and a single infusion of infliximab during her six-day hospital stay. The SAE was felt by the Investigator to be related to azathioprine and not to the study drug.

eMG Patient 494-09

The patient, an 83 year old male, was in remission for three months before entry into the study and had a baseline DAI score of 0. The patient completed the study after being exposed to the study drug for 183 days. The patient was admitted to the hospital with fatigue, chest pain, "missing" heartbeats, and palpitations 16 days after completing the study. The patient's past medical history included a history of left bundle branch block and first degree AV block. In-hospital work-up revealed worsening left ventricular systolic function and second degree AV block. Both events were considered resolved and deemed unrelated to the study drug by the Investigator upon the patient's hospital discharge (5 days after admission).

Placebo Patient 569-08

The patient, a 53 year old Caucasian male, was in remission for 3 months before entry into the study. Approximately, three months into the study the patient experienced weakness and chest pain while shoveling snow. The patient was hospitalized and diagnosed with severe angina. While

hospitalized, the patient was also diagnosed with right bundle branch block, arterial hypertension, and acute heart failure. The patient was treated with nitrates, beta-blockers, aspirin, enalapril, trimetazidine, and heparin. After two and one-half weeks, the patient was discharged and the event was considered resolved. The patient continued the study after this event and completed the study after 184 days of exposure to the study drug. The SAE was felt by the Investigator to be not related to the study drug.

Placebo patient 626-03

The patient, a 49 year old Caucasian female, was in remission for 3 months before entry into the study and had a baseline DAI of 0. The patient had a past medical history significant for hypothyroidism, acid reflux disease, chronic sinusitis, asthma, depression, and sciatica and a past surgical history of hernia repair. After 24 days of exposure, the patient experienced abdominal pain and vomiting. The patient was hospitalized and diagnosed with small bowel obstruction due to holes in pre-existing mesh from a previous hernia repair. During hospitalization the patient was treated with midazolam, hydromorphone, oxycodone, morphine, acetaminophen, ondansetron, metoclopramide, lorazepam, sumatriptan, cephalexin, metronidazole, piperacillin, magnesium hydroxide, heparin, and naloxone. The study drug was interrupted for six days. The patient resumed the study drug and completed the study after 225 days of exposure. The SAE was felt by the Investigator to be not related to the study drug.

Patients Reporting Serious Adverse Events

MPUC3004			
SAEs	eMG N=161 (%)	Placebo N=91 (%)	Total N=252 (%)
All SAEs	2 (1.2)	2 (2.2)	4 (1.6)
Acute pancreatitis	1 (0.6)	0	1 (0.4)
Atrioventricular block, second degree Ventricular dysfunction	1 (0.6)	0	1 (0.4)
Angina Pectoris	0	1 (0.1)	1 (0.4)
Small bowel obstruction	0	1 (0.1)	1 (0.4)

Source: Data listing 16.2.7.3, MPUC3004 Clinical Study Report

Study Discontinuations due to Treatment Emergent Adverse Events

TEAEs leading to study discontinuation were more frequent in the placebo group than in the eMG group (23.1% versus 14.3%). In total, 17.5% of patients in Study MPUC3004 withdrew due to TEAEs. The overwhelming majority of these discontinuations occurred in the GI SOC (approximately 93 % of total withdrawals due to TEAEs). The most common preferred term associated with early withdrawal was ulcerative colitis.

Patients with TEAEs Leading to Study Withdrawal

Study MPUC3004			
MedDRA System Organ Class Preferred Terms	eMG N=161 (%)	Placebo N=91 (%)	Total N=252 (%)
Total Number of Patients with TEAE leading to Study Withdrawal	23 (14.3)	21 (23.1)	44 (17.5)
Gastrointestinal Disorders	20 (12.4)	21 (23.1)	41 (16.3)
Colitis ulcerative	16 (9.9)	17 (18.7)	33 (13.1)
Abdominal pain	0	2 (2.2)	2 (0.8)
Diarrhea	1 (0.6)	1 (1.1)	2 (0.8)
Constipation	1 (0.6)	0	1 (0.4)
Flatulence	0	1 (1.1)	1 (0.4)
Hematochezia	1 (0.6)	0	1 (0.4)
Nausea	0	1 (1.1)	1 (0.4)
Rectal hemorrhage	1 (0.6)	0	1 (0.4)
General Disorders and Administration Site Conditions	1 (0.6)	0	1 (0.4)
Pyrexia	1 (0.6)	0	1 (0.4)
Investigations	3 (1.9)	0	3 (1.2)
Alanine aminotransferase increased	2 (1.2)	0	2 (0.8)
Aspartate aminotransferase increased	1 (0.6)	0	1 (0.4)
Creatinine renal clearance decreased	1 (0.6)	0	1 (0.4)
Alkaline phosphatase increased*	1 (0.6)	0	1 (0.4)

Source: Summary Table 14.3.1.9, Section 14.3.1, Volume 104 of 189, with modifications by Clinical Reviewer*

A Patient reporting more than one adverse event for a particular MedDRA Preferred Term (PT) or System Organ Class (SOC) is counted only once for that PT or SOC. Alkaline phosphatase not included on summary table, but narratives, study report write-up, and CRFs support its inclusion in the table.

Of the laboratory abnormalities associated with early withdrawal, all occurred in patients receiving the eMG study drug. Laboratory abnormalities resulting in premature study withdrawal in the eMG treatment group included an alkaline phosphatase elevation to 832 U/L (normal range 40-135 U/L), AST elevation to 107 U/L (normal range 0-37 U/L), and an ALT elevation to 63 U/L (normal range 0-47 U/L) all occurring in the same patient. Other laboratory abnormalities included a creatinine clearance decreased to 55.5 mL/min (normal range 80-120 mL/min) and an ALT level elevated to 122 U/L and normal AST coded in the CRF as elevated.

Clinical Reviewer's Comment: The finding in Study MPUC3004 that all liver enzyme abnormalities occurred in eMG patients while none occurred in placebo patients provides some evidence that the use of eMG may be associated with abnormal liver function tests and further strengthens our recommendation to include a hepatic warning on the label.

Common Adverse Events

In study MPUC3304, TEAE incidence was higher in placebo patients (64%) than in eMG patients (53%). The most common TEAEs in both groups were ulcerative colitis (11% eMG, 22% placebo) and headache (11% eMG, 8% placebo). The majority of TEAEs occurred in the gastrointestinal system MedDRA SOC (32% eMG, 45% placebo). The most common gastrointestinal system TEAEs other than ulcerative colitis were diarrhea (7% eMG, 7%

placebo), abdominal pain (5% eMG, 7% placebo), upper abdominal pain (6% eMG, 3% placebo). All these GI symptoms are commonly associated with ulcerative colitis.

TEAEs Reported by ≥2% of Patients in Any Treatment Group

Study MPUC3004			
MedDRA System Organ Class Preferred Term	eMG N=161 (%)	Placebo N=91 (%)	Total N=252 (%)
Total Number of Patients with any TEAE	86 (53.4%)	58 (63.7%)	144 (57.1)
Gastrointestinal Disorders	52 (32.3)	41 (45.1)	93 (36.9)
Colitis Ulcerative	17 (10.6)	20 (22.0)	37 (14.7)
Diarrhea	11 (6.8)	6 (6.6)	17 (6.7)
Abdominal Pain	8 (5.0)	6 (6.6)	14 (5.6)
Abdominal Pain Upper	10 (6.2)	3 (3.3)	13 (5.2)
Nausea	7 (4.3)	5 (5.5)	12 (4.8)
Flatulence	1 (0.6)	6 (6.6)	7 (2.8)
Hemorrhoids	5 (3.1)	2 (2.2)	7 (2.8)
Rectal hemorrhage	4 (2.5)	3 (3.3)	7 (2.8)
Constipation	4 (2.5)	3 (3.3)	7 (2.8)
Dyspepsia	3 (1.9)	2 (2.2)	5 (2.0)
Hematochezia	3 (1.9)	2 (2.2)	5 (2.0)
Hemorrhoidal hemorrhage	2 (1.2)	2 (2.2)	4 (1.6)
Stomach discomfort	2 (1.2)	2 (2.2)	4 (1.6)
General Disorders and Administration Site Conditions	8 (5.0)	6 (6.6)	14 (5.6)
Pyrexia	5 (3.1)	1 (1.1)	6 (2.4)
Fatigue	2 (1.2)	3 (3.3)	5 (2.0)
Pain	0	2 (2.2)	2 (0.8)
Infections and Infestations	32 (19.9)	15 (16.5)	47 (18.7)
Sinusitis	6 (3.7)	3 (3.3)	9 (3.6)
Influenza	5 (3.1)	1 (1.1)	6 (2.4)
Nasopharyngitis	3 (1.9)	3 (3.3)	6 (2.4)
Upper respiratory tract infection	5 (3.1)	1 (1.1)	6 (2.4)
Urinary tract infection	4 (2.5)	2 (2.2)	6 (2.4)
Bronchitis	0	2 (2.2)	2 (0.8)
Pharyngitis	0	2 (2.2)	2 (0.8)
Nervous System Disorders	21 (13.0)	9 (9.9)	30 (11.9)
Headache	17 (10.6)	7 (7.7)	24 (9.5)
Dizziness	3 (1.9)	2 (2.2)	5 (2.0)
Psychiatric Disorders	3 (1.9)	2 (2.2)	5 (2.0)
Insomnia	1 (0.6)	2 (2.2)	3 (1.2)
Respiratory, Thoracic and Mediastinal Disorders	9 (5.6)	4 (4.4)	13 (5.2)
Sinus pain	0	2 (2.2)	2 (0.8)

Source: Summary Table 14.3.1.4, Section 14.3.1, MPUC3004 Clinical Study Report

Conclusion

Overall, Study MPUC3004 appears to be underpowered to tell a difference in efficacy between eMG and placebo. Calculation of the primary efficacy measure using the original definition of relapse resulted in results that were only modestly statistically significant, p=0.046. The late

Clinical Review
Aisha E. Peterson, MD, MPH, MBA
NDA 22-301
Apriso (mesalamine)

stage protocol amendment which decreased the planned study enrollment by 50 patients is problematic and the Applicant's reason for making this change is unclear.

Our Statistical reviewer performed a sensitivity analysis with 43 additional subjects in Study MPUC3004 (300 total subjects as planned). For this analysis, she assumed that these additional subjects would have a success rate equal to the observed placebo response rate of 68% (revised definition of relapse). Her results showed that the resultant success rates would be 78% eMG, 67 placebo, $p=0.06$. This result represents a failure of the primary endpoint.

10.3 STUDY PROTOCOL MPUC3005

10.3.1 Protocol Summary

Title: A Multi-Center, Open-Label, Treatment Extension Trial to Evaluate the Long-Term Safety and Tolerability of Mesalamine Pellet Formulation

Study Centers

A total of 370 patients from 66 centers participated in this study.

Patient Selection

Study MPUC3005 was an open-label extension study. Patients who successfully completed studies MPUC3003 and MPUC3004 along with new patients were eligible to participate in Study MPUC3005. Successful participation was defined as: compliance with study-related procedures, $\geq 70\%$ compliance with taking study medication per-protocol, and not withdrawn from lead-in study due to study drug-related AE(s). The study population of Study MPUC3005 included 271 patients in remission who successfully participated in lead in clinical study MPUC3003 or MPUC3004. In addition, 99 new patients who did not participate in the lead-in studies, but were in remission, were also enrolled in the study.

The safety population for this study included only 365 of the 370 enrolled patients because 5 patients did not have a post-baseline safety assessment at the time of the interim analysis.

Study period

The study was planned for all patients to remain on open-label medication for at least 24 months, until regulatory approval of eMG, or until the study was terminated by the Applicant, whichever came first. The study began 22 December 2005. The interim clinical data cutoff date was 09 May 2007.

Objectives

The primary study objective was to evaluate the long-term safety and tolerability of treatment with encapsulated mesalamine granules (eMG).

Study Design

This ongoing study was designed as a Phase 3 multicenter, open-label, treatment-extension study evaluating the long-term safety and tolerability of eMG at 1.5 g given once daily (QD; 4 capsules total) in approximately 400 to 500 patients with demonstrated remission from UC. Eligible patients had successfully participated in a lead-in study (MPUC3003 or MPUC3004) or were new patients who were in remission from UC.

This study consisted of a Treatment phase and a Follow-up visit two weeks after study completion.

MO Comment: The study design is adequate to capture safety data of long term use of eMG.

10.3.2 Inclusion Criteria

Patient has successfully participated in Study MPUC3003 or MPUC3004 and has enrolled in this study within 30 days of the end of treatment for the previous study. Or, if patient has not participated in a previous study or has rolled over in this study after more than 30 days after completing the previous study, the patient must meet the same inclusion criteria as Studies MPUC3003 and MPUC3004.

1. Age 18 years or greater
2. Males or non-pregnant, non-lactating females of non-child-bearing potential or agreeing to an acceptable form of birth control as outlined in the protocol.
3. Historically confirmed diagnosis of mild to moderate UC in remission at least one month, but not more than 12 months with a history of at least one flare within the past 12 months.
4. Confirmed current remission defined as a rectal bleeding score on revised Sutherland DAI of 0 (none) *and* sigmoidoscopy score of 0 to 1 for mucosal appearance (0=intact mucosa; 1=erythema, decreased vascular pattern, granularity, no mucosal hemorrhage)

10.3.3 Exclusion Criteria

1. History of infectious, ischemic, or immunologic disease involving the GI tract.
2. History of a significant medical condition, including, but not limited to, psychiatric conditions, impaired immune function, HIV, in-born errors of metabolism, hepatitis B or C, unstable cardiovascular disease, unstable renal disease, coagulopathy, or unstable pulmonary disease.
3. History of current or malignancy or same within the last five years, except basal cell carcinoma of the skin, or if female, cervical carcinoma in situ that has been surgically excised.
4. History of any prior bowel surgery, except appendectomy.

5. Any of the following laboratory abnormalities: Serum Cr or BUN >1.5 ULN, CrCl <60 mL/min, twice the ULN for ALT, AST, or total bilirubin.
6. Current excessive alcohol use or drug dependence.
7. History of allergy or intolerance to aspirin, mesalamine, or other salicylates.
8. Personal history of phenylketonuria or history of parent's having the same.

10.3.4 Efficacy Analyses

There were no efficacy analyses conducted for this long-term, open-label safety and tolerability study.

10.3.5 Safety Analyses

The following safety endpoints were evaluated during the study:

- Incidence of TEAEs
- Time to onset of TEAEs
- Percentage of patients who prematurely discontinue the study
- Changes from baseline in clinical laboratory parameters
- Changes from baseline in vital sign measurements

10.3.6 Treatment

All patients receive 1.5g once daily of eMG (dispensed as four 0.375 mg capsules) once daily in the morning. The study was designed to last 24 months.

10.3.7 Monitoring

Patients entered the study as rollover patients from Studies MPUC3003 or MPUC3004 or as new patients. There were two types of rollover patients—direct and delayed. A direct rollover patient enrolled in Study MPUC3005 within 7 days of Visit 4/EOS of the lead in study, MPUC3003 or MPUC3004. For direct rollover patients, the EOS visit for the lead-in study was used as the baseline (Visit 1) visit for Study MPUC3005. And the two week follow-up visit for the lead-in studies was waived for those direct rollover patients.

Delayed rollover patients entered Study MPUC3005 more than seven days and no more than 30 days after Visit 4/EOS of the lead-in study. Delayed rollover patients were required to have an

in-office MPUC3005 study Visit 1 (Day1). During this visit, concomitant medications were recorded and it was reconfirmed that these patient continued to meet open-label eligibility criteria. In addition, safety laboratory tests including hematology, blood chemistry, and urinalysis were performed. For females of childbearing potential, a serum pregnancy test was performed. Vital sign measurements were obtained. Journals to record AEs and concomitant medications were dispensed. In addition, these patients were observed taking their first dose of study medication.

For the purposes of Study MPUC3005, patients from lead-in studies who enrolled in Study MPUC3005 more than 30 days after the completion of the lead-in study were classified as new patients. Study MPUC3005 Visit 1 for new patients involved all of the monitoring described above for delayed rollover patients and also included obtaining a complete medical history, physical examination, and sigmoidoscopy.

Visit 2 (Month 1) was conducted in-office and involved obtaining vital sign measurements and performing safety laboratory tests. Visit 3 (Month3) involved vital sign measurement, safety laboratory testing and urine pregnancy testing for females of childbearing potential. After Visit 3, visits were conducted every 3 months for the remainder of the study. At Month 24 or at the time of study discontinuation, each patient was seen in office for an end of treatment visit. This visit involved vital sign measurement, safety laboratory testing, urine pregnancy testing, physical examination, and sigmoidoscopy. The follow-up visit was scheduled to occur 14 ± 3 days after the last dose of study drug. During this visit, vital sign measurement and safety laboratory testing was conducted.

At Week 2 (Day 14 ± 3), Month 2 (Day 56 ± 3), Month 4 (Day $112\pm$), and Month 5 (Day 140 ± 3) patients were contacted by telephone. During these visits, AEs and concomitant medications were assessed and recorded.

It should also be noted that at each in-person study visit and telephone contact, AEs and concomitant medications were assessed and recorded.

Unscheduled visits could occur at any time at the discretion of the investigator to assess symptoms of possible UC flare. Assessments performed at this visit were symptom directed at the investigator's discretion.

10.3.8 Control Procedures

This open-label study was not randomized. All patients received the same study treatment, 1.5 g eMG once daily in the morning. There was no placebo control.

Prior and Concomitant Therapy

Existing, permitted, concomitant treatment were not to be changed during the course of the study. All concomitant treatments were recorded in the patient file and the CRF. Prohibited concomitant medications were as follows:

Prohibited concomitant medications were as follows:

Any experimental drugs

Psyllium-containing intestinal regulators

Lactulose or similar preparation which lowers stool pH

Warfarin

Rifampin

Probenecid/sulphinpyrazone due to possible attenuation of uricosuric effects

Spirolactone due to possible attenuation of tuberculostatic effects

Clinical Reviewer's Comment: This open-label study allowed the concomitant use of immunosuppressants including steroids, azathioprine, and TNF blockers.

Compliance

Treatment compliance was assessed during scheduled in-office visits. Site coordinators determined compliance by counting the capsules remaining in the bottles and directly questioning patients. Patients were instructed to record compliance in a daily diary. The study monitor confirmed capsule counts during monitoring visits. Upon study completion, all unused, partially used, and fully used (empty) bottles and cartons along with a packing slip were returned to Cardinal Health Clinical Services for final drug reconciliation.

Patient compliance was calculated during each study interval and at the end of the study using the following formula: $100 * (\text{number of capsules dispensed} - \text{number of capsules returned}) / (4 * \text{number of days of exposure})$. A patient was considered compliant if he or she took at least 70% of the study drug.

10.3.9 Safety Evaluation

The primary measure of safety was the incidence of treatment-emergent adverse events (TEAEs). The safety and tolerability of the study medication was also assessed by monitoring laboratory test results (hematology, chemistry, calculated creatinine clearance, and urinalysis), physical examination, reported concomitant medications, and vital signs.

10.3.10 Protocol Amendments

Protocol Amendment 1 dated 14 December 2005 was introduced for the following main reasons:

1. To allow the enrollment of new patients who did not participate in lead-in studies MPUC3003 or MPUC3004.
2. To include study assessment (flexible sigmoidoscopy and calculation of Sutherland DAI) for new patients.

Protocol Amendment 2 was introduced 24 July 2006. This date is after the study began, but before study completion. The Amendment was introduced for the following main reasons:

1. To clarify the duration of study treatment.
2. To define activities to be conducted at the end of the study
3. To provide additional exclusion criteria for new patients.

Protocol Amendment 3 was introduced 15 July 2007. This date is after the study began, but before study completion. The Amendment was introduced for the following main reasons:

1. To clarify the visit schedule.
2. To allow patients who had a previous cholecystectomy to participate in the study. Initially, the only previous abdominal surgery allowed was appendectomy.
3. To allow the use of furosemide during study treatment

10.3.11 Statistical Methods

Data Set Analyzed

Data from all patients in study MPUC3005 who had baseline visits and at least one other study visit. For the safety analysis of this study, all patients who took at least one dose study drug were used.

10.3.12 Study Results

At the time of the original submission, 365 were included in the safety population for Study MPUC3005. Of these, 271 rolled over from a lead-in study and 99 enrolled as new subjects. At the Time of the 120-Day Safety Update, 387 subjects had enrolled in the study. The data included below in the study results represents data included in the Interim Study Report as part of the original NDA Submission. The Integrated Review of Safety in Sections 6 and 7 above contains data as of the clinical cut-off date of the 120-Day Safety Update.

10.3.12.1 *Demographics and Baseline Disease characteristics*

Overall, the distribution of male and female patients appears reasonable in Study MPUC3005. Approximately 47% of these patients are male. As in previous studies, the numbers of patients age 65 and older is small (12.3%) making it more difficult to adequately assess the safety and tolerability in this group. The patients continue to be primarily White.

Demographics, Study MPUC3005

Study MPUC3005		eMG/ N=365
Demographic Subgroup		
Sex (n,%)		
Male		171 (46.8)
Female		194 (53.2)
Age (years) (n,%)		
<65		320 (87.7)
≥65		45 (12.3)
Mean (SD)		47.2 (13.7)
Median (min,max)		48 (19, 82)
Race ^ (n,%)		
AI/AN*		1 (0.3)
Asian		1 (0.3)
Black/AA**		18 (4.9)
Native Hawaiian or Islander	Pacific	1 (0.3)
White		342 (93.7)
Ethnicity (n,%)		
Hispanic or Latino		13 (3.6)
Not Hispanic or Latino		350 (95.9)
Country (n,%)		
Russia		162 (44.4)
United States		203 (55.6)
Weight (lbs) (n,%)		
N		362
Mean (SD)		172.5 (37.3)
Median (min,max)		160.4 (100.0, 355.0)

Source: Table 14.1.2, Clinical Study Report MPUC3005

^Patients were allowed to check more than one race and so percentages may be greater than 100%

* American Indian/Alaskan Native

** African-American

The patients in Study MPUC3005 entered the study with a mean revised DAI score of 0.8, which reflects the inclusion criteria that patients had to be in remission of UC. Similar to the lead-in studies, there was inappropriate study entry of at least one patient with a DAI score of 7 at baseline.

Baseline Disease Characteristics, Study MPUC3005

Disease Characteristic	MPUC3005 Patients N=365
Duration of disease (weeks)	
N	363
Mean (SD)	372.1 (405.2)
Median (min,max)	229.0 (4.0, 2182.0)
Time since most recent flare (weeks)	
N	360
Mean (SD)	43.7 (21.9)
Median (min,max)	44.0 (0.0, 107.0)
Duration of current remission (weeks)	
N	350
Mean (SD)	24.9 (20.1)
Median (min,max)	36.0 (0.0, 93.0)
Disease severity	
0	189 (51.8)
≥1	167 (45.8)
Normal Number of Stools Daily	
N	361
Mean (SD)	1.7 (1.1)
Median (min,max)	1 (1, 8)
Revised Sutherland DAI total score	
N	356
Mean (SD)	0.8 (1.1)
Median (min, max)	0 (0, 7)
Revised Sutherland DAI Component Scores Mean (SD)	
N	356
Stool Frequency	0.1 (0.4)
Rectal Bleeding	0.0 (0.2)
Mucosal Appearance	0.4 (0.6)*
Physician's rating of disease severity	0.2 (0.4)
Baseline Renal Function (n,%) (Cockcroft-Gault formula)	
Normal (≥90 mL/min)	238 (65.2)
Mild (60-<90 mL/min)	115 (31.5)
Moderate (30-<60 mL/min)	8 (2.2)
Severe (<30 mL/min)	0

Source: Table 14.1.3, Clinical Study Report MPUC3005

* N=357

Compliance

Overall treatment compliance cannot be calculated because the study is still on-going. At the time of the original NDA submission, the mean calculated study compliance was 93.8% .

10.3.12.2 Efficacy Analyses

No efficacy analyses were performed as part of Study MPUC3005.

10.3.12.3 Safety Analyses

The interim study report safety population included 365 patients.

Extent of Exposure

The mean exposure time was 297.3 days which represents approximately the same number of person-years given that the number of patients was 365. Most patients had received study drug for 52 to 78 weeks.

Concomitant Medications

During this open-label trial to assess safety and tolerability a host of concomitant medications were allowed, including other 5-ASA medications and immunosuppressants. See exclusion criteria above.

Adverse Events

During Study MPUC3005, 61.6% of patients experienced a TEAE. Of these, 18.1% were mild, 33.7% were moderate, and 9.0% were severe. The most commonly reported TEAEs were headache (9.0%), nasopharyngitis (8.8%), diarrhea (7.7%), UC (5.2%), and a sinusitis (5.2%). Eighteen patients, 4.9%, experienced 22 SAEs. Of these SAEs, only one was considered by the Investigator to be possibly related to the study drug. There were no deaths reported.

Patients Reporting TEAEs , Severity and Relatedness

Category	MPUC3005 N=365
Patients Experiencing any TEAE	225 (61.6)
Patients Experiencing any Serious TEAE	18 (4.9)
TEAEs by Severity	
Mild	66 (18.1)
Moderate	123 (33.7)
Severe	33 (9.0)
Missing	3 (1.3)
Patients Experiencing TEAE possibly related to study drug, per Investigator	35 (9.6)
TEAEs Resulting in Study Discontinuation	37 (10.1)
Deaths	0

Source: Summary Table 14.3.1.1, MPUC3005 Interim Clinical Study Report

Serious Adverse Events

During MPUC3005, 22 serious adverse events (SAEs) occurred in 18 (4.9%) study patients. Of these, only one was felt to be related to the study drug—worsening UC.

Patients Reporting Serious Adverse Events, Study MPUC3005

SAEs System Order Class Preferred Term	Study MPUC3005 N=365
All SAEs	18 (4.9)
Cardiac Disorders	1 (3)
Atrial fibrillation	1 (0.3)
Gastrointestinal Disorders	9 (2.5)
Ulcerative colitis	6 (1.6)
Diverticular perforation	1 (0.3)
Ileus	1 (0.3)
Periproctitis	1 (0.3)
General Disorders	1 (0.3)
Chest pain	1 (0.3)
Infections and Infestations	5 (1.4)
Cellulitis	3 (0.8)
Abscess limb	1 (0.3)
Diverticulitis	1 (0.3)
Localized infection	1 (0.3)
Lower Respiratory Tract Infection	1 (0.3)
Tooth abscess	1 (0.3)
Neoplasms Benign, Malignant and Unspecified	5 (1.4)
Breast Cancer	3 (0.8)
Colon Cancer	1 (0.3)
Lung Neoplasm Malignant	1 (0.3)

Source: ISS Tables 2.7.4.11.1 and 2.7.4.11.2, and Summary Table 14.3.1.4.

Note: A subject reporting more than one AE for a particular Preferred Term (PT) or SystemOrderClass(SOC) is counted only once for that PT or SOC.

Below, are brief narratives of patients experiencing SAEs in MPUC3005. Patients who experienced the SAE of ulcerative colitis flare have been omitted. Unless specified, the Investigator categorized these events as not related to the study drug.

3003-553-01

The patient, a 51 year old White male, was in remission from UC for 8 months before enrolling in Study MPUC3003 as a placebo patient. He successfully completed Study MPUC3003 and enrolled in the open-label extension study MPUC3005. The patient had a known past medical history of mitral valve prolapse, paroxysmal atrial fibrillation, and hypercholesterolemia. Approximately 8 months after beginning eMG, the patient experienced chest pain with radiation to left arm and shoulder, palpitations, shortness of breath, and chest pressure. Emergency room evaluation concluded that the patient was not having a myocardial infarction. EKG showed incomplete right bundle branch block and atrial fibrillation. Approximately 18 months after being on eMG, the patient had a second episode of atrial fibrillation. The subject continued on the study drug without interruption during both of these events. The investigator felt that these SAEs were not related to the study drug.

3004-564-04

The patient, a 55 year old white male, successfully completed Study MPUC3003 and entered into the open-label extension study three weeks after study completion with a DAI score of 0. After 291 days of exposure to eMG, the patient was hospitalized with acute subcutaneous perirectal abscess which was successfully opened and drained the day of admission. The patient continues in the study.

3004-565-07

The patient, a 30 year old white female, successfully completed study MPUC3004 before entering the open-label extension study MPUC3005. Three months into the study, the patient was hospitalized with severe lower abdominal pain. The patient was found to have a uterine perforation and an extrauterine pregnancy was noted. The perforation was thought to be related to the extraction of an intrauterine device that had been performed approximately three weeks prior to the event. The subject interrupted treatment with the study drug for two days and then continued in the study.

3004-566-35

The patient, a 42 year old white male, successfully completed study MPUC3004 as a placebo patient and enrolled in the open-label extension study. After 49 days of exposure to eMG, the patient was hospitalized with a diagnosis of moderately differentiated adenocarcinoma of the colon with ulceration penetrating all layers of the colon and surrounding fatty tissues. The patient underwent a sub-total colectomy. The patient was withdrawn from the study.

9999-591-96

The patient, a 63 year old white male, entered the open-label study as a new patient. She had a DAI score of 3 at baseline. After 161 days on eMG, the patient was hospitalized with pulmonary congestion and was diagnosed with an acute exacerbation of chronic obstructive pulmonary disease. With treatment, the event resolved and the patient continued in the study.

3003-592-06

The patient, a 51 year old white female, successfully completed Study MPUC3003 as an eMG patient and enrolled in the open-label extension study. After approximately 180 days of exposure to eMG, the patient was hospitalized with sharp flank pain and fever. The patient was found to have diverticulitis in the sigmoid colon with perforation and localized abscess. During hospitalization, the abscess was percutaneously drained. The event was considered resolved. However, the patient discontinued from the study.

9999-599-03

The patient, a 71 year old white male, entered the open-label study as a new patient with a DAI score of 0 at baseline. After 8 days of exposure to eMG the patient had an accident during which a wire cleaning brush became embedded in his hand. The patient was diagnosed with cellulitis and limb abscess. The patient was hospitalized for antibiotic treatment as well as incision and drainage. The event resolved and the patient continued in the study.

3003-618-01

The patient, a 38 year old white female, successfully completed MPUC3003 as a placebo patient before enrolling in the open-label study. After 118 days of exposure to eMG the patient tested positive for pregnancy and discontinued the study drug. Subsequent to discontinuing the study medication, the patient experienced a spontaneous abortion.

3003-618-02

The patient, a 68 year old white female, successfully completed MPUC3003 as an eMG patient before enrolling in the open-label extension study. After 306 days of exposure to the study drug, the patient discontinued the study due to the new diagnosis of ductal carcinoma. The patient had a right partial mastectomy and axillary node dissection.

Study Discontinuations due to Treatment Emergent Adverse Events

TEAEs leading to study discontinuation in Study MPUC3005 have occurred in 10.1% of patients. Most of these TEAEs were gastrointestinal disorders. Of those, most were ulcerative colitis flares. Due to the on-going nature of this study, it is expected that the numbers of adverse withdrawals in the Final Study Report will be higher than the numbers presented below.

Patients with TEAEs Leading to Study Withdrawal, Study MPUC3005

MedDRA System Organ Class Preferred Terms	Number of patients N=365
Total Number of Patients with TEAE leading to Study Withdrawal	37 (10.1)
Gastrointestinal Disorders	22 (6.0)
Colitis Ulcerative	14 (3.8)
Abdominal pain	2 (0.5)
Constipation	2 (0.5)
Hemorrhagic diarrhea	2 (0.5)
Abdominal distension	1 (0.3)
Abdominal pain upper	1 (0.3)
Crohn's disease	1 (0.3)
Diarrhea	1 (0.3)
Dyspepsia	1 (0.3)
Hematochezia	1 (0.3)
Loose stools	1 (0.3)
Pancreatitis	1 (0.3)
Rectal hemorrhage	1 (0.3)
Infections and infestations	1 (0.3)
Diverticulitis	1 (0.3)
Investigations	1 (0.3)
Creatinine renal clearance decreased	1 (0.3)
Hemoglobin decreased	1 (0.3)
Platelet count decreased	1 (0.3)
Red blood cell count decreased	1 (0.3)
Musculoskeletal And Connective Tissue Disorders	1 (0.3)
Back pain	1 (0.3)
Neoplasms benign, malignant and unspecified	1 (0.3)
Lung neoplasm malignant	1 (0.3)
Nervous System Disorders	3 (0.8)
Headache	2 (0.3)
Dizziness	1 (0.3)
Pregnancy, puerperium, and perinatal conditions	1 (0.3)
Pregnancy	1 (0.3)
Psychiatric disorders	1 (0.3)
Insomnia	1 (0.3)
Renal and urinary disorders	1 (0.3)
Dysuria	1 (0.3)
Skin and subcutaneous tissue disorders	4 (1.1)
Alopecia	2 (0.5)
Rash	2 (0.5)

Source: Summary Table 13.3.1.5, Study MPUC3005 Interim Study Report

Common Adverse Events

The percentage of patients reported a TEAE in this open-label study, 61.6%, is consistent with the percentage of eMG subjects reporting a TEAE in the lead-in studies—64.1% MPUC3003, 53.4% MPUC3004. Given the longer duration of this on-going study, it is expected that the final percentage of patients reporting a TEAE will be higher than those reported in the six-month lead-in studies. Of the reported adverse events, most were gastrointestinal disorders (29.6%) or infections (32.6%). As expected headache, continued to be commonly reported among study patients (9.0%). See Table 15 below.

TEAEs Reported by ≥3% of Patients, Study MPUC3005

MPUC3005	
MedDRA System Organ Class Preferred Term	eMG N=365 (%)
Total Number of Patients with a TEAE	225 (61.6)
Gastrointestinal Disorders	108 (29.6)
Diarrhea	29 (7.7)
Ulcerative colitis	19 (5.2)
Abdominal Pain	16 (4.4)
Constipation	12 (3.3)
Nausea	11 (3.0)
Infections and Infestations	119 (32.6)
Nasopharyngitis	32 (8.8)
Sinusitis	19 (5.2)
Upper respiratory tract infection	17 (4.7)
Gastroenteritis viral	15 (4.1)
Urinary Tract Infection	12 (3.3)
Musculoskeletal And Connective Tissue Disorders	50 (13.7)
Arthralgia	14 (3.8)
Back pain	12 (3.3)
Nervous System Disorders	48 (13.2)
Headache	33 (9.0)

Source: Summary Tables 14.3.1.2 and 14.3.1.3, MPUC3005 Interim Clinical Study Report

Conclusion

Overall, Study MPUC305 was appropriately designed with appropriate inclusion criteria. Specifically, the use of steroids, azathioprine, and 6-mercaptopurine were allowed by study patients. This more appropriately represents how the post-marketing uses of the product. The study duration appears adequate to monitor for adverse events.

10.4 List and Description of Investigators

Included below are all investigators who screened patients for pivotal studies MPUC3003, MPUC3004, and MPUC3005.

Clinical Review
 Aisha E. Peterson, MD, MPH, MBA
 NDA 22-301
 Apriso (mesalamine)

10.4.1 MPUC3003 Clinical Investigators

Site Number	Principal Investigator	Site Address
071	J. Mark Provenza	Louisiana Research Center, LLC 3217 Mabel St. Shreveport, LA 71103
092	H. Tatum	Oklahoma Gastroenterology Associates 1145 South Utica, Suite 701 Tulsa, OK 74104
106	M. Mazen Jamal	Long Beach VA Medical Center 5901 East 7 th Street, 111G Long Beach, CA 90822
157	James W. Dimitroff	St. Louis Center for Clinical Research 10012 Kennerly Rd., Suite 101 St. Louis, Missouri 63128
186	M. Nagrani	United Medical Research 612 Palmetto Street New Smyrna Beach, FL 32168
194	Marc F. Catalano	Wisconsin Center for Advanced Research 2801 W. Kinnickinnic River Pkwy, Suite 1030 Milwaukee WI 53215
208	Dale E. Merrell, M.D	Borland Groover Clinic-Research Dept. 4800 Belfort Road Jacksonville, Florida 32256
214	Ronald Pruitt, MD	4230 Harding Road Suite 309 Nashville, TN 37205
265	Barry P. Kaufman, MD,	AGA Clinical Research Associates, LLC 3205 Fire Road Egg Harbor Township, NJ 08234
271	Robert W. Schuman, M.D.	195 Columbia Turnpike, Suite 110 Florham Park, NJ 07932
306	Mitchell A. Mah'moud	Boice-Willis Clinic 901 N. Winstead Ave., Suite 530 Rocky Mount, NC 27804

Clinical Review
 Aisha E. Peterson, MD, MPH, MBA
 NDA 22-301
 Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
335	Jawahar L. Taunk	Advanced Gastroenterology Associates 34041 US Hwy. 19 N., Suite A Palm Harbor, FL 34684
338	Howard N. Guss	Shore Health Group 3200 Sunset Ave., Suite 208 Ocean, NJ 07712
398	Richard Alan Wright	University of Louisville Division of Gastroenterology/Hepatology 550 S. Jackson Street, ACB 3 rd floor Louisville, KY 40202
415	Subhash C. Gumber	Triangle Medical Research Associates 530 New Waverly Place, Suite 200 Cary, NC 27511
417	D. Rider	Rider Research Group 350 Parnassus Ave., Suite 900 San Francisco, CA 94117
435	Michael F. Kestell	Spokane Digestive Disease Center, P.S. 105 W. 8 th Ave, Suite 6010 Spokane, WA 99204
459	Mark A. Ringold	New River Valley Research Institute 110 Akers Farm Road Christiansburg, VA 24073
483	Stefano P. Marcuard	Carolina Research Carolina Digestive Diseases, PA 800 Moye Boulevard Greenville, North Carolina 27834
505	Gary Culp Richter	Consultative Gastroenterology 550 Peachtree Street, Suite 1750 Atlanta, GA 30308
514	John P. Cello	San Francisco General Hospital 1001 Potrero Ave, NH 3D San Francisco, CA 94110
520	Wayne B. Schonfeld	4700M Sheridan Street Hollywood, Florida 33021
543	Simon Lichtiger	1755 York Avenue New York, NY 10128
545	Michael Galambos	Digestive Healthcare of Georgia 95 Collier Road, NW, Suite 4085 Atlanta, GA 30309

Site Number	Principal Investigator	Site Address
546	David B. Rausher	The Atlanta Center for Gastroenterology 2665 N. Decatur Road, Suite 550 Decatur, GA 30033
547	Shahriar Sedghi	Gastroenterology Associates of central Georgia 610 Third Street, Suite 204 Macon, GA 31201
553	Robert W. Braun	720 SW Lane Street Topeka, KS 66606
557	Victor Lawrienko	Covenant Clinic 2710 St. Francis Drive, Suite 510 Waterloo, IA 50702
559	John Sabel	499 E. Hampden Ave Suite 420 Englewood, Colorado 80113
560	Farid Naffah	Farid Naffah 9225 East Market Street Warren, OH 44484
561	Andrey Yu. Baranovsky	Saint-Petersburg Medical academy of Postgraduate Education City Clinical Hospital # 31 3, prospect Dinamo, 197110, St- Petersburg, Russia
562	Evgeny I. Tkachenko	State Medical Academy 47, Piskariovsky prospect, 195067 St. - Petersburg, Russia
563	Oleg N. Minushkin	Educational Scientific Center President of the Russian Federation, City Clinical Hospital #51 7/33, Alyabieva str., Moscow 121309, Russia
571	Evgeny L. Nasonov	Institute of Rheumatology of Russian Academy of Medical Sciences 34 a, Kashirskoye Shosse, Moscow, 115522. Russia
572	Boris D. Starostin	City Polyclinic #38, Centre for Gastroenterology No. 1 26, Kavalergardskaya, 193015, St. Petersburg, Russia,

Clinical Review
 Aisha E. Peterson, MD, MPH, MBA
 NDA 22-301
 Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
579	William A. Kaye	Metabolic Research Institute, Inc. 1515 N. Flagler Drive Suite 440 West Palm Beach, FL 33401
583	Lenin J. Peters	Bethany Medical Center 507 Linsay Street High Point, NC 27262
592	Walid F. Makdisi	Gastroenterology Associates of Tidewater 112 Gainsborough Square, Suite 101 Chesapeake, VA 23320
596	A. Rosen	Sinai Medical Office Building 2411 West Belvedere Ave., Suite 306 Baltimore, MD 21215
597	Diego T. Torres, II	Peninsula research, Inc 305 Clyde Morris Blvd - Suite 250 Ormond Beach, Fl 32174
604	Steven J. Wegley	11027 Meridian Ave. N., #100 Seattle, WA 98133
605	P. Winkle	Orango County Clinical Research 11741 Valley View Street Cypress, CA 90630
607	Umedchandra K. Shah	Mid Atlantic Medical Research Centers Philip J. Bean Medical Center 24035 Three Notch Road Hollywood, MD 20636
613	C. Badii	Advent Clinical Research Centers 2750 Bahia Vista Street, Suite 105 Sarasota, FL 34239
618	Glenn L. Gordon	Center for Digestive & Liver Diseases, Inc 714 Medical Park Drive Mexico, MO 65265-3726
631	B. Hrach	Barbara Hrach, MD 1482 E. Valley Road, Suite 154 Santa Barbara, CA 93108
647	John Corless	ACCR/CGC Research Department Charleston Gastroenterology Specialist 1962 Charlie Hall Blvd. Charleston, SC 2914

Clinical Review
Aisha E. Peterson, MD, MPH, MBA
NDA 22-301
Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
859	Nikolay N. Olondar	District Military Clinical Hospital 63, Suworovsky pr., St. Petersburg, 193163, Russia

Clinical Review
Aisha E. Peterson, MD, MPH, MBA
NDA 22-301
Apriso (mesalamine)

10.4.2 Study MPUC3004 Clinical Investigators

Site Number	Principal Investigator	Site Address
022	Joseph Duncan Fitterer	105 W 8 th Ave., Suite 6050 Spokane, WA 99204
041	David B. Stanton	Community Clinical Trials 505 S. Main Street, Suite 1030 Orange, CA 92868
074	David J. Sales	Northwest Gastroenterologists S.C. 1415 S. Arlington Heights Road Arlington Heights, Illinois 60005
108	Donald R. Abraham	Newport Beach Orange Coast Endoscopy Center 1525 Superior Ave., Suite 114 Newport Beach, CA 92663
117	Simon Behar	Medical Research Unlimited 590 B 25 St., Suite 503 Hialeah, FL 33013
124	Michael D. Kreines	Consultants for Clinical Research, Inc. 2925 Vernon Place, Suite 200 Cincinnati, OH 45219
198	Ronald P. Fogel	30795 23 Mile Road, Suite 207 Chesterfield, MI 48047
216	Dennis S. Riff	AGMG Clinical Research 1211 W. La Palma Ave., Suite 602,306 Anaheim, CA 92801
396	C. Stephen Yarborough	Hillcrest Clinical Research, LLC 717 SE Main Street, Suite B Simpsonville, SC 29681
419	Salam F. Zakko	Connecticut Gastroenterology Institute Brewster Road Bristol, CT 06010
445	Mark A. Bonner	First Care Family Doctors South 2523 E. Huntsville Road Fayetteville, AR 72701
460	Dallas N. Shone	2204 Pavilion Drive Kingsport, TN 37660

Clinical Review
Aisha E. Peterson, MD, MPH, MBA
NDA 22-301
Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
463	Syam P. Gaddam	Digestive and Liver Disease Specialists A Medical Group, Inc. 11922 Seacrest Drive, Suite A Garden Grove, CA 92840
476	Abdul Moosa	1007 S. Broadway Laporte, TX 77571
485	Edward H. Cheng	VA Medical Center 79 Middleville Road, Suite 111E Northport, NY 11768
486	Philip G. Holtzapfle	SUNY Upstate Medical University 750 East Adams St. Syracuse, NY 13210
494	Uma K. Murthy	Veteran's Affairs Medical Center 800 Irving Avenue Syracuse, NY 13210
496	Atilla Ertan	6560 Fannin Street, Suite 2208 Houston, TX 77030
497	Samuel Castillo	1044 N. Mozart, Suite 500 Chicago, IL 60622
498	Robert D. Kaplan	LeBauer Research Associates, P.A. 520 North Elam Avenue Greensboro, NC 27403
499	Shawkat Kero	Clinical Research of Tampa Bay, Inc. 11373 Cortez Blvd., Suite 401 Brooksville, FL 34613
503	Rajendra Prasad Gupta	1871 Pennington Road Trenton, NJ 08618
518	Frederick M. Braunstein	2200 Burdett Avenue, Suites 201 and 205 Troy, NY 12180
532	Angelo G. Coppola, Jr.	Little Rock Diagnostic Clinic 10001 Lile Drive Little Rock, AR 72205
558	Michael Perkel	Digestive Care Associates 1700 Hospital S. Drive, Suite 502 Austell, GA 30106
564	Alexander V. Lakhin	Lipetsk Regional Clinical Hospital 6A Moskovskaya str. 398055, Lipetsk, , Russia

Clinical Review
 Aisha E. Peterson, MD, MPH, MBA
 NDA 22-301
 Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
565	Andrey P. Rebrov	Saratov State Medical University Department of Hospital Therapy Saratov Regional Clinical Hospital 1 Smirnovskoye ravine Saratov, 410053, Russia
566	Yuri G. Shvarz	Saratov State Medical University Department of Faculty Therapy Clinical Hospital No. 3 137 Bolshaya Sadovaya str. Saratov, 410053, Russia
568	Andrey V. Kalinin	Burdenko Main Military Clinical Hospital 3 Hospital sq. Moscow, 105229, Russia
569	Boris F. Nemtsov	Kirov State Medical Academy Department of Hospital Therapy Kirov Regional Clinical Hospital 42 Vorovskogo str. Kirov, 610027, Russia
573	Vyacheslav Yu. Golofeevsky	Dept. of Internal Medicine (Hospital Therapy) Military Medical Academy District Military Hospital 63 Suvorovsky pr. St. Petersburg, 193163, Russia
586	Bradley L. Freilich	6675 Holmes, Suite 430 Kansas City, MO 64131
591	Sardar D. Khan	Houston Digestive Diseases Clinic 714 FM 1960 W., Suite 201 Houston, TX 77090
598	W. Michael Priebe	Tacoma Digestive Disease Research Center, LLC 1112 6 th Avenue, Suite 200 Tacoma, WA 98405
599	Willard Roger Carlisle	Birmingham Gastroenterology Associates One Independence Plaza, Suite 900 Birmingham, AL 35209
615	I. Rajjman	Digestive Associates of Houston, PA 6620 Main Street, Suite 1510 Houston, TX 77030

Clinical Review
Aisha E. Peterson, MD, MPH, MBA
NDA 22-301
Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
626	Ramona Rajapakse	Stony Brook University Hospital 100 Nicolls Road Department of Gastroenterology, HSC T17, Room 060 Stony Brook, NY 11794-8173
636	I. Kalvaria	Lovelace Scientific Research 5741 Bee Ridge Road, Suite 560 Sarasota, FL, 34233
888	Gennady V. Tsodikov	Moscow Regional Scientific-Research Clinical Institute named after M.F. Vladimirsky 6 ½ Shchepkina str. Moscow, 129110, Russia
889	Igor Khalif	State Scientific Center for Coloproctology 2 Selyam Adil str. Moscow 123423, Russia

10.4.3 Study MPUC3005 Clinical Investigators

Site Number	Principal Investigator	Site Address
022	Joseph D. Fitterer	105 W. 8 th Ave., Suite 6050 Spokane, WA 99204
041	David B. Stanton	Community Clinical Trials 505 S. Main Street, Suite 1030 Orange, CA 92868
074	David J. Sales	Northwest Gastroenterologists S.C. 1415 S. Arlington Heights Road Arlington Heights, Illinois 60005
092	Harvey A. Tatum	1145 South Utica, Suite 701 Tulsa, OK 74104
106	M. Mazen Jamal	Long Beach VA Medical Center 5901 E. 7 th Street #111 Long Beach, CA 90822
117	Simon Behar	Medical Research Unlimited 590 East 25 th Street, Suite #503 Hialeah, FL 33013
124	Michael D. Kreines	Consultants for Clinical Research, Inc. 2925 Vernon Place, Suite 200 Cincinnati, OH 45219
157	James W. Dimitroff	St. Louis Center for Clinical Research 10012 Kennerly Rd. Suite 101 St. Louis, Missouri 63128
186	Mark Nagrani	612 Palmetto Street New Smyrna Beach, FL 32168
194	Marc F. Catalano	Wisconsin Center for Advanced Research Gastroenterology Consultants, Ltd. 2801 W. Kinnickinnic River Parkway, Suite 1030 Milwaukee, WI 53215
198	Ronald P. Fogel	30795 23 Mile Road, Suite 207 Chesterfield, MI 48047
208	Dale E. Merrell	Borland Groover Clinic-Research Department 4800 Belfort Road Jacksonville, FL 32256

Clinical Review
 Aisha E. Peterson, MD, MPH, MBA
 NDA 22-301
 Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
214	Ronald Pruitt	4230 Harding Road Suite 309 Nashville, TN 37205
216	Dennis S. Riff	AGMG Clinical Research 1211 W. La Palma Ave., Suite 602,306 Anaheim, CA 92801
265	Barry Kaufman	3205 Fire Road Egg Harbor Township, NJ 08234
271	Robert W. Schuman	Affiliates in Gastroenterology, PA 195 Columbia Turnpike Suite 110 Columbia Turnpike, NJ 07932
306	Mitchell A. Mah'moud	Boice-Willis Clinic 901 N. Winstead Ave., Suite 340 Rocky Mount, NC 27804
335	Jawahar L. Taunk	Advanced Gastroenterology Associates 34041 US Hwy. 19, N Suite A Palm Harbor, FL 34684
338	Howard N. Guss	3200 Sunset Avenue #208 Ocean, NJ 07712
396	C. Stephen Yarborough	Hillcrest Clinical Research, LLC 717 SE Main Street, Suite B Simpsonville, SC 29681
417	Dean Rider	Rider Research Group 350 Parnassus Suite 900 San Francisco, CA 94117
419	Salam F. Zakko	Connecticut Gastroenterology Institute Brewster Road Bristol, CT 06010
435	Michael F. Kestell	Spokane Digestive Disease Center, P.S. 105 W. 8 th Ave., Suite 6010 Spokane, WA 99204
445	Mark A. Bonner	FirstCare Family Doctors South 2523 E. Huntsville Road Fayetteville, AR 72701
459	Mark A. Ringold	New River Valley Research Institute 110 Akers Farm Road Christiansburg, VA 24073

Clinical Review
Aisha E. Peterson, MD, MPH, MBA
NDA 22-301
Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
463	Syam P. Gaddam	Digestive and Liver Disease Specialists, A Medical Group, Inc. 11922 Seacrest Drive, Suite A Garden Grove, CA 92840
476	Abdul Moosa	1007 S. Broadway Laporte, TX 77571
483	Stefano P. Marcuard	Carolina Research Carolina Digestive Diseases, PA 704 W.H. Smith Boulevard Greenville, NC 27834
494	Uma K. Murthy	Syracuse Veteran's Affairs Medical Center 800 Irving Avenue Syracuse, NY 13210
498	Robert D. Kaplan	LeBauer Research Associates, P.A. 520 N. Elam Avenue Greensboro, NC 27403
499	Shawkat Kero	Clinical Research of Tampa Bay, Inc. 11373 Cortez Blvd., Suite 401 Brocksville, FL 34613
505	Gary Richter	550 Peachtree Street NE Suite 1750 Atlanta, GA 30308
518	Frederick M. Braunstein	Upstate Gastroenterology Associates 2200 Burdett Avenue Suite 201 Troy, NY 12180
520	Wayne B. Schonfeld	4700 M Sheridan Street Hollywood, FL 33021
543	Simon Lichtiger	1755 York Avenue New York, NY 10128
546	David B. Rausher	Atlanta Center for Gastroenterology 2665 N. Decatur Rd., Suite 550 Decatur, GA 30033
547	Shahriar Sedghi	610 Third Street, Suite 204 Macon, GA 31201
553	Robert W. Braun	Cotton-O'Neil Clinical Research Center Cotton-O'Neil Digestive Health Center 720 SW Lane Street Topeka, KS 66606

Clinical Review
Aisha E. Peterson, MD, MPH, MBA
NDA 22-301
Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
557	Victor Lawrinenko	2710 St. Francis Drive, Suite 510 Waterloo, Iowa 50702
558	Michael Perkel	Digestive Care Associates 1700 Hospital S. Drive, Suite 502 Austell, GA 30106
560	Farid Naffah	9225 East Market Street Warren, Ohio 44484
561	Andrey Yu. Baranovsky	Clinical Hospital # 31 3, Dynamo prospect, 197110 St. Petersburg, Russia
562	Evgeny I. Tkachenko	State Medical Academy named after I.I. Mechnikov 47 Piskariovsky prospect, 195067, St. Petersburg, Russia
563	Oleg N. Minushkin	Educational Scientific Centre of the Medical Centre Management Department of President of the Russian Federation, City Clinical Hospital #51 7/33 Alyabieva str., Moscow 121309, Russia
564	Alexander V. Lakhin	Lipetsk Regional Clinical Hospital 6A Moskovskaya str. Lipetsk, 398055, Russia
565	Andrey P. Rebrov	Saratov State Medical University Department of Hospital Therapy Saratov Regional Clinical Hospital 1 Smirnovskoya ravine Saratov, 410053, Russia
566	Yuri G. Shvarz	Saratov State Medical University Department of Faculty Therapy Clinical Hospital No. 3 137 Bolshaya Sadovaya str. Saratov, 410053, Russia
568	Andrey V. Kalinin	Burdenko Main Military Clinical Hospital 3 Gospitalnaya Square Moscow, 105229, Russia
569	Boris F. Nemtsov	Kirov State Medical Academy Department of Hospital Therapy Kirov Regional Clinical Hospital 42 Vorovskogo str. Kirov, 610027, Russia

Clinical Review
Aisha E. Peterson, MD, MPH, MBA
NDA 22-301
Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
571	Evgeny L. Nasonov	Institute of Rheumatology of the Russian Academy of Medical Sciences 34 A, Kashirskoye shosse, 115522, Moscow, Russia
572	Boris D. Starostin	City polyclinic No. 38, Centre for Gastroenterology No.1, 26 Kavalergardskaya, St. Petersburg, Russia 193015
573	Vyacheslav Yu. Golofeevsky	Dept. of Internal Medicine (Hospital Therapy) Military Medical Academy District Military Hospital 63 Suvorovsky prospect St. Petersburg, 191163, Russia
583	Lenin Peters	507 Lindsay Street 2 nd Floor High Point, NC 27262
591	Sardar D. Khan	714 FM 1960 W. #201 Houston, TX 77090
592	Walid F. Makdisi	Gastroenterology Associates of Tidewater 112 Gainsborough Square, Suite 101 Chesapeake, VA 23320
596	Alan A. Rosen	2411 W. Belvedere Avenue Suite 306 Baltimore, MD 21215
597	Diego T. Torres II	Peninsula Research, Inc. 305 Clyde Morris Blvd., Suite 250 Ormond Beach, FL 32174
598	W. Michael Priebe	Tacoma Digestive Disease Research Center, LLC 1112 6 th Avenue, Suite 200 Tacoma, WA 98405
599	W. Roger Carlisle	Birmingham Gastroenterology Associates, P.C. One Independence Plaza, Suite 900 Birmingham, AL 35209
604	Steven J. Wegley	11027 Meridian Ave. N., #100 Seattle, WA 98133

Clinical Review
Aisha E. Peterson, MD, MPH, MBA
NDA 22-301
Apriso (mesalamine)

Site Number	Principal Investigator	Site Address
607	Umedchandra K. Shah	Mid Atlantic Medical Research Centers Philip J. Bean Medical Center 24035 Three Notch Road Hollywood, MD 20636
613	Cyrus A Badii	Center for Digestive Diseases 3325 S. Tamiami Trail, Suite 200 Sarasota, FL 34239
618	Glenn L. Gordon	Center for Digestive & Liver Diseases, Inc. 714 Medical Park Drive Mexico, MO 65265-3726
626	Ramona Rajapakse	Stony Brook University Hospital 100 Nicolls Road Department of Gastroenterology, HSC T17, Room 060 Stony Brook, NY 11794-8173
636	Issac Kalvaria	Lovelace Scientific Resources, Inc. 2089 Hawthorne Street Sarasota, FL 34239
647	John K. Corless	ACCR/CGC Research Department Charleston Gastroenterology Specialists 1962 Charlie Hall Blvd. Charleston, SC 29414

10.5 Line-by-Line Labeling Review

Discussions between the Applicant and CDER have resolved major issues with regard to the label. Several significant changes have been made to the Applicant's proposed labeling. These include the following:

~~_____~~ b(4)

~~_____~~ b(4)

~~_____~~ b(4)

~~_____~~ b(4)

11 REFERENCES

¹ Gisbert JP, Gonzalez-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis.* 2007;13:629-638.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Aisha E Peterson
10/30/2008 12:10:47 PM
MEDICAL OFFICER

John Hyde
10/30/2008 12:48:16 PM
MEDICAL OFFICER