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RESEARCH**

APPLICATION NUMBER:

22-301

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name mesalamine
Trade Name Apriso
Therapeutic Class Locally acting aminosalicylate
Applicant Salix Pharmaceuticals, Inc.

Priority Designation S

Formulation 0.375 g delayed-release capsules
Dosing Regimen 1.5 g (four 0.375 g capsules)
once daily
Indication Maintenance of remission of
Ulcerative Colitis (UC)
Intended Population Adults ages 18 years and older
currently in remission from UC

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Apriso, encapsulated mesalamine granules (eMG), be approved for the maintenance of remission of ulcerative colitis in patients 18 years of age and older. Treatment duration in the prospective, placebo-controlled trials was 6 months.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There is no applicable activity related to risk management for this New Drug Application (NDA).

1.2.2 Required Phase 4 Commitments

Safety and effectiveness have not been established in pediatric patients. The Applicant is required to perform clinical studies to evaluate the safety and effectiveness of mesalamine granules in the pediatric population. Specifically, the Applicant has agreed to conduct studies to evaluate the safety and effectiveness of at least two dosing regimens in patients in remission of ulcerative colitis who are five years of age or older. Studies in those ages birth to less than five years have been waived.

The Applicant agreed to submit the final study report by June 1, 2013.

1.2.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Two pivotal, Phase 3 studies were submitted by Salix Pharmaceuticals, Inc. to evaluate the clinical efficacy and safety of eMG (encapsulated mesalamine granules) for the maintenance of remission of ulcerative colitis (UC) in patients ages 18 years and over for consecutive therapy up to six months. In addition, a single open-label long-term extension study, MPUC3005, was submitted as part of this NDA submission.

1.3.2 Efficacy

Two pivotal Phase 3 studies were submitted by the Applicant to provide data for the efficacy review in support of the maintenance of remission of ulcerative colitis indication being sought. These studies—MPUC3003 and MPUC3004--were randomized, double-blind, placebo-controlled, parallel group, multi-center studies conducted in Russia and the United States. Both studies used identical inclusion and exclusion criteria, efficacy endpoints, and study schedules. The only difference between the two studies was the total number of patients randomized—305 in MPUC3003 and 257 in MPUC3004. Both studies randomized patients in a 2:1 ratio (eMG:placebo). The distribution of demographic and baseline disease characteristics were similar across treatment groups.

The primary efficacy endpoint for both studies was the number and proportion of patients who remained relapse-free at Month 6/End of Study (EOS). Relapse (or treatment failure) was defined as a rectal bleeding score of 1 or more AND a mucosal appearance score of 2 or more as described in the revised Sutherland Disease Activity Index (see Section 6 for a detailed description of this index). In addition, patients who experienced symptoms of a UC flare or restarted medications used to treat UC were counted as relapses. In the original protocol, patients who prematurely discontinued a study for any reason were counted as relapses. However, in a late-stage protocol amendment, premature discontinuations were only counted as relapses if they discontinued for an adverse event related to UC. Efficacy was analyzed using the intent-to-treat (ITT) population, all randomized patients who received at least one dose of the study drug.

In study MPUC3003, 305 patients were randomized and received at least one dose of study medication (209 eMG; 96 placebo). At Month 6/EOS, 78.9% of eMG subjects and 58.3% of placebo subjects remained relapse-free ($p < 0.001$). If we analyze the primary efficacy results using the original definition of relapse (i.e., all premature withdrawals counted as relapses), at Month 6/EOS, 68.4% of eMG patients and 51.0% of placebo patients remained relapse-free ($p < 0.001$). Both results are highly statistically significant.

In study MPUC3004, 257 patients were randomized and received at least one dose of study medication (164 eMG, 93 placebo). At Month 6/EOS, 79.9% of eMG patients remained relapse-free, compared with 67.7% of placebo patients ($p = 0.029$). If we analyze the primary efficacy results using the original definition of relapse, at Month 6/EOS, 71.3% of eMG patients and 59.1% of placebo patients remained relapse free ($p = 0.046$).

For both studies, analysis of the primary endpoint was repeated controlling for gender, age group (<65, ≥ 65), race (White, non-White), and baseline disease severity category (0, ≥ 1). The results remained statistically significant. For subgroup analysis, studies MPUC3003 and MPUC3004 were combined. Subgroup analysis by baseline disease category showed a statistically significant difference (eMG over placebo) in both baseline disease categories, both genders, and both countries. However, statistically significant differences (eMG over placebo) were only seen in the <65 age group and the White race group. The numbers of patients the ≥ 65 age group and the white race group were very small.

Seven secondary endpoints were defined *a priori* and tested using a hierarchical approach. In Study MPUC3003, only the first secondary endpoint, the number and proportion of patients in each level of change from baseline in rectal bleeding score at months 1, 3, and 6, was found to have a statistically significant difference between the eMG and placebo groups ($p=0.008$). In Study MPUC3004, a statistically significant difference between eMG and placebo groups was not found for any of the secondary endpoints. Once a secondary endpoint failed to reach statistical significance, further endpoints in the hierarchy were deemed exploratory (and not inferential) in nature.

1.3.3 Safety

The study drug, eMG, was evaluated in 557 unique patients whose UC was in remission in controlled and open-label studies in the US and Russia. Overall, adverse events in the eMG clinical development program were similar to those attributable to other mesalamine formulations. The majority of adverse events were related to the gastrointestinal system or were events common to the general population (i.e., headache, nasopharyngitis, and sinusitis).

Two populations were used for the safety analyses: the RCT population and the All eMG population. These populations were taken from the larger safety population which included all patients who received at least one dose of the study drug (eMG or placebo) and provided at least one post-baseline safety assessment. The RCT population included all safety patients in studies MPUC3003 and MPUC3004. The All eMG population included all patients in MPUC3003 and MPUC3004 who received eMG in addition to all patients from study MPUC3005, an open-label extension study.

RCT Population

In the RCT population, 59% of patients treated with eMG reported a treatment-emergent adverse event (TEAE), compared with 64% of placebo patients. Of these, the most commonly reported TEAEs were colitis ulcerative and headache (a known possible mesalmine adverse event) in both treatment groups. Eight patients (1.4%) reported a total of eight serious adverse events (SAEs). Four SAEs (1.1%) were reported in eMG patients, and 4 SAEs (2.2%) were reported in placebo patients. Only one patient in this population withdrew from the study due to an SAE.

All eMG Population

In the All eMG population, 69% of patients experienced a TEAE. Of these, the most commonly reported were also ulcerative colitis and headache. Twenty-six patients reported a SAE. Of the 22 SAEs that occurred in Study MPUC3005, 10 patients withdrew due to the SAE. It should be noted that, Study MPUC3005 is on-going and the results included in this review are as of the 12-Day Safety Update clinical cut-off date of 14 January 2008.

Four supportive studies using mesalamine formulations similar to eMG were submitted with NDA 22-301—SAG-2, SAG-15, SAG-26, and SAG-27. The TEAEs reported and their incidences were similar to those found in the primary studies—MPUC3003, MPUC3004, and MPUC3005.

A query of the Adverse Events Reporting System (AERS) revealed several cases of mesalamine use associated with liver failure. These spontaneous case reports along with post-marketing data from other mesalamine products prompted a recommendation that a liver impairment warning be added to mesalamine labeling.

There were no deaths reported in any of the submitted primary or supportive studies.

1.3.4 Dosing Regimen and Administration

This reviewer recommends that the proposed dosage of eMG for the maintenance of remission from ulcerative colitis of 1.5 g once daily taken as four 0.375 g capsules orally be accepted. Treatment duration in the prospective, placebo-controlled trials was 6 months. The use of eMG beyond six months has been studied in only one study, MPUC3005. Capsules of eMG can be taken without regard for the timing of food intake, but should not be co-administered with antacids.

1.3.5 Drug-Drug Interactions

In an *in vitro* study using human liver microsomes, mesalamine and its metabolites were not shown to inhibit the major CYP enzymes CYP1A2, CYP2C9, CYPsC19, CYP2D6, and CYP3A4 (Study Report XT055039). There are no known drug interactions with mesalamine products.

1.3.6 Special Populations

The safety and efficacy of eMG has not been established in the pediatric population. The Applicant requested a partial waiver of pediatric studies. The waiver included the age group of birth to less than five years of age. The Applicant reasons that studies are impossible or highly impractical because the pool of patients in this age group with ulcerative colitis eligible to take medication for maintenance of remission is too small. Given that pediatric ulcerative colitis has been designated an orphan indication and Colazal was granted a waiver for the age group birth to less than five years of age, the Applicant argues that their waiver request should also be granted. The Food and Drug Administration's (FDA) Pediatric Review Committee (PeRC) granted the Applicant's waiver for studies in patient's less than five years of age.

The Applicant also requested a deferral of pediatric studies for ages greater than five years and less than 18 years of age. The Applicant has committed to designing and implementing a safety, effectiveness, and pharmacokinetic study with mesalamine granules of at least two dosing regimens for in patients in remission of ulcerative colitis who are five years of age or older at study entry. The Applicant has agreed to submit a study protocol to the Agency by June 1, 2009 and initiate the study by January 1, 2010. The Applicant has also agreed to submit the final study report for this study by June 1, 2013.

In non-clinical studies with mesalamine, the kidney has been identified as the primary organ of toxicity. Therefore, it is recommended that all patients have an evaluation of renal function prior to initiation of mesalamine products and periodically while on therapy. Current mesalamine labeling states in the Warning and Precautions section that “Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported...”

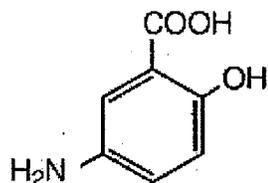
Studies using eMG contained few patients with renal insufficiency, hepatic insufficiency, age >65 years, non-white race, or pregnant or nursing women. Despite the lack of non-White patients in the eMG studies, currently available information on the use of other mesalmine products in non-white patients does not suggest that eMG will have a different efficacy or safety profile in this group. Caution should be taken when prescribing eMG to the elderly as this group of patients is more likely to have concomitant renal and/or hepatic insufficiency. It is recommended that the drug product, eMG, be assigned to pregnancy category B and should, therefore, only be used by pregnant women if clearly needed. This recommendation is based on pre-clinical reproduction studies and is consistent with the labeling of other mesalamine products.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Trade Name: Apriso
Generic Name: Mesalamine (5-aminosalicylic acid; 5-ASA)
Code Name: eMG
Chemical Name: 5-amino-2-hydroxybenzoic acid

Structural formula:



Therapeutic Class: Anti-inflammatory
Formulation: Encapsulated granules
Proposed indication: Maintenance of remission of UC

Encapsulated mesalamine granules, formerly referred to as mesalamine pellets, are 1 mm granules of 5-ASA. The granules are contained in a hard gelatin capsule shell. The formulation is designed to offer delayed release of mesalamine controlled by a [] coating which dissolves when exposed to pH 6, but resists dissolution in the stomach where the pH is lower. In addition, extended release is controlled by a [] coating over the granules which uniformly releases and distributes mesalamine in the lumen of the colon. This mesalamine formulation does not contain phthalates.

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The exact mechanism of action of mesalamine is unknown, but it appears to act topically rather than systemically. Oral mesalamine formulations have been accepted as a first line treatment for the induction and maintenance of remission of ulcerative colitis for over 40 years.

2.2 Currently Available Treatment for Indication

Currently approved oral products for the maintenance of remission from ulcerative colitis include systemic steroids, sulfasalazine, mesalamine products, and biologics. Specific products are included below:

Asacol® 400 mg (delayed-release mesalamine)

Eudragit-S coated mesalamine tablets approved for adults 1.6 g/day

Lialda® (mesalamine)

Mesalamine coated with a multimatrix (MMX) system

Pentasa® (mesalamine)

Ethylcellulose-coated microgranules available in 250 mg and 500 mg tablets

Colazal®, Colazide® (balsalazide)

5-ASA linked to 4-aminobenzol-b-alanine by azo-bond

Azulfidine® and Azulfidine EN-tabs®

sulfasalazine sodium, prodrug of mesalamine and sulfapyridine

Dipentum® (osalazine, prodrug of mesalamine)

Remicade® (Infliximab)

Biologic TNF α inhibitor

2.3 Availability of Proposed Active Ingredient in the United States

Various oral and rectal mesalamine formulations are approved for marketing in the U.S.

2.4 Important Issues With Pharmacologically Related Products

The current labeling of other mesalamine products includes the following warning and precautions:

- Renal impairment, including renal failure
- Acute exacerbation of colitis
- Hypersensitivity reactions
- Pyloric stenosis

2.5 Presubmission Regulatory Activity

In 2003, the Applicant met with the Agency to gain agreement with their plan to submit NDA 22,301 as a 505(b)(2) application referencing the pharmacology and toxicology studies of Canasa and Asacol. At the meeting, the Agency requested that the Applicant do additional

studies to characterize the [] with regard to safety pharmacology and toxicity as it differed from the [] coating used in the referenced products. See Table 1 for a summary of key Applicant and Agency interactions related to IND 62,113 and NDA 22-301.

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Table 1: Pre-submission Regulatory History, NDA 22,301

Date Meeting Type	Regulatory Action(s)
August 20, 2003 Pre-IND Meeting	<ul style="list-style-type: none"> Agency agreed with Applicant's plan to submit application as 505(b)(2) with Asacol, NDA 19-651, and Canasa, NDA 21-252, as references. Agency agreed with Applicant's proposed pharmacokinetic studies and strategy for dose evaluation for the Phase 3 clinical studies. Agency requested that additional safety pharmacology and toxicology data be submitted regarding the drug product excipient []
October 30, 2003	<ul style="list-style-type: none"> IND 62,113 submitted for Phase 1 pharmacokinetic studies.
October 6, 2004 End of Phase 2 Meeting	<ul style="list-style-type: none"> Agency requested revision of remission definition as follows: Removal of friability from endoscopic definition of remission Inclusion of absence of rectal bleeding. Agency agreed to 6-month study duration and sample size of pivotal Phase 3 studies. Agency agreed that comparative dissolution profiles between the loose mesalamine pellets used in Salix Phase 1 studies and the mesalamine granules encapsulated in hard gelatin capsules to be used in Phase 3 studies appeared similar, but needed to be evaluated in more detail by Clinical Pharmacology and Biopharmaceutics in a forth-coming IND.
November 9, 2005 Type C Meeting	<ul style="list-style-type: none"> Agency concluded that proposed studies would not provide adequate information for chronic use of [] Agency asked for specific toxicology studies with []
October 29, 2007 Pre-NDA Meeting	<ul style="list-style-type: none"> Agency recommended that Applicant completes dissolution testing (see above) or provides data or scientific information in the NDA to justify why it is not necessary. Agency agreed that proposed statistical analysis plans appear acceptable. Agency agreed that summaries of the finding of carcinogenicity studies conducted by Dr. Falk Pharma and submitted under a different NDA in lieu of the full data sets for the studies may be submitted in the NDA.

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2.6 Other Relevant Background Information

Mesalamine has been available worldwide for the treatment of inflammatory bowel disease (IBD) for more than 20 years and as the active component in sulfasalazine for more than 50 years.

In 2002, Salix Pharmaceuticals, Inc. acquired the US rights for mesalamine granules from Dr. Falk Pharma. The originator's product, Falk mesalamine granules (FMG), has been modified in [] to produce eMG. [] The resultant

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product was known as Salix mesalamine granules (SMG). Next, the granules were over-encapsulated in hard gelatin capsules. The current US marketing application applies only to this product known as encapsulated mesalmine granules (eMG).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

According to the CMC reviewer, the information provided by the Applicant is sufficient to assure the identity, strength, purity, and quality of the drug product.

3.2 Animal Pharmacology/Toxicology

NDA 22,301 is an application for which one or more of the investigations relied upon by the Applicant for approval “were not conducted by or for the Applicant and for which the Applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted” (21 USC 355(b)(2)). NDA 22-301 references the following applications: IND 62,113 (mesalamine granules), NDA 19-651 (Asacol®, mesalamine), and NDA 21-242 (Canasa®, mesalamine).

Non-clinical studies showed that eMG has the potential for causing adverse effects on the kidney in patients taking the drug. Repeat dose toxicology studies in rats and dogs showed the kidney to be the major organ of toxicity. Oral doses of 40 mg/kg/day produced minimal to slight tubular injury at doses of 160 mg/kg/day or higher in rats produced renal tubular degeneration, tubular mineralization, and papillary necrosis. Other treatment-related findings in rats, included hemorrhagic changes in the gastric mucosa at 640 mg/kg, mucosal/submucosal fibrosis of the stomach and inflammation of the urinary bladder at 360 mg/kg, and ulceration of the stomach at 320 mg/kg.

Studies of [] the outer coating used for eMG, were requested by the Division. [] was well-tolerated in dogs. No target organ of toxicity was identified and a NOAEL was not established.

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For more detail, see the Pharmacology/Toxicology Review and Evaluation dated September 25, 2008 by Dr. Shushanta Chakder.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Two pivotal studies (MPUC3003 and MPUC3004) provided the majority of the data for the efficacy and safety review. In addition, an on-going, open-label, 12-24 month extension study

(MPUC3005) also provided additional data to evaluate the safety and tolerability of the study drug.

Supportive data from three studies (SAG-2/15/26) using Falk mesalamine granules (FMG) to treat *active* ulcerative colitis (a different indication than the proposed indication of maintenance of remission) were also submitted for review. In addition, Study SAG-27 using FMG for the indication of maintenance of remission was also submitted for review by the Applicant. The data provided by the SAG studies was viewed as supportive and useful only in terms of the information they provided in regards to safety and tolerability. Further, two pharmacokinetic studies (MPPK1001 and MPPK1002) in healthy using Salix mesalamine granules (SMG) were also submitted. Safety data from these studies was briefly reviewed.

4.2 Tables of Clinical Studies

Table 2 below summarizes the primary studies used in the review of this NDA to evaluate the efficacy and safety of TRADE NAME.

Table 2: Primary Clinical Studies Submitted in Support of NDA 22,301

Study Identifier	Objective of Study	Ulcerative Colitis Indication	Study Design	Test Product	Number of patients	Treatment Duration
MPUC3003	To assess the safety and efficacy of eMG 1.5 g once daily versus placebo	Maintenance of remission	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Four 0.375 g eMG capsules once daily or placebo	eMG: 209 Placebo: 96	6 months
MPUC3004	To assess the safety and efficacy of eMG 1.5 g once daily versus placebo	Maintenance of remission	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Four 0.375 g eMG capsules once daily or placebo	eMG: 164 Placebo: 93	6 months
MPUC3005	To assess the safety and tolerability of eMG 1.5 g once daily	Maintenance of remission	Multicenter, open-label, extension	Four 0.375 g eMG capsules once daily	365	24 months, regulatory approval, or Applicant termination

4.3 Review Strategy

The Applicant submitted paper copies of NDA 22,301 in the Common Technical Document (CTD) format. In this application, efficacy data for the study drug was generated from two pivotal studies, MPUC3003 and MPUC3004. The reviewer thoroughly reviewed the pivotal studies both individually and together as pooled data with equal regard to efficacy and safety.

These results were compared to the results reported in the Applicant's integrated safety and efficacy reports and with the drug's established safety profile.

Data for the safety analyses for the study drug were generated from the same studies as the efficacy analysis with the addition of the open-label, extension study, MPUC3005. The Applicant submitted additional clinical studies using a related mesalamine product, Falk Mesalamine Granules (FMG). The efficacy data from these additional clinical studies were not reviewed. Instead, these studies were reviewed only for the additional safety data that they provided.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) performed clinical site audits for this application. The two domestic sites with the largest number of patients from each pivotal study were selected for audit. Three Russian sites were also selected for inspection. The selected Russian sites had the largest number of patients (Sites 565 and 572) or were located in the same facility as a site with a large number of patients which would make that site readily available for inspection.

DSI recommended that data from each of the sites can be used in support of the NDA. (See DSI Clinical Inspection Summary dated August 28, 2008).

Table 3: Sites Selected for DSI Inspection

Investigator	Site No.	No. of Patients	Location	Rationale
Dr. Boris D. Starostin	572	30	Russia	Large number of patients
Dr. Andrey P. Rebrov	565	19	Russia	Large number of patients
Dr. Yuri G. Shvarz	566	30	Russia	Large number of patients
Dr. Glenn L. Gordon	618	12	U.S.	Largest number of patients at single US center for protocol MPUC3003
Dr. Dr. Salam F. Zakko	419	11	U.S.	Largest number of patients at single US center for protocol MPUC3004

4.5 Compliance with Good Clinical Practices

According to the Applicant, all of the studies were conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human patients (21 CFR 50), IRBs (21 CFR 56) and the obligations of clinical investigators (21 CFR 312). All studies were also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs), which is

consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

4.6 Financial Disclosures

For studies MPUC3003, MPUC3004, and MPUC3005 the Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

The Applicant also certified that all investigators who participated in MPUC3003 did not have financial arrangements nor financial interests required to be disclosed in accord with 21 CFR 54.2(b). A single investigator who enrolled patients in studies _____ held an equity interest that needed to be disclosed. This investigator held 35,000 shares of Salix (the Applicant) stock at the time of his participation in these studies. b(6)

_____ The Applicant felt that the potential impact of this investigator's participation in the study results was minimal.

Clinical Reviewer's Comment: It is agreed that the investigator with disclosed financial interests has limited potential to impact the outcome of studies _____ given the small number of patients he enrolled into the studies. b(6)

5 CLINICAL PHARMACOLOGY

The Applicant submitted 11 Phase 1 and Phase 2 trials, three Phase 3 trials, and one *in vitro* drug interaction study in support of this NDA. Of the 11 Phase 1/2 trials submitted, three studies were found by the clinical pharmacology reviewer to be the most relevant: a relative BA study using Asacol BID and mesalamine granules QD (MPPK1001), a food effect study (MPPK1002), and a single and multiple dose PK study (MPPK1003). Studies MPPK1001 and MPPK1002 used mesalamine granules equivalent to eMG (based on *in vitro* dissolution studies). Study MPPK1003 used eMG.

The other studies were conducted using Dr. Falk mesalamine granules in sachet (FMG). This formulation is manufactured in Europe, while eMG and SMG are manufactured in the US. This difference in manufacturing sites requires an *in vivo* bioequivalence (BE) study which was not done. Therefore, with the exception of Study BIO/SAG-16, the studies conducted using FMG are considered supportive only and were not reviewed. Study BIO/SAG-16 was reviewed because of a labeling claim based on the study.

5.1 Pharmacokinetics

Two pharmacokinetic studies were performed by Salix to evaluate the pharmacokinetic properties of eMG: Study MPPK1001 and Study MPPK1002.

Study MPPK1001 was a Phase 1, single-center, open-label, randomized, crossover study in 30 healthy patients to study the relative bioavailability of SMG and Asacol. The study had three treatment phases each lasting four days. The treatment groups were 0.8 g Asacol® twice daily, 0.8 g Salix Mesalamine Granules (SMG) twice daily and 1.6 g SMG once daily. Treatment phases were separated by a washout period of at least seven days. The mean AUC and C_{max} of 5-ASA and its metabolite N-Acetyl-5-aminosalicylic acid (N-Ac-5-ASA) were higher for SMG 0.8g BID and SMG 1.6 g QD than for Asacol 0.8 g BID. Intact tablets were recovered from stool samples of 50% of subjects after Asacol treatment leading the Applicant to conclude that Asacol PK parameters were not reliable.

Study MPPK1002 was a Phase 1, open-label, randomized, balanced, 2-treatment 2-period, 2-sequence, crossover study of a single dose of SMG (1.6g, 2x 0.8g) administered orally in 30 patients following an overnight fast and following ingestion of a high-fat meal (breakfast). Plasma, urine, and fecal samples were collected to assess the effect of a high fat meal on the pharmacokinetics of mesalamine and N-Ac-5-ASA. Absorption of the administered dose was not affected by a high fat meal.

For more detailed study results and conclusions, see the full Clinical Pharmacology review by Dr. Insook Kim.

5.2 Pharmacodynamics

Asacol (mesalamine) is thought to exert its pharmacologic effects topically on the GI tract. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, i.e. prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxyecosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

The clinical pharmacology reviewer for this application was Dr. Insook Kim. See her review for detailed pharmacodynamic information.

5.3 Exposure-Response Relationships

Studies to assess exposure-response relationships were not conducted as part of the clinical pharmacology program.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Apriso (eMG) is a locally acting aminosalicylate indicated for the maintenance of remission of ulcerative colitis in patients 18 years of age and older.

6.1.1 Methods

The clinical efficacy of eMG was evaluated in two pivotal, Phase 3, placebo-controlled studies--MPUC3003 (Study 3) and MPUC3004 (Study 4). Both studies were of identical designed and used the same inclusion/exclusion criteria, study schedule, and efficacy endpoints. The only difference between the two studies was the number of patients randomized. Initially, both studies were planned to randomize 300 patients. Study 3 randomized 305 patients. For Study 4, the number of planned patients was changed from 300 to 250 in Protocol Amendment 2. Statistical evaluations indicated that a total of 250 patients would provide at least 80% power ($\beta=0.20$) to reject the null hypothesis of no difference between eMG and placebo. Therefore, the study was terminated at 257 randomized patients.

The primary eligibility criteria selected in MPUC3003 and MPUC3004 were based on eligibility criteria used in the pivotal Asacol Delayed Release Tablets (mesalmine) efficacy trial for maintenance of remission from UC.

Clinical Reviewer's Comment: The study design, dosage, and treatment period are consistent with current practice and similar to various approved mesalamine products. It is concerning that the required sample size was changed after the initiation of Study 4.

6.1.2 General Discussion of Endpoints

Primary Efficacy Endpoint

In both pivotal studies, the primary efficacy endpoint was remaining relapse-free at Month 6 or the end-of-study (EOS). To be eligible for the study, patients had to have a confirmed diagnosis of UC and be in remission for at least one month, but not more than 12 months. For those patients who withdrew before study completion, this EOS visit occurred on the day of withdrawal (or as close to it as possible). Relapse (or treatment failure) was defined as a rectal bleeding score of 1 or more **and** a mucosal appearance score of 2 or more as described in the revised Sutherland Disease Activity Index. Early termination was not considered a relapse by the Applicant unless the reason was lack of efficacy or discontinuation due to a UC-related adverse event (AE). 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 forward (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 that changed this definition was made July 16, 2007 which was after the completion of Study 3 and during Study 4, but before unblinding of the data.

Clinical Reviewer's Comment: The original primary endpoint that considered all patients who terminated the study prematurely as having relapsed is more conservative than the amended definition and is included in this review for primary efficacy endpoint calculations for comparison.

The number and proportion of relapse-free patients after 6 months of treatment/EOS was summarized by treatment group using the ITT population (all randomized subjects who had taken at least one dose of study medication). For all endpoints, comparisons between treatment groups were based on a Cochrane-Mantel Haenszel (CMH) 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, i.e., those patients without a major protocol violation. Only the primary result obtained from the ITT population was considered to be inferential.

The Sutherland Disease Activity Index (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." Study patients self-reported rectal bleeding and stool frequency symptoms for scoring.

Secondary efficacy analyses were performed using only the ITT population. Statistical tests on secondary endpoints were performed in a hierarchical fashion using the CMH test controlling for country. The p-value for comparison between baseline and Month 6/EOS values were calculated. 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 of the revised Sutherland DAI >1 and rectal bleeding=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 was 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.

Table 4: Revised Sutherland Disease Activity Index

Index	Score
Stool frequency	0 Normal
	1 1 to 2 stools/day more than normal
	2 3 to 4 stool/day more than normal
	3 >4 stools/day more than normal
Rectal bleeding	0 None
	1 Streaks
	2 Obvious blood
	3 Mostly blood
Mucosal Appearance	0 Intact mucosa with preserved or distorted blood vessels
	1 Erythema, decreased vascular pattern, granularity, no mucosal hemorrhage
	2 Mucosal hemorrhage without blood in the lumen or gross ulceration, marked erythema, absent vascular pattern, small ulcers
	3 Blood in lumen, gross ulceration, exudates
Physician's rate of disease activity	0 Normal
	1 Mild
	2 Moderate
	3 Severe
Maximum Score	12

Sutherland LR, Martin F. 5-aminosalicylic acid enemas in treatment of distal ulcerative colitis and proctitis in Canada. Dig Dis Sci 1987;32(12 Suppl): 64S-66S.

6.1.3 Study Design

Both pivotal studies (MPUC3003 and MPUC3004) were randomized, double-blind, placebo-controlled, parallel group, multi-center, Phase 3 studies designed to compare the efficacy and safety of 1.5g eMG versus placebo given in a 2:1 ratio (eMG:placebo).

Both studies were identical in design and used the same inclusion and exclusion criteria, efficacy endpoints, and study schedule. The only difference between the two studies is the number of patients randomized. Both studies were planned to randomize 300 patients in a 2:1 ratio (eMG:placebo). However, the planned number of patients for Study MPUC3004 was changed to 250 in Protocol Amendment 2. The Applicant's Amendment stated that statistical evaluation revealed that 250 patients were adequate to prove a power of at least 80% ($\beta=0.20$).

Clinical Reviewer's Comment: The study design is appropriate for the study and provides a reasonable assessment of benefit. It is unclear why the sample size calculations were not done prior to enrolling patients in the study or if they were, why the sample size required differed.

6.1.4 Efficacy Findings

The Agency's statistical reviewer verified the Applicant's computations and concurs with the overall results of the submitted efficacy analyses. The inferential efficacy analyses were performed on the intention-to-treat (ITT) population. The null hypothesis of no treatment difference was rejected if the resulting p-value was less than 0.05. To assess the effect of protocol compliance on drug efficacy, analysis of the primary endpoint was also done using the per-protocol (PP) population. This population included all patients in the ITT population without a major protocol deviation.

While agreeing with the Applicant's overall efficacy conclusions, the statistical reviewer did call into question the Applicant's rationale for decreasing the sample size of Study MPUC3004 after the study started. To further appreciate the possible implications of reducing the sample size, the statistical reviewer performed a sensitivity analysis of Study MPUC3004. For this analysis, it was assumed that the additional 43 subjects who would have enrolled in Study MPUC3004 achieved a success rate equal to the observed placebo response rate (68% using the ITT population). The calculated p-value for this analysis was found to be 0.06, non-statistically significant.

Primary Efficacy Analyses

Analysis of the primary endpoint utilizing a Cochran-Mantel-Haenszel (CMH) test, controlling for country, reveals that the difference in the proportion of relapse-free patients at Month 6/EOS between the eMG and placebo groups is statistically significant in both studies. This significance holds whether we use the Applicant's original or amended definition of relapse as defined above.

Table 5: Primary Efficacy Analysis by Study

Relapse-free at Month 6/EOS					
Study Population	Definition of Relapse	eMG	Placebo	95% CI for Difference	p-value
MPUC3003					
ITT	Revised	165/209=78.9%	56/96=58.3%	21% (9.5%, 32%)	<0.001
PP	Revised	157/200=78.5%	55/93=59.1%		<0.001
	Original	143/209=68.4%	49/96=51.0 %	17% (5.5%, 29.2%)	<0.001
MPUC3004					
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
	Original	117/164= 71.3%	55/93=59.1%	12% (0%, 24.5%)	0.046

Source: Statistical Reviewer's Table

In study MPUC3003, 305 patients were randomized and received at least one dose of study medication (209 eMG: 96 placebo). At Month 6/EOS, 78.9% of eMG subjects and 58.3% of placebo subjects remained relapse-free ($p < 0.001$). If we analyze the primary efficacy results using the original definition of relapse (i.e., all premature withdrawals counted as relapses), at Month 6/EOS, 68.4% of eMG patients and 51.0% of placebo patients remained relapse-free ($p < 0.001$). Both results are highly statistically significant.

In study MPUC3004, 257 patients were randomized and received at least one dose of study medication (164 eMG, 93 placebo). At Month 6/EOS, 79.9% of eMG patients remained relapse-free, compared with 67.7% of placebo patients ($p = 0.029$). If we analyze the primary efficacy results using the original definition of relapse, at Month 6/EOS, 71.3% of eMG patients and 59.1% of placebo patients remained relapse free ($p = 0.046$). See Table 5 and Figures 1 and 2 below.

Figure 1: Efficacy Results of Pivotal Studies, Revised Definition of Relapse

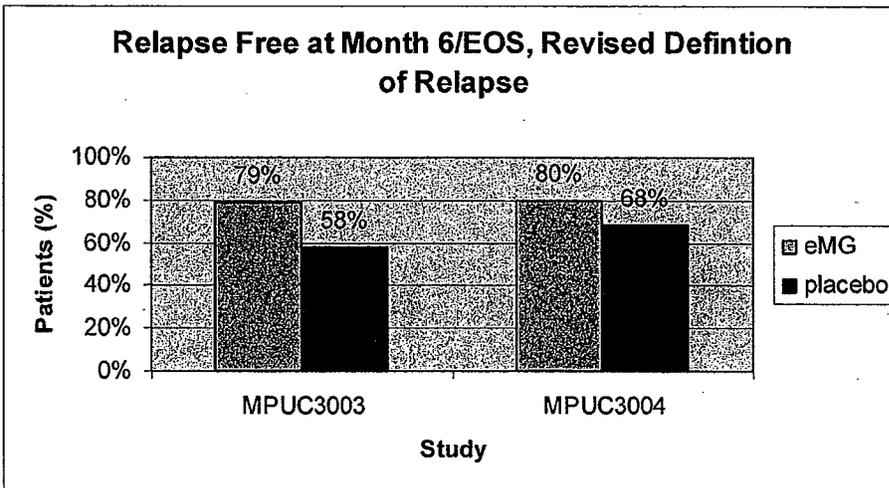
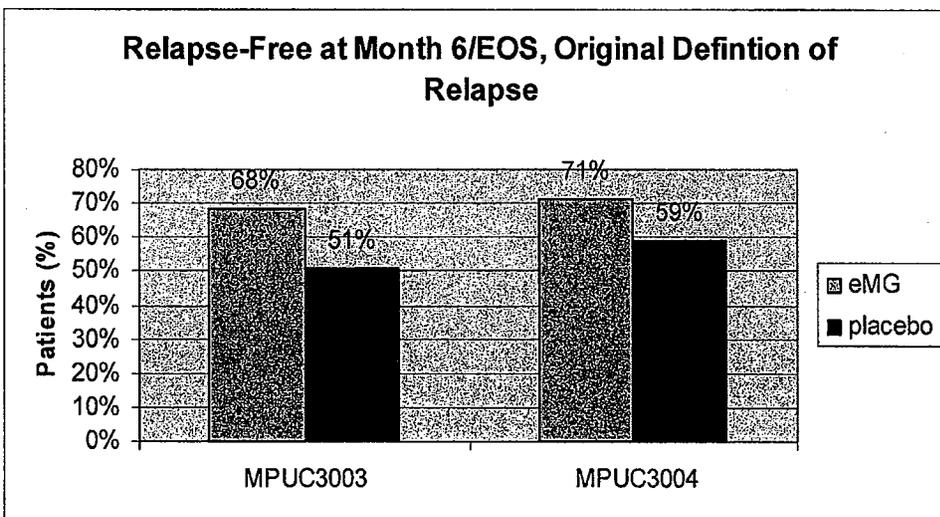


Figure 2: Efficacy Results of Pivotal Studies, Original Definition of Relapse



Clinical Reviewer's Comment: Counting all relapses as treatment failures, as was planned in the original protocols for Studies MPUC3003 and MPUC3004, provides a more rigorous efficacy analysis. For Study MPUC3004, the marginal statistical significance of the results obtained suggest that the study was not adequately powered to show a difference between eMG and placebo using the original definition of treatment failure. It would have been helpful if the Applicant had not made a late-stage decision to decrease the Study MPUC3004 sample size.

Primary Efficacy Analyses by Subgroup (Pooled Pivotal Studies)

Primary efficacy analysis was conducted for the following important subgroups: country, sex, race, age, baseline disease severity, and renal function as measured by creatinine clearance. For sub-group analysis, results from studies MPUC3003 and MPUC3004 were pooled and the revised definition of relapse was used. See Table 6 below.

Table 6: Primary Efficacy Analysis by Subgroup, ITT Population

Subgroup	eMG	Placebo	P Value
Country			
USA	130/172=75.6%	48/91=52.7%	<0.001
Russia	166/201= 82.6%	71/98=72.4%	0.042
Gender			
Male	132/166=79.5%	69/101=68.3%	0.039
Female	165/207=79.7%	50/88=56.7%	<0.001
Age Group			
< 65	270/334=80.8%	103/166=62.0%	<0.001
>= 65	26/39=66.7%	16/23=70%	0.81
Race			
White	274/344=79.6%	112/175=64.0%	<0.001
Non-White	21/28=75.0%	7/14=50.0%	0.11
Baseline Disease Severity Category			
Normal or None >=1	134/156=85.9%	47/72=65.3%	<0.001
Normal or None >=1	162/217=74.7%	72/117=61.5%	0.01
Renal Impairment			
Normal (≥90 ml/min)	192/240=80.0%	78/134=58.2%	<0.001
Mild (60-90 ml/min)	97/122= 79.5%	36/51= 70.6%	0.205
Moderate (30-<60 ml/min)	4/6=66.7%	3/3= 100.0%	0.320

Sources: Appendix D, Table 2.7.3.2 and Statistical Review's Table

Analysis of the primary endpoint by sex revealed that both females and males in the eMG group had statistically significant greater treatment success compared with the placebo group (p<0.001 and p=0.041, respectively). Further, the percentage of successes in the male eMG group (80%) and the female eMG group (79%) were nearly identical. However, there was a higher placebo effect seen in the male patients than in the female patients (68% versus 57%). Similarly, when analyzed by country, results from Russia (p=0.042) and from the USA (p=<0.001) showed eMG patients had statistically significant greater treatment success than placebo patients.

In patients less than 65 years of age, a higher proportion of eMG patients than placebo (p=0.039) remained in remission at Month 6/EOS. The number of patients aged 65 and older and the numbers of white patients included in the study were very small and provided inadequate power to detect a difference in efficacy between the eMG and placebo groups.

Medical Reviewer's Comment:

Despite the lack of statistically significant efficacy results, the experience of other mesalamine products and the overall safety profile of mesalamines would, in my opinion, make the use of eMG in non-whites and those age 65 and older appropriate. For labeling, monitoring of blood cell counts in the geriatric population is recommended due to the higher incidences of blood dyscrasias seen in this group. Further, "Geriatric Use" section of labeling should remind prescribers that caution should be exercised with the use of mesalamine in those patients with renal and/or hepatic impairment, both of which are more common in the geriatric population.

Secondary Efficacy Analyses

Seven secondary endpoints were defined *a priori* as described in Section 6.1.2 above. All secondary endpoint analyses were conducted using the ITT Population. In testing multiple secondary endpoints, the Applicant used a hierarchical approach to control for Type 1 error. Only a single secondary endpoint was found to be statistically significant in either study MPUC3003 and MPUC3004—change from baseline to Month6/EOS rectal bleeding score in Study MPUC3003.

In Study MPUC3003, analysis of the first secondary endpoint in the hierarchy demonstrated that the difference in the overall change from baseline in revised Sutherland DAI rectal bleeding scores between the eMG and placebo groups was statistically significant (p=0.008). In the eMG group, 81.3% of patients maintained their baseline rectal bleeding score compared with 66.7% of placebo patients. None of the other secondary efficacy endpoints reached the level of statistical significance

In Study MPUC3004, the first secondary endpoint did not reach the level of statistical significance and therefore no other secondary endpoints were tested.

Table 7: Secondary Efficacy Endpoints, Pivotal Studies

Study 3003	Mesalamine	Placebo	P-Value
Change from Baseline in Rectal Bleeding			0.01
-1	0 (0%)	1 (1%)	
0	170 (81%)	64 (67%)	
1	22 (10.5%)	11 (11%)	
2	16 (8%)	19 (20%)	
3	1 (0.5%)	1 (1%)	
Change from Baseline in Mucosal Appearance			0.41
-1	32 (15%)	13 (13.5%)	
0	129 (62%)	51 (53%)	
1	32 (15%)	20 (21%)	
2	14 (7%)	11 (11%)	
3	2 (1%)	1 (1%)	
Study 3004			
Change from Baseline in Rectal Bleeding			0.38
-1	1 (0.6%)	1 (1%)	
0	138 (84%)	69 (74%)	
1	12 (7%)	13 (14%)	
2	12 (7%)	9 (10%)	
3	1 (1%)	1 (1%)	

Source: Statistical Reviewer's Table

6.1.5 Clinical Microbiology

Not Applicable

6.1.6 Efficacy Conclusions

In this reviewer's opinion, both pivotal studies, MPUC3003 and MPUC3004, successfully demonstrated that eMG is effective in the maintenance of remission from ulcerative colitis. The chosen dose of 1.5 g once daily was shown to be superior over placebo for the stated indication. The efficacy profile was similar between sexes and nationalities (Russian, US). Limited enrollment of patients over 65 years of age and non-whites makes statistically significant efficacy comparisons in these subgroups difficult. However, the consistent, reproducible efficacy demonstrated by eMG makes efficacy extrapolation to these groups appropriate at this time. Post-marketing surveillance of these special subgroups will be important.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Encapsulated mesalamine granules were evaluated in 557 patients whose UC was in remission in controlled and open-label trials in the US and Russia. During the two randomized, controlled trials, 367 patients were exposed to eMG (206 in MPUC3003 and 161 in MPUC3004). During the ongoing open-label trial MPUC3005, 197 eMG patients and 83 placebo patients from Studies MPUC3003 and MPUC3004 were permitted to enroll. In addition, 107 new patients not previously in either randomized study enrolled in MPUC3005.

Study MPUC3005 is an ongoing, open-label study to evaluate the safety and tolerability of long-term eMG use. The study is planned for 24 months or regulatory approval of eMG (whichever comes first). Patients enter the study either as rollover patients from lead-in studies MPUC3003 and MPUC3004 or as new patients. Patients from the lead-in studies were eligible to enter Study MPUC3005 if during the lead-in study they had been compliant with study-related procedures, $\geq 70\%$ compliance with taking study medication per-protocol, and not withdrawn due to a study drug-related AE(s).

Two analysis populations were used for all analyses in the integrated summary of safety: the RCT population and the All eMG population. These sub-populations were taken from the larger Safety Population, which included all patients who received at least one dose of the study drug (eMG or placebo) and provided at least one post-baseline safety assessment. The two primary studies, MPUC3003 and MPUC3004, were combined into the RCT population based on the fact that the study designs are identical. Data from patients receiving the placebo drug product were captured in this RCT population. The All eMG population excludes those patients from MPUC3003 and MPUC3004 receiving the placebo drug product and includes all patients in MPUC3005, the open-label extension study. During MPUC3003 and MPUC3004 randomized patients received 1.5 g eMG or matching placebo once. During MPUC3005, all patients received 1.5g eMG once daily.

Across all three studies, a total of 354 patients in the All eMG population were exposed to eMG 1.5 once daily for more than six months, and 250 subjects were exposed to eMG for more than one year. The overall mean exposure to eMG was 245 days in the RCT population and 352 days in the All eMG population. The mean exposure time for eMG patients in the RCT population was 145.0 days and the mean exposure amount was 211 g. For Study MPUC3005, the mean exposure time was 335 days and the mean exposure amount was 482 g.

The Applicant submitted a 120-day Safety Update which included all available data for all patients in Study MPUC3005 up to 14 January 2008 (clinical cutoff date). In addition, the Applicant submitted a summary of SAES reported from October 2001 through February 2008 with Dr. Falk formulations of mesalamine (pellets, tablets, enemas). For more details, see Section 7.1.17.

In the RCT population, fewer patients treated with eMG reported a treatment-emergent adverse event (TEAE) compared with patients treated with placebo (59.4 % versus 63.8%, respectively). A recurrence of UC was the most frequently reported TEAE in either treatment group. A larger percentage of placebo patients experienced *common* TEAEs, those occurring in greater than 3% of any treatment arm (49.2% versus 42.0%). Gastrointestinal disorders were the most frequent TEAEs in both treatment groups and were more frequent with placebo treatment than with eMG treatment (64.9% versus 46.6%, respectively). Serious adverse events were reported in 4 (1.1%) of eMG patients in the eMG group and 4 (2.2%) of patients in the placebo group.

In the All eMG population, 68.6% of patients reported at least one TEAE. A recurrence of ulcerative colitis was the most commonly reported TEAE. In this population 13.5% of all patients reported a TEAE which investigators characterized as possibly related to the study medication. Serious adverse events occurred in 22 patients (4.1%).

The majority of AEs in both the RCT and All eMG populations were mild or moderate in severity. Only 5.6% of the TEAEs were considered by investigators to be severe in the RCT population, compared with 10.1% in the All eMG population.

7.1.1 Deaths

There were no deaths reported in the eMG Phase 2 or Phase 3 studies.

7.1.2 Other Serious Adverse Events

RCT Population

In the RCT population, eight patients reported a total of eight SAEs. This represents an overall incidence of 1.44% in the RCT population. Four SAEs occurred in patients taking placebo and four SAEs occurred in patients taking eMG.

In the eMG patients, SAEs included distal esophagitis (MPUC3003, 562-18), UC flare (MPUC3003, 505-02), pancreatitis (MPUC3004, 419-04), and second degree atrioventricular

block (AV block) with worsening left ventricular function (MPUC3003, 494-09). According to the reviewed CRFs, none of these patients discontinued the study due to the SAE. The patient with pancreatitis and the patient with distal esophagitis each withdrew secondary to an AE of UC flare and not the SAE. The patient with AV block only temporarily discontinued the study drug during hospitalization and then resumed the study. The patient with UC flare is reported by the Applicant to have discontinued due to an AE of UC flare and not the SAE UC flare (see below).

Clinical Reviewer's Comment: Review of the accompanying CRF for patient 505-02 revealed that the patient discontinued the study due to an AE of UC flare and six days later was hospitalized for UC flare which elevated this original AE to an SAE. The Applicant's rationale is that the six day separation between study drug discontinuation and hospital admission makes the reason for study discontinuation the AE of UC flare and not the SAE.

In the placebo patients, SAEs included UC flare (MPUC3003, 561-06), right arm cellulitis (MPUC3003, 208-08), myocardial infarction (MPUC 3004, 569-08), and small bowel obstruction (MPUC3004, 626-03). Of these, only patient 561-06 withdrew from the study due to the SAE. The other three patients continued the study.

For brief narratives of all eMG patients experiencing SAEs, see Appendix 10 individual study reports (10.1.12.3 and 10.2.12.3).

Table 8: SAEs in the Safety Population

System Organ Class Preferred Terms	RCT Treatment Group		All eMG
	eMG N=367 (%)	Placebo N=185 (%)	eMG N=557 (%)
All SAEs	4 (1.1)	4 (2.2)	26 (4.7)
Cardiac Disorder	1 (0.3)	1 (0.5)	2 (0.4)
Atrial Fibrillation	0	0	1 (0.2)
AV Block, second degree	1 (0.3)	0	1 (0.2)
Ventricular Dysfunction	1 (0.3)	0	1 (0.2)
Angina Pectoris	0	1 (0.5)	0
Gastrointestinal Disorders	3 (0.8)	2 (1.1)	11 (2.0)
Colitis Ulcerative	1 (0.3)	1 (0.5)	7 (1.3)
Acute Pancreatitis	1 (0.3)	0	1 (0.2)
Diverticular Perforation	0	0	1 (0.2)
Ileus	0	0	1 (0.2)
Esophagitis	1 (0.3)	0	0
Periproctitis	0	0	1 (0.2)
Small Intestinal Obstruction	0	1 (0.5)	0
General Disorders and Administration Site Conditions	0	0	1 (0.2)
Chest Pain	0	0	1 (0.2)
Infections and Infestations	0	1 (0.5)	6 (1.1)
Cellulitis	0	0	3 (0.5)
Abscess Limb	0	0	1 (0.2)
Diverticulitis	0	0	1 (0.2)
Localized Infection	0	0	1 (0.2)
Lower Respiratory Infection	0	0	1 (0.2)
Tooth Abscess	0	0	1 (0.2)
Opportunistic Infection	0	1 (0.5)	0
Neoplasms Benign, Malignant and Unspecified	0	0	3 (0.5)
Breast Cancer	0	0	1 (0.2)
Colon Cancer	0	0	1 (0.2)
Lung Neoplasm Malignant	0	0	1 (0.2)
Nervous System Disorders	0	0	1 (0.2)
Convulsion	0	0	1 (0.2)
Pregnancy, Puerperium and Perinatal Conditions	0	0	2 (0.4)
Abortion Spontaneous	0	0	1 (0.2)
Ectopic Pregnancy	0	0	1 (0.2)
Reproductive System and Breast Disorders	0	0	1 (0.2)
Uterine Perforation	0	0	1 (0.2)
Vascular Disorders	0	0	1 (0.2)
Deep Vein Thrombosis	0	0	1 (0.2)

Source: ISS Tables 2.7.4.11. and 2.7.4.11.2, Appendix C

Note: A patient reporting more than one adverse event for a particular MedDRA Preferred Term or System Organ Class is counted only once for that MedDRA Preferred Term or System Organ Class.

All eMG Population

In the All eMG population, a total of 26 patients (4.7%) experienced a total of 26 SAEs. This number includes the four SAEs described above experienced by patients randomized to receive eMG in the RCT population. The remaining 22 All eMG patients who experienced SAEs during MPUC3005 entered the study as new patients (n=5), as eMG patients from the RCT population

(n=11), or as placebo patients from the RCT population (n=6). Most of the SAEs experienced by All eMG patients during the 24-month open-label extension study were in the GI SOC (11 patients) and the infections and infestations SOC (6 patients).

Of the 22 patients who experienced SAEs in study MPUC3005, 10 of those patients withdrew from the study due to the SAE. Four patients withdrew due to the SAE of UC flare (9999-518-910, 3004-564-07, and 3004-569-11). Three patients withdrew due to cancer diagnoses—3004-124-05 (lung cancer), 3004-566-35 (colon cancer), and 3003-618-02 (breast cancer). One patient withdrew due to the diagnosis of deep vein thrombosis, the treatment of which required the use of a prohibited medication. One patient withdrew after testing positive for pregnancy. That pregnancy actually ended in spontaneous abortion. One patient withdrew due to diverticulitis and subsequent diverticular perforation. For brief narratives of non-UC SAEs experienced by patients in Study MPUC3005 before the clinical cutoff date (14 January 2008), see Appendix 10.3.12.3.

MO Comment: The percentage of patients who experienced a SAE in the All eMG group was higher than for either of the groups in the RCT population. This is likely due to the extended length of time over which the patients in MPUC3005 used eMG. Twenty-two of the 26 patients who experienced an SAE in the All eMG population experienced that SAE as part of the on-going open label extension study, MPUC3005.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

RCT Population

In the RCT population, premature discontinuations occurred more frequently in the placebo group (42.7%) compared with the eMG group (28.3%). For both eMG and placebo patients, the primary reason for withdrawal was lack of efficacy (12.3% eMG, 20.5% placebo) and TEAE (10.6% eMG, 16.2% placebo).

Table 9: Disposition of Patients in Pivotal Studies

	RCT Population		RCT Total N (%)	MPUC3005 N (%)
	eMG N (%)	Placebo N (%)		
Safety population	367	185	552	387
Completed Study	263 (71.7)	106 (57.3)	369 (66.8)	6 (1.6)
Discontinued Study	104 (28.3)	79 (42.7)	183 (33.2)	96 (24.8)
AE	39 (10.6)	30 (16.2)	69 (12.5)	24 (6.2)
Lost to follow-up	3 (0.8)	4 (2.2)	7 (1.3)	10 (2.6)
Lack of efficacy	45 (12.3)	38 (20.5)	83 (15.0)	29 (7.5)
Patient request	8 (2.2)	1 (0.5)	9 (1.6)	18 (4.7)
Patient non-compliant	1 (0.3)	0	1 (0.2)	5 (1.3)
Other	8 (2.2)	6 (3.2)	14 (2.5)	10 (2.6)
<i>AE or lack of efficacy</i>	84 (22.9)	68 (36.8)	152 (27.5)	53 (13.7)
Continued into MPUC3005	197 (53.7)	83 (44.9)	280 (50.7)	-

Source: ISS Table 2.7.4.1, Appendix C

All eMG Population

The disposition of eMG patients from the RCT trial is described above. The long-term extension study, MPUC3005, enrolled 387 patients. By the 120 Day Safety Update, 96 patients (24.8%) had withdrawn and 6 patients (1.6%) had completed the study. Most of the discontinuations were due to lack of efficacy (7.5%) and adverse events (6.2%).

Clinical Reviewer's Comment: Review of the submitted CRFs and narratives reveals that there was some inconsistency in categorizing patients who withdrew from the study because of a UC flare. Some patients were coded as "withdrew due to AE" while others were coded as "withdrew due to lack of efficacy". For a uniform analysis, it was decided to re-evaluate the AE incidence by combining all patients who withdrew due to lack of efficacy with all patients who withdrew due to AE. See Table 9 above for this analysis. If we consider lack of efficacy to be an AE, the fact that more placebo patients withdrew due to AEs than eMG patients continues to hold. The percentage of patients who discontinued due to AE out of all total discontinuations becomes 83% (152/183) as opposed to 38% (69/183) as the previous analysis shows.

7.1.3.2 Adverse events associated with dropouts

In both populations, discontinuations associated with dropouts were due primarily to gastrointestinal symptoms and abnormal laboratory values. See Table 10 below.

TABLE 10: RCT and All eMG Populations, Patient Discontinuation due to TEAE

MedDRA System Organ Class Preferred Terms	RCT		All eMG
	eMG N=367	Placebo N=185	eMG N=557
Total Discontinuations due to TEAE	40 (10.9%)	32 (17.3%)	66 (11.8%)
Gastrointestinal Disorders	30 (8.2%)	30 (16.2%)	44 (7.9%)
Colitis Ulcerative	23 (6.3%)	26 (14.1%)	34 (6.1%)
Diarrhea	3 (0.8%)	1 (0.5%)	3 (0.5%)
Nausea	1 (0.3%)	1 (0.5%)	1 (0.2%)
Abnormal Feces	0	1 (0.5%)	0
Flatulence	0	1 (0.5%)	0
Hematochezia	1 (0.3%)	0	1 (0.2%)
Hemorrhoids	1 (0.3%)	0	1 (0.2%)
Rectal Hemorrhage	1 (0.3%)	0	1 (0.2%)
General Disorders and Administration Site Conditions	0	0	1 (0.2%)
Fatigue	0	0	1 (0.2%)
Investigations	7 (1.9%)	2 (1.1%)	8 (1.4%)
Alanine Aminotransferase Increased	2 (0.5%)	2 (1.1%)	2 (0.4%)
Aspartate Aminotransferase Increased	2 (0.5%)	0	2 (0.4%)
Creatinine Renal Clearance Decreased	2 (0.5%)	0	2 (0.4%)
Blood Alkaline Phosphatase Increased	1 (0.3%)	0	0
Hemoglobin Decreased	0	0	1 (0.2%)
Platelet Count Decreased	0	0	1 (0.2%)
Musculoskeletal and Connective Tissue Disorders	1 (0.3%)	0	4 (0.8%)
Muscle Cramp	1 (0.3%)	0	1 (0.2%)
Neoplasms, Benign, Malignant and Unspecified	0	0	3 (0.6%)
Breast Cancer	0	0	1 (0.2%)
Colon Cancer	0	0	1 (0.2%)
Lung Neoplasm Malignant	0	0	1 (0.2%)
Nervous System Disorders	1 (0.3%)	0	2 (0.4%)
Headache	1 (0.3%)	0	2 (0.4%)
Reproductive System and Breast Disorders	1 (0.3%)	0	1 (0.2%)
Ovarian Cyst	1 (0.3%)	0	1 (0.2%)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.3%)	0	1 (0.2%)
Dyspnea	1 (0.3%)	0	1 (0.2%)
Skin and Subcutaneous Tissue Disorders	0	0	4 (0.7%)
Alopecia	0	0	2 (0.4%)
Rash	0	0	1 (0.2%)
Swelling Face	0	0	1 (0.2%)
Vascular Disorders	0	0	1 (0.2%)
Deep Vein Thrombosis	0	0	1 (0.2%)

Source: ISS Table 2.7.4.12.1 and 2.7.4.13.1, Note: Each patient is counted only once for each Preferred Term or System Organ Class.
*As of 120-Day Safety Update Clinical Cutoff Date

RCT Population

In the RCT population, discontinuation due to TEAEs occurred in 40 patients (10.9%) receiving eMG and 32 patients (17%) receiving placebo. A full 75% of TEAEs resulting in discontinuation in the eMG group and 94% of TEAEs in the placebo group were in the Gastrointestinal disorders MedDRA system organ class (SOC). The most common preferred term recorded for these GI disorders in both treatment groups was ulcerative colitis. The incidence of GI TEAEs was almost twice as high in the placebo group as in the eMG group which is consistent with the proposed action of mesalamine.

The only other SOC with incidence of discontinuations due to TEAEs greater than 1% was the SOC Investigations. In the Investigations SOC, 6 eMG patients (2%) and 2 placebo patients (1%) experienced abnormal laboratory values leading to discontinuation. See below for details of eMG patients in the RCT population who discontinued the study due to a laboratory abnormality.

Patient 3003-572-19

The patient's total duration of exposure to eMG was 90 days. Upon enrollment, the patient had a slightly elevated alkaline phosphatase level at 210 U/L (normal range: 40-135 U/L). At Study Visit 4, the patient's level was 297 and the patient was discontinued from the study.

Patient 3003-572-26

The patient's total duration of exposure to eMG was 170 days. On Study Day 171, the patient was permanently withdrawn from the study due to a decreased creatinine clearance. The patient's calculated creatinine clearance was 66.03 mL/min (normal range: 80-120 mL/min) at screening, 88.04 mL/min at Visit 3 and 52.83 mL/min at Visit 4 when the patient was discontinued from the study. At the two-week follow-up visit, the patient had a calculated creatinine clearance of 66.03 mL/min. This event was considered related to study therapy by the Investigator.

Patient 3003-859-06

The patient's total duration of exposure to eMG was 183 days. The patient completed Study MPUC3003 and at each study visit was found to have a normal AST level. However, at the two-week follow-up visit the patient was noted to have an AST level of 83U/L (normal range 0-47 U/L).

Patient 3004-568-08

The patient's total duration of exposure to eMG was 37 days. At Study Visit 2, the patient was noted to have an elevated ALT level of 122 U/L (normal range=0-37 U/L) and a mildly elevated AST level. The patient was withdrawn from the study and at the End of Study Visit, the ALT value was 19 U/L.

Patient 3004-573-07

The patient's total duration of exposure to eMG was 113 days. At Study Visit 2, the patient was noted to have an elevated AST level of 107 U/L, an elevated ALT level of 63 U/L, and an elevated Alkaline phosphatase level of 446 U/L. At this point, the patient was withdrawn from

the study. At a two-week follow-up visit, AST and ALT levels were elevated at 125 U/L and 198 U/L respectively. The patient's total bilirubin was 1.4 mg/dL. The patient's alkaline phosphatase level was increased to 832 U/L (6.2 x ULN). The patient was not followed to resolution.

Clinical Reviewer's Comment: In the Table 10 above, patients were only counted once for each PT or SOC. Therefore, patients with multiple reasons for study discontinuation are represented only under a single preferred term. For example, patient 3004-573-07 who experienced an elevated AST, ALT, and alkaline phosphatase is only represented once in the table under the PT increased ALT. It would seem more logical for the Applicant to have placed this patient under the PT increased alkaline phosphatase given that the patient's highest level was 6.2 times the upper limit of normal.

Patient 3004-573-34

The patient's total duration of exposure to eMG was 175 days. At screening, the patient was noted to have a calculated creatinine clearance of 61.3 mL/min. At Visit 1, the calculated creatinine clearance was noted to be 56.2 mL/min (PCS is defined as less than 60 mL/min). At visit 2, the value was 66.6 mL/min. At Visit 4, the value was noted to be 55.5 mL/min. However, by the time of the two-week follow-up visit, the level was noted to be 74.0 mL/min.

All eMG population

In the All eMG population, discontinuation due to TEAEs occurred in 66 patients (12%). Of these TEAEs, 67% were in the Gastrointestinal Disorders SOC. The most common preferred term recorded for these GI disorders was ulcerative colitis. The only other SOC with incidence of discontinuations due to TEAEs greater than 1% was the Investigations SOC.

In the Investigations SOC, 8 patients (1.4%) experienced abnormal laboratory values leading to discontinuations. Some of these laboratory abnormalities leading to discontinuation have been described above. Below are descriptions of the laboratory abnormalities leading to withdrawals to date in Study MPUC3005.

Patient 9999-543-92

The patient's total duration of exposure to eMG was 213 days. The patient was noted to have facial swelling and proteinuria and was discontinued from the study. The patient had 30 mg/dL proteinuria at baseline (normal value=0 mg/dL) and remained at this level during the entire study. A review of urine and blood glucose levels found them to be substantially elevated during Visits 3 and 4, and at follow-up. Additionally, the presence of bacteria was noted in the urine throughout the study.

Creatinine clearance and BUN levels remained normal throughout the study. The facial swelling and proteinuria were considered related to study therapy by the Investigator.

Clinical Reviewer's Comment: Patient 9999-543-92 was a poorly controlled diabetic whose urine results show bacteria throughout the study which could represent colonization versus active infection.

Patient 3003-547-04

The patient's total duration of exposure was 508 days during studies MPUC3003 and MPUC3005. At the Month 1 visit Study MPUC3005, the patient's platelet count was noted to be $172 \times 10^9/L$ (normal range $150-400 \times 10^9/L$). Over the course of the study, the patient's platelet count gradually decreased to a low of 128 at the Month 15 visit. Due to this gradual drop in platelet count, the patient was withdrawn from the study. At the follow-up visit, the platelet count was 134

Patient 3003-572-01

Total duration of exposure to eMG=237 days. The patient participated in Study MPUC3003 as a placebo patient and then entered Study MPUC3005. The patient had a past medical history of anemia and was treated with ferrous sulfate before and during study participation. At Visit 1 of Study MPUC3003, the patient's hemoglobin (Hgb) was found to be 7.3 g/dL (normal 11.5-15.5 g/dL). At Visit 1 of Study MPUC3005, the patient's Hgb was found to be 9.2 g/dL (normal 11.5-15.5 g/dL). After approximately 8 months, the patient's Hgb was found to be 5.4 g/dL and the patient was withdrawn from the study. In the opinion of the investigator, the AE was related to the study drug. The blood sample collected at the follow-up visit clotted before arriving at the lab. No additional follow-up recorded.

7.1.3.3 Other significant adverse events

Apart from AEs that resulted in discontinuation, there were no other significant AEs.

Table 11: Overall Summary of TEAE Incidence in the RCT Safety Population

	eMG N=367 (%)	Placebo N=185 (%)	All eMG N=557
All TEAEs	218 (59.4)	118 (63.8)	388 (69.7)
Serious TEAEs	4 (1.1)	4 (2.2)	26 (4.7)
TEAEs by Severity			
Mild	93 (25.3)	53 (28.6)	127 (22.8)
Moderate	103 (28.1)	56 (30.3)	190 (34.1)
Severe	22 (6.0)	9 (4.9)	67 (12.0)
Related TEAEs, per Investigator	39 (10.6)	25 (13.5)	69 (12.4)
TEAEs Resulting in Study Discontinuation	40 (10.9)	32 (17.3)	66 (11.8)
Deaths	0	0	0

Source ISS Tables 2.7.4.6.1 and 2.7.4.6.2
*As of 120-Day Safety Update Clinical Cut-off date

7.1.4 Other Search Strategies

The safety data from each primary Phase 3 study were reviewed. In addition, the interim safety data from the on-going open-label study was also reviewed. The CRFs and narratives of patients who discontinued due to TEAEs and all patients experiencing SAEs were reviewed. The results were compared to the Applicant's integrated summary of safety. For certain types of AEs, the reviewer did additional analyses using combinations of MedDRA terms (see section 7.1.5.2 and 7.1.5.3).

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the two primary, Phase 3, randomized, controlled studies, safety monitoring included physical examination, vital sign monitoring, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), and regularly assessing patients for the presence of AEs. Regular clinic visits were planned for Screening, Day 1, Month 1, Month 3, and Month 6. Telephone contacts were planned for Week 2, Month 2, and Month 5. Patients also had an in-office follow-up visit two week after the end of the study.

In Study MPUC3005, patients were seen for their initial visit at varying times depending on rollover status, See Appendix 10.3 for details. Patients were then seen at Month 1, 3, and every 3 months for up to 24 months. Patients were also seen for unscheduled visits at any time to assess a UC flare. Patients also had a follow-up visit two weeks after the end of the study.

All AEs, without regard to causality, or severity, were assessed and recorded in each patient's CRF and medical record. The Applicant encouraged investigators to complete SAE reports thoroughly and to assign an assessment of causality at the time of the initial report. All AEs and SAEs were followed until resolution, stabilization, until the event was otherwise explained, or until the patient was lost to follow-up.

Investigators were not required to actively seek new AEs in study participants once the study was completed. However, if the investigator learned of any SAE after the study, and such an event was reasonably related to the study drug, the Investigator was instructed to notify the Applicant.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary, Version 7.1. Treatment-emergent AEs were defined as any event with a start date occurring on or after treatment Day 1 or, if the event involved a pre-existing condition, worsening of the condition after treatment Day 1. By convention, a patient with events coded under the same preferred term more than once was counted only once for the summary of that event with the most severe intensity or maximum relationship to study drug.

Clinical Reviewer's Comment: Review of the AE datasets in combination with selected patient narratives and CRFs revealed that there were some inconsistencies in the coding of events to preferred terms. Specifically, there was inconsistency in coding the most common TEAE—ulcerative colitis flare. For example, for a patient whose narrative described ulcerative colitis flare, the preferred terms used might have included frequent bowel movements, diarrhea, abnormal feces, and/or abdominal pain and not the most appropriate preferred term—ulcerative colitis. In an attempt to better understand the possible number of patients experiencing an ulcerative colitis flare during the studies, the preferred terms associated with UC including diarrhea, abdominal pain, hematochezia, and rectal hemorrhage were combined with the term colitis ulcerative. See section 7.1.5.3 and Table 10 below.

7.1.5.3 Incidence of common adverse events

TEAEs occurring in greater than 3% of patients in any treatment group were considered *common* TEAEs. In general, the types and incidence of common TEAEs observed were similar between eMG and placebo groups in the RCT population, and between these groups and the All eMG population. The most common TEAEs for all groups occurred in the GI SOC.

Clinical Reviewer's Comment: The cut-off value of 3% was chosen because it provided a reasonable means of determining which TEAEs may have some association to the study drug given the size of the study population. With only 185 placebo patients in the RCT trials, events occurring in only two placebo patients reached the level of 1%. The number TEAEs reaching 1% incidence was large.

RCT Population

The incidence of the TEAE colitis ulcerative was more than twice as high in the placebo group (24%) as compared to the eMG group (11%). Many of the TEAEs listed in this SOC such as diarrhea, abdominal pain, hematochezia, and rectal hemorrhage likely also represent symptoms of UC rather than independent TEAEs. If the UC-related preferred terms are combined under the preferred term colitis ulcerative, the possible incidence of the TEAE colitis ulcerative triples to nearly 31% in the eMG group and 46% in the placebo group. In the eMG group, the incidence of headache was 11%, while the incidence was only 8% in the placebo group. Headache is a known adverse event associated with the use of mesalamine.

All eMG Population

Incidence rates for common TEAEs in the GI SOC were fairly similar between patients using eMG in the RCT population and those patients in the All eMG population. However, in the Infections and Infestations SOC, the incidence of nasopharyngitis in the All eMG population was 9%, which was more than twice as much as the eMG (4%) and placebo (3%) groups of the RCT population. Similarly, the incidences of sinusitis, upper respiratory tract infections, viral respiratory tract infection, and bronchitis were approximately two to three times as high in the All eMG population as the eMG and placebo groups of the RCT population.

The incidence rate for headache in the all eMG population was 14%, which was higher than the both the placebo (8%) and the eMG (11%) groups of the RCT population.

Clinical Reviewer's Comment: The preferred term "Influenza" was combined with the preferred term "Influenza-like illness" in an attempt to better appreciate the incidence of the flu syndrome which is generally a clinical and not a laboratory diagnosis. The terms are also combined for the adverse reaction frequency table in the proposed labeling.

7.1.5.4 *Common adverse event tables*

Table 12: TEAEs Occurring in at Least 3% of the RCT or All eMG Populations

b(4)

Clinical Reviewer's Comment: For the proposed labeling, we are proposing the following modifications to Table 12:

b(4)

7.1.5.5 Identifying common and drug-related adverse events

In each patient's CRF, investigators had to select between two categories for relationship to study drug. Those categories were 'possibly related' and 'not related.'

RCT Population

The incidence of TEAEs considered possibly related to the study drug was comparable between the placebo group (14%) and the eMG group (11%). About half as many patients in the eMG group had TEAE GI disorders that were considered by the investigator to be possibly related to the study drug compared with patients in the placebo group (7% eMG, 14% placebo). All possibly related events in the placebo group were in the GI SOC. The possibly-related preferred term with the highest incidence was colitis ulcerative, 14% placebo versus 11% eMG.

Outside the GI SOC, the possibly-related preferred term with the highest incidence was headache, 2% eMG group versus 0% placebo group.

All eMG Population

At the time of the 120 Day Safety Update, 385 patients (69%) experienced a total of 2,065 adverse events. Of these, 190 events (9%) experienced by 69 patients (12%) were considered by investigators to be possibly related to the study drug. This incidence is similar to the incidence in each group of the RCT population. The most common adverse event judged by investigators to be possibly related was ulcerative colitis (3%).

Clinical Reviewer's Comment: Information from approved mesalamine products along with substantial review of the adverse event data in this Application including narratives of selected patients lead me to believe that headache, UC flare and symptoms associated with UC, alkaline phosphatase elevation, AST elevation, and ALT elevations are all events possibly related to eMG use. See Section 7.1.5.6 for details regarding patients reporting liver enzyme elevations. This information provides additional evidence to support a hepatic impairment warning to the proposed labeling.

Table 13: TEAEs Considered Related per Investigator in ≥1% of RCT Patients

	eMG N=367 (%)	Placebo N=185 (%)	All eMG* N=557
MedDRA System Organ Class			
Preferred Term			
All System Organ Class	39 (10.6)	25 (13.5)	69 (12.4)
Gastrointestinal Disorders	26 (7.1)	25 (13.5)	48 (8.6)
Colitis Ulcerative	13 (3.5)	15 (8.1)	17 (3.1)
Abdominal Pain	4 (1.1)	1 (0.5)	9 (1.6)
Constipation	3 (0.8)	0	6 (1.1)
Diarrhea	4 (1.1)	2 (1.1)	9 (1.6)
Nausea	3 (0.8)	1 (0.5)	7 (1.3)
Abdominal Pain Upper	5 (1.4)	2 (1.1)	9 (1.6)
Flatulence	2 (0.5)	2 (1.1)	4 (0.7)
Hematochezia	4 (1.1)	2 (1.1)	4 (0.7)
Dyspepsia	0	2 (1.1)	2 (0.4)
Loose Stools	0	2 (1.1)	1 (0.2)
Nervous System Disorders	8 (2.2)	1 (0.5)	13 (2.3)
Headache	7 (1.9)	0	11 (2.0)

Source: ISS Tables 2.7.4.15.1 and 2.7.4.15.2, Appendix C
*As of 120-Day Safety Update Clinical Cut-off date

7.1.5.6 Additional analyses and explorations

Renal manifestations are a well-known possible adverse event associated with the use of mesalamine products. A recently published literature review reports that nephrotoxicity, in patient's taking 5-ASA, occurs at a mean rate of 0.26% per patient-year. Nephrotoxicity is most often reported within the first year and the most common form is interstitial nephritis with nonspecific signs and symptoms.¹ In an attempt to capture possible nephrotoxicity, the Applicant included an analysis of TEAEs involving the renal system using appropriate MedDRA preferred terms.

To explore the possibility that renal impairment associated with mesalamine use is dose related, DGP requested a search of the Adverse Event Reporting System (AERS). Ann Corken Mackey, Safety Evaluator in the Division of Adverse Event Analysis, conducted the review and concluded that renal impairment associated with mesalamine use is not dose-related.

Based on the mechanism of action of 5-ASA and the incidence of AEs related to the pancreatic and hepatic systems seen in association with the use of other mesalamine products, TEAEs of these systems were also analyzed.

Pericarditis and myocarditis are mentioned in current mesalamine labeling as possible rare adverse reactions. None of these adverse events were reported by any of the patients in the Study MPUC30034, MPUC3004, or MPUC3005.

RCT Population

In the RCT population, 31 patients developed a total of 37 TEAEs (22 eMG patients, 9 placebo patients) related to the renal, pancreatic, or hepatic organ systems.

The renal TEAE with the highest incidence was hematuria, 2.5% in the eMG group compared with 0.54% in the placebo group. Renal events included gross and microscopic hematuria (9 eMG patients; 1 placebo patient), decreased creatinine clearance (3 eMG patients), WBC positive urine (3 eMG patients, 0 placebo patients), urine abnormality (1 eMG patient, 1 placebo patient), pyelonephritis (0 eMG patients, 1 placebo patient), and proteinuria (1 eMG patient, 1 placebo patient).

In the RCT population, a single eMG patient (0.3%) developed pancreatitis compared with no patients in the placebo group. Patient 3004-419-04 (eMG group) a 33-year-old, female was hospitalized due to acute pancreatitis. The episode was felt to be secondary to azathioprine used to treat a UC flare. For a more detailed description of this event, see Appendix 10.1, MPUC Clinical Study Results.

The highest reported alkaline phosphatase level in an eMG-treated patient was 832 (6.2 x ULN). This patient was the only patient in Studies MPUC3003, 3004, or 3005 to have a potentially clinically significant change in the level of alkaline phosphatase reported (≥ 2.5 x ULN). The highest reported AST level was 126 U/L.

No patients in either the placebo or eMG groups developed other significant hepatobiliary disorders in the RCT population.

All eMG Population

In the All eMG population, 38 patients (6.8%) developed a total of 52 TEAEs of special interest. In addition to the renal TEAEs experienced by eMG patients during the RCT trials, during MPUC3005, 3 additional patients had gross/microscopic hematuria, 1 additional patient had WBC positive urine, and a single additional patient had proteinuria. During MPUC3005, no additional eMG patients experienced decreased creatinine clearance, urine abnormality, or pyelonephritis.

So far, a single patient has developed pancreatitis during MPUC3005. Patient 3003-561-12 completed Study MPUC3003 and rolled over into Study MPUC3005. After 98 days of exposure to the open-label drug, the patient experienced an exacerbation of chronic pancreatitis and was withdrawn from the study. The patient was treated as an outpatient with pancreatin and omeprazole.

A single patient has developed jaundice during MPUC3005.

Table 14: TEAEs of Special Interest

MedDRA SOC	eMG	Placebo	All eMG
Preferred Term	N=367 (%)	N=185 (%)	N=557
All System Organ Classes	22 (6.0)	9 (4.9)	38 (6.8)
Gastrointestinal Disorders			
Pancreatitis	1 (0.3)	0	2 (0.)
Hepatobiliary Disorders			
Jaundice	0	0	1 (0.2)
Infections and Infestations			
Pyelonephritis	0	1 (0.5)	0
Investigations			
Creatinine Renal Clearance Decreased	3 (0.8)	0	7 (1.3)
Aspartate Aminotransferase Increased	4 (1.1)	4 (2.2)	6 (1.1)
Alanine Aminotransferase Increased	3 (0.8)	4 (2.2)	6 (1.1)
White Blood Cells Urine Positive	2 (0.5)	0	3 (0.5)
Blood Urine Present	3 (0.8)	1 (0.5)	3 (0.5)
Blood Bilirubin Increased	1 (0.3)	0	2 (0.4)
Red Blood Cells Urine Positive	1 (0.3)	0	1 (0.2)
Bacteria Urine	0	0	1 (0.2)
Urine Ketone Body Present	0	0	1 (0.2)
White Blood Cells Urine	1 (0.3)	0	1 (0.2)
Renal And Urinary Disorders			
Hematuria	5 (1.4)	0	8 (1.4)
Proteinuria	1 (0.3)	1 (0.5)	2 (0.4)
Urine Abnormality	1 (0.3)	1 (0.5)	1 (0.2)
Metabolism And Nutrition Disorders			
Hypokalemia	0	0	2 (0.4)

Source: ISS Tables 2.7.4.16.1 and 2.7.4.16.2, Appendix C
*As of 120-Day Safety Update Clinical Cut-off date

7.1.6 Less Common Adverse Events

A review of less common AEs did not identify any specific patterns or safety signals.

7.1.7 Laboratory Findings

Hematology and clinical chemistry parameters were assessed in the RCT population at screening and Months 1, 3, 6/EOS. During the open-label extension study, MPUC3005, changes from baseline parameters were calculated at months 1,3,6, and every 3 months thereafter. In addition, a final value was calculated at Month 24/EOS.

In order to describe shifts, baseline and final values were categorized as low, normal, or high. Shifts from baseline to the final evaluation were summarized. A change in a safety laboratory investigation value could represent a TEAE if the change was clinically relevant or if, during treatment, a parameter was observed to go from a normal value to a pathological one, or if a known pathologic value worsened. The investigator was responsible for deciding whether a

change in a laboratory parameter was clinically significant and, therefore, represented an adverse event.

7.1.7.1 Overview of laboratory testing in the development program

Criteria for identifying clinically potentially clinically significant (PCS) laboratory are outlined below in Tables 15 and 16 below.

Table 15: Patients with PCS Changes in Hematology Parameters

Laboratory Parameter	Laboratory Criteria	eMG N=367	Placebo N=185	All eMG N=557
Hemoglobin (g/dL)	<10 AND ≥3 decrease; or >20	1 (0.3%)	1 (0.5%)	8 (1.4)
Hematocrit (%)	<30 AND ≥10 decrease; or >60	0	0	6 (1.1)
Platelets (x 10 ⁹ /L)	<100 or ≥700	0	1 (0.5%)	3 (0.5)
White Blood Cells (x 10 ⁹ /L)	<2.3 or >16.2	4 (1.1%)	3 (1.6%)	15 (2.7)

Source: ISS Table 2.7.4.24.1

*As of 120-Day Safety Update Clinical Cut-off date

Table 16: Patients with PCS changes in Clinical Chemistry Parameters

Laboratory Parameter	Laboratory Criteria	eMG N=367 (%)	Placebo N=185 (%)	All eMG N=557
Creatinine (mg/dL)	>2.5	0	0	0
Calculated creatinine clearance (mL/min)	≤50	0	2 (1.1%)	1 (0.18)
Alkaline phosphatase (U/L)	≥2.5 x ULN	1 (0.3%)	0	2 (0.36)
ALT (U/L)	≥3 x ULN	3 (0.8%)	1 (0.5%)	5 (0.90)
AST (U/L)	≥3 x ULN	2 (0.5%)	0	4 (0.72)
Total bilirubin (mg/dL)	>2.0	3 (0.8%)	2 (1.1%)	8 (1.4)

Source: ISS Table 2.7.4.25.1

*As of 120-Day Safety Update Clinical Cut-off date

Clinical Reviewer's Comment: A review of the Applicant's categorization of potentially clinically significant laboratory criteria appears reasonable.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable.

7.1.7.3 Standard analyses and explorations of laboratory data

RCT Population

The number and magnitude of laboratory abnormalities was not substantial enough at the time of this review to warrant further investigation of a possible safety signal.

All eMG Population

The number and magnitude of laboratory abnormalities was not substantial enough at the time of this review to warrant further investigation of a possible safety signal.

7.1.7.3.1 Analyses focused on measures of central tendency

RCT Population

A review of the mean data for laboratory parameters found no significant changes for any group across the course of the studies.

All eMG Population

A review of the mean data for laboratory parameters found no significant changes for any group across the course of the studies.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

RCT Population

There was a trend for the mean percentage of basophils to increase from normal to high in 16.0% of placebo patients and 12.3 % of eMG patients. There is likely no clinical significance to this laboratory finding. No other trends were noted in the hematology shift parameters.

A trend was also seen from normal to high in the total cholesterol values. In 11% of eMG patients and 13% of placebo patients cholesterol levels increased over the course of the RCT studies from normal to high. Over that same period 11% of eMG patients and 11% of placebo patients had a change in total cholesterol from high to normal. It is unlikely to be related to eMG as the percentage is higher in the placebo group. No other trends were seen in the clinical chemistry shift parameters.

Changes in urinalysis parameters for both eMG and placebo patients were unremarkable.

All eMG Population

The trend for basophils to increase from normal to high was also seen in the All eMG population. At month 6, 10.4% of patients had a shift from normal to high. At month 12, 15% of patients had a shift from normal to high. At Month 12, only 8% of patients had a shift from normal to high. As mentioned previously, it is unlikely that this change in basophils has any clinical significance.

Similar to the RCT population, total cholesterol values in the All eMG population trended from normal to high in 12% of patients at 6 months, 12% of patients at 12 months, and 15% of patients at 24 months.

Changes in urinalysis parameters were unremarkable.

MO Comment: The month 24 hematology and clinical chemistry laboratory values may not present a complete picture because at month 24, only 105 patients were tested, compared with 399 patients at month 6. Similarly, for the urinalysis values at month 24, only 105 patients were tested.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

RCT Population

Eight patients discontinued the study due to laboratory abnormalities (6 eMG, 2 placebo). Two eMG patients (0.5%) and two placebo patients (1%) discontinued due to an increase in alanine aminotransferase (ALT). Two eMG patients (0.5%) discontinued due to an increase in aspartate aminotransferase (AST). And two eMG patients (0.5%) discontinued due to a decrease in creatinine clearance. Overall, the incidence of discontinuations due to laboratory abnormalities was low (2% eMG, 1% placebo). See Table 10 above.

All eMG Population

Apart from the six eMG patients who discontinued due to laboratory abnormalities during the RCT studies, an additional 2 patients had withdrawn due to laboratory abnormalities in Study MPUC3005 at the time of the 120-day safety update. One patient withdrew due to decreased hemoglobin (0.2%); another patient withdrew due to decreased platelet count (0.2%).

There were no cases found meeting the requirements to be termed “Hy’s Law” cases. That is, there were no cases found of transaminase elevations combined with increased bilirubin without evidence of obstruction (increased alkaline phosphatase).

7.1.7.4 Additional analyses and explorations

No additional analyses and explorations were indicated.

7.1.7.5 Special assessments

None.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In the randomized controlled clinical trials, MPUC3003 and MPUC304, vital signs included sitting blood pressure (mm Hg), heart rate (beats per minute), body weight, and oral temperature. Vital signs were collected at each scheduled study visit including screening and follow-up. Scheduled study visits were planned to occur on Study Day 1, Month 1, Month 3, Month 5 and Month 6/EOS. In the on-going, open-label study, MPUC3005, vital signs were collected every 3 months at the end of the study.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital sign data were examined from both primary Phase 3, placebo-controlled trials, MPUC3003 and MPUC3004. In addition, to explore the long-term effects of eMG administration, vital sign data from open-label extension study MPUC3005 was also examined. No clinically significant changes were seen in any of these Phase 3 clinical trials.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Overall, mean changes in vital signs from screening to last visit were minimal with no clinically significant mean changes noted. A review vital sign changes revealed no clinically significant differences between subgroups.

Table 17: Mean change from baseline to End of Treatment

Parameter	RCT eMG	RCT Placebo	All eMG
Systolic BP (mm Hg)	-0.2	0.2	-0.5
Diastolic BP (mm Hg)	0.0	-0.7	-0.2
Pulse (bpm)	0.8	0.4	0.0
Oral Temp (°F)	-0.04	0.03	-0.02
Weight (lb)	-0.31	-0.07	1.4

Source: Table 2.7.4.26.1, 2.7.4.27.1

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

No clinically significant changes in vital sign measurements were seen.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no dropouts due to vital sign abnormalities in this clinical program.

7.1.8.4 Additional analyses and explorations

The 120-day Safety Update provided by the Applicant included additional data from the ongoing MPUC3005 study available for all patients up to 14 January 2008. Additional data were also included (only in the database) for some patients up to 08 February 2008. Additionally, the 120-day Safety Update included, for the first time, safety summaries for SAG-27/UCR, a long-term, double-blind, randomized, multicenter supportive study conducted by Dr. Falk Pharma with mesalamine granules (Falk formulation, FMG) for the maintenance of remission of UC. This FMG product is not the to-be-marketed product and bio-equivalence has not been established.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 *Overview of ECG testing in the development program, including brief review of preclinical results*

None of the included Phase 3 trials included ECG testing.

7.1.9.2 *Selection of studies and analyses for overall drug-control comparisons*

Not applicable. No ECG data submitted for any of the studies.

7.1.9.3 *Standard analyses and explorations of ECG data*

Not Applicable. No ECG data submitted for any of the studies

7.1.10 Immunogenicity

Not Applicable. The Applicant did not provide any clinical or adverse event data regarding immunogenicity in this application.

7.1.11 Human Carcinogenicity

The Applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application. Three study subjects were diagnosed with cancer during treatment with eMG.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Given past experience with the 5-ASA drug class and the proposed mechanism of action, abuse is not expected. Drug abuse was not reported during the submitted eMG trials. No formal withdrawal or rebound studies were performed.

7.1.14 Human Reproduction and Pregnancy Data

Pregnant and lactating females were excluded from participating in studies MPUC3003, 3004 and 3005. During the studies, patients were required to use an acceptable method of birth control. Despite these measures, three pregnancies were reported in the Phase 3 clinical studies submitted with this NDA in patients taking eMG. And a single pregnancy was reported in a patient taking placebo.

Patient 563-19, a 38-year-old female patient in study MPUC3003 took blinded eMG from 07 March 2006 to 14 May 2006 when she terminated the study drug. The patient was permanently discontinued from the study on 16 May 2006. The pregnancy was terminated via therapeutic abortion on _____

b(6)

Patient 3003-618-01, a 38-year-old, white female took open-label eMG in Study MPUC3005 from 16 March 2006 to 11 July 2006. On this date she was withdrawn from the study due to pregnancy. _____ the patient had a spontaneous abortion.

b(6)

Patient 999-565-07, a 30-year-old, white female, received open-label eMG starting on March 2006. On 08 June 2006 she experienced severe lower abdominal pain. A subsequent hysteroscopy revealed a uterine perforation and an extra-uterine pregnancy was noted. The extra-uterine perforation was thought to be related to the extraction of an intrauterine device performed on _____

b(6)

Placebo patient 566-18 in Study MPUC3004 was a 41-year-old female. The patient started the placebo on 10 October 2005 and discontinued the drug on 03 April 2006. The pregnancy was terminated via therapeutic abortion on _____ The patient later enrolled in MPUC3005.

b(6)

7.1.15 Assessment of Effect on Growth

Pediatric patients were excluded from the submitted Phase 3 studies. Therefore, no height/weight data was reviewed.

7.1.16 Overdose Experience

No case of overdose has been reported during any of the clinical trials submitted with this NDA. In addition, no case of overdose has been reported for mesalamine granules (Dr. Falk Pharma, Salofalk tablets, Salix clinical studies).

A case of possible intentional overdose with Pentasa® (mesalamine) was reported in the US in 2007. The spontaneous case report from a medical examiner (forensic pathologist, M.D.) describes a completed suicide in a 17-year-old female who may have taken 14 of her brother's Pentasa (mesalamine) pills. According to the medical examiner, there was no evidence of disease or injury on autopsy and all toxicology (blood, urine and vitreous fluid) evaluations came back negative for everything except trace amounts of salicylates. It should be noted that a small amount of white powdery substance found near the patient tested positive for cocaine. No concomitant medications were reported. The medical examiner listed the cause of death as "undetermined."

7.1.17 Postmarketing Experience

The drug product eMG has not been marketed for use in any country at the time of this submission. However, eMG is an encapsulated formulation that is similar to Falk Mesalamine Granules (FMG). Dr. Falk Pharma has approval to market FMG in 25 countries in Europe, Asia, and South America. Dr. Falk Pharma has not withdrawn any of its mesalamine formulations from any market due to safety concerns.

A summary of SAEs reported with Dr. Falk Pharma formulations of mesalamine (pellets, tablets, enemas) from 15 October 2001 through 29 February 2008 was submitted with this NDA application. These SAEs were obtained from spontaneous reporting to Dr. Falk Pharma, clinical studies, and the literature. During the above reporting period, there were three deaths reported in patients treated with mesalamine.

A ten year old boy taking mesalmine (dose and route unknown) for Crohn's disease for an unknown period of time died from a case of acute hepatic failure (confirmed by autopsy). Very little information was available and the relationship to the study drug was qualified as "not assessable" due to insufficient information.

A 71-year-old male was found dead at home after receiving Salofalk Granustix® 1g/d for one year. The patient received the medication as part of a study on the prevention of colorectal polyps by 5-ASA after polypectomy. The patient had a past medical history significant for cerebral infarction, arteriosclerosis, peripheral vascular disease, carotid artery stenosis, compensated heart failure, and compensated renal insufficiency. Concomitant medications included acetyl salicylic acid (100 mg), captopril, furosemide, and triamterene. The causal relation was qualified as "unassessable."

A 47-year-old-female taking an unknown generic mesalmine for ulcerative colitis developed anaphylactic shock with asystole two days following a change of medication from Salofalk® to generic mesalamine. At the time of the incident, the patient was not taking any concomitant medication. The patient's past medical history was not reported. The patient was taken to the hospital, at which time an acute hemorrhagic anterior infarction of the left ventricle of the heart was diagnosed. The MI was treated with stenting and the anaphylaxis was treated with vasopressin. On the third day following the event, the patient died. The causal relationship was qualified as "possible."

As part of the review of this NDA, we requested a brief search of the Adverse Events Reporting System (AERS) by Ann Corken Mackey, Division of Adverse Events Analysis 1 for cases of liver failure in patients taking mesalamine. Thirteen cases were retrieved. Many of these case reports were incomplete. The cases with the greatest amount of information reported are presented below. It should be noted that these accumulated case reports cannot calculate incidence or estimates of drug risk.

Case 1: A 32 year-old patient treated with mesalamine 1.5 g/day for Crohn's disease was hospitalized with fulminant hepatitis and an AST level of 12,000 U/L and an ALT of 8,000u/L. The patient had a prior medical history of fulminant hepatitis. On the evening of admission, the patient was noted to have ALT and AST levels of about 2,500 U/L. The day after admission the patient was reported to have recovered.

Clinical Reviewer's Comment: This patient with known history of liver disease appeared to recover from fulminant hepatitis immediately after the discontinuation of mesalamine. This case provides temporal plausibility for an association between liver failure and mesalamine use.

Case 2: An 80-year old patient treated with mesalamine 4 g/day for 17 days presented with neutropenia and fever leading to hepatic and cardiac failure. The patient died due this event. The patient's past medical history was not reported.

Case 3: An 83 year old patient treated with mesalmine, 800 mg per day for two years, was hospitalized with jaundice and died due to end stage liver disease. The patient's past medical history was positive for chronic liver disease and possible cirrhosis.

Case 4: A 23-year old patient with a history of UC treated with mesalamine 800 mg per day was admitted to the hospital and subsequently died after a two month history of vomiting. Four days after the onset of the vomiting, diclofenac was taken for four days. Asacol was started at the same time as Diclofenac and continued intermittently until death. At post-mortem, the patient was found to have liver histology consistent with Reye's Syndrome.

Case 5: A 48-year old patient treated with mesalamine 4.8 g per day to treat UC was hospitalized with UC exacerbation and drug-induced hepatitis. The patient reports being on a liver transplant list. It is unclear whether the medication was discontinued. This was a spontaneous self-report.

Clinical Reviewer's Comment: Due to the serious nature of the possible association of liver failure with mesalamine use, a liver warning should be included with the prescribing information for this product.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Safety data for eMG were collected from three Phase 3 clinical studies for the proposed indication of maintenance of remission from UC. Studies MPUC3003 and MPUC3004 were designed to evaluate the use of the medication for six months duration. In addition, long-term safety and tolerability data were evaluated in a long-term, open-label extension study, MPUC3005. In evaluating the safety and tolerability of eMG, emphasis has been placed on

studies MPUC3003 and MPUC3004. Their randomized, placebo-controlled designs allow for unbiased assessment of the safety of eMG.

7.2.1.1 Study type and design/patient enumeration

The two pivotal studies (MPUC3003 and MPUC3004) along with interim data from the ongoing, open-label, 12-34 month extension study (MPUC3005) provided the majority of the data for the safety review (See Table 2: Primary Clinical Studies Submitted in Support of NDA 22,301).

7.2.1.2 Demographics

Table 18: Demographic data—RCT and All eMG Populations of Primary Studies

Demographic Subgroup	RCT POPULATION		All eMG
	eMG N=367	Placebo N=185	MPUC3003/4/5 N=557
Sex (n,%)			
Male	162 (44.1)	100 (54.1)	257 (46.1)
Female	205 (55.9)	85 (45.9)	300 (53.9)
Age (years) (n,%)			
<65	328 (89.4)	163 (88.1)	491 (88.2)
≥65	39 (10.6)	22 (11.9)	66 (11.8)
Mean (SD)	46.5 (13.7)	45.4 (14.1)	46.7 (13.9)
Median (min,max)	46 (18,82)	46 (18,82)	47 (18,82)
Race[^] (n,%)			
AI/AN [*]	5 (1.4)	0	5 (0.9)
Asian	3 (0.8)	2 (1.1)	4 (0.7)
Black/AA ^{**}	21 (5.7)	12 (6.5)	32 (5.7)
Native Hawaiian ⁺	0	0	1 (0.2)
White	341 (92.9)	171 (92.4)	518 (93.0)
Ethnicity (n,%)			
Hispanic or Latino	7 (1.9)	4 (2.2)	19 (3.4)
Not Hispanic or Latino	360 (98.1)	181 (97.8)	538 (96.6)
Country (n,%)			
Russia	198 (54.0)	96 (51.9)	246 (44.2)
United States	169 (46.0)	89 (48.1)	311 (55.8)
Weight (lbs) (n,%)			
Mean (SD)	166.52 (36.00)	168.63 (33.03)	169.93 (37.39)
Median (min,max)	160.6 (101.1, 337.2)	166.0 (81.6, 273.0)	165.0 (101.2, 355.0)
Height (inches) (n,%)			
Mean (SD)	66.48 (3.89)	67.30 (3.58)	66.70 (3.85)
Median (min,max)	66.1 (57.0, 76.4)	67.5 (56.3, 75.0)	66.3 (57.0, 76.4)
Baseline Renal Function (n,%) (Cockcroft-Gault formula)			
Normal (≥90 mL/min)	234 (63.8)	131 (70.8)	361 (64.8)
Mild (60-<90 mL/min)	122 (33.2)	50 (27.0)	176 (31.6)
Moderate (30-<60 mL/min)	6 (1.6)	3 (1.6)	11 (2.0)
Severe (<30 mL/min)	0	0	0

Source: ISS Tables 2.7.4.2.1 and 2.7.4.2.2, Appendix C

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

^{*}American Indian/Alaskan Native

^{**}African-American

⁺Other Pacific Islander included

Clinical Reviewer's Comment: The randomization procedure produced demographically balanced eMG and placebo groups.

7.2.1.3 Extent of exposure (dose/duration)

For patients in Study MPUC3005, exposure was calculated as of the clinical cut-off date, 14 January 2008. In the RCT population, the mean exposure to eMG was 145.0 days, with a mean cumulative eMG dose of 211.3g.

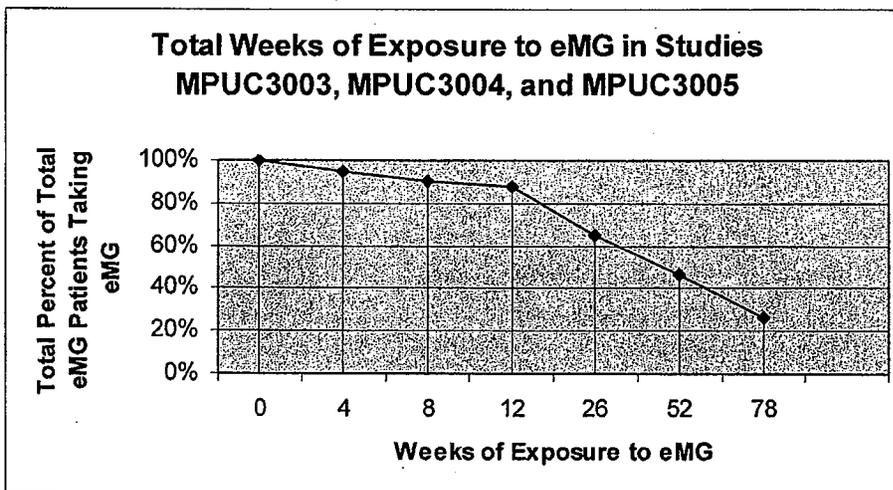
In the ALL eMG population, the mean exposure to eMG was 352 days, with a median exposure duration of 335 days. A total of 354 patients were exposed to eMG 1.5 g once daily for more than 6 months, and 250 patients were exposed for more than one year. Patients in the All eMG population had cumulative exposure of eMG up to 1285g, with a mean cumulative exposure of 482.9g, and approximately 527 person-years of exposure. Placebo patients who rolled over to MPUC3005 from a lead-in study had a mean exposure to eMG of 402.7 days, with a mean cumulative dose of 550g.

Table 19: Extent of Exposure to eMG: RCT and All eMG Populations

Exposure Duration (days)	RCT Population eMG	Placebo	All eMG Population
Mean (SD)	145.0 (55.1)	125.9 (66.0)	352.0 (231.3)
Median (min, Max)	169 (3, 224)	162 (3, 215)	335 (1, 868)
Cumulative eMG dose (grams)	N=364	N=185	N=543
Mean (SD)	211.3 (80.5)	0	482.9 (329.1)
Median (min,max)	246 (2,315)	0	396 (2, 1285)
Number of patients on study drug n(%)			
1-4 weeks	29 (7.9)	32 (17.3)	23 (5.0)
5-8 weeks	24 (6.5)	14 (7.6)	26 (4.7)
9-12 weeks	12 (3.3)	4 (2.2)	15 (2.7)
13-16 weeks	13 (3.5)	15 (8.1)	
17-24 weeks	104 (28.3)	49 (26.5)	
25 weeks to maximum duration	185 (50.4)	71 (38.4)	
13-26 weeks			124 (22.3)
27-52 weeks			104 (18.7)
53-78 week			113 (20.3)
79 weeks to maximum duration			137 (24.6)

Source: ISS Table 2.7.4.5.1 and 2.7.4.5.2, Appendix C, 120-Day Safety Update

Figure 2: Extent of Exposure to eMG in Studies MPUC3003, MPUC3004, and MPUC3005



Clinical Reviewer's Comment: The mean duration and cumulative dose exposure experienced by patients in the RCT studies was adequate for evaluation. The long-term extension study provides additional exposure data which is useful for predicting safety in patients taking courses of therapy exceeding the six month duration of the primary efficacy studies.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The primary studies relevant to the safety evaluation have been outlined under Section 7.2.1.1 of this review. In addition, supportive data from three studies (SAG-2/15/26) using Falk mesalamine granules (FMG) to treat *active* ulcerative colitis (a different indication than the proposed indication of maintenance of remission) were also submitted for review. The Applicant also submitted the full study report for SAG-27 which used FMG for maintenance of remission of UC. The entire study report was not submitted until April 2008 along with the 120-Day Safety Update. The study was not fully integrated into the ISS until a subsequent July 2008 submission by the Applicant. Further, the study drug used in these studies is different from the to-be-marketed formulation. Therefore, data from these studies was viewed as supportive and useful only in terms of the information it provided in regard to safety and tolerability. In addition, two pharmacokinetic studies (MPPK1001 and MPPK1002) in healthy volunteers using Salix mesalamine granules (SMG) were also submitted. Safety data from these studies were briefly reviewed.

Table 20: Summary of Secondary Clinical Safety Studies

Study Name	Study Type	Study Drug	Number of Patients in Safety Population	Study Duration	Indication
SAG-2	Randomized, double-blind, parallel group	FM 0.5 g TID FM 1 g TID FM 1.5 g QD	319	8 weeks	Treatment of active disease
SAG-15	Randomized, double-blind, parallel group	FMG 0.5g TID Mesalamine 0.5g TID	233	8 weeks	Treatment of active disease
SAG-26	Randomized, double-blind, parallel group	FMG 3 g QD FMG 1 g TID	380	8 weeks	Treatment of active disease
SAG-27	Randomized, double-blind, comparative group	FMG 3.0 g QD FMG 1.5g QD FMG 0.5 g QD	647	52 weeks	Maintenance of remission

SAG-2

Study SAG-2 was a randomized, double-blind, parallel group study. There were three groups (FMG 0.5 g TID, 1 G TID, and 1.5 G TID) who participated in the study planned for 8 weeks. A total of 321 patients with mildly to moderately active UC participated in the study. There were no deaths reported for any study patient. Twelve patients experienced 14 SAEs during the study. Of those SAEs, two (abnormal liver function and pancreatitis) were attributed to the study drug by the investigator. Both SAEs occurred in the highest dosage group, 1.5 g TID.

The most common AE in all three dosage groups was headache. The next most common AEs were associated with ulcerative colitis (abdominal pain and colitis ulcerative aggravated). Ten patients experienced abnormal hepatic function. Of these ten cases, eight were attributed to the study drug by the investigator. Twenty-seven patients prematurely discontinued the study due to AEs. The most common AE leading to discontinuation was aggravated UC.

SAG-15

Study SAG-15 was a randomized, double-blind, parallel-group study of FMG 0.5 g TID compared to Salofalk Tablets 0.5 g TID. Salofalk tablets are a mesalmine formulation not approved in the United States. The study was conducted in 233 patients with mildly to moderately active UC for 8 weeks. Both groups had the option to increase the dose to 1 g TID after Day 14 if adequate response was not achieved.

No patients died during the study. No SAES were reported in the FMG group. The most frequently reported adverse events were influenza like symptoms, headache, and ulcerative colitis.

SAG-26

SAG-26 was a double-blind, double-dummy, randomized, multi-center, comparative study using a four-stage, group sequential adaptive design with sample size adjustments after the planned interim analyses. FMG 3 g QD was compared with FMG 1 g TID. There were no deaths during the study and six patients (4 QD, 2 TID) experienced SAES. None of the SAES were attributed to the study drug by the investigator. Five SAEs were aggravation of ulcerative colitis (4 QD, 1 TID). A single SAE in the QD group was coded as viral upper respiratory tract infection. And a single SAE in the TID group was coded as measles.

In the 3 g QD group, 28.8% of patients reported an AE compared with 32.3% of patients in the 1 g FMG TID group. The most frequently reported AEs were headache, UC, and nasopharyngitis.

MO Comment: The AE incidence and most frequently reported AEs in SAG-26 are similar to those found in the primary studies MPUC3003, MPUC3004, and MPUC3005.

SAG-27

SAG-27 was a double-blind, double-dummy, randomized, multi-center, 12-month comparative study of three separate dosing regimens of FMG for the maintenance of remission of UC. Patients were randomized in a 1:1:1 ratio to receive FMG either as 3.0 g QD, 1.5 g QD, or 0.5 g TID. The study was conducted at centers in Croatia, the Czech Republic, Estonia, Germany, Hungary, Israel, Latvia, Lithuania, Poland, Russia, the Slovak Republic, Slovenia, and Ukraine.

A total of 647 patients received study drug. Of those, 151 patients (18.9% 3.0g QD; 28.8% 1.5 g QD, 22.5% 0.5 g TID) prematurely discontinued the study. The primary reason for premature discontinuation was lack of efficacy.

A total of 146 TEAEs occurred in 41% of 3.0 g QD patients, 55.2% of 1.0 g QD patients, and 48.2% of 0.5 G TID patients. The most commonly reported TEAEs were colitis ulcerative (3.0 g QD: 15.7%, 1.5 g QD: 34.0%, 0.5 g TID: 24.3%); nasopharyngitis (3.0 g QD: 2.8%, 1.5 g QD: 3.8%, 0.5 g TID: 4.1%); and headache (3.0 g QD: 1.4%, 1.5 g QD: 0.9%, 0.5 g TID: 3.2%). All other preferred terms occurred in less than 3% of patients per treatment group. Two patients had an AE of pregnancy and both resulted in healthy babies. Related TEAEs, as assessed by study investigators, occurred in

Adverse events leading to study discontinuation occurred in 9.2% of 3.0g QD patients, 22.2% of 1.5 g QD patients and 14.7% of 0.5 g TID patients. Colitis ulcerative was the most commonly reported AE associated with discontinuation (83 patients). Twenty-two SAEs occurred in 21 patients (see Table X). None of the SAES were reported as associated with the study drug by the investigators. No patients died during this study.

Table 21: SAG-27, TEAEs Occurring in at Least 3% of Patients

MedDRA SOC	3.0 g QD N=217 (%)	1.5 g QD N=212 (%)	0.5 g TID N=218 (%)
Any TEAE	89 (41.0)	117 (55.2)	105 (48.2)
Gastrointestinal Disorders			
Colitis ulcerative	34 (15.7)	72 (34.0)	53 (24.3)
Diarrhea	2 (0.9)	1 (0.5)	0
Abdominal Pain	4 (1.8)	2 (0.9)	0
Abdominal Pain Upper	2 (0.9)	2 (0.9)	0
Infections and Infestations			
Nasopharyngitis	6 (2.8)	8 (3.8)	9 (4.1)
Nervous System Disorders			
Headache	3 (1.4)	2 (0.9)	7 (3.2)

Source: ISS Tables 2.7.4.11.1 and 2.7.4.8.1, Appendix C

Table 22: SAG-27, SAEs by Treatment Group

Treatment Group	SAE
FMG 3.0 g QD, N=217	Appendicitis
	Acute tonsillitis
	Rectal hemorrhage
	Colitis Ulcerative
	Duodenal Ulcer Hemorrhage
	Inguinal hernia
	Myocardial Infarction
FMG 1.5 g QD, N=212	Pregnancy
	Acute sinusitis
	Knee Arthroplasty
	Periorbital Edema
	Post-traumatic spinal cord contusion, cervical region
	Colitis ulcerative
	Intervertebral disc disorder
FMG 0.5 g TID, N=218	Appendicitis
	Colitis ulcerative
	Limb injury
	Benign breast neoplasm
	Colitis ulcerative
	Acute myocardial infarction
	Appendicitis
Pregnancy	

Source: Integrated Clinical Study Report, Table 50, p.106

Clinical Reviewer's Comment: SAG-27 is the only secondary study that was designed to study the same indication as the submitted application—maintenance of remission of ulcerative colitis. However, the study drug used in SAG-27, FMG, was a different formulation than the study drug submitted for this application, eMG.

Study SAG-27 was submitted by the Applicant as a "primary" study in support of the application for approval. However, the study report was not submitted until the 120-Day safety update and at that time was not fully integrated into the safety summary. A fully integrated safety summary was not received until July 28. As such, only the safety information from SAG-27 was reviewed and the study was viewed as supportive and not primary.

7.2.2.2 Post-marketing experience

The Applicant submitted a post-marketing review which included information reported spontaneously to Dr. Falk Pharma from 15 October 2001 through 29 February 2008 for all Salofalk mesalmine formulations—pellets (granules), enemas, and caplets.

The most frequently reported SAEs included cholestatic hepatitis and pancreatitis. Other common SAEs (≥ 2 to < 5) included nausea, diarrhea, fever, headache, interstitial nephritis, acute myocardial infarction, anaphylactic reaction, renal insufficiency, and Steven-Johnson syndrome (in descending order).

Table 23: SAEs with Dr. Falk Pharma Mesalamine Formulations February 2008

MedDRA System/Order Class	Total SAEs	Total Patients
Blood and Lymphatic System Disorders	6	6
Cardiac Disorders	6	5
Congenital Familial, and Genetic Disorders	1	1
Ear and Labyrinth Disorders	0	0
Eye Disorders	0	0
Gastrointestinal Disorders	14	13
General Disorders and Administrative Site Conditions	12	11
Hepatobiliary Disorders	8	8
Immune System Disorders	3	3
Infections and Infestations	2	2
Injury, Poisoning, and Procedural Complications	1	1
Investigations	2	1
Metabolism and Nutrition Disorders	1	1
Musculoskeletal and Connective Tissue Disorders	5	5
Neoplasms Benign, Malignant & Unspecified	0	0
Nervous System Disorders	4	3
Renal and Urinary Disorders	6	6
Reproductive System and Breast Disorders	1	1
Respiratory, thoracic, and Mediastinal Disorders	8	7
Skin and Subcutaneous tissue Disorders	6	6
Vascular Disorders	0	0

Source: 120 Day Safety Update, Module 5.3.5.3.2, Section 4.11.2.1, p. 144

Along with NDA 22,301 the Applicant submitted a safety data review that included information for 5-ASA products in scientific literature, commercial marketing experiences, and unpublished scientific papers. The Agency requested this information in accordance with 21 CFR 314.50 (d)(5)(iv). The submitted information was reviewed and no new safety signal was identified.

Current mesalamine labeling identifies pericarditis as a rare possible adverse event. The Agency's Office of Surveillance and Epidemiology, Division of Adverse Event Analysis (DAEA) conducted a search of the Adverse Event Reporting System (AERS) and the literature to identify cases of pericardial effusion in which pericarditis was *not* reported. The search found 18 cases of pericardial effusion in which pericarditis was not concomitantly reported. There were no deaths in this case series. In a February 2008 report, DAEA recommended that mesalamine labeling be updated to include pericardial effusion in the post-marketing Adverse Events section. There were no new cases of pericardial effusion reported during the primary studies submitted with this NDA.

7.2.2.3 Literature

This review does not contain a significant review of the scientific literature on either mesalamine or UC. Where literature has been used, references have been cited.

7.2.3 Adequacy of Overall Clinical Experience

The design of the pivotal studies and safety monitoring were acceptable. The database is sufficiently large to allow for adequate assessment of the baseline safety profile of eMG. Rare events (in less than 1/1000) patients may not have been detected. Additionally, the length of exposure to eMG does not permit the adequate assessment of the rate and risk of events that may need long exposures to develop.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Agency did not request and this application did not include any new animal studies.

7.2.5 Adequacy of Routine Clinical Testing

The protocol defined clinical testing and safety assessments appear adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see the clinical pharmacology review by Dr. Insook Kim.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The studies were adequately designed to allow for safety analyses. The submitted studies also adequately monitored for possible renal, pancreatic, and hepatic adverse events—events known to be associated with 5-ASA. The studies did not reveal any new safety signals. The three key studies (MPUC3003, MPUC3004, and MPUC3005) showed 1.5 g eMG to be relatively safe and well tolerated.

The submitted studies did not contain TQT studies.

7.2.8 Assessment of Quality and Completeness of Data

The primary source data provided was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The AE analyses in the 120-Day safety update from an ongoing open-label, long-term safety study (MPUC3005) and the original integrated summary of clinical safety (12/31/2008) show an overall similarity. The occurrence of AEs in the six month studies and the open-label extension studies was relatively low. Most AEs were in the GI SOC and there were no deaths in any of the studies. Laboratory test and vital sign results were unremarkable.

The 120-Day Safety Update also included the full study report for SAG-27. This study was not fully integrated into the update until a later submission received by the Agency on 24 July 2008. The safety information from SAG-27 was similar to the information from the three key studies and the study did not provide evidence of any new safety signals.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Overall, eMG appears to have a safety profile comparable to other mesalamine products.

In the RCT studies, SAES were more common in the placebo group (2.2%) than in the eMG group (1.1%). In the All eMG population, 5% of patients experienced an SAE. Most of these SAEs were associated with the gastrointestinal system or were infectious in nature.

Most TEAEs in both the RCT and All eMG populations were mild or moderate in intensity.

Withdrawals due to TEAEs were more common in the placebo group (17%) than in the eMG group (11%) in the RCT population. In the All eMG population, 12% of patients experienced at least one TEAE. Most of TEAEs leading to withdrawal were in the gastrointestinal system with most of those being flare of ulcerative colitis.

Overall incidence of TEAEs seen with eMG therapy (59%) was lower than that seen with placebo therapy (64%) in the RCT population. For patients in the All eMG population, the overall incidence of TEAEs was 70%. The most common TEAEs reported in the RCT population (>3% in either group) and occurring at a rate greater than placebo were headache, diarrhea, upper abdominal pain, nausea, nasopharyngitis, influenza, and sinusitis. Because of the difficulty in differentiating influenza from influenza-like illness in a clinical setting, these preferred terms were combined.

The most common adverse events previously associated with mesalamine products in patients with UC are the same adverse events most commonly associated with this new mesalamine preparation. These TEAEs include headache, UC symptoms (e.g. diarrhea, abdominal pain, nausea/vomiting), and symptoms common to the population at large (e.g. sinusitis, nasopharyngitis).

Previous mesalamine preparations have been associated with hepatic, pancreatic, and renal AEs. In the All eMG population, 6.8 % of patients developed a TEAE related to these organ systems. Given the results of a recent AERS database review, the labeling for eMG should include a hepatic failure warning especially for patients with previous liver disease.

Overall, eMG appears to be a relatively safe product when used once daily at a dose of 1.5g.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Across the three studies using the to-be-marketed mesalamine formulation (Studies MPUC3003, 3004, and 3005), 557 patients received eMG at a dose of 1.5 g once daily for a mean duration of exposure of approximately 352 day and a mean cumulative dose of approximately 483 g.

7.4.1.1 Pooled data vs. individual study data

The incidence of TEAEs in pooled data has been reviewed and is summarized in previous sections. Individual study data is summarized in Appendix 10 of this review. The submitted pivotal studies had identical study designs and were carried out in similar patient populations. The only difference between the studies was the number of patients; Study MPUC3004 had approximately 50 fewer patients than Study MPUC3003.

7.4.1.2 Combining data

This review pools studies by simple combination of numerators and denominators and does not employ other pooling procedures.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Only a single dose of study drug (1.5 g once daily) was used in the submitted primary studies (MPUC3003, MPUC3004, and MPUC3005). Therefore, no dose dependence of adverse findings was able to be conducted.

7.4.2.2 Explorations for time dependency for adverse findings

No particular explorations for time dependency of adverse events were conducted.

7.4.2.3 Explorations for drug-demographic interactions

A review of TEAE incidence by demographic subgroup revealed that the incidence of TEAEs was double in the US sub-group as compared to the Russian sub-group. This trend was seen the eMG and placebo treatment groups. It is unclear whether this large difference in incidence of TEAEs occurred reflected a true difference in TEAE incidence. It is possible that there was some difference in the way TEAEs were reported in Russia as compared to the US or cultural differences making it more likely for a person in the US to report an adverse event.

A conclusion about the differences in the incidence of TEAEs between racial group and between age groups is difficult because the numbers of non-white patients and patients ≥ 65 years old were very small. The numbers of male and female patients were about equal. The incidence of TEAEs between these two groups was also very similar with 61.8% of men and 60.0% of women reporting TEAEs.

Table 24: Percentage of Patients with TEAE in RCT Population by Demographic Subgroup

Sub-group	Treatment Group		All Patients
	eMG	Placebo	
White	58.1 %	63.7%	60.0 %
Non-White	76.0 %	64.3 %	78.1 %
Russia	40.4 %	47.9 %	42.9 %
U.S.	81.7 %	80.9 %	81.4 %
Male	58.0 %	68.0 %	61.8 %
Female	60.5 %	58.8 %	60.0 %
<65 years	59.1 %	65.0 %	61.1 %
≥ 65 years	61.5 %	54.5 %	59.0 %

Source: ISS Appendix C, Tables 2.7.4.7.4, Table 2.7.4.7.6, Table 2.7.4.7.2, Table 2.7.4.7.3

7.4.2.4 Explorations for drug-disease interactions

No particular explorations for drug-disease interactions were conducted.

7.4.2.5 Explorations for drug-drug interactions

No clinical studies exploring drug-drug interaction were conducted. *In vitro* studies have shown that eMG does not interfere with the metabolism of drugs using the hepatic CYP enzymes.

7.4.3 Causality Determination

The overall safety data submitted in support of this NDA did not suggest that the use of eMG is associated with any new safety signal. The overall safety profile was as expected according to

the drug class. Liver failure cases associated with mesalamine use found during a recent query of the AERS database warrant a hepatic impairment warning particularly in patients with pre-existing liver disease.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dosage for the maintenance of remission of ulcerative colitis in adults is four 0.375 g capsules to be taken once daily for a total daily dose of 1.5 g. The drug can be taken without regard to the timing of food intake as evidenced by submitted PK studies.

It is recommended that all patients have an evaluation of renal function prior to the initiation of eMG and periodically while on therapy. Caution should be exercised when using eMG in patients with known renal dysfunction or history of renal disease.

Reports from post-marketing reporting systems for mesalamine suggest a higher incidence of blood dyscrasias, i.e., agranulocytosis, neutropenia, pancytopenia, in patients who were 65 years or older. Caution should be taken to closely monitor blood cell counts during mesalmine therapy in this population.

Post-marketing reporting systems also suggest a possible association between mesalamine use and hepatic impairment particularly in patients with liver disease. Therefore, caution should be taken when prescribing eMG to this population.

8.2 Drug-Drug Interactions

There are no known drug interactions with mesalamine, and no drug-drug interaction studies were performed in this clinical development program other than the in vitro studies of the CYP enzymes previously discussed. See section 1.3.5.

8.3 Special Populations

The safety and effectiveness of eMG in pediatric patients has not been established; however, the Applicant has planned pediatric studies. The submitted studies excluded patients with known renal or hepatic impairment. Pregnant women and nursing mothers were also excluded from the submitted clinical trials. Further, the number of non-white patients and patients ≥ 65 years old was insufficient to make a determination of whether efficacy or safety differences exist in these sub-groups of the population.

Included in the labeling is a hepatic impairment warning which cautions prescribers when using eMG in patients with liver disease. No liver, renal, or pancreatic studies were conducted as part

of this Application despite the known association with mesalamine and these organ systems seen in post-marketing reports.

8.4 Pediatrics

Safety and efficacy have not been established in pediatric patients.

Partial waiver was granted for patients age 0 to less than 5 years old. A deferral for pediatric studies in patients age 5 to 17 years old will be granted with the approval of this drug with final study reports to be submitted by June 1, 2013. The Applicant has agreed that the submitted studies will investigate the safety, effectiveness, and pharmacokinetic characteristics of at least two doses of granulated mesalamine.

8.5 Advisory Committee Meeting

No Advisory Committee meeting was held for this new drug application.

8.6 Literature Review

A brief review of the scientific literature was conducted with regard to current scoring system currently used in ulcerative colitis.

8.7 Postmarketing Risk Management Plan

For this NDA, there are no applicable issues related to risk management.

8.8 Other Relevant Materials

Review of this application included consultation from the Office of Surveillance and Epidemiology (OSE) Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Scientific Investigations (DSI).

The Division of Gastroenterology products requested a review of the Adverse Events Reporting System (AERS) to identify cases of liver failure associated with the use of mesalamine. Eight cases were found. A full safety review of AERS and the literature for evidence that the use of mesalamine is associated with hepatic impairment is on-going and will not be completed before the end of this review cycle.

During this review cycle, the Division of Adverse Event Analysis 1 (DAEA1) also completed two reviews related to mesalamines.

The Division of Gastroenterology Products requested Ann Corken Mackey, RPh, MPH, from DAEA1, to conduct a search of the AERS database and the literature for evidence that

pericardial effusion *not* associated with pericarditis is associated with mesalamine use. The safety evaluator concluded that there was sufficient evidence that pericardial effusion is associated with mesalamine use. She further recommended that pericardial effusion be included in mesalmine class labeling as a possible adverse reaction.

The Division of Gastroenterology Products also requested the safety evaluator to conduct a search for evidence that hypersensitivity and renal impairment associated with mesalamine use are dose-related. The safety evaluator concluded that the AERS database did not provide enough information in each report to determine if an AE was due to an increase/decrease in mesalmine dosing. Based on reports in the medical literature, the safety evaluator concluded that the risk of mesalamine-induced renal impairment does not appear to be dose-related.

Both safety reviews (February 25, 2008 and March 19, 2008) are filed under other NDAs 19-651, 20-049, 22-000, 21-252, 19-618, and 19-919 in DFS.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

Overall, this reviewer concludes that Studies MPUC3003 and MPUC3004 adequately demonstrate the efficacy of eMG over placebo and recommends that TRADENAME 0.375g tablets given once daily in the morning be approved for the maintenance of remission in adult patients with ulcerative colitis with revisions to the proposed labeling.

The two pivotal studies MPUC3003 and MPUC3004 demonstrate eMG to be efficacious in the maintenance of remission of ulcerative colitis as compared with placebo. Study MPUC3003, the larger of the two studies, provided a more statistically significant difference in rates of treatment success (maintenance of remission) between the eMG (68%) and placebo (51%). The results for Study MPUC3003 were highly statistically significant, $p < 0.001$.

Enrollment in Study MPUC3004 was terminated at 250 patients due to a late stage protocol amendment. In this study, the success (maintenance of remission) rate in the eMG group (71%) was better than placebo (59%), but just barely reached the level of statistical significance, $p = 0.046$ when counting all premature discontinuation as relapses, the *a priori* definition of relapse. However, the results were more statistically significant, $p = 0.029$, when using the revised definition of relapse which counts only those patients who withdrew for UC-related TEAEs as relapses, the revised definition of relapse.

The pooled results of both studies show that the rate of treatment success in the eMG treatment groups did not vary by gender (approximately 80% treatment success in both males and females). However there was a higher placebo effect rate in males than in females (68.3% males, 56.7% females). Efficacy results between eMG and placebo groups did vary somewhat by country. For patients in the United States (difference=22.9%, $p < 0.001$), the evidence was

stronger for greater efficacy of eMG compared with placebo than for patients in Russia (difference=10.2%, p=0.042). There were insufficient numbers of non-White patients and patients age 65 years and older to make conclusions regarding the efficacy of eMG in these groups. However, this review does not believe additional studies are warranted given the wide post-marketing experience of other mesalamine products.

Safety

Across the three primary studies to evaluate the safety of eMG (MPUC3003, MPUC3004, and MPUC3005), 557 patients received TRADENAME 0.375 (1.g/day) for a mean duration of exposure of 352 days (SD 231.3 days) and a mean cumulative eMG dose of 482.9 g (SD 329.1). A total of 354 patients were exposed to eMG 1.5 once daily for more than 6 months, while 250 patients were exposed for more than one year.

SAEs occurred in 4.7% of all patients exposed to eMG. A large percentage of these SAEs involved the gastrointestinal system. There were no SAEs related to the hepatic or renal systems. The majority of AEs were mild or moderate in severity with 10.1% of AEs judged to be severe.

Withdrawals due to AEs occurred in 11.8% of eMG patients. The majority of adverse discontinuations occurred as a result of recurrence of ulcerative colitis.

The overall incidence of adverse events seen in patients taking eMG was 68.6%. Recurrence of ulcerative colitis (10.4%) was the most commonly reported AE. The other most commonly reported adverse events reported were headache (13.8%), diarrhea (9.7%), abdominal pain (7.7%), nasopharyngitis (8.8%), and back pain (5.0%).

No evidence of change in renal function was identified based on the studies submitted. In patients receiving eMG, 7 patients (1.3%) experienced a decrease in renal creatinine clearance. However, only 1 (0.18%) of these patients had a decrease to ≤ 50 mL/min (a level of potential clinical significance). Similarly, the number of patients with potentially clinically significant changes in liver enzymes was low—ALT (0.90%), AST (0.72%), alkaline phosphatase (0.36%), total bilirubin (1.4%).

A review of the Adverse Event Reporting System by the Office of Surveillance and Epidemiology (OSE) found 13 cases of liver failure associated with mesalamine use. Some of these had a past medical history of hepatic impairment. Some of these cases ended in death. This reviewer feels that these hepatic events are serious enough to require the inclusion of a hepatic warning on mesalamine labeling.

The data are adequate for safety labeling as revised based on recommendations provided in Section 9.4.

9.2 Recommendation on Regulatory Action

This reviewer recommends that 0.375 g eMG tablets given at a dose of 1.5 g once daily be approved for the treatment of adults patients with ulcerative colitis for the maintenance of remission. The information in this submission provides substantial evidence to support the proposed indication.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There is no special applicable activity related to risk management for this New Drug Application.

9.3.2 Required Phase 4 Commitments

Safety and efficacy have not been established in pediatric patients. Partial waiver was granted for patients less than five years of age. The Applicant has agreed to study the safety, effectiveness and pharmacokinetic parameters of at least two dose regimens of mesalamine granules in patients ages 5 to 17 years old.

9.3.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

9.4 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:

Section 2 Dosage and Administration

- ⇒ Direction that eMG should be taken orally once "in the morning" was added as this was the direction given to patients in all submitted studies of eMG.
- ⇒ Instruction that eMG should not be co-administered with antacids was added as the Agency's Labeling and Nomenclature Committee is requesting this of all delayed release formulations. This information was also included in Section 7, Drug Interactions.
- ⇒ Instruction that an evaluation of renal function is recommended before initiating therapy with eMG was added.

Section 5 Warnings and Precautions

⇒ The Hepatic Impairment statement was clarified cautioning the administration of eMG in patients with pre-existing liver disease due to the results of a recent AERS query.

⇒ [redacted]

b(4)

Section 6.1 Adverse Reactions

⇒ It was decided to include only information on eMG, [redacted]

b(4)

⇒ The adverse reactions table [redacted]

b(4)

It was decided that the table should include all treatment-emergent adverse reactions occurring at a rate of at least 3% and at a rate greater than placebo.

⇒ The term influenza in the adverse reactions table was lumped with the term influenza-like illness. This was done to fully appreciate the incidence of the clinically-relevant syndrome of flu as opposed to the specific etiologic agent of the influenza virus.

Section 14.1 Clinical Studies

⇒ It was decided that the primary efficacy results presented would be those calculated using the Applicant's original definition of relapse which included all premature discontinuations as relapses.

9.5 Comments to Applicant

No further comments need to be conveyed to the Applicant.

10 APPENDICES

10.1 STUDY PROTOCOL MPUC3003

10.1.1 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 305 patients from 48 centers participated in this study. There were 42 study sites in the United States and six in Russia. The US sites had an average of 4.1 patients per site for a total of 160 randomized patients. The Russian sites had an average of 24.2 patients randomized per site for a total of 145 randomized patients.

See Appendix 10.6 for a chart of study centers and investigators participating in Study MPUC3003.

Study period

20 December 2004 to 26 April 2007.

Objectives

The primary study objective was to assess the ability of encapsulated mesalamine 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.

10.1.2 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).

10.1.3 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, mesalmine, 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.

10.1.4 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 July 16, 2007, after the completion of Study MPUC3003, but before unblinding of the data. Efficacy results using both this original definition and the revised definition are presented in the Efficacy Results section 10.1.12.2 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.

10.1.5 Secondary Efficacy Endpoints

Secondary efficacy analyses were performed using all randomized patients who received at least one dose of the 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.

10.1.6 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.

10.1.7 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 *C. 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 *Clostridium 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 AÉ 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.

10.1.8 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.

10.1.9 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.

10.1.10 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 July 16, 2007. This date is after study completion. The Amendment was introduced for the following main reasons:

1. To change the definition of relapse, one of the study's primary endpoints, to no longer include patients terminating early for reasons other than lack of efficacy or UC-related AE.
2. To enumerate secondary endpoints allowing hierarchical testing.
3. To change the ITT population from all randomized patients to all randomized patients who received at least one dose of study drug
4. To define major protocol deviations that excluded patient from the PP population
5. To add a sensitivity analysis to the primary efficacy analysis using the PP population
6. To add a modified last observation carried forward procedure for imputing missing values of primary and secondary efficacy endpoints for patients who terminated early.

MO Comment:

The initial definition of relapse included patients who discontinued the study for any reason; not only those who discontinued for lack of efficacy or UC-related AEs. This protocol amendment was made after study completion. The reason for this change in the definition of the primary efficacy endpoint after study completion is unclear. However, the Applicant's submission states

that no planned analyses were changed once the data were unblinded. Therefore, the study results were viewed as valid.

10.1.11 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.

10.1.12 Study Results

10.1.12.1 Demographics and Baseline Disease Characteristics

Overall, the eMG and placebo treatment groups did not vary significantly with regard to demographic characteristics. There were slightly more males (55%) than females in the placebo group and slightly more females (56%) in the eMG treatment group. In both treatment groups, the majority of patients were younger than 65 years of age (89% eMG, 88% placebo). In both treatment groups, the majority of patients were of white race (90% eMG, 89% placebo). Likewise, the number of patients from Russia and the US were similar and nearly evenly distributed across treatment groups. See Demographics Table below.

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 310 weeks (approximately 6 years). In both groups, patients had identical mean time since most recent flare, 26 weeks (six months). The mean baseline Sutherland DAI score was slightly in the placebo group than in eMG group (1.0 vs 0.8). It should be noted that the placebo mean baseline DAI score may have been somewhat inflated by a patient with a baseline DAI score of 11 who was erroneously randomized in the study and whose score was averaged with the others.

Demographics by Treatment Group

Demographic Subgroup	MPUC3003 ITT Population		
	IMG N=209	Placebo N=96	All Patients N=305
Sex (n,%)			
Male	92 (44.0)	53 (55.2)	145 (47.5)
Female	117 (56.0)	43 (44.8)	160 (52.5)
Age (years) (n,%)			
<65	185 (88.5)	84 (87.5)	269 (88.2)
≥65	24 (11.5)	12 (12.5)	36 (11.8)
Mean (SD)	46.9 (13.6)	45.5 (14.4)	46.5 (13.8)
Median (min,max)	47 (18,82)	46 (21,82)	46 (18,82)
Race[^] (n,%)			
AI/AN [*]	4 (1.9)	0 (0.0)	4 (1.3)
Asian	1 (0.5)	0 (0.0)	1 (0.3)
Black/AA ^{**}	19 (9.1)	11 (11.5)	30 (9.8)
White	188 (90.0)	85 (88.5)	273 (89.5)
Ethnicity (n,%)			
Hispanic or Latino	3 (1.4)	0 (0.0)	3 (1.0)
Not Hispanic or Latino	206 (98.6)	96 (100.0)	302 (99.0)
Country (n,%)			
Russia	99 (47.4)	46 (47.9)	145 (47.5)
United States	110 (52.6)	50 (52.1)	160 (52.5)
Weight (lbs) (n,%)			
N	208	96	304
Mean (SD)	168.5 (37.5)	172.4 (35.10)	169.7 (36.7)
Median (min,max)	164.0 (110.0, 337.2)	166.7 (107.9, 273.0)	165.0 (107.8, 337.2)
Height (inches) (n,%)			
N	208	96	304
Mean (SD)	66.5 (3.8)	67.7 (3.5)	66.9 (3.7)
Median (min,max)	66.0 (110.0, 337.2)	67.7 (59.8, 74.8)	66.5 (57.0, 76.4)
Body Mass Index (kg/m²)			
N	208	96	304
Mean (SD)	26.8 (5.53)	26.4 (4.8)	26.7 (5.3)
Median (min, max)	25.2 (17.3, 47.9)	25.8 (16.9, 39.2)	25.5 (16.9, 47.9)

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

Baseline Disease Characteristics by Treatment Group

Study MPUC3003			
Category	eMG N=209	Placebo N=96	All Patients N=305
Duration of disease (weeks)			
Mean (SD)	310.0 (321.9)	312.5 (310.7)	310.8 (217.9)
Median (min,max)	190.0 (11.0, 1785.0)	216.0 (6.0, 1466.0)	199.0 (6.0, 1785.0)
Time since most recent flare (weeks)			
N	207	96	303
Mean (SD)	25.6 (13.0)	25.6 (13.0)	25.6 (13.0)
Median (min,max)	24.0 (4.0, 60.0)	24.0 (6.0, 60.0)	24.0 (4.0, 60.0)
Duration of current remission (weeks)			
N	207	95	302
Mean (SD)	16.8 (11.1)	16.2 (11.0)	16.6 (11.1)
Median (min,max)	13.0 (2.0, 57.0)	13.0 (0.0, 48.0)	13.0 (0.0, 57.0)
Disease severity			
0	85 (40.7)	33 (34.4)	118 (38.7)
≥1	124 (59.3)	63 (65.6)	187 (61.3)
Normal Number of Stools Daily			
Mean (SD)	1.8 (1.0)	1.8 (0.9)	1.8 (1.0)
Median (min,max)	2 (1,7)	2 (0,5)	2 (0,7)
Revised Sutherland DAI total score			
Mean (SD)	0.8 (0.8)	1.0 (1.3)	0.8 (1.0)
Median (min, max)	1 (0,3)	1 (0,11)*	1 (0,11)*
Revised Sutherland DAI Component Scores			
Mean (SD)			
Stool Frequency	0.1 (0.2)	0.1 (0.4)	0.1 (0.3)
Rectal Bleeding	0.0 (0.0)	0.0 (0.2)	0.0 (0.1)
Mucosal Appearance	0.5 (0.5)	0.7 (0.5)	0.6 (0.5)
Physician's rating of disease severity	0.2 (0.4)	0.2 (0.5)	0.2 (0.4)
Baseline Renal Function (n,%) (Cockcroft-Gault formula)			
Normal (≥90 mL/min)	136 (65.1)	69 (71.9)	205 (67.2)
Mild (60-<90 mL/min)	70 (33.5)	26 (27.1)	96 (31.5)
Moderate (30-<60 mL/min)	1 (0.5)	1 (1.0)	2 (0.7)
Severe (<30 mL/min)	0 (0.0)	0 (0.0)	0 (0.0)

* Patient 618-06 with total DAI score of 11, a rectal bleeding score of 2, and a mucosal appearance score of 3 at baseline was mistakenly randomized by the study site.

Source: Sponsor Table 11, MPUC3003 Clinical Study Report

A larger percentage of eMG patients completed Study MPUC3003 as compared with the placebo group (68.9% versus 51.0%). Reasons for study discontinuation are presented in the Patient Disposition table below.

Patient Disposition, Study MPUC3003

	RCT Population		
	eMG N=209 (%)	Placebo N=96 (%)	Total N=305 (%)
Safety population	206	94	300
Completed Study	144 (68.9)	49 (51.0)	193 (63.3)
Discontinued Study	65 (31.1)	47 (49.0)	112 (36.7)
AE	30 (14.4)	24 (25.0)	54 (17.7)
Lost to follow-up	3 (1.4)	2 (2.1)	5 (1.6)
Lack of efficacy	20 (9.6)	16 (16.7)	36 (11.8)
Patient request	8 (3.8)	2 (2.1)	10 (3.3)
Did not meet entry criteria	0	2 (2.1)	2 (0.7)
Use of excluded medications	2 (1.0)	0	2 (0.7)
Protocol violation	1 (0.5)	1 (1.0)	2 (0.7)
Pregnancy	1 (0.5)	0	1 (0.3)
Noncompliance	0	0	0
Continued into MPUC3005			

Source: Table 14.1.1 MPUC3003 Clinical Study Report

Compliance

Treatment compliance was comparable between treatment groups. The mean calculated study compliance was 96.2% in the eMG group and 96.7% in the placebo group.

10.1.12.2 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 July 16, 2007, after the completion of Study MPUC3003, but before unblinding 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, 78.9% of patients in the eMG group and 58.3% 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 remain highly statistically significant.

MPUC3003 Primary Endpoint Efficacy Results

Relapse-free at Month 6/EOS					
Study Population	Definition of Relapse	eMG	Placebo	95% CI for Difference	p-value
MPUC3003	Original	143/209=68.4%	49/96=51.0%	17% (5.5%, 29.2%)	<0.001
ITT	Revised	165/209=78.9%	49/96=51.0%	21% (9.5%, 32%)	<0.001
PP	Revised	157/200=78.5%	55/93=59.1%		<0.001

Source: Statistical Reviewer's Calculations

Secondary Endpoints

The statistical analyses of the secondary endpoints were performed in a hierarchical fashion. Placebo and eMG results were compared using the CMH test controlling for country. According to the Applicant's statistical analysis plan, if statistical significance was not achieved for any secondary endpoint, all subsequent endpoints would be considered exploratory (and not inferential) in nature. In study MPUC3003, only the results from the first endpoint, number and proportion of patients in each level of change from baseline in rectal bleeding score, provides results that can be treated as inferential. All other end points must be considered exploratory in nature.

Except for the second secondary endpoint, all other secondary endpoints reach nominal statistical significance and provide additional support for the primary endpoint. The second secondary endpoint involving mucosal appearance did not reach the level of statistical significance. This result suggests that mucosal appearance alone does not predict the presence of relapse. However, due to its place as second in the hierarchy, the information from all other endpoints must be viewed as exploratory and not inferential.

Secondary endpoint six, Month 6 Cumulative relapse-free probability, has the smallest 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.

Secondary Endpoint Efficacy Analyses

Study 3003	Mesalamine	Placebo	P-Value
Change from Baseline in Rectal Bleeding			0.01
-1	0 (0%)	1 (1%)	
0	170 (81%)	64 (67%)	
1	22 (10.5%)	11 (11%)	
2	16 (8%)	19 (20%)	
3	1 (0.5%)	1 (1%)	
Change from Baseline in Mucosal Appearance			0.41*
-1	32 (15%)	13 (13.5%)	
0	129 (62%)	51 (53%)	
1	32 (15%)	20 (21%)	
2	14 (7%)	11 (11%)	
3	2 (1%)	1 (1%)	
Change from Baseline in Physician's Rating of Disease Severity			0.005
-2	1 (1%)	0 (0%)	
-1	16 (8%)	6 (6%)	
0	146 (70%)	55 (57%)	
1	35 (17%)	17 (18%)	
2	10 (5%)	18 (19%)	
3	1 (1%)	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 (%)	147 (70%) 62 (30%)	51 (53%) 45 (47%)	0.003
Mean change from baseline in the Sutherland DAI at Month 6/EOS Mean (SD)	0.9 (2%)	2.0 (3%)	0.001
Relapse-free duration Month 6 Cumulative relapse-free probability (SE)	0.77 (0%)	0.56 (1%)	<0.001
Stool Frequency at Month 6/EOS Patients in each level of change from baseline Change from Baseline in Mucosal Appearance			0.005
-1	4 (2%)	1 (1%)	
0	167 (80%)	64 (67%)	
1	20 (10%)	11 (12%)	
2	8 (4%)	11 (12%)	
3	10 (5%)	9 (9%)	

Source: Table 13, MPUC3003 Clinical Study Report
*From Statistical Reviewer's Calculation, See Statistical Review

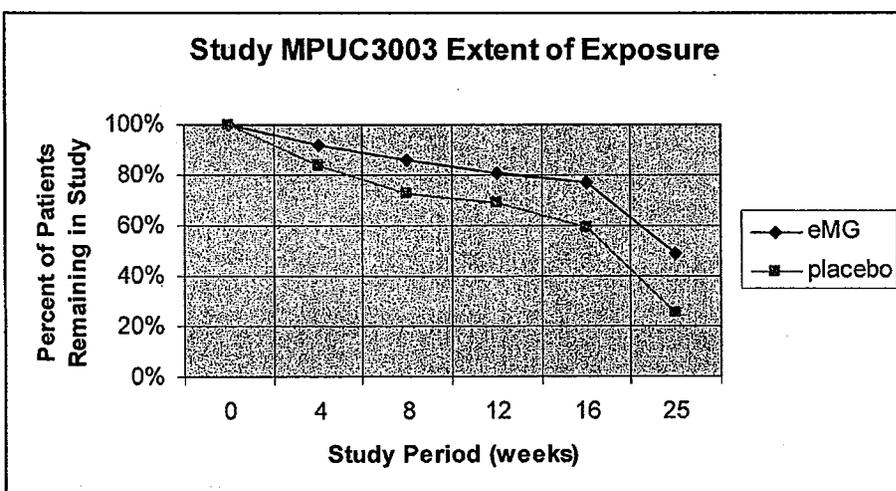
10.1.12.3 Safety Analyses

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 MPUC3003 included 300 patients (206 eMG, 94 placebo).

Extent of exposure

As expected, study attrition occurred in both treatment groups. Approximately half (49%) of eMG patients remained in the study for greater than 25 weeks, compared with only 26% of placebo patients. In both groups, the majority of patients remained in the study for greater than 16 weeks (77% eMG, 60% placebo). Study withdrawal during Week 1 through Week 4 occurred in 8% of eMG patients and 16% of placebo patients.

Clinical Reviewer's Comment: The difference in extent of exposure between active drug and placebo patients is expected if the investigational drug product is efficacious. These results support the efficacy conclusions for eMG.



Concomitant Medications

Overall, 48.5% of eMG patients, and 37.2% of placebo patients used concomitant medications during Study MPUC3003. Slightly less than half of these medications were used for GI symptoms. In the Table below, the alimentary tract and metabolism medication groups were combined. A review of all 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 and is included in this group. 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 MPUC3003		
Medication Class Medication Name	eMG N=206 (%)	Placebo N=96 (%)
Alimentary Tract & Metabolism	41 (19.9)	15 (16.0)
Bisacodyl	5 (2.4)	2 (2.1)
Fortrans	3 (1.5)	2 (2.1)
Magnesium citrate	0 (0.0)	2 (2.1)
Magnesium hydroxide	0 (0.0)	2 (2.1)
Mesalazine	0 (0.0)	2 (2.1)
Anti-infectives for Systemic Use	34 (16.5)	10 (10.6)
Levofloxacin	7 (3.4)	1 (1.1)
Amoxicillin	7 (3.4)	0 (0.0)
Influenza vaccines	5 (2.4)	2 (2.1)
Cefalexin	1 (0.5)	2 (2.1)
Pneumococcal vaccine	0 (0.0)	2 (2.1)
Blood and Blood Forming Organs	2 (1.0)	4 (4.3)
Ferrous sulfate	0 (0.0)	2 (2.1)
Nervous System & Pain Medications	64 (31.1)	22 (23.4)
Ibuprofen	11 (5.3)	3 (3.2)
Paracetamol	23 (11.2)	8 (8.5)
Vicodin	5 (2.4)	2 (2.1)
Propacet	1 (0.5)	2 (2.1)
Sumatriptan	0 (0.0)	2 (2.1)
Respiratory & Allergy Medications	26 (12.6)	5 (5.3)
Diphenhydramine hydrochloride	2 (1.0)	4 (4.3)

*Note: A patient with more than one medication by a given medication name is counted only once for that medication name.
Source: Summary Table 14.3.6.3, and Table 32 MPUC3003 Clinical Study Report p. 114*

A similar number of patients in both the eMG and placebo treatment groups reported taking GI medications during the study (19.9% eMG, 16.6% placebo). Most of the GI-related concomitant medications are for indications that may or may not be related to UC. The frequency of nervous system and pain medicine use is greater in the eMG group (31.1%) compared to the placebo group (23.4%). This could be expected given that headache is known side effect of mesalmine use.

Adverse Events

In study MPUC3003, 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

MPUC3003			
Category	eMG N=206 (%)	Placebo N=94 (%)	Total N=300
Patients Experiencing any TEAE	132 (64.1)	60 (63.8)	192 (64.0)
Patients Experiencing any Serious TEAE	2 (1.0)	2 (2.1)	4 (1.3)
TEAEs by Severity			
Mild	53 (25.7)	17 (18.1)	70 (23.3)
Moderate	62 (30.1)	39 (41.5)	101 (33.7)
Severe	17 (8.3)	4 (4.3)	21 (7.0)
Patients Experiencing TEAE possibly related to study drug, per Investigator	28 (13.6)	15 (16.0)	43 (14.3)
TEAEs Resulting in Study Discontinuation	31 (15.0)	26 (27.7)	57 (19.0)
Deaths	0	0	0

Source: Summary Table 14.3.1.1, Section 14.3.1

Serious Adverse Events

Serious adverse events occurred in 1% of eMG patients and 2% of placebo patients. All serious adverse events led to study discontinuation except for the SAE of opportunistic infection. Below are brief narratives of the four patients experiencing an SAE in Study MPUC3003.

eMG Patient 505-02

The patient, a 29 year old African American female, was in remission for two months before entry into the study and had a baseline DAI score of 0. The patient experienced bloody stools and an unscheduled sigmoidoscopy during Study Visit 4 revealed a diffuse area of erythematous, eroded, and granular mucosa in the rectum and sigmoid colon. At that time, the patient's total DAI score was 5 (SF=2, RB=0, MA=1, PRDA=2) and the patient was withdrawn from the study. The patient received study drug for 78 days prior to study discontinuation. The patient was treated with balsalazide for the UC flare. This event was considered related to the study drug.

Six days after discontinuing the study drug, the patient returned to the clinic reporting vomiting and diarrhea (of 3 days duration) and was admitted to the hospital with worsening UC of moderate intensity and treated with prednisone and balsalazide. This event represents the reported SAE and it was felt to be unrelated to the study drug by the investigator.

eMG Patient 562-18

The patient, a 71 year old Caucasian female, was in remission for nine months before entry into the study and had a baseline DAI score of 0. The patient had a history of GERD and distal esophagitis and experienced heartburn of moderate intensity and was treated with ranitidine and omeprazole. Eventually, the patient had to be hospitalized and on endoscopy was found to have an incomplete closure of the esophagogastric orifices and a hiatal hernia. Final diagnoses included chronic gastritis, erosive duodenitis, and questionable Barrett's syndrome.

The patient continued study medication while in the hospital until a rectoscopic exam revealed erosions and edema with hyperemic mucous cover with a poor vascular pattern and contact

bleeding. The patient's total DAI score was 5 (RB=1, MA=2, SF=1, PRDA=1) and the patient was withdrawn from the study. The patient received study medication for 148 days. This SAE was believed to be unrelated to the study drug.

Placebo patient 208-08

The patient, a 29 year old male, was in remission for 9 months before entry into the study and had a baseline DAI score of 2. After 22 weeks on the study drug, the patient was hospitalized due to an opportunistic infection secondary to pre-existing lymphedema of the right arm. The patient was treated with IV antibiotics and pain medication. The patient remained on the study drug throughout the hospitalization.

Placebo patient 561-06

The patient, a 35-year-old Caucasian male, was in remission for 1 month before entry into the study and had a baseline DAI score of 1. On Study Day 125, the patient was admitted to the hospital with an exacerbation of UC. Sigmoidoscopy revealed erosive proctitis which was treated with prednisolone, sulfasalazine, sulpiride, and folic acid. The patient was discharged 13 days later and remained on the study drug throughout the hospitalization. The patient completed the study and during the End of Study (Visit 4) sigmoidoscopy, the patient was found to have a total DAI score of 8 (SF=2, RB=2, MA=2, PRDA=2). The Investigator believed this event to be possibly related to the study drug.

Patients Reporting Serious Adverse Events

MPUC3003			
SAEs	eMG N=204 (%)	Placebo N=96 (%)	eMG N=300 (%)
All SAEs	2 (1.0)	2 (2.1)	4 (1.3)
Gastrointestinal Disorders			
Colitis Ulcerative	1 (0.5)	1 (1.0)	2 (0.7)
Esophagitis	1 (0.5)		
Infections and Infestations			
Opportunistic Infection		1 (1.0)	1 (0.4)

Study Discontinuations due to Treatment Emergent Adverse Events (TEAEs)

TEAEs leading to study discontinuation were more frequent in the placebo group than in the eMG group. In total, 19% of patients in Study MPUC3003 withdrew due to TEAEs. The most common SOC of TEAEs leading to withdrawal was gastrointestinal disorders. And the most common preferred term of TEAEs leading to withdrawal was ulcerative colitis.

Patients with TEAEs Leading to Study Withdrawal

Study MPUC3003			
MedDRA System Organ Class (Preferred Terms)	eMG N=206 (%)	Placebo N=94 (%)	Total N=300 (%)
Total Number of Patients with TEAE leading to Study Withdrawal	31 (15.0)	26 (27.7)	57 (19.0)
Gastrointestinal Disorders	24 (11.7)	24 (25.5)	48 (16.0)
Colitis Ulcerative	20 (9.7)	23 (24.5)	43 (14.3)
Abnormal feces	0	1 (1.1)	1 (0.3)
Diarrhea	1 (0.5)	0	1 (0.3)
Hematochezia	1 (0.5)	0	1 (0.3)
Hemorrhoids	1 (0.5)	0	1 (0.3)
Nausea	1 (0.5)	0	1 (0.3)
Investigations	3 (1.5)	2 (2.1)	5 (1.7)
Alanine aminotransferase increased	0	2 (2.1)	2 (0.7)
Creatinine renal clearance decreased	1 (0.5)	0	1 (0.3)
Aspartate aminotransferase increased	1 (0.5)	0	1 (0.3)
Blood alkaline phosphatase increased	1 (0.5)	0	1 (0.3)
Musculoskeletal And Connective Tissue Disorders	1 (0.5)	0	1 (0.3)
Muscle cramp	1 (0.5)	0	1 (0.3)
Nervous System Disorders	1 (0.5)	0	1 (0.3)
Headache	1 (0.5)	0	1 (0.3)
Reproductive system and breast disorders	1 (0.5)	0	1 (0.3)
Ovarian cyst	1 (0.5)	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.5)	0	1 (0.3)
Dyspnea	1 (0.5)	0	1 (0.3)

Source: Summary Table

14.3.1.9, Section 14.3.1, MPUC3003 Clinical Study Report

Although headache is a common adverse reaction associated with mesalamine use, in this study the incidence of study withdrawal due to headache was quite low with less than 1% of eMG patients withdrawing due to headache and no placebo patients withdrawing due to headache. This may suggest that headache is a tolerable adverse reaction that does not in most cases prevent patients from taking mesalmine medications.

Laboratory abnormalities resulting in premature study withdrawal in the eMG treatment group included an alkaline phosphatase elevation to 297 U/L (normal range 40-135 U/L), an AST level elevated to 83 U/L (normal range 0-47), and creatinine clearance decreased to 52.8 mL/min (normal range 80-120 mL/min). The magnitude of the liver enzyme elevations was mild and there is likely little clinical significance. For brief patient narratives of all eMG patients with laboratory abnormalities leading to study discontinuation, see Section 7.1.3.2.

Common Adverse Events

The proportion of patients experiencing a TEAE was 64% in both treatment groups. The most common MedDRA System Order Class (SOC) for TEAEs was Gastrointestinal Disorders. The proportion of patients experiencing GI TEAEs was higher in the placebo group (48%) than in the eMG group (38%). The most common MedDRA Preferred Term (PT) for TEAEs was ulcerative colitis. In the placebo group, 27% of patients reported UC as a TEAE compared with only 11% in the eMG group. After UC, headache was the most commonly reported PT. Headache was reported more frequently in the eMG group (11%) than in the placebo group (7%). This is expected given that headache is a known adverse reaction associated with the use of mesalamine products. See Table below.

TEAEs Reported by $\geq 2\%$ of Patients in Any Treatment Group, MPUC3003

MedDRA System Organ Class Preferred Term	EMC N=206 (%)	Placebo N=94 (%)	Total N=300 (%)
Total Number of Patients with a TEAE	132 (64.1)	60 (63.8)	192 (64.0)
Gastrointestinal Disorders	78 (37.9)	45 (47.9)	123 (41.0)
Colitis Ulcerative	23 (11.2)	25 (26.6)	48 (16.0)
Diarrhea	18 (8.7)	7 (7.4)	25 (8.3)
Abdominal Pain	15 (7.3)	6 (6.4)	21 (7.0)
Constipation	7 (3.4)	5 (5.3)	12 (4.0)
Hematochezia	11 (5.3)	6 (6.4)	17 (5.7)
Abdominal Pain Upper	8 (3.9)	3 (3.2)	11 (3.7)
Flatulence	6 (2.9)	5 (5.3)	11 (3.7)
Abnormal Feces	7 (3.4)	2 (2.1)	9 (3.0)
Frequent Bowel Movements	5 (2.4)	3 (3.2)	8 (2.7)
Hemorrhoids	4 (1.9)	4 (4.3)	8 (2.7)
Loose stools	4 (1.9)	4 (4.3)	8 (2.7)
Nausea	7 (3.4)	1 (1.1)	8 (2.7)
Dyspepsia	5 (2.4)	1 (1.1)	6 (2.0)
Rectal hemorrhage	2 (1.0)	4 (4.3)	6 (2.0)
Abdominal tenderness	1 (0.5)	2 (2.1)	3 (1.0)
Hemorrhoidal hemorrhage	1 (0.5)	2 (2.1)	3 (1.0)
Abdominal discomfort	0	2 (2.1)	2 (0.7)
Dry mouth	0	2 (2.1)	2 (0.7)
General Disorders and Administration Site Conditions	12 (5.8)	3 (3.2)	15 (5.0)
Fatigue	2 (1.0)	3 (3.2)	5 (1.7)
Pyrexia	4 (1.9)	0	4 (1.3)
Infections and Infestations	50 (24.3)	15 (16.0)	65 (21.7)
Influenza	8 (3.9)	5 (5.3)	13 (4.3)
Nasopharyngitis	10 (4.9)	3 (3.2)	13 (4.3)
Sinusitis	6 (2.9)	3 (3.2)	9 (3.0)
Respiratory Tract Infection Vial	5 (2.4)	2 (2.1)	7 (2.3)
Urinary Tract Infection	5 (2.4)	1 (1.1)	6 (2.0)
Tooth abscess	0	2 (2.1)	2 (0.7)
Investigations	18 (8.7)	11 (11.7)	29 (9.7)
Aspartate aminotransferase increased	1 (0.5)	4 (4.3)	5 (1.7)
Alanine aminotransferase increased	0	4 (4.3)	4 (1.3)
Blood alkaline phosphatase increased	1 (0.5)	2 (2.1)	3 (1.0)
Musculoskeletal And Connective Tissue Disorders	17 (8.3)	9 (9.6)	26 (8.7)
Arthralgia	4 (1.9)	5 (5.3)	9 (3.0)
Back pain	6 (2.9)	2 (2.1)	8 (2.7)
Nervous System Disorders	27 (13.1)	9 (9.6)	36 (12.0)
Headache	23 (11.2)	7 (7.4)	30 (10.0)
Psychiatric Disorders	7 (3.4)	6 (6.4)	13 (4.3)
Insomnia	5 (2.4)	6 (6.4)	11 (3.7)
Respiratory, Thoracic and Mediastinal Disorders	17 (8.3)	1 (1.1)	18 (6.0)
Nasal congestions	5 (2.4)	0	5 (1.7)
Skin and Subcutaneous Tissue Disorders	12 (5.8)	4 (4.3)	16 (5.3)
Pruritis	1 (0.5)	3 (3.2)	4 (1.3)

Source: Table 13.2.1.4, Section 14.3.1, MPUC3003 Clinical Study Report

Conclusion

Overall, Study MPUC3003 was appropriately designed to evaluate the efficacy and safety of eMG. Calculation of the primary efficacy measure, using both the original and revised definitions of relapse resulted in results that were highly statistically significant ($p < 0.001$) and give confidence that there is a difference in treatment outcomes between the eMG and placebo groups.

Safety findings are consistent with other mesalamine products.