

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-301
Drug Name: Encapsulated Mesalamine Granules, 0.375 g (eMG)
(5-aminosalicylic acid or 5-ASA)
Indication(s): Maintenance of Remission of Ulcerative Colitis
Applicant: Salix Pharmaceuticals
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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on data from two randomized and controlled studies, Encapsulated Mesalamine Granules, 0.375 g (eMG) (5-aminosalicylic acid or 5-ASA) taken once a day for six months appear to be efficacious for maintenance of remission of Ulcerative Colitis, as assessed by relapse-free rate, the primary endpoint. The results from Study MCUP3003 provided clearer evidence of efficacy compared to Study MCUP 3004. Both studies failed to show consistent secondary endpoint efficacy. For Study MCUP3004, the trial completed at approximately the same time the protocol was amended to reduce the sample size; thus interpretation of even the primary result is problematic, and, at best, that study should be considered as showing marginal efficacy in support of the first trial.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted results from two, Phase 3, double-blind, randomized, parallel-group, placebo-controlled, multi-center trials to investigate the efficacy and safety of Encapsulated Mesalamine (5-aminosalicylic acid or 5-ASA), Granules (eMG) for maintenance of remission of Ulcerative Colitis (UC). The studies were conducted in males and non-pregnant females ages 18 years and older, with mildly to moderately active UC who had previously demonstrated remission of UC. Study MPUC3003 enrolled 160 U.S. subjects and 145 in Russia; Study MPUC3004 enrolled 103 in the U.S. and 154 in Russia.

The primary efficacy analysis endpoint was the proportion of subjects who were relapse-free after six months of treatment. 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 (DAI). In addition, subjects who experienced a UC flare or initiated medication used previously to treat UC were also considered treatment failures. Subjects were randomized 2:1 to receive the test product (eMG) or placebo. Secondary endpoints included rectal bleeding score, mucosal appearance score, physicians' rating of disease activity, and individual components of the Sutherland DAI.

1.3 Statistical Issues and Findings

For Study MPUC3003, the primary efficacy comparison shows a highly statistically significant difference between Mesalamine and placebo ($p < .001$). For Study MPUC3004, the primary efficacy results were also statistically significant ($p = .029$).

The sponsor's imputation strategy assigned treatment failures to subjects who terminated the study early but only if the reason for drop-out was related to lack of efficacy or a UC-related adverse event. This approach to handling drop-outs was changed in late-stage protocol amendments after study completion; the original plan was to consider all subjects who terminated early as treatment failures. The results from this more conservative analysis do not change the efficacy conclusions for the first study; however, the efficacy results for Study MPUC3004 are marginal ($p = .046$).

To control for experiment-wise type I error, the sponsor planned a hierarchical testing strategy for the secondary endpoints, although the order of testing was specified in a protocol amendment after completion of studies but prior to unblinding. For Study MPUC3003, only the first secondary endpoint (change from baseline in rectal bleeding score) showed a statistically significant improvement from baseline. None of the secondary endpoints were statistically significant in Study MPUC3004.

The planned sample size for Study MPUC3004 was reduced in a late-stage protocol amendment. A total of 257 patients instead of the planned 300 were analyzed. This could be interpreted as an unplanned or early stopping of the study. Even though the decision appears to have been made prior to breaking the blind, the study completion date precedes the protocol amendment date. A sensitivity analysis shows that if the additional 43 subjects were enrolled and had a 68% treatment success rate for both treatment groups (consistent with the observed placebo rate) then the primary ITT analysis would have failed ($p = .06$). This may suggest that the study was terminated early to avert possible failure of the primary endpoint.

The reviewer performed several subgroup analyses using the combined study data. These results suggest a smaller effect size for the Russian and males subpopulations but can be attributed to higher placebo response rates. Efficacy results are consistent across baseline disease severity as well as time on remission.

2 INTRODUCTION

2.1 Overview

Encapsulated mesalamine (5-aminosalicylic acid or 5-ASA) granule is a capsule oral dosage form of mesalamine developed by Salix Pharmaceuticals, Inc., as a once daily (QD) dosing regimen in the maintenance of remission of ulcerative colitis (UC). The proposed dosage and administration is four 0.375 g eMG capsules (1.5 g/day) administered QD _____ for subjects in remission of UC. Several mesalamine-containing dosage forms have been approved in the United States for use in UC over the last twenty years. However, there is, currently, no marketed mesalamine product in the US with QD dosing for the maintenance or remission of UC.

b(4)

Disease activity in the two trials MPUC3003 and MPUC 3004 was measured using the revised Sutherland DAI. The Sutherland DAI was selected because it represents a historical standard for assessing the symptoms of UC (rectal bleeding, mucosal appearance, physician's rating, and stool frequency). No standard scoring system for measuring UC disease activity has been validated for clinical use. At the request of the agency and to clarify the diagnosis of UC remission, two changes were made to the Sutherland definition of mucosal appearance for protocols MPUC3003 and MPUC 3004 before the studies were started. For these studies, the term "mild friability" was removed from the mucosal appearance score of 1, and the term "moderate friability" was removed from the mucosal appearance score of 2 as defined in Sutherland, et al., 1987. (See end-of-phase 2 meeting minutes dated October 6, 2004.)

The sponsor conducted two similar, Phase 3, double-blind, randomized, parallel-group, placebo-controlled, multi-center trials to investigate the efficacy and safety of Encapsulated Mesalamine

(5-aminosalicylic acid or 5-ASA) Granules (eMG) for the Maintenance of Remission of Ulcerative Colitis for the duration of 6 months (Study MPUC3003 and Study MPUC 3004). Subjects were randomized 2:1 to receive the test product (eMG) or placebo. A total of 305 subjects (209, 68.5% in eMG and 96, 31.5% in placebo) from 45 centers took part in study MPUC3003, and a total of 257 patients (164, 63.8% in eMG and 93, 36.2% in placebo) from 37 sites participated in study MPUC 3004. The primary analysis efficacy endpoint was the proportion of subjects who were relapse-free after 6 months of treatment, where relapse was defined by the revised Sutherland Disease Activity Index as a rectal bleeding score ≥ 1 and a mucosal appearance score ≥ 2 .

To be eligible for these studies, subjects were to have a historically confirmed diagnosis of UC in remission for at least 1 month and not more than 12 months, and a confirmed current remission of UC defined as a rectal bleeding score of 0 and a mucosal appearance score of 0 or 1 using a revised Sutherland Disease Activity Index (DAI). Subjects were also required to have a history of at least one flare with symptoms within the past 1 to 12 months that required therapeutic intervention but not to have taken steroids or immunosuppressive agents within 30 days of screening.

The sponsor also submitted interim safety data from an ongoing open-label extension safety study (MPUC3005) which includes subjects who participated in Study 3003 and 3004 as well as new subjects who did not participate in the pivotal studies. Refer to the Medical Officer's review for the safety assessment.

Table 1: Description of the Efficacy Studies

Study #	Study Description	Dose/Regimen	# of Subjects
MPUC3003	Males and non-pregnant women in remission from UC for at least 1 month and not more than 12 months (US and Russia)	1.5 g eMG or Placebo /QD	Total ITT: 305 eMG: 209 Placebo: 96
MPUC3004	Males and non-pregnant women in remission from UC for at least 1 month and not more than 12 months (US and Russia)	1.5 g eMG or Placebo /QD	Total ITT: 257 eMG: 164 Placebo: 93

In this review, for the sake of brevity, the two studies will be referred to as study 3003 or study 3004.

2.2 Data Sources

This NDA was submitted in CTD (paper) format. However, the datasets were provided electronically and are located at: \\FDSWA150\NONECTD\N22301\N_000\2007-12-21

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design:

The sponsor conducted two, Phase 3, double-blind, randomized, parallel-group, placebo-controlled, multi-center trials to investigate the efficacy and safety of Encapsulated Mesalamine (5-aminosalicylic acid or 5-ASA), Granules (eMG) for the Maintenance of Remission of Ulcerative Colitis (UC) for the duration of 6 months (StudyMPUC3003 and Study MPUC 3004) in males and non-pregnant females ages 18 and older with mildly to moderately active UC. Subjects were to have a confirmed diagnosis of UC in remission for at least 1 month and not more than 12 months, as discussed above.

Subjects were randomized 2:1 to receive the test product, eMG or placebo once daily. A total of 305 subjects (209, 68.5% in eMG and 96, 31.5% in placebo) from 45 centers took part in study MPUC3003 and a total of 257 patients (164, 63.8% in eMG and 93, 36.2% in placebo) from 37 sites participated in study MPUC 3004. Study MPUC3003 enrolled 160 U.S. subjects and 145 in Russia; Study MPUC3004 enrolled 103 (U.S.) and 154 (Russia).

The primary efficacy analysis population is Intent-to-Treat (ITT), which is defined as all subjects who were randomized to the study and had taken at least one dose of the study medication.

Primary Objective:

The primary objective of the pivotal studies was to evaluate the efficacy and safety of eMG compared to placebo in men and non-pregnant women for maintenance of remission from UC as measured by rectal bleeding and endoscopic mucosal appearance after 6 months.

Primary Endpoints:

The primary analysis efficacy endpoint is the proportion of subjects who were relapse-free after six months of treatment. 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 (DAI), shown in Table 2.

In addition, subjects who experienced a UC flare or initiated medication used previously to treat UC were also considered treatment failure.

Table 2: The Revised* Sutherland Disease Activity Index Scores

Stool Frequency	0 = Normal 1 = 1 to 2 stools/day more than normal 2 = 3 to 4 stools/day more than normal 3 = >4 stools/day more than normal
Rectal Bleeding	0 = None 1 = Steaks of blood 2 = Obvious blood 3 = Mostly blood
Mucosal Appearance	0 = Intact mucosa with preserved or distorted 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 Rating of Disease Activity	0 = Normal 1 = Mild 2 = Moderate 3 = Severe
Maximum Score	12

* for protocols 3003 and 3004 the Sutherland DAI was revised to remove the term "mild friability" from the mucosal appearance score of 1 and to remove the term "moderate friability" from the mucosal appearance score of 2.

Secondary Endpoints:

Seven secondary endpoints were defined in the protocol. Protocol amendment 02, dated July 16, 2007 for Study 3003 and amendment 02 dated August 9, 2007 for study 3004, modified and ordered the secondary endpoints for hierarchical testing in order to control for the type I error. It should be noted that these amendments occurred after study enrollment completed but, according to the sponsor, prior to unblinding. The seven secondary efficacy endpoints, in hierarchical order are:

- 1) Rectal Bleeding: The number and proportion of subjects in each level of change from baseline in rectal bleeding score at months 1, 3 and 6.
- 2) Mucosal Appearance: The number and proportion of subjects in each level of change from baseline in mucosal appearance score at month 6.
- 3) Physician's Rating Of Disease Activity
- 4) The Sutherland DAI Score ≤ 2 with no Individual Component >1 and a Rectal Bleeding Score of 0
- 5) Mean Change from Baseline in the Revised Sutherland DAI Score at Month 6
- 6) Relapse-Free Duration
- 7) An Assessment of the Revised Sutherland DAI Score for Stool Frequency.

If testing of the primary endpoints showed statistical significance, then testing was to be conducted for the secondary endpoints until a non-significant p-value was found at $p > 0.05$. Once a non-significant result was obtained, the testing was to be stopped.

For each study, the final statistical analysis plan (SAP) refers to the analysis of the primary endpoint using the Per-Protocol (PP) population as a secondary analysis. However, in their submission, the sponsor has presented the PP analyses as sensitivity analyses for the primary. In the SAP, this PP analysis was not considered part of the hierarchical testing.

Randomization:

Eligible subjects received a unique identifier by a consecutively assigned subject ID number by the order of enrollment within each study center. Treatments were assigned randomly via a randomization schedule using a 2:1 (2 eMG : 1 Placebo) ratio.

Sample Size Calculation:

For each study, the sample size was based on the assumption that 70% of the mesalamine-treated subjects and 50% of the placebo-treated subjects would be relapse-free at the end of 6 month of treatment. Study 3003 was designed to provide at least 90% power (Beta= 0.1) to detect this treatment difference between eMG and placebo in the proportion of subjects who were relapse-free after 6 weeks using a 2-sided significance level of 5% (alpha= 0.05) and 2:1 allocation ratio. A total of 200 subjects were randomized to the eMG and 100 randomized to the placebo arm.

In Protocol Amendment 02, dated August 9, 2007, Study 3004 was revised to reduce the number of planned subjects from 300 to 250. Based on the sponsor's calculations, a total of 250 subjects would provide at least 80% power (beta=0.20) to reject the null hypothesis of no difference between eMG and placebo. A total of 257 patients (164, 63.8% in eMG and 93, 36.2% in placebo) participated in study 3004. The sponsor states this amendment occurred prior to breaking the study blind, but the study completion date is shown as August 8, 2007.

Statistical Methodology:

Statistical testing of the primary endpoint was done using 2-sided Chi-square test with an alpha level of 0.05. A Cochran-Mantel-Haenszel (CMH) test, controlling for country was performed. For the categorical secondary endpoint variables a 2-sided Chi-square was used. For all continues variables an Analysis of Variance or Analysis of Covariance was used, appropriately.

Analysis Population:

The primary analyses were performed on the ITT population, which was defined as all subjects who were randomized to the study and had taken at least one dose of study medication.

Handling of Missing Data

Last observation carried forward (LOCF) was applied for subjects who terminated the study early, except that subjects who terminated due to lack of efficacy or UC-related adverse events were classified as treatment failures. After study completion but before unblinding, the sponsor held data reviews to determine reasons for early study terminations. This imputation method was changed from the original protocols which stipulated that all subjects who dropped out early would be considered treatment failures, regardless of the reason for early termination. This

change appeared in Amendment 2 dated July 16, 2007 for study 3003 and Amendment 2 dated August 9, 2007, for study 3004.

As noted above, these protocol changes occurred after the studies were completed. This reviewer performed the primary analyses using both the original and modified methods for handling dropouts. The results are shown in the next section, under “Analyses of the Primary Endpoint.”

3.2 Efficacy Results

Patient Disposition, Demographics and Baseline Characteristics:

Subjects were randomized 2:1 to receive the test product (eMG) or placebo once daily in subjects who had demonstrated remission of UC. A total of, 305 subjects (209, 68.5% in eMG and 96, 31.5% in placebo) from 45 centers took part in study MPUC3003, and a total of 257 patients (164, 63.8% in eMG and 93, 36.2% in placebo) from 37 sites participated in study MPUC3004. Table 3 shows the disposition of the subjects by study.

Both studies were conducted concurrently. Study 3003 began on December 20, 2004 and completed on April 26, 2007. Study 3004 was initiated on December 24, 2004 and was completed on August 8, 2007.

Table 3: Disposition of Subjects by Study (Reviewer’s Table)

Randomized	Study 3003			Study 3004		
	eMG (n=209)	Placebo (n=96)	Total (N=305)	eMG (n=164)	Placebo (n=93)	Total (N=257)
Completed the Study	113 (54.07)	29 (30.2)	142 (46.6)	95 (66.4%)	48 (33.6%)	143 (55.6%)
Withdraw Early	65/209=31%	47/96=49%	112/305=37%	45/164=27%	36/93=39%	81/257=32%
Reason for Withdrawal						
Adverse Event	30	24	54	9	6	15
Lost to Follow-Up	3	2	5	2	3	5
Lack of Efficacy	20	16	36	25	22	47
Subject Request	8	2	10	2	1	3
Noncompliance				1	0	1
Other	4	3	7	6	4	10

As it is shown in Table 3, most drop-outs occurred as a result of adverse events and/or lack of efficacy. In both studies, drop-out rates were similar, although the eMG groups had slightly higher drop-out rates compared to the placebo groups.

Table 4 presents the demographics and baseline characteristics of the subjects by study.

Table 4: Demographics and Baseline Characteristics of Subjects by Study

	Study 3003			Study 3004		
	Mesalamine (n=209)	Placebo (n=96)	Total (N=305)	Mesalamine (n=164)	Placebo (n=93)	Total (N=257)
Sex						
Male	92/209=44%	53/96=55%	145/305=48%	74/164=45%	48/93=52%	122/257=47%
Female	117/209=56%	43/96=45%	160/305=52%	90/164=55%	45/93=48%	135/257=53%
Age						
Mean (Std)	46.9 (13.6)	45.5 (14.4)		45.7 (14)	45.6 (14.1)	
< 65	185/209=89%	84/96=88%	269/305=88%	149/164=91%	82/93=88%	231/257=90%
≥ 65	24/209=11%	12/96=13%	36/305=12%	15/164=9%	11/93=12%	26/257=10%
Race						
White	188/209=90%	85/96=89%	273/305=90%	156/163=96%	90/93=97%	246/256=96%
Non-White	21/209=10%	11/96=11%	32/305=10%	7/163=4%	3/93=3%	10/256=4%
Baseline Disease * Severity Category						
Normal or None	85/209=41%	33/96=34%	118/305=39%	71/164=43%	39/93=42%	110/257=43%
≥ 1	124/209=59%	63/96=66%	187/305=61%	93/164=57%	54/93=58%	147/257=57%
Baseline Remission Dur.						
≤ 13 Weeks	110/209=53%	49/96=51%	159/305=52%	94/164=57%	44/93=47%	138/257=54%
> 13 Weeks	99/209=47%	47/96=49%	146/305=48%	70/164=43%	49/93=53%	119/257=46%
Baseline BMI						
Mean (Std)	26.8 (5.5)	26.4 (4.8)		26 (4.6)	26 (4.4)	
Country						
US	110/209=53%	50/96=52%	160/305=52%	62/164=38%	41/93=44%	103/257=40%
Russia	99/209=47%	46/96=48%	145/305=48%	102/164=62%	52/93=56%	154/257=60%

*Disease Severity: Sum of all DAI scores, ranging from 0 (normal) to 12 (maximum score).

In both studies, the distribution of subjects in both treatment groups were balanced with respect to demographics and baseline characteristics, such as gender, age and age category, race (White vs. non-Whites), baseline disease severity, baseline remission duration (≤ 13 Weeks vs. > 13 Weeks), baseline BMI and country (U.S. vs. Russia).

Analyses of the Primary Endpoints:

In the original protocols, the population for the primary analyses were to include all subjects who discontinued the study early counted as relapse or ‘failure’. However, the sponsor changed this definition in protocol amendments dated after the completion of the studies, and assigned relapse to early terminators only if they dropped out due to lack of efficacy or UC-related adverse events.

Primary analyses using both methods of imputation were done by the reviewer. Table 5 shows the sponsor’s as well as the reviewer’s efficacy analysis results of the primary endpoint variable.

Table 5: Primary Efficacy Endpoint*

	Mesalamine	Placebo	95% CI for Difference	P-Value
Study 3003				
No Relapse (S ITT)**	165/209=79%	56/96=58%	21% (9.5%, 32%)	<0.001
No Relapse (PP)	157/200=78.5%	55/93=59%		<0.001
No Relapse (R ITT)***	143/209=68.4%	49/96=51%	17% (5.5%, 29.2%)	<0.001
Study 3004				
No Relapse (S ITT)**	131/164=80%	63/93=68%	12% (1.1%, 24%)	0.029
No Relapse (PP)	129/161=80%	58/86=67%		0.027
No Relapse (R ITT)***	117/164=71%	55/93=59%	12% (0%, 24.5%)	0.046

* The primary analysis efficacy endpoint is the proportion of subjects who were relapse-free after 6 months of treatment. 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 (DAI).

**Sponsor's ITT analysis (early dropouts as relapse only lack of efficacy or if UC-related AE occurred).

***Reviewer's ITT analysis, all early withdrawals as relapse.

The primary efficacy endpoint comparisons based on sponsor's revised imputation strategy shows a highly statistically significant difference between Mesalamine and placebo in study 3003 ($p < 0.001$). Study 3004, also, demonstrated statistically significant results ($p = 0.029$). When these analyses were repeated using per-protocol population the results were comparable to that of the intent-to-treat population. The reviewer's findings were consistent with the sponsor's results.

Based on the more conservative approach where all early drop-outs are classified as having relapse, the overall efficacy conclusions for the ITT analyses are not changed; however, the results for study 3004 are only marginally significant at $p = .046$. (Based on Fisher's exact test, $p = .054$.)

This reviewer performed additional analyses of the primary endpoint, each analysis adjusting for a single factor [(country, site, gender, age group (< 65 or ≥ 65), race (White/Non-White) and baseline severity category ($0, \geq 1$)] using the CMH Chi-square test. For Study 3003, each analysis showed highly significant differences between treatment groups ($p < 0.001$). For Study 3004, these same analyses resulted in statistical significance ($0.03 < p < 0.046$).

Analyses of the Secondary Endpoints:

The sponsor analyzed the secondary endpoints using the ITT population with a LOCF imputation method. The sponsor had specified in the SAP's that if statistical significance was not achieved for any of the secondary endpoints, all subsequent secondary endpoints would be considered exploratory in nature. For study 3003, the second secondary endpoint (mucosal appearance) failed testing, and for study 3004, the first secondary endpoint (rectal bleeding) failed testing.

Table 6 presents the reviewer's analysis of the first two secondary endpoints. The reviewer's analysis method for the endpoint is based on a Chi-square test; however results are consistent with those of the sponsor. In both studies for both the treatment arms, the majority of subjects

had no change from baseline for either bleeding or mucosal appearance. This is noted in the table in bold font. The sponsor's results for the other secondary endpoints, Physician's rating and the Sutherland DAI component scores are shown in the Appendix.

Table 6: Secondary Efficacy Endpoint (Reviewer's Results)

Study 3003 Change from Baseline	Mesalamine (n=209)	Placebo (n=96)	P-Value
Rectal Bleeding n (%)			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%)	
Mucosal Appearance n (%)			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%)	

*Sponsor's p-value=0.008, using CMH controlling for country

**Sponsor's p-value=0.098, using CMH controlling for country

Table 6, Cont'd: Secondary Efficacy Endpoint (Reviewer's Results)

Study 3004 Change from Baseline	Mesalamine (n=164)	Placebo (n=93)	P-Value
Rectal Bleeding n (%)			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%)	
Mucosal Appearance n (%)			(not testable)
-1	26 (15.9%)	13 (14.0%)	
0	104 (63.4%)	56 (60.2%)	
1	18 (11.0%)	14 (15.1%)	
2	16 (9.8%)	10 (10.8%)	
3	0 (0%)	0 (0%)	

For Study 3003, based on the hierarchical testing, only rectal bleeding showed a statistical significant result. In Study 3004, rectal bleeding did not show a statistically significant difference between eMG and placebo. Therefore, all secondary results for study 3004 should be considered exploratory.

Additional Analyses:

In consultation with the clinical reviewer, I conducted additional analyses of bleeding and mucosal appearance status at the end of the study as assessed by binary analysis. A rectal bleeding score of 0 is defined as "No Bleeding". A mucosal appearance score of 0 was considered as "Normal". Tables 7 and 8 show the results of these exploratory analyses by study.

Table 7: Bleeding

Study 3003	Mesalamine (n=209)	Placebo (n=96)	P-Value
Bleeding			<0.01
Yes	64 (31%)	44 (46%)	
No	145 (69%)	52 (54%)	
Study 3004	Mesalamine (n=164)	Placebo (n=93)	
Bleeding			0.01
Yes	44 (27%)	39 (42%)	
No	120 (73%)	54 (58%)	

Table 8: Mucosal Appearance

Study 3003	Mesalamine (n=209)	Placebo (n=96)	P-Value
Mucosal Appearance			0.06
Normal	91 (44%)	31 (32%)	
Not Normal	118 (56%)	65 (68%)	
Study 3004	Mesalamine (n=164)	Placebo (n=93)	
Mucosal Appearance			0.2
Normal	89 (54%)	43 (46%)	
Not Normal	75 (46%)	50 (54%)	

I also analyzed time-to-relapse for the PP populations. The Kaplan-Meier graphs for studies 3003 and 3004 are presented in the Appendix. These results are exploratory but present another way of illustrating the lower relapse rates for the treated group. Notice the events extend beyond the double-blind period of six months.

Given that Study MPUC3004 terminated before completing its originally planned enrollment, a sensitivity analysis was performed with the additional 43 subjects that the study would have enrolled had it not terminated. If we assume these subjects would have had a success rate equal to the observed placebo response of 68% (Table 5), then using the ITT population, the success rates would be 151/193 (78%) and 73/107 (67%) for Mesalamine and Placebo, respectively, $p = 0.06$. This may suggest that the trial may have been stopped early to avoid a potential failure of its primary endpoint.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age and Other Special/Subgroup Populations

Both studies were combined in order to facilitate the subgroup analyses. These analyses were, solely, for exploratory purposes. As noted in Table 9 below, a smaller effect size is indicated for the Russian subpopulation (p=0.042) which appears to be due to the higher placebo response rate. Efficacy is also weaker for the male population (p=0.039) again possibly due to the higher placebo response for males. In the subpopulation of age groups for ≥ 65 the results are not statistically significant (p=0.81) however, the subgroup size is small for that age group. Efficacy results are consistent across baseline disease severity as well as time on remission.

Table 9: Table Analysis of Primary Endpoint Variable (No-Relapse) by Subgroup (Both Studies Combined)

	Mesalamine	Placebo	P-Value
Country			
USA	130/172=75.5%	48/91=53%	<0.001
Russia	166/201=82.6%	71/98=72%	0.042
Gender			
Male	132/166=80%	69/101=68%	0.039
Female	165/207=79%	50/88=57%	<0.001
Age Group			
< 65	270/334=81%	103/166=62%	<0.001
≥ 65	26/39=67%	16/23=70%	0.81
Race			
White	274/344=80%	112/175=64%	<0.001
Non-White	21/28=75%	7/14=50%	0.11
Baseline Disease Severity Category*			
Normal or None	134/156=86%	47/72=65%	<0.001
≥ 1	162/217=75%	72/117=62%	0.01
Baseline Remission Duration			
≤ 13 Weeks	159 (78%)	57 (61%)	0.003
> 13 Weeks	137 (81%)	62 (65%)	0.003

*Disease Severity: Sum of all DAI scores, ranging from 0 (normal) to 12 (maximum score).

The table below shows the primary analysis cross-classified by both gender and country. These data suggest lack of efficacy for the Russia-males subgroup, again due to high placebo response.

Table 10: Primary Endpoint Variable (No Relapse) by Country by Gender (Both Studies Combined)

United States	eMG	Placebo	P-value
Males	62/82=76%	30/51=56%	0.04
Females	68/90=76%%	18/40=45%	0.03

Russia	eMG	Placebo	P-value
Males	70/84=83%	39/50=78%	0.44
Females	96/117=82%	32/48=67%	0.03

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary efficacy endpoint comparisons showed a highly statistically significant difference between Mesalamine and placebo in study 3003 ($p < .001$). Study 3004, also, demonstrated statistically significant results ($p = .029$). When these analyses were repeated using the per-protocol population, the results were similar to that of the intent-to-treat population.

The sponsor's imputation strategy assigned treatment failures to subjects who terminated the study early but only if the reason for drop-out was efficacy related or due to a UC-related adverse event. The reviewer performed the more conventional and conservative analysis of the ITT population assigning treatment failure to all subjects who terminated early. These results did not change the efficacy conclusions for study 3003; however, the efficacy results for study 3004 were marginal ($p = .046$).

The reviewer performed additional analyses of the primary endpoint, each analysis adjusting for a single factor: country, site, gender, age group (< 65 or ≥ 65), race (White/Non-White) and baseline severity category (0, ≥ 1). These results are consistent with the primary analysis for each study.

To control for type I error, the sponsor planned a hierarchical testing strategy for the secondary endpoints, although the order of testing was specified in a protocol amendment dated after completion of studies but prior to unblinding. For Study MPUC3003, only the first secondary endpoint (change from baseline in rectal bleeding score) shows statistically significant improvement from baseline. None of the secondary endpoints were statistically significant in Study MPUC3004.

The sample size for study 3004 was reduced in a late-stage protocol amendment. A total of 257 patients instead of the planned 300 were analyzed. This could be interpreted as an unplanned or early stopping of the study. Even though the decision appears to have been made prior to breaking the blind, the study completion date is prior to the protocol amendment date. There is no formal way to adjust the p-value for early study termination. However, a sensitivity analysis shows that if the additional 43 subjects were enrolled and had a 68% treatment success rate for both treatment groups (consistent with the observed placebo rate) then the primary ITT analysis would have failed ($p = .06$). In view of these results and the lack of efficacy demonstrated for all secondary endpoints, study 3004 should be considered supportive with marginal demonstration of efficacy.

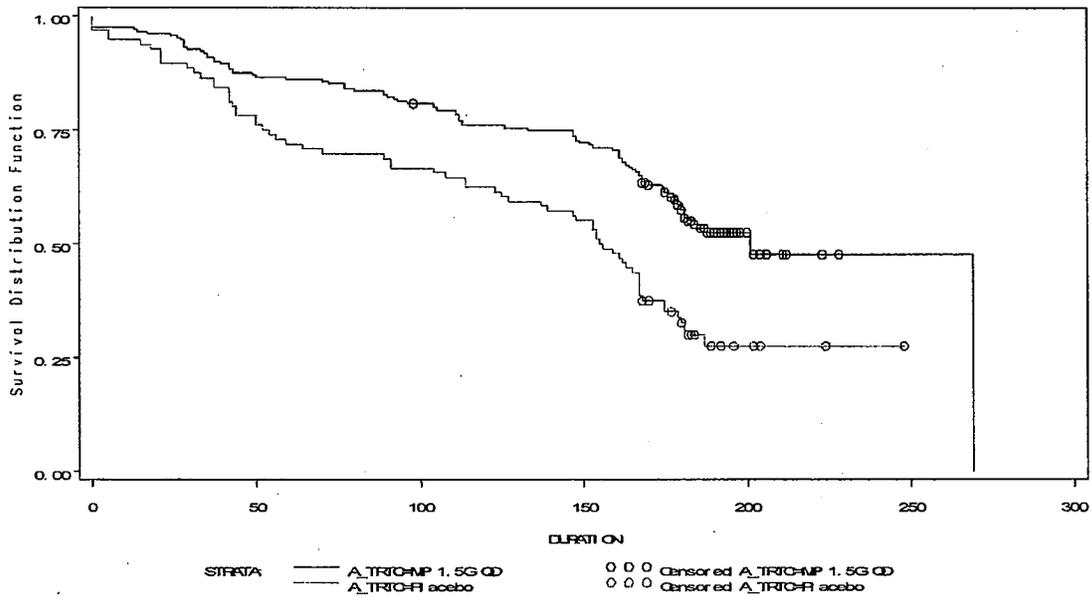
5.2 Conclusions and Recommendations

Based on data from two randomized and controlled studies, and from a statistical perspective, the results reported in this submission support the conclusion that Encapsulated Mesalamine Granules, 0.375 g (eMG) (5-aminosalicylic acid or 5-ASA) taken once a day for a total of six months appear to be efficacious for maintenance of remission of Ulcerative Colitis. However, the results from Study MCUP3003 provides clearer evidence of efficacy; due to late-stage study design changes and lack of any secondary endpoint efficacy, the results from Study MPUC3004 should be considered supportive and not showing substantial efficacy.

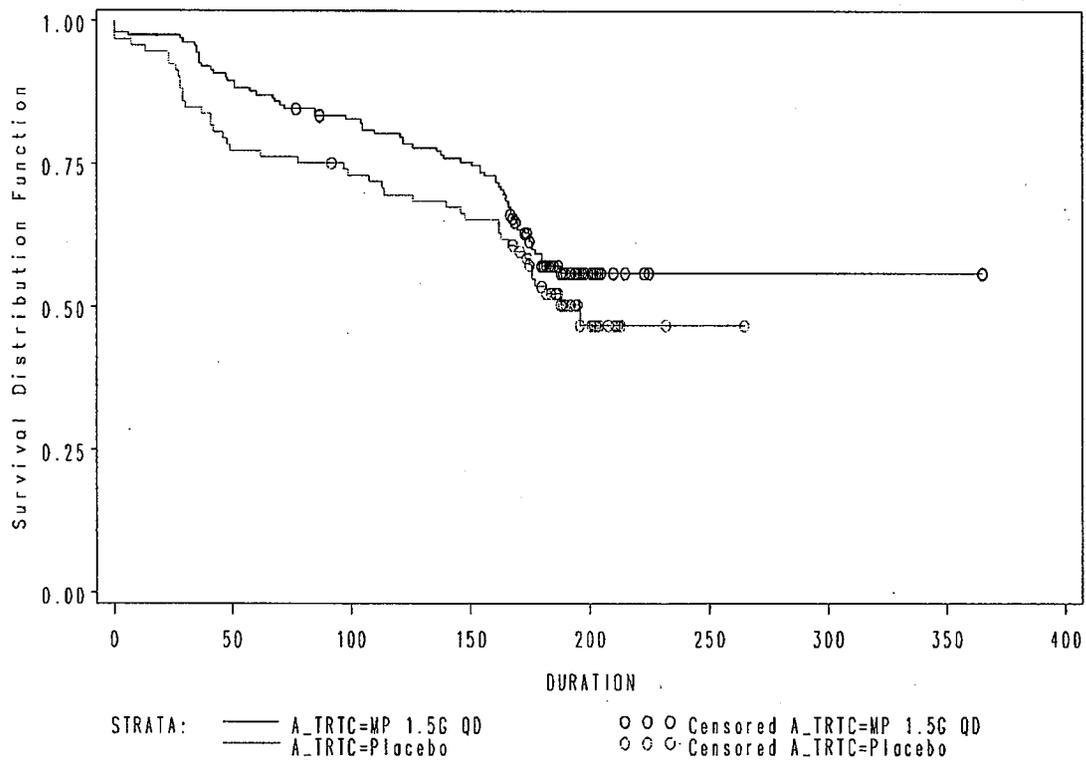
APPENDIX

Graphs 1 and 2 present Kaplan-Meier curves for relapse-free duration for Studies 3003 and 3004.

Graph 1: Study 3003 - Kaplan-Meier Estimates for Relapse-Free Duration – Per-Protocol Population (Reviewer’s results)



Graph 2: Study 3004 - Kaplan-Meier Estimates for Relapse-Free Duration – Per-Protocol Population (Reviewer’s results)



**Numerical Results for Remaining Secondary Endpoints (Source: Sponsor)
Study 3003**

	Mesalamine (n=209)	Placebo (n=96)
Number and Proportion of Subjects in Each Level of Change from Baseline in Physician's Rating Of Disease Activity (at 6 months)		
-3	0 (0%)	0 (0%)
-2	1 (0.5%)	0 (0%)
-1	16 (7.7)	6 (6.3)
0	146 (69.9)	55 (57.3)
1	35 (16.7)	17 (17.7)
2	10 (4.8)	18 (18.8)
3	1 (0.5)	0 (0%)
Number and Proportion of Subjects Maintaining the Southerland DAI Score ≤ 2 with no Individual Component >1 and a Rectal Bleeding = 0 (at 6 months)		
Success	147 (70.3)	51 (53.1)
Failure	62 (29.7)	45 (46.9)
Mean (SD) Change from Baseline in the Revised Sutherland DAI Score (at Month 6)	0.9 (2.4)	2.0 (3.3)
Relapse-Free Duration (at 6 months)		
At Risk (at the beginning of the interval)	167	66
Relapses (during the interval)	17	14
Cumulative Relapse-Free Probability (SE)*	0.77 (0.03)	0.56 (0.05)
Number and Proportion of Subjects in Each Level of Chang from Baseline in Stool Frequency Score (at month 6)		
-3	0 (0)	0 (0)
-2	0 (0)	0 (0)
-1	4 (1.9)	1 (1.0)
0	167 (79.9)	64 (66.7)
1	20 (9.6)	11 (11.5)
2	8 (3.8)	11 (11.5)
3	10 (4.8)	9 (9.4)

Numerical Results for Remaining Secondary Endpoints (Source: Sponsor)
Study 3004

	Mesalamine (n=164)	Placebo (n=93)
Number and Proportion of Subjects in Each Level of Change from Baseline in Physician's Rating Of Disease Activity (at 6 months)		
-3	0 (0)	0 (0)
-2	1 (0.6)	0 (0)
-1	16 (9.8)	10 (10.8)
0	122 (74.4)	60 (64.5)
1	16 (9.8)	16 (17.2)
2	8 (4.9)	7 (7.5)
3	1 (0.6)	0 (0)
Number and Proportion of Subjects Maintaining the Southerland DAI Score ≤ 2 with no Individual Component >1 and a Rectal Bleeding = 0 (at 6 months)		
Success	118 (72.0)	54 (58.1)
Failure	46 (28.0)	39 (41.9)
Mean (SD) Change from Baseline in the Revised Sutherland DAI Score (at Month 6)	0.7 (2.4)	1.2 (2.7)
Relapse-Free Duration (at 6 months)		
At Risk (at the beginning of the interval)	136	68
Relapses (during the interval)	12	11
Cumulative Relapse-Free Probability (SE)*	0.79 (0.03)	0.56 (0.09)
Number and Proportion of Subjects in Each Level of Chang from Baseline in Stool Frequency Score (at month 6)		
-3	0 (0)	0 (0)
-2	0 (0)	0 (0)
-1	12 (7.3)	4 (4.3)
0	124 (75.6)	67 (72.0)
1	11 (6.7)	8 (8.6)
2	14 (8.5)	9 (9.7)
3	3 (1.8)	5 (5.4)

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/s/

Shahla Farr
9/29/2008 02:45:13 PM
BIOMETRICS

Mike Welch
9/29/2008 04:17:31 PM
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Concur with review.