CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-830

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

NDA/Serial Number:	21-830
Drug Name:	Asacol 800 (mesalamine) delayed-release tablets
Indication(s):	Treatment of moderately active ulcerative colitis
Applicant:	P&G Pharmaceuticals, Inc.
Date(s):	Submitted October 22, 2007
Review Priority:	Standard
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Keywords: NDA review, clinical studies, adaptive strategy, non-inferiority

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1. EXECUTIVE SUMMARY

1.1 **Conclusions and Recommendations**

As concluded in the original statistical review of study 2000082, that study did not provide substantial evidence to conclude superiority of Asacol 4.8 mg/day over the 2.4 mg/day dose. The many unplanned design changes implemented near the end of that study and the inconsistencies in subgroup efficacy results were problematic in determining the strength of evidence. At best, study 2000082 provided only supportive evidence of efficacy.

Study 2006444 gives principle support for efficacy of the 4.8 g/day dose as demonstrated by a treatment difference of 4.6% in favor of 4.8 g/day with 95% confidence interval of (-1.9%, 11.2%). Additionally, the lower limit of this confidence interval is smaller than the pre-specified non-inferiority margin of 10% and is close to 1.0%, a margin obtained from the historical placebo-controlled study for patients with moderate disease. Thus, Asacol 800 dosed at 4.8 g/day should be considered efficacious compared to placebo.

1.2 **Brief Overview of Clinical Studies**

1.2.1 **Study 2006444**

Study 2006444 was submitted to support a Complete Response to the Agency Approvable Letter dated August 29, 2005. This was a double-blind, randomized, multi-center, multi-national, active-control study in patients who were experiencing a moderate active flare of UC and was submitted to address deficiencies found in studies 2000082 and 2000083 in the original NDA submission (October 22, 2004).

The original primary objective was to confirm the clinical benefits of Asacol 4.8 g/day (800 mg tablet) compared to Asacol 2.4 g/day (400 mg tablet) in patients with moderately active ulcerative colitis. The secondary objectives of this study were to evaluate changes in each of the individual assessments and composite scores of the Physician's Global Assessment (PGA) and Ulcerative Colitis Disease Activity Index (UCDAI).

Patients were randomly assigned to receive either Asacol 2.4 g/day (400 mg tablet) or Asacol 4.8 g/day (800 mg tablet) for 6 weeks. Patients were randomized to one of the two treatment groups in a 1:1 ratio and were stratified by gender.

The primary efficacy parameter was the proportion of patients who achieved treatment success, defined as improvement from baseline at Week 6. Improvement was defined as either a complete response (remission) or partial response (improvement) to treatment. A complete response was defined by the PGA showing complete resolution or normalization of symptoms based on stool frequency, rectal bleeding, and sigmoidoscopy. A partial response was defined as improvement from baseline in the PGA and no worsening in any of the three component endpoints.

Secondary efficacy endpoints included patient improvement at Week 3 and 6 in individual symptom and composite scores of the PGA and UCDAI. Quality of life assessments were also made with the Inflammatory Bowel Disease Questionnaire at Weeks 3 and 6.

During the course of this study, the statistical hypothesis was changed to non-inferiority. If non-inferiority was confirmed, then the superiority of the 4.8 g/day dose to the 2.4 g/day dose would be tested.

The primary analysis was based on the intent-to-treat (ITT) population defined as all randomized patients.

1.3 **Statistical Issues and Finding**

The sponsor has submitted two pivotal studies to support an indication for Asacol, 4.8 g/day for treatment of moderately active ulcerative colitis. These are studies 2000082 (contained in the original NDA 21-830) and study 2006444 (contained in this Complete Response).

In the original submission, the sponsor submitted studies (2000083 and 2000082) (ASCEND I and ASCEND II) comparing efficacy and safety of Asacol 800 dosed 4.8 g/day versus Aascol dosed 2.4 g/day in treatment of patients with moderately active ulcerative colitis.

Based on subgroup results from the completed study 2000083, the sponsor amended ongoing study 200082 on February 18, 2003 when 96% of the intended sample size had been enrolled. Under the amended protocol, only patients with moderate disease at baseline (PGA=2) were to be enrolled; the sponsor increased the sample size and changed the focus of the primary analysis to the subgroup of patients with moderate active ulcerative colitis at baseline.

For study 2000082, superiority was seen among all patients enrolled with moderate disease at baseline. However, the success rates were much higher than those for patients enrolled before the amendment than after the amendment for patients with moderate disease at baseline (71.4% vs. 54.7% for 2.4 g/day and 75.6% vs. 69.9% for 4.8 g/day).

Study 2000082 showed a slightly better rate of treatment success at week 6 for the 4.8 g/day group compared to the 2.4 g/day group, with a nominal p-value of 0.046, adjusted for time of enrollment. From a statistical perspective, this result was not statistically persuasive, and the sponsor's adaptive changes to study 2000082 were considered to be post hoc. It was concluded that superiority of the higher dose was not clearly established, and another phase 3 study would be required.

In complete response to the August 29, 2005 Approvable Letter, the sponsor submitted results for Study 2006444 (ASCEND III) which was originally designed as a superiority trial. As this study was approaching completion (January 2007) the sponsor learned that a

4.8 g/day regimen of mesalamine (Lialda) had been approved on January 16, 2007 in the absence of incremental benefit of 4.8 g/day over 2.4 g/day, though both doses were shown to be superior to placebo.

Subsequently, study 2006444 was amended (IND 26,093 Serial #262) on March 2, 2007 to increase the sample size to from 470 to 770 patients, while the primary analysis plan was changed to first test for non-inferiority of the two treatment regimens.

The sponsor's 10% non-inferiority margin was not pre-specified in the amendment dated March 2, 2007 but was discussed at the March 17, 2007 meeting with the sponsor. At that time, no agreement on the 10% margin had been reached, and it was concluded that the sponsor would provide additional justification in the submission.

The ITT analysis for study 2006444 demonstrated statistical non-inferiority between Asacol 800 (4.8 g/day) and Asacol 2.4 g/day for treatment outcome at Week 6 with a lower limit of confidence interval of -1.9%. Per protocol analysis demonstrated statistical non-inferiority with a lower limit of confidence interval of -2.3%. Both lower limits were smaller than the pre-specified 10%.

From this reviewer's sensitivity analysis, the treatment differences ranged from 4.1% to 5.4% with the lower limits of 95% confidence intervals ranged from -1.1% and -2.5%. In this reviewer's opinion, the sponsor's results can be considered robust since the lower confidence limit (-1.9%) is between -1.1% and -2.5%.

Furthermore, from the placebo-controlled study C14 conducted for Asacol under NDA 19-651, lower limits of 95% confidence intervals of differences between 2.4 g/day and placebo was 3% for ITT analysis and 7% for patients with mild to moderate disease. For the subgroup of patients with moderate disease in Study C14, the lower confidence limit was 2%.

A 50% discount applied to the lower limit to establish a non-inferiority margin yields a margin ranging from 1.5% to 3.5% for patients with mild to moderate disease and about 1.0% for patients with moderate disease. However, the confidence interval of treatment difference for the subgroup of patients with moderate disease may not be reliable due to potential bias.

2. INTRODUCTION

2.1 **Overview**

In the original application for NDA 21-830, the sponsor submitted two studies, ASCEND I and ASCEND II, (Protocols 2000083 and 2000082) to compare the efficacy and safety of Asacol 4.8 g/day (800 mg tablet) and Asacol 2.4 g/day (400 mg tablet) in patients with mildly to moderately active ulcerative colitis (UC).

Efficacy results from the study 2000083, which complete first, failed to show a statistical difference between treatment groups; however an exploratory subgroup analysis of subjects with moderately active UC indicated an advantage for the 4.8 g/day dose group.

Based on this finding, the second study (2000082) was amended to increase enrollment of patients with moderate disease and to focus on the subgroup of subjects in the study with moderate to active UC at baseline. This amendment was made after about 96% of the originally planned study size was enrolled; the Agency agreed to the amendment in a fax dated March 17, 2003, but indicated that final recommendations for the 4.8 g/day dose would be made based on review findings and that consistent and statistically significant efficacy outcomes would be expected.

The results for study 2000082 showed a statistical difference between dose groups for the subgroup of subjects with moderate disease at baseline. However, superiority was not shown for the entire patient population (ITT); there was treatment gender interaction observed with main benefit being driven by male subjects; and success rates were actually higher for subjects enrolled prior to the amendment as compared to after the amendment.

It was concluded by the statistical reviewer that study 2000082 did not have a well-defined adaptive design, and the results could not provide substantial evidence to conclude superiority of the 4.8 g/day dose; it was recommended the sponsor conduct another study. (For additional details, refer to the statistical review of NDA 21-830 dated Aug 5, 2005.)

This review addresses the sponsor's Complete Response submitted October 22, 2007. The sponsor has provided results from an additional study (Protocol 2006444, ASCEND III) in response to the Medical Division's request in the August 29, 2005 Approvable Letter for at least one additional adequate and well-controlled clinical study to:

- Demonstrate the added clinical benefit of Asacol 800 tablets at a dose of 4.8 g/day compared to Asacol 400 mg at 2.4 g/day in moderate active ulcerative colitis patients.

- Explain why Asacol 800 mg at 4.8 g/day was more efficacious than Asacol 400 mg at 2.4 g/day in male patients.

ASCEND III was initiated in June 2006. As the study was approaching completion (January 2007) the sponsor learned that a 4.8 g/day regimen of mesalamine (Lialda) had been approved on January 16, 2007 in the absence of incremental benefit of 4.8 g/day over 2.4 g/day, even though both doses were superior to placebo.

A formal request for a Type A meeting was submitted on January 26, 2007. A Type C meeting was granted on February 2, 2007 for March 16, 2007. During the interim, e-mail, subject "change in study design Asacol" was sent from Dr. Zorich of P&G to Dr. Harvey, Director, DGP. The sponsor decided to amend protocol 2006444 in advance of the March 16 meeting to allow the study to continue unabated, without any pause in enrollment.

Subsequently, protocol 2006444 (ASCEND III) was amended (IND 26,093 Serial #262) on March 2, 2007 to increase the sample size to 770 patients, while the primary analysis plan was changed to add an additional test for non-inferiority of the two treatment regimens.

2.2 **Date Sources**

The sponsor submitted Complete Response Dated October 22, 2007. This response provided the results from an additional study (Protocol #2006444, ASCEND III) of Asacol 800 dosed 4.8 g/day versus Asacol dosed 2.4 g/day for the treatment of patients with moderately active ulcerative colitis (UC). EDR path: \\Fdswa150\nonectd\N21830\N_000\2007-10-22

Three statistical information requests were generated by this reviewer and provide additional data sources for this review. The sponsor replies were submitted to the EDR on December 7, 2007, February 22, 2008, and March 31, 2008 located at: \\Fdswa150\nonectd\N21830\N_000.

3. STATISTICAL EVALUATION

3.1 **Evaluation of Efficacy**

3.1.1 **Study 2006444 (ASCEND III)**

3.1.1.1 **Description of Study**

This was a double-blind, randomized, multi-center, multi-national, active-control study in patients who were experiencing a moderate active flare of UC.

The original primary objective was to confirm the clinical benefits of Asacol 4.8 g/day (800 mg tablet) compared to Asacol 2.4 g/day (400 mg tablet) in patients with moderately active ulcerative colitis.

The treatment comparison was changed to add a non-inferiority comparison. If non-inferiority was confirmed, then the superiority of the 4.8 g/day dose to the 2.4 g/day dose would be tested.

The secondary objectives of this study were to evaluate the change in each of the individual assessments and composite score (PGA and Ulcerative Colitis Disease Activity Index [UCDAI]) at Week 6, evaluate the change in the individual assessments of stool frequency, rectal bleeding, and PFA at Week3, and evaluate treatment success in patients with left-sided disease at Week 6.

In this study, the PFA no longer was a component of the PGA. The PGA was based on stool frequency (patient recall from previous 3 days), rectal bleeding (patient recall from previous 3 days), and sigmoidoscopy findings.

Patients were screened according to inclusion and exclusion criteria within 7 days before receiving study drug. The Baseline visit was within 7 days after the Screen Visit. Visits 1 and 2 were scheduled at 3 and 6 weeks, respectively, from Day 1 of dosing. A visit window of ±3 calendar days was permitted.

Patients were eligible to participate in the study who:

a) were between 18 and 75 years of age, inclusive at Screening;
b) had a confirmed diagnosis of moderately active ulcerative colitis, extending proximally beyond 15 cm from the anal verge, as confirmed by flexible sigmoidoscopy or colonoscopy performed within 7 days prior to the Baseline Visit.
c) had a confirmed diagnosis of moderately active disease (PGA=2) at the Baseline Visit;
d) had, at the Baseline Visit, a score of at least 1 in both the stool frequency and rectal bleeding clinical assessments and a score of at least 2 in the Sigmoidoscopy Assessment Score;

Patients were randomly assigned to receive either Asacol 2.4 g/day (400 mg tablet) or Asacol 4.8 g/day (800 mg tablet) for 6 weeks. Patients were randomized to one of the two treatment groups in a 1:1 ratio and were stratified by gender.

It was assumed that the true rate of improvement for the overall patient (males and females) in the 2.4 g/day treatment group was 40% and in the 4.8 g/day group was 60%. To detect a true difference of 20% between these two groups with a 2-sided test, type I error of 0.025 and power 90%, it required 163 patients per group (a total of 326 patients) to complete the study with a treatment outcome at Week 6.

It was also of interest to compare the treatment difference in male patients only, as Studies 2000082 and 2000083 (original NDA submission) suggested that the 4.8 g/day dose of Asacol might not provide additional efficacy over the 2.4 g/day dose in female patients. To calculate the sample size required for male patients only, it was assumed the true rate of improvement for males in the 2.4 g/day treatment group was 40% and for male in the 4.8 g/day group was 65%. To detect a true difference of 25% between these two groups of male patients with a 2-sided test, type I error of 0.025 and power 90%, it required 105 patients per group (a total of 210 male patients) to complete the study with a treatment outcome at Week 6.

It was assumed that male and female patients would enroll at approximately the same rate (50% male and 50% female). If the enrollment rate for male and female patients were not similar, recruitment would continue until a total of 210 male patients (and at least 326 patients total, male and female) had completed the study with a treatment outcome at Week 6 in order to ensure there were sufficient patients for the primary efficacy analysis and male study population analyses. The dropout rate was estimated to be 10%-15%; consequently, enrollment of approximately 470 patients was expected to result in at least 420 completed patients, the number of completed patients needed for the analysis.

3.1.1.2 **Sponsor's Analysis**

A total of 775 patients were randomized (383 for 2.4 g/day [400 mg] and 392 for 4.8 g/day [800 mg]). More than 90% of the patients completed the study in both treatment groups (347 for 2.4 g/day [400 mg] and 353 for 4.8 g/day [800 mg]). The main reason for discontinuation was adverse events (15 for 2.4 g/day [400 mg] and 15 for 4.8 g/day [800 mg]).

Table below included data sets analyzed for all randomized, intent-to-treat, and per protocol patients.

Study Populations

Category	2.4g/day Asacol (400 mg Tablet)	4.8g/day Asacol (800 mg Tablet)
All Randomized Patients	383	392
Patients Not Dosed	0	3
Intent-to-treat Patients	383	389
Patients without Week 6 Outcome	17	20
Patients with Week 6 Outcome	366	369
Per Protocol Patients	348	359
Per Protocol Exclusions[a]	35	33
Compliance	13	14
Exclusion Criteria	13	10
Excluded Medication	2	1
Inclusion Criteria	2	0
No Week 6 Outcome	17	23

[a] Patients may be counted in more than 1 exclusion category.
Corresponding data can be found in Appendix 13.2.3, Listings 1, 2 and 3, and Appendix 13.2.5, Listing 1.
/ASACOL/2006444/ANAL/stdypop.sas; SAS 8.2 20JUL07 13:23 AI9318.

ITT study population included all patients who were randomized and took at least one dose of study medication. ITT population included 772 patients (383 for 2.4 g/day [400 mg] and 392 for 4.8 g/day [800 mg]). Per Protocol population included 707 patients (348 for 2.4 g/day [400 mg] and 359 for 4.8 g/day [800 mg]).

3.1.1.2.1 **Planned Analysis**

The primary efficacy parameter was the proportion of patients who achieved treatment success, defined as improvement from baseline at Week 6. Improvement was defined as either a complete response (remission) or partial response (improvement) to treatment. A complete response was defined as a Physician's Global Assessment (PGA) of zero (PGA)=0, i.e., complete resolution or normalization of the following symptoms: stool frequency, rectal bleeding, and Sigmoidoscopy Assessment Score, and. A partial response was defined as improvement from baseline in the PGA and no worsening in any of the 3 component endpoints.

Secondary efficacy endpoints included patient improvement at Week 3, change from baseline in UCDAI, sigmoidoscopic and clinical improvement (stool frequency, rectal bleeding, PGA, and PFA), and quality of life (Inflammatory Bowel Disease Questionnaire) at Weeks 3 and 6.

The intent-to-treat analyses (ITT) were the primary analyses. All randomized patients were included in the ITT analyses.

3.1.1.2.2 **Treatment Group Comparability**

A summary of the demographic characteristics at baseline, baseline ulcerative colitis history, and baseline disease state characteristics of treatment subjects by randomized treatment are presented in Appendix Table 1.

As seen from Appendix Table 1, overall, demographic characteristics at baseline were generally similar across the two treatment groups with the exception of age (0.0668).

3.1.1.2.3 **Sponsor's Analysis of Primary Efficacy Variable**

3.1.1.2.3.1 **ITT Analysis**

A summary of patients with treatment success at Week 6 for ITT analysis is given below. In this analysis, patient with missing observations was considered to be "failure."

Superiority of Treatment Outcome at Week 6: Missing Observations Set to Treatment Failure (Intent-to-treat)

Treatment Outcome	2.4g/day Asacol (400 mg Tablet) (N = 383) n (%)	4.8g/day Asacol (800 mg Tablet) (N = 389) n (%)	Total (N = 772) n (%)	p-value[a]	4.8 - 2.4 Difference in Success Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
Success	251 (65.5%)	273 (70.2%)	524 (67.9%)			
Failure	132 (34.5%)	116 (29.8%)	248 (32.1%)			
Total	383	389	772	0.1684	4.6	(-1.9, 11.2)

N = number of patients in treatment group
n (%) = number and percentage (n/Total x 100) of patients in treatment group with specified outcome
[a] 4.8g/day compared to 2.4g/day stratified by sex using the Cochran-Mantel-Haenszel test.
[b] Difference between Asacol 800 (4.8g/day) and Asacol 2.4g/day
[c] Confidence interval for the difference in success rates between 4.8g/day compared to 2.4g/day with no stratification.
Corresponding data can be found in Appendix 13.2.6, Listing 2.
/ASACOL/2006444/ANAL/mch.sas; SAS 8.2 20JUL07 13:23 AI9318.

As seen in the table above, the ITT analysis demonstrated statistical non-inferiority between Asacol 800 (4.8 g/day) and Asacol 2.4 g/day with an lower limit confidence interval of -1.9%.

3.1.1.2.3.2 **Per Protocol Analysis**

A summary of patients with treatment success at Week 6 for Per Protocol analysis is given below. In this table the difference in success rates is the 2.4 minus 4.8 dose.

Per Protocol Analysis
Non-Inferiority of Treatment Outcome at Week 6
(Per Protocol Patients)

Treatment Outcome	2.4g/day Asacol (400 mg Tablet) (N=348) n (%)	4.8g/day Asacol (800 mg Tablet) (N=359) n (%)	Total (N=707) n (%)	2.4 - 4.8 Difference in Success Rate[a]	95% Confidence Interval for 2.4 - 4.8[b]
Success	247 (71.0%)	270 (75.2%)	517 (73.1%)		
Failure	101 (29.0%)	89 (24.8%)	190 (26.9%)		
Total	348	359	707	-4.2	(-10.8, 2.3)

N = number of patients in treatment group with treatment outcome at Week 6
n (%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome.
[a] Difference between 2.4g/day and 4.8g/day
[b] Confidence interval for the difference in success rates between 2.4g/day compared to 4.8g/day with no stratification.
Corresponding data can be found in Appendix 13.2.6, Listing 2 and Appendix 13.2.3, Listing 2.
/ASACOL/2006444/ANAL/mch.sas; SAS 8.2 20JUL07 13:23 AI9318.

As seen in the table above, the per protocol analysis demonstrated statistical non-inferiority between Asacol 2.4 g/day and Asacol 800 (4.8 g/day)with an upper limit confidence interval of 2.3%.

3.1.1.2.3.3 **Subgroup Analysis**

Results from all subgroup analysis of treatment outcome at Week 6 by are shown in the Appendix, Figure 1. These results show that treatment effects were consistent across the subgroups examined. Note that in this figure, the differences are for the 4.8 dose minus the 2.4 dose.

3.1.1.2.4 **Sponsor's Analyses of Secondary Efficacy Variables**

Secondary efficacy endpoints included sigmoidoscopic and clinical improvement (stool frequency, rectal bleeding, PGA, and PFA), and quality of life (Inflammatory Bowel Disease Questionnaire) at Weeks 3 and 6.

3.1.1.2.4.1 **Improvement in Individual Clinical and Sigmoidoscopic Assessment**

Summary of treatment outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6 is given in Appendix Table 2.

As seen Appendix Table 2, at Week 3, significantly more patients receiving Asacol 800 (4.8 g/day) experienced improvement in stool frequency versus Asacol 2.4 g/day (400 mg). There were no treatment differences for improvement either at Week 3 or Week 6 for other individual clinical and sigmoidoscopic assessment.

3.1.1.2.4.2 **Change in UCDAI**

The mean change from baseline in UCDAI was statistically significant for both the 4.8 g/day group and 2.4 g/day group, however, the difference between the two groups was not statistically significant.

3.1.1.3 **Reviewer's Comments and Evaluation**

3.1.1.3.1 **Study Design**

This study was originally designed for superiority of Asacol 4.8 g/day versus Asacol 2.4 g/day in improvement for the overall patient population and males. The study was initiated in June 2006. As the study was approaching completion (January 2007) the sponsor learned that a 4.8 g/day regimen of mesalamine (Lialda) had been approved on January 16, 2007 in the absence of incremental benefit of 4.8 g/day over 2.4 g/day, even though both doses were superior to placebo.

The sponsor decided to amend this study in advance of its meeting with FDA on March 16 to allow the study to continue without any pause in enrollment. Subsequently, the study was amended on March 2, 2007 to increase the sample size from 470 to 770 patients, while the primary analysis was changed to add a test for non-inferiority of the two treatment regimens.

At the time of the amendment (March 2, 2007), a total of 552 patients had enrolled in the study, well over the 470 patients required in the protocol. The protocol was amended to add 300 more patients to increase the sample size to 770 patients.

It is unclear whether the sponsor knew that the superiority objective was likely to fail if the study ended as planned with 470 patients. However, as it turned out, the study failed superiority with a p-value of 0.4595 at the time of the amendment. The treatment difference was 3.0% with 95% C.I. (-4.8%, 10.8%). The sponsor's added of the additional 300 patients had the effect of narrowing the 95% confidence interval to (-1.9%, 11.2%).

It can be stated that the sponsor performed an "adaptive strategy" in changing their design during the course of the study. This is not a pre-specified adaptive design which is normally required for confirmatory interpretation of the statistical results. From this reviewer's perspective, this is considered a post hoc study design change. To explore adjustment of type I error, however, this reviewer requested the sponsor calculate a 95% confidence interval of treatment difference using an adaptive adjustment method [Cui, Hung, Wang, (1999) Modification of Sample Size in Group Sequential Clinical Trial]. These results are given in section 3.1.1.3.6.2.

3.1.1.3.2 **Non-inferiority Margin**

The non-inferiority margin was not pre-specified in the amendment dated March 2, 2007 but was communicated to the Agency at the sponsor meeting of March 17, 2007. At that time, the sponsor's 10% non-inferiority margin had not been justified and no agreement on sponsor's 10% non-inferiority margin was reached. The sponsor was to provide additional justification for the margin at the time of submission.

The sponsor provided some justification based on an historical study (C14) in Section 2.5.4 (Overview of Efficacy) in their submission. Treatment outcomes at Week 6 for this study are given below for patients with mild-to-moderately active UC and patients with moderately active UC. Patients with missing observations were set to "treatment failure."

Summary of Treatment Outcome at Week 6 for Study C14

ITT Analysis

	Placebo		Asacol 2.4 g/day		Difference	
Population	Rate	95% CI	Rate	95% CI	Rate	95%CI
Mild to Moderate	11/52 (21%)	(11%, 35%)	22/53 (42%)	(28%, 56%)	20%	(3%, 38%)
Moderate	8/24 (33%)	(16%, 55%)	15/24 (63%)	(41%, 81%)	29%	(2%, 56%)

Compiled from Table 2.5.4.2
Missing observations set to treatment failure.

As seen from the table above, for patients with mild to moderate disease in C14, the treatment difference was 20%, 95% CI (3%, 38%). For subgroup of patients with moderate disease in Study C14, the treatment difference was 29%, 95% CI (2%, 56%). The lower limits were similar for patients with mild to moderate and moderate disease.

But, for patients with mild to moderate disease in C14, the results from this reviewer's analysis (ref. Statistical Review and Evaluation for NDA 19-651 Asacol Tablet 400 mg dated February 26, 1991) showed that the mean rate for patient improvement at Week 6 was 49% (21/43) and 23%,(10/44) for Asacol 2.4 g/day and placebo, respectively. The treatment difference was 26% with 95% CI (7%, 46%).

So, the lower limits for 95% confidence intervals ranged from 3% to 7% for patients with mild to moderate disease in C14. Applying a 50% discount to the lower confidence limit to establish the non-inferiority margin, the margin should have ranged from 1.5% to 3.5% for patients with mild to moderate disease.

This confidence interval of treatment difference however is susceptible to bias since it was based on a subgroup of patients with moderate disease. It is unclear whether it can be assumed that the non-inferiority margin for patients with moderate disease is similar to that for patients with mild to moderate disease.

3.1.1.3.3 **Sensitivity Analysis for Primary Efficacy Endpoint**

This reviewer performed a sensitivity analysis including three analyses listed below.

1) "true" ITT analysis including all randomized patients; patients without Week 6 outcome were assumed to be "failure."
2) ITT LOCF analysis
3) Analyzable analysis including only patients with known Week 6 outcome.

The result of this sensitivity analysis is given below.

Summary of Treatment Outcomes at Week 6
Study 2006444

Analysis	4.8 g/day Asacol 800	2448 g/dayAsacol	Difference	95% C.I.
"True" ITT	273/392 (69.6%)	251/383 (65.5%)	4.1%	(-2.5%, 10.7%)
ITT LOCF	275/391 (70.3%)	252/383 (65.8%)	4.5%	(-2.0%, 11.1%)
Analyzable	273/369 (74.0%)	251/366 (68.6%)	5.4%	(-1.1%, 11.9%)

Tabulated by reviewer.

As seen from the table above, the treatment differences range from 4.1% to 5.4% with the lower limits of 95% confidence intervals ranging from -1.1% and -2.5%. The sponsor's result can be considered to be robust as their lower confidence limit (-1.9%) is between -1.1% and -2.5%.

3.1.1.3.4 **Primary Efficacy Endpoint**

The primary efficacy endpoint in this study was less stringent as compared to Studies 2000082 and 2000083,

Unlike Studies 2000082 and 2000083, in this study, the physician's functional assessment (PFA) was not a component of the PGA. The PGA was based on stool frequency (patient recall from previous 3 days), rectal bleeding (patient recall from previous 3 days), and sigmoidoscopy findings.

In Studies 2000082 and 2000083, a partial response was defined as improvement from baseline in the PGA, accompanied by improvement in at least one other category of symptoms (stool frequency, rectal bleeding, PFA, or sigmoidoscopy score) and no worsening in all remaining categories.

But, in this study, a partial response was defined as improvement from baseline in the PGA and no worsening in any of the 3 component endpoints.

Per this reviewer's request, the sponsor incorporated the changes in PFA into the definition of treatment success for the primary endpoint using the same algorithm as was used Studies 2000082 and 2000083. The results are given below.

Superiority of Treatment Outcome at Week 6: Missing Observations Set to Treatment Failure
Includes PFA Assessment in Treatment Outcome
Study 2006444
(Intent-to-Treat Patients)

Treatment / Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 383) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 389) n (%)	Total (N = 772) n (%)	p-value (a)	4.8 -2.4 Difference in Response Rates (b)	Confidence Interval for 4.8 - 2.4 (c)
Success	250 (65.3%)	271 (69.7%)	521 (67.5%)			
Failure	133 (34.7%)	118 (30.3%)	251 (32.5%)			
Total	383	389	772	0.1946	4.4	(-2.2, 11.0)

N = number of patients in treatment group who met the inclusion criteria.
n (%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome.
(a) 4.8 g/day compared to 2.4 g/day, stratified by sex using the Cochran-Mantel-Haenszel test.
(b) Risk difference between 4.8 g/day and 2.4 g/day.
(c) Confidence interval for the risk difference in response rates between 4.8 g/day and 2.4 g/day with no stratification.
/ASACOL/2006444/ANALVAL/EFFICACY/FDA/main_eff_pfa.sas; on 05DEC07 16:06 by TY1006.

As seen from this table, including PFA assessment in treatment outcome, the ITT analysis demonstrated statistical non-inferiority between Asacol 800 (4.8 g/day) and Asacol 2.4 g/day with a lower limit confidence interval of -2.2%.

3.1.1.3.5 Demographic and Baseline Information Before and After the Protocol Amendment

Per this reviewer's request, the sponsor provided the patient populations by demographic and baseline characteristics before and after the amendment. Demographic and baseline characteristics are given in Appendix Table 3 and Table 4 for before and after protocol amendment, respectively.

As seen from Appendix Tables 3 and 4, the patient populations were consistent before and after the amendment for demographic and baseline characteristics with exception for age. There was statistically significant treatment difference in age after the amendment (mean age 39.8 for Asacol 400 mg and 44.1 for Asacol 800 mg).

Ulcerative colitis history is given in Appendix Table 5 and Table 6 for before and after protocol amendment, respectively.

As seen in Appendix Tables 5 and 6, the patient populations were consistent before and after the amendment for ulcerative colitis history with exception for length of disease history, steroid use, sulfa-free oral 5-ASAs, any oral 5-ASAs, rectal therapies, and relapse frequency. There were slight treatment differences in sulfa-free oral 5-ASAs and any oral 5-ASAs before the amendment and in length of disease history, steroid use, and rectal therapies after the amendment.

Baseline disease state characteristics are given in Appendix Table 7 and Table 8 for before and after protocol amendment, respectively.

As seen in Appendix Tables 7 and 8, the patient populations were consistent before and after the amendment for baseline disease state characteristics with exception for stool frequency score and rectal bleeding score. There were slight treatment differences in stool frequency score before the amendment.

3.1.1.3.6 Results of Analyses of Primary Efficacy Endpoint Before and After the Protocol Amendment

Per this reviewer's request, the sponsor provided results of analyses of efficacy before and after the protocol amendment.

3.1.1.3.6.1 Primary Efficacy Endpoint

A summary of patients with treatment success at Week 6 for ITT and Per Protocol analyses are given in Appendix Table 9 and Table 10 before the amendment and after the amendment, respectively.

As seen in Appendix Tables 9 and 10, ITT analysis indicated statistical non-inferiority between Asacol 2.4 g/day and Asacol 800 (4.8 g/day). The upper limit of the confidence interval of the differences (the 2.4 dose group minus the 4.8 dose group) showed 4.8% before the amendment and 3.5 after the amendment.

The per protocol analysis was consistent with statistical non-inferiority between Asacol 2.4 g/day and Asacol 800 (4.8 g/day) with an upper limit confidence interval of 7.3%. before the amendment. The 95% confidence interval of the treatment difference after the amendment was (-26.1, -2.0) which did not contain zero

3.1.1.3.6.2 95% Confidence Interval adjusting for Protocol Amendment

Per this reviewer's request, the sponsor calculated a 95% confidence intervals of treatment difference between Asacol 2.4 g/day and Asacol 800 (4.8 g/day) adjusting for protocol amendment using three methods; Cochran-Mantel-Haenszel, Adaptive Adjustment, and DerSimonian and Laird methods. The results for these methods are given below.

Method for Calculating Confidence Interval	*95% two-sided Confidence Interval*
Cochran-Mantel-Haenszel method	(-11.15%, 1.85%)
Adaptive Adjustment Method	(-11.43%, 1.96%)
Primary Analysis of 2006444	(-11.2%, 1.9%)
DerSimonian and Laird	(-11.30%, 1.86%)

These results showed the upper confidence limits were similar and close to 2.0%.

3.1.1.3.6.3 Secondary Efficacy Endpoints

A summary of distribution of treatment outcomes for physician's global assessment and individual symptoms at Weeks 3 and 6 are given in Appendix Table 11 and Table 12 before the amendment and after the amendment, respectively.

As seen from Appendix Table 11 and Table 12, treatment differences were inconsistent before and after amendment for physician's global assessment and individual symptoms.

Treatment difference after amendment tends to larger that those before amendment with exception for PFA at Week 3.

3.2 **Evaluation of Safety**

3.2.1 **Study 2006444**

The percent of patients with AEs and percent of patients who withdrew due to AEs were the same for both treatment groups (20.6% and 3.9%, respectively). Both treatments were well-tolerated, with a mean of 0.4 and 0.3 AE's per patients in the 4.8 g/day and 2.4 g/day groups, respectively. Refer to the medical officer's review for more detail regarding the safety results.

4. FINDING IN SPEC IAL/SUBGROUP POPULATION

4.1 **Gender, Race and Age**

The summary of primary efficacy endpoint by gender and race and age is given the Appendix Figure 1.

4.2 **Other Special/Subgroup Population**

The summary of primary efficacy endpoint evaluation by other special/subgroup population is given Appendix, Figure 1.

5. SUMMARY AND CONCLUSIONS

5.1 **Statistical Issues and Collective Evidence**

The sponsor has submitted two pivotal studies to support an indication for Asacol, 4.8 g/day for treatment of moderately active ulcerative colitis. These are studies 2000082 (contained in the original NDA 21-830) and study 2006444 (contained in this Complete Response.).

In the original submission, the sponsor submitted studies (2000083 and 2000082) (ASCEND I and ASCEND II) comparing efficacy and safety of Asacol 800 dosed 4.8 g/day versus Aascol dosed 2.4 g/day in treatment of patients with moderately active ulcerative colitis.

Based on subgroup results from the completed study 2000083, the sponsor amended ongoing study 200082 on February 18, 2003 when most of the intended sample size (96%) had been enrolled. Under the amended protocol, only patients with moderate disease at baseline (PGA=2) were to be enrolled; the sponsor increased the sample size and changed the focus of the primary analysis to the subgroup of patients with moderate active ulcerative colitis at baseline.

For study 2000082, superiority was seen among all patients with moderate disease at baseline enrolled in the study. However, superiority was not demonstrated for patients enrolled after the amendment. The success rates were much higher than those for patients enrolled before the amendment than after the amendment for patients with moderate disease at baseline (71.4% vs. 54.7% for 2.4 g/day and 75.6% vs. 69.9% for 4.8 g/day).

Study 2000082 showed a slightly better rate of treatment success at week 6 for the 4.8 g/day group compared to the 2.4 g/day group, with a nominal p-value of 0.0463, adjusted for time of enrollment. From a statistical perspective, this result was not statistically persuasive, and the sponsor's adaptive changes to study 2000082 are considered to be post hoc. It was concluded that superiority of the higher dose was not clearly established, and a second phase 3 study would be required.

In complete response to the August 29, 2005 Approvable Letter, the sponsor submitted results for Study 2006444 (ASCEND III) which was originally designed as a superiority trial. As this study was approaching completion (January 2007) the sponsor learned that a 4.8 g/day regimen of mesalamine (Lialda) had been approved on January 16, 2007 in the absence of incremental benefit of 4.8 g/day over 2.4 g/day, even though both doses were shown to be superior to placebo.

Subsequently, study 2006444 was amended (IND 26,093 Serial #262) on March 2, 2007 to increase the sample size to from 470 to 770 patients, while the primary analysis plan was changed to first test for non-inferiority of the two treatment regimens.

The sponsor's 10% non-inferiority margin was not pre-specified in the amendment dated March 2, 2007 but was discussed at the March 17, 2007 meeting with the sponsor. At that time, no agreement on the 10% margin had been reached, and it was concluded that the sponsor would provide additional justification in the submission.

The ITT analysis for study 2006444 demonstrated statistical non-inferiority between Asacol 800 (4.8 g/day) and Asacol 2.4 g/day for treatment outcome at Week 6 with a lower limit of confidence interval of -1.9%. Per protocol analysis demonstrated statistical non-inferiority with a lower limit of confidence interval of -2.3%. Both lower limits were smaller than the pre-specified 10%.

From this reviewer's sensitivity analysis, the treatment differences ranged from 4.1% to 5.4% with the lower limits of 95% confidence intervals ranged from -1.1% and -2.5%. In this reviewer's opinion, the sponsor's results can be considered robust since the lower confidence limit (-1.9%) is between -1.1% and -2.5%.

Furthermore, from the placebo-controlled study C14 conducted for Asacol under NDA 19-651,, lower limits of 95% confidence intervals of differences between 2.4 g/day and placebo was 3% for ITT analysis and 7% for patients with mild to moderate disease. For the subgroup of patients with moderate disease in Study C14, the lower confidence limit was 2%.

A 50% discount applied to the lower limit to establish a non-inferiority margin yields a margin ranging from 1.5% to 3.5% for patients with mild to moderate disease and about 1.0% for patients with moderate disease. However, the confidence interval of treatment difference for the subgroup of patients with moderate disease may not be reliable due to potential bias.

5.2 **Conclusions and Recommendations**

As concluded in the original statistical review of study 2000082, that study did not provide substantial evidence demonstrating superiority of the 4.8 mg/day dose over the 2.4 mg/day dose. The many design changes specified near the end of that study and the inconsistencies in efficacy results were problematic. At best, the results from study 2000082 can provide supportive evidence of efficacy.

The results for study 2006444 provide principle support for efficacy of the 4.8 g/day dose as demonstrated by a treatment difference of 4.6% in favor of 4.8 g/day with 95% confidence interval of (-1.9%, 11.2%). Additionally, the lower limit of this confidence interval is smaller than the pre-specified non-inferiority margin of 10% and is close to 1.0%, a margin obtained from the historical placebo controlled study for patients with moderate disease. Thus, Asacol 800 dosed at 4.8 g/day should be considered efficacious compared to placebo.

6. APPENDIX

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 2006444

Characteristics	(All Randomized Patients) 2.4 g/day mesalamine (400 mg Tablet) (N=383)	4.8 g/day mesalamine (800 mg Tablet) (N=392)	Between Treatment p-value
Sex			0.8259
Male	216 (56.4%)	218 (55.6%)	
Female	167 (43.6%)	174 (44.4%)	
Race			0.5804
White	368 (96.1%)	380 (96.9%)	
Black	6 (1.6%)	3 (0.8%)	
Other Races	9 (2.4%)	9 (2.3%)	
Age (yrs)			0.0696
Mean (SD)	42.4 (13.6)	44.1 (13.3)	
Age			0.4845
18 to 64	355 (92.7%)	358 (91.3%)	
≥65	28 (7.3%)	34 (8.7%)	
Height (cm)			0.5570
N	381	392	
Mean (SD)	171.4 (9.2)	171.0 (9.3)	
Weight (kg)			0.9127
N	381	392	
Mean (SD)	73.9 (15.6)	74.0 (15.5)	
Smoking History			0.7474
Never smoked	239 (62.4%),	242 (61.7%)	
Previously smoked	103 (26.9%)	113 (28.8%)	
Currently smokes	41 (10.7%)	37 (9.4%)	
Disease Extent			0.2349
N	379	387	
Proctosigmoiditis	183 (48.3%)	185 (47.8%)	
Left-sided colitis	136 (35.9%)	139 (35.9%)	
Pancolitis	44 (11.6%)	35 (9.0%)	
Extensive	16 (4.2%)	28 (7.2%)	
Disease diagnosis			0.4796
Newly diagnosed	307 (80.2%)	322 (82.1%)	
Previous diagnosed	76 (19.8%)	70 (17.9%)	

Compiled by this reviewer. P-values were obtained by this reviewer.
Chi-square test was used for sex, age group, and race. ANOVA was used for age, height, and weight

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 2006444 (Continued)

Characteristics	(All Randomized Patients) 2.4 g/day mesalamine (400 mg Tablet) (N=383)	4.8 g/day mesalamine (800 mg Tablet) (N=392)	Between Treatment p-value
Prior Treatment			
Steroids	157 (41.0%)	158 (40.3%)	0.8459
Immunomodulators	17 (4.4%)	17 (4.3%)	0.9448
Sulfasalazine	196 (51.2%)	210 (53.6%)	0.5042
Sulfa-free oral 5-ASAs	240 (62.7%)	252 (64.3%)	0.6390
H2 antagonist	4 (1.0%)	2 (0.05%)	0.3963
Proton Pump Inhibitor	15 (3.9%)	17 (4.3%)	0.7687
Bioligic use	3 (0.8%)	4 (1.0%)	0.7272
Rectal therapies	188 (49.1%)	194 (49.5%)	0.9105
UC Relapse Frequency			0.2883
Newly diagnosed	76 (19.8%)	70 (17.9%)	
More than once a month	21 (5.5%)	12 (3.1%)	
Once every 6 months	108 (28.2%)	123 (31.4%)	
Once every 6 to 12 months	122 (31.9%)	118 (30.1%)	
Less than once a year	56 (14.6%)	69 (17.6%)	
Physician's Global Assessment Score			
2 (Moderate activity)	383 (100.0%)	391 (100.0%)	
Stool Frequency Score			0.4244
1 (1 to 2 greater than normal)	53 (13.8%)	50 (12.89%)	
2 (3 to 4 greater than normal)	271 (70.8%)	292 (74.7%)	
3 (≥ 5 greater than normal)	59 (15.4%)	49 (12.5%)	
Rectal Bleeding Score			0.7044
1 (Streak, less than ½ times)	112 (29.2%)	120 (30.7%)	
2 (Obvious, most of time)	266 (69.5%)	268 (68.5%)	
3 (Blood alone)	5 (1.3%)	3 (0.8%)	
Patient's Functional Assessment Score			0.3340
0 (Generally well)	16 (4.2%)	24 (6.1%)	
1 (Fair)	172 (44.9%)	177 (45.3%)	
2 (Poor)	191 (49.9%)	189 (48.3%)	
3 (Terrible)	4 (1.0%)	1 (0.3%)	

Compiled by this reviewer. P-values were obtained by this reviewer.
Chi-square test was used for sex, age group, and race. ANOVA was used for age, height, and weight

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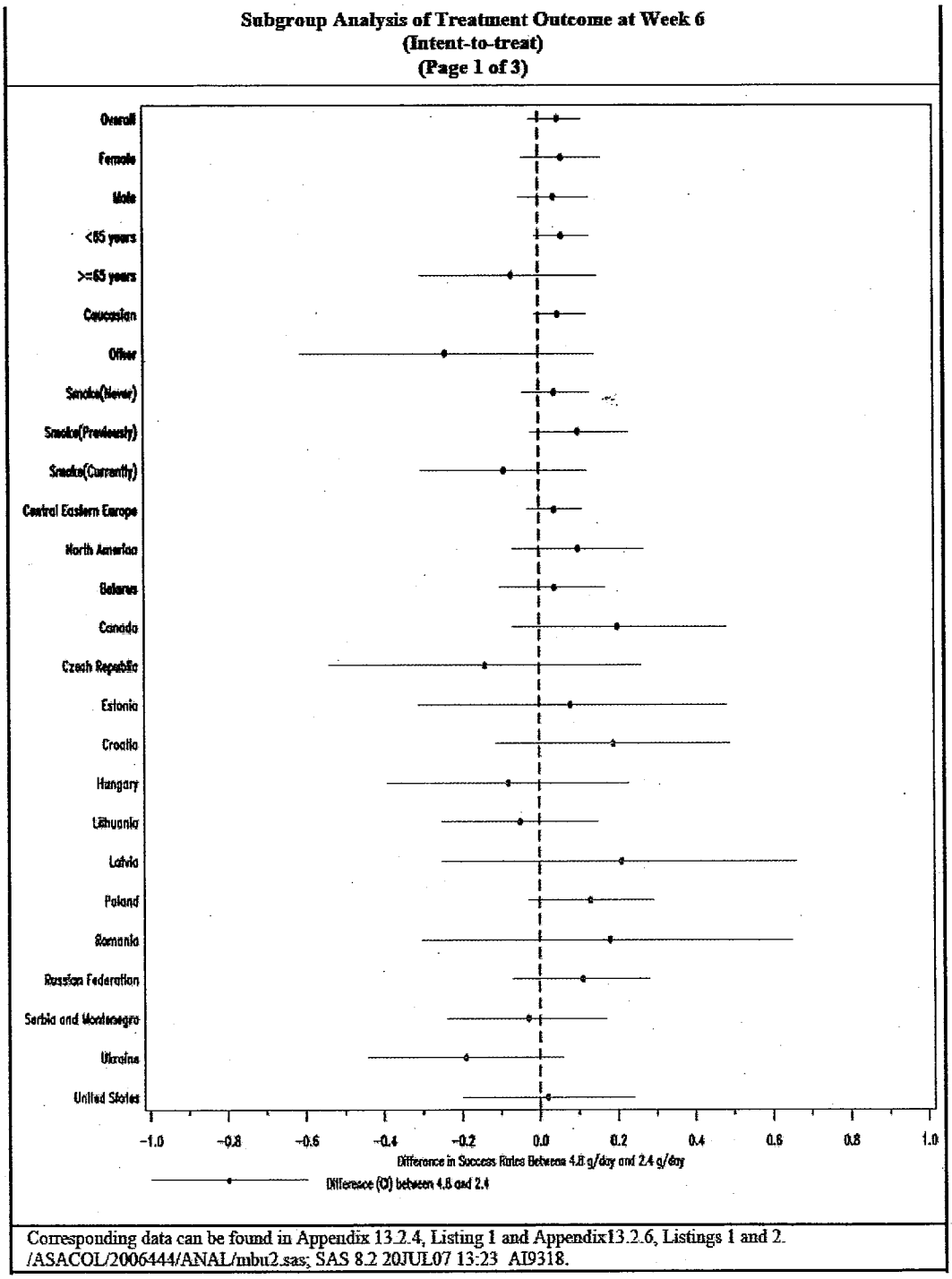
Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 2006444 (Continued)

Characteristics	(All Randomized Patients) 2.4 g/day mesalamine (400 mg Tablet) (N=383)	4.8 g/day mesalamine (800 mg Tablet) (N=392)	Between Treatment p-value
Sigmoidoscopy Score			0.3037
1 (Mild)	1 (0.5%)	0 (0.0%)	
2 (Moderate)	364 (95.0%)	371 (94.6%)	
3 (Severe)	17 (4.4%)	21 (5.4%)	
UCDAI Score			0.6306
N			
Mean (SD)	7.8 (0.68)	7.8 (0.68)	

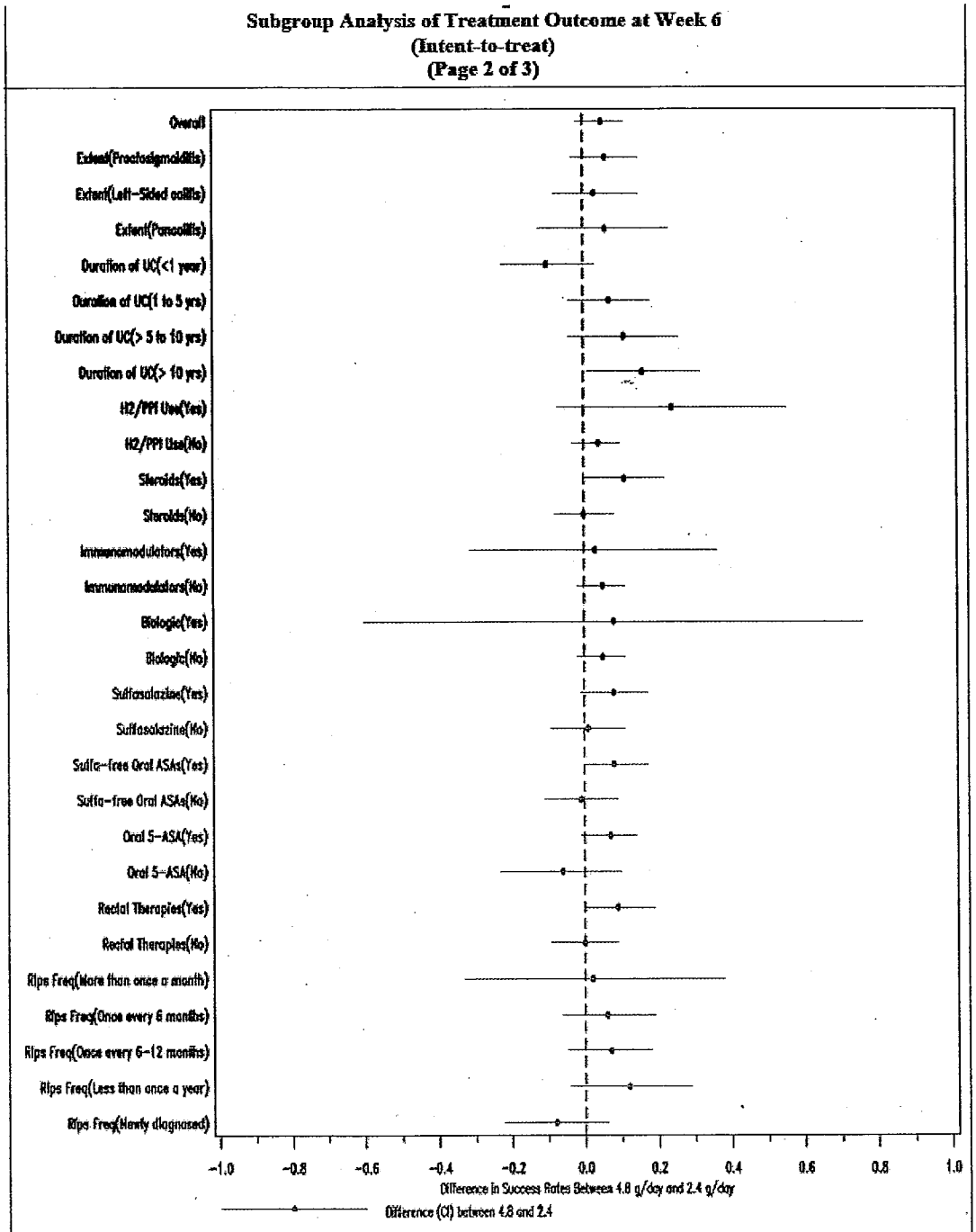
Compiled by this reviewer. P-values were obtained by this reviewer.
Chi-square test was used for sex, age group, and race. ANOVA was used for age, height, and weight

Figure 1 Subgroup Analysis of Treatment Outcome at Week 6 for ITT Analysis -- Protocol 2006444



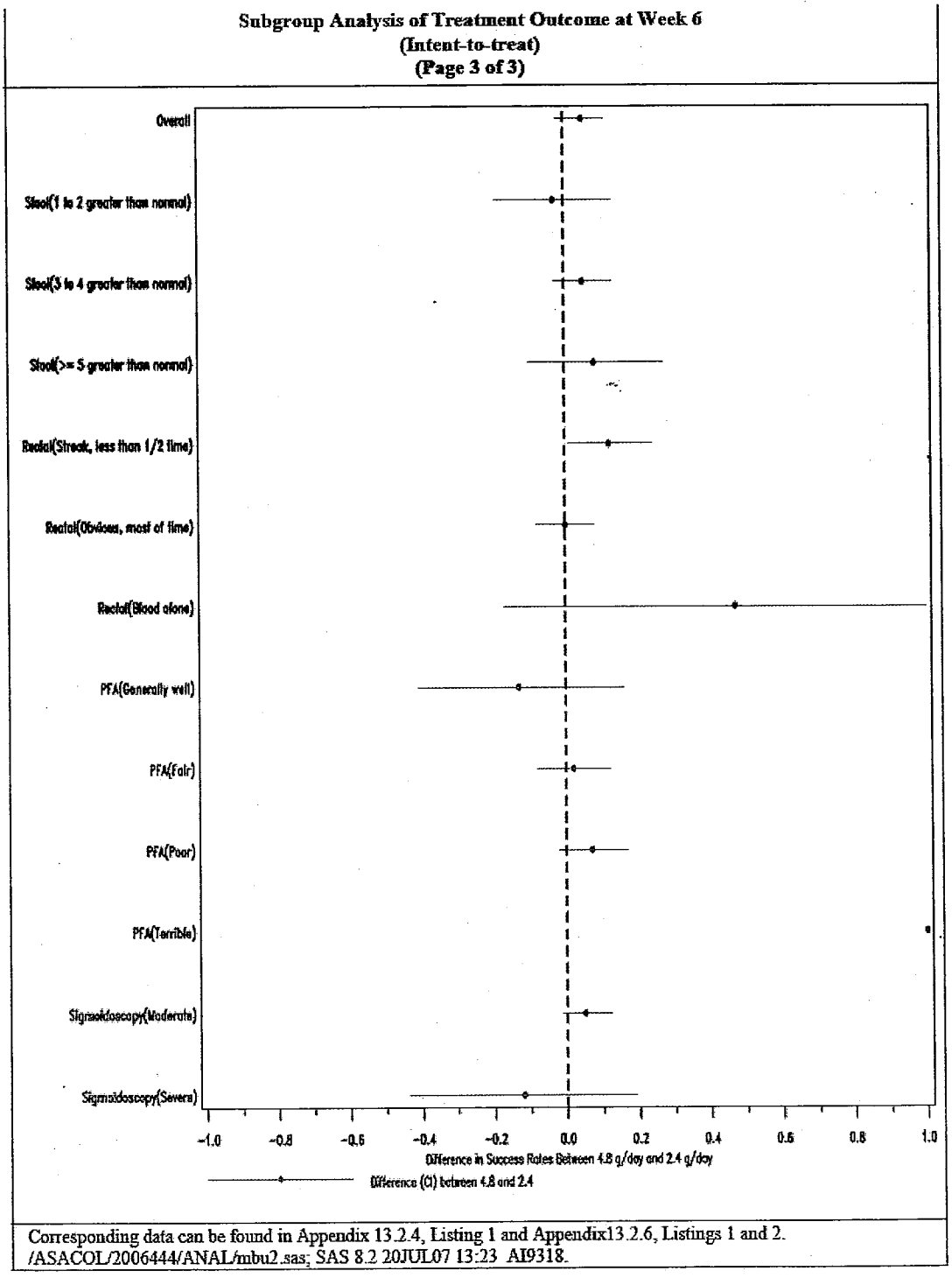
Corresponding data can be found in Appendix 13.2.4, Listing 1 and Appendix13.2.6, Listings 1 and 2. /ASACOL/2006444/ANAL/mbu2.sas; SAS 8.2 20JUL07 13:23 AI9318.

Figure 1 Subgroup Analysis of Treatment Outcome at Week 6 for ITT Analysis --- Protocol 2006444 (Continued)



Corresponding data can be found in Appendix 13.2.4, Listing 1 and Appendix13.2.6, Listings 1 and 2. /ASACOL/2006444/ANAL/mbu2.sas; SAS 8.2 20JUL07 13:23 AI9318.

Figure1 Subgroup Analysis of Treatment Outcome at Week 6 for ITT Analysis ---Protocol 2006444 (Continued)



Corresponding data can be found in Appendix 13.2.4, Listing 1 and Appendix13.2.6, Listings 1 and 2.
/ASACOL/2006444/ANAL/mbu2.sas; SAS 8.2 20JUL07 13:23 AI9318.

Table 2 Distribution of Treatment Outcomes for PGA and Individual Symptoms at Weeks 3 and 6 -- Protocol 2006444

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6
Excluding Patients With Both Baseline and Visit Scores of Zero
(Intent-to-treat)

Parameter	Visit	Outcome	2.4g/day Asacol (400 mg Tablet) n (%)	4.8g/day Asacol (800 mg Tablet) n (%)	Total n (%)	CMH General Association p-value[a]	4.8 - 2.4 Difference in Improvement Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
PGA	Week 6	I	252 (73.0%)	276 (79.3%)	528 (76.2%)			
		NI	93 (27.0%)	72 (20.7%)	165 (23.8%)			
		Total	345	348	693	0.0528	6.3	(-0.1, 12.6)
Stool Frequency	Week 3	I	237 (66.0%)	279 (76.4%)	516 (71.3%)			
		NI	122 (34.0%)	86 (23.6%)	208 (28.7%)			
		Total	359	365	724	0.0019	10.4	(3.9, 17.0)
	Week 6	I	258 (74.4%)	280 (79.3%)	538 (76.9%)			
		NI	89 (25.6%)	73 (20.7%)	162 (23.1%)			
		Total	347	353	700	0.1186	5.0	(-1.3, 11.2)
Rectal Bleeding	Week 3	I	278 (77.4%)	283 (77.5%)	561 (77.5%)			
		NI	81 (22.6%)	82 (22.5%)	163 (22.5%)			
		Total	359	365	724	0.9736	0.1	(-6.0, 6.2)
	Week 6	I	276 (79.5%)	298 (84.4%)	574 (82.0%)			
		NI	71 (20.5%)	55 (15.6%)	126 (18.0%)			
		Total	347	353	700	0.0934	4.9	(-0.8, 10.6)

PGA = Physician's Global Assessment; PFA = Patient's Functional Assessment
n (%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome
I = Improved
NI = Not improved
[a] 4.8g/day compared to 2.4g/day, stratified by sex using the Cochran-Mantel-Haenszel test.
[b] Difference between Asacol 800 (4.8g/day) and Asacol 2.4g/day
[c] Confidence interval for the difference in success rates between 4.8g/day and 2.4g/day with no stratification
Corresponding data can be found in Appendix 13.2.6, Listings 1 and 2.
/ASACOL/2006444/ANAL/adv2.sas; SAS 8.2 20JUL07 13:23 AI9318.

Table 2 Distribution of Treatment Outcomes for PGA and Individual Symptoms at Weeks 3 and 6 ---Protocol 2006444 (Continued)

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6
Excluding Patients With Both Baseline and Visit Scores of Zero
(Intent-to-treat)
(Page 2 of 2)

Parameter	Visit	Outcome	2.4g/day Asacol (400 mg Tablet) n (%)	4.8g/day Asacol (800 mg Tablet) n (%)	Total n (%)	CMH General Association p-value[a]	4.8 - 2.4 Difference in Improvement Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
PFA	Week 3	I	223 (63.9%)	244 (70.7%)	467 (67.3%)			
		NI	126 (36.1%)	101 (29.3%)	227 (32.7%)			
		Total	349	345	694	0.0562	6.8	(-0.1, 13.8)
	Week 6	I	243 (72.3%)	254 (76.0%)	497 (74.2%)			
		NI	93 (27.7%)	80 (24.0%)	173 (25.8%)			
		Total	336	334	670	0.2667	3.7	(-2.9, 10.3)
Sigmoidoscopy with CFT	Week 6	I	106 (30.7%)	105 (30.2%)	211 (30.4%)			
		NI	239 (69.3%)	243 (69.8%)	482 (69.6%)			
		Total	345	348	693	0.8823	-0.6	(-7.4, 6.3)

PGA = Physician's Global Assessment; PFA = Patient's Functional Assessment
n (%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome
I = Improved
NI = Not improved
[a] 4.8g/day compared to 2.4g/day, stratified by sex using the Cochran-Mantel-Haenszel test.
[b] Difference between Asacol 800 (4.8g/day) and Asacol 2.4g/day
[c] Confidence interval for the difference in success rates between 4.8g/day and 2.4g/day with no stratification
Corresponding data can be found in Appendix 13.2.6, Listings 1 and 2.
/ASACOL/2006444/ANAL/adv2.sas; SAS 8.2 20JUL07 13:23 AI9318.

Table 3 Demographic and Baseline Characteristics ITT Analysis Before March 2, 2007 --- Protocol 2006444

Demographic and Baseline Characteristics
(Intent-to-treat Before March 2, 2007)
(Page 1 of 2)

Parameter Statistic/Category	2.4 g/day Asacol (400 mg tablet) (N=271)	4.8 g/day Asacol (800 mg tablet) (N=281)	p-value
Age			0.5201
n	271	281	
Mean (SD)	43.4 (13.67)	44.1 (13.36)	
Median	42.0	44.0	
Min,Max	18,75	19,75	
Age Group	271 (100.0%)	281 (100.0%)	1.0000
<65 years	248 (91.5%)	257 (91.5%)	
>=65 years	23 (8.5%)	24 (8.5%)	
Height (cm)			0.6336
n	269	281	
Mean (SD)	171.08 (9.289)	170.70 (9.206)	
Median	170.00	170.00	
Min,Max	145.0,202.0	152.0,200.0	
Weight (kg)			0.9066
n	269	281	
Mean (SD)	73.97 (16.294)	73.82 (15.015)	
Median	72.80	73.00	
Min,Max	42.0,131.1	37.0,134.3	
Race	271 (100.0%)	281 (100.0%)	0.7500
Caucasian	261 (96.3%)	273 (97.2%)	
Black	5 (1.8%)	3 (1.1%)	
Indian (Asian)	3 (1.1%)	3 (1.1%)	
Asian (Oriental)	1 (0.4%)	0 (0.0%)	
Multi-Racial	1 (0.4%)	2 (0.7%)	
Sex	271 (100.0%)	281 (100.0%)	0.8643
Male	150 (55.4%)	153 (54.4%)	
Female	121 (44.6%)	128 (45.6%)	
Smoking History	271 (100.0%)	281 (100.0%)	0.3965
Currently	29 (10.7%)	22 (7.8%)	
Never	176 (64.9%)	181 (64.4%)	
Previously	66 (24.4%)	78 (27.8%)	

N = number of patients within specified treatment.
n(%) = number and percentage of patients in category and treatment group.
Categorical p-values are chi-square test and continuous p-values are one-way ANOVA.
/ASACOL/2006444/FDA_04DEC2007/ANAL/eff_demog.sas; SAS 8.2 05DEC07 14:03 AW2116.

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Table 4 Demographic and Baseline Characteristics ITT Analysis After March 2, 2007 --- Protocol 2006444

Demographic and Baseline Characteristics
(Intent-to-treat After March 2, 2007)
(Page 1 of 2)

Parameter Statistic/Category	2.4 g/day Asacol (400 mg tablet) (N=112)	4.8 g/day Asacol (800 mg tablet) (N=108)	p-value
Age			0.0169
n	112	108	
Mean (SD)	39.8 (13.00)	44.1 (13.45)	
Median	40.5	45.0	
Min,Max	18,74	19,73	
Age Group	112 (100.0%)	108 (100.0%)	0.1876
<65 years	107 (95.5%)	98 (90.7%)	
>=65 years	5 (4.5%)	10 (9.3%)	
Height (cm)			0.8355
n	112	108	
Mean (SD)	172.28 (9.098)	172.02 (9.396)	
Median	172.35	172.35	
Min,Max	150.0,198.0	154.0,195.0	
Weight (kg)			0.6316
n	112	108	
Mean (SD)	73.81 (13.737)	74.79 (16.248)	
Median	74.00	74.75	
Min,Max	46.0,105.0	43.0,120.0	
Race	112 (100.0%)	108 (100.0%)	0.7339
Caucasian	107 (95.5%)	105 (97.2%)	
Black	1 (0.9%)	0 (0.0%)	
Indian (Asian)	2 (1.8%)	1 (0.9%)	
Multi-Racial	2 (1.8%)	2 (1.9%)	
Sex	112 (100.0%)	108 (100.0%)	1.0000
Male	66 (58.9%)	64 (59.3%)	
Female	46 (41.1%)	44 (40.7%)	
Smoking History	112 (100.0%)	108 (100.0%)	0.7699
Currently	12 (10.7%)	15 (13.9%)	
Never	63 (56.3%)	58 (53.7%)	
Previously	37 (33.0%)	35 (32.4%)	

N = number of patients within specified treatment.
n(%) = number and percentage of patients in category and treatment group.
Categorical p-values are chi-square test and continuous p-values are one-way ANOVA.
/ASACOL/2006444/FDA_04DEC2007/ANAL/eff_demog.sas; SAS 8.2 05DEC07 14:03 AW2116.

Table 5 Ulcerative Colitis History ITT Analysis Before March 2, 2007--- Protocol 2006444

Ulcerative Colitis History
(Intent-to-treat Before March 2, 2007)
(Page 1 of 2)

Parameter Category	2.4 g/day Asacol (400 mg tablet) (N=271) n (%)	4.8 g/day Asacol (800 mg tablet) (N=281) n (%)	p-value
Disease Extent at Baseline	268 (100.0%)	276 (100.0%)	0.9378
Proctosigmoiditis	120 (44.8%)	126 (45.7%)	
Left-Sided Colitis	102 (38.1%)	101 (36.6%)	
Pancolitis(Pancolitis + Extensive)	46 (17.2%)	49 (17.8%)	
Length of Disease History	271 (100.0%)	281 (100.0%)	0.6098
<1 year	73 (26.9%)	62 (22.1%)	
1 to 5 yrs	97 (35.8%)	106 (37.7%)	
>5 to 10 yrs	55 (20.3%)	63 (22.4%)	
>10 yrs	46 (17.0%)	50 (17.8%)	
Steroids (oral or IV)	271 (100.0%)	281 (100.0%)	0.5492
No	154 (56.8%)	152 (54.1%)	
Yes	117 (43.2%)	129 (45.9%)	
Immunomodulators	271 (100.0%)	281 (100.0%)	0.6791
No	258 (95.2%)	270 (96.1%)	
Yes	13 (4.8%)	11 (3.9%)	
Biologics	271 (100.0%)	281 (100.0%)	1.0000
No	269 (99.3%)	279 (99.3%)	
Yes	2 (0.7%)	2 (0.7%)	
Sulfasalazine	271 (100.0%)	281 (100.0%)	0.6080
No	125 (46.1%)	123 (43.8%)	
Yes	146 (53.9%)	158 (56.2%)	
Sulfa-free oral 5-ASAs	271 (100.0%)	281 (100.0%)	0.1860
No	108 (39.9%)	96 (34.2%)	
Yes	163 (60.1%)	185 (65.8%)	
Any oral 5-ASAs	271 (100.0%)	281 (100.0%)	0.0791
No	43 (15.9%)	30 (10.7%)	
Yes	228 (84.1%)	251 (89.3%)	
Rectal Therapies	271 (100.0%)	281 (100.0%)	0.3086
No	142 (52.4%)	135 (48.0%)	
Yes	129 (47.6%)	146 (52.0%)	

N = number of patients within specified treatment.
n(%) = number and percentage of patients in category and treatment group.
p-value corresponds to the test of no treatment difference using chi-square test.
/ASACOL/2006444/FDA_04DEC2007/ANAL/eff_demog.sas; SAS 8.2 05DEC07 14:03 AW2116.

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Table 5 Ulcerative Colitis History ITT Analysis Before March 2, 2007 (Continued)

Ulcerative Colitis History
(Intent-to-treat Before March 2, 2007)
(Page 2 of 2)

Parameter Category	2.4 g/day Asacol (400 mg tablet) (N=271) n (%)	4.8 g/day Asacol (800 mg tablet) (N=281) n (%)	p-value
Relapse Frequency	271 (100.0%)	281 (100.0%)	0.3206
Newly diagnosed	50 (18.5%)	45 (16.0%)	
Less than once a year	31 (11.4%)	47 (16.7%)	
Once every 6-12 months	91 (33.6%)	87 (31.0%)	
Once every 6 months	82 (30.3%)	90 (32.0%)	
More than once a month	17 (6.3%)	12 (4.3%)	

N = number of patients within specified treatment.
n(%) = number and percentage of patients in category and treatment group.
p-value corresponds to the test of no treatment difference using chi-square test.
/ASACOL/2006444/FDA_04DEC2007/ANAL/eff_demog.sas; SAS 8.2 05DEC07 14:03 AW2116.

Table 6 Ulcerative Colitis History ITT Analysis After March 2, 2007 --- Protocol 2006444

Ulcerative Colitis History
(Intent-to-treat After March 2, 2007)
(Page 1 of 2)

Parameter Category	2.4 g/day Asacol (400 mg tablet) (N=112) n (%)	4.8 g/day Asacol (800 mg tablet) (N=108) n (%)	p-value
Disease Extent at Baseline	111 (100.0%)	108 (100.0%)	0.8308
Proctosigmoiditis	63 (56.8%)	59 (54.6%)	
Left-Sided Colitis	34 (30.6%)	37 (34.3%)	
Pancolitis(Pancolitis + Extensive)	14 (12.6%)	12 (11.1%)	
Length of Disease History	112 (100.0%)	108 (100.0%)	0.1597
<1 year	38 (33.9%)	36 (33.3%)	
1 to 5 yrs	34 (30.4%)	42 (38.9%)	
>5 to 10 yrs	17 (15.2%)	19 (17.6%)	
>10 yrs	23 (20.5%)	11 (10.2%)	
Steroids (oral or IV)	112 (100.0%)	108 (100.0%)	0.1445
No	72 (64.3%)	80 (74.1%)	
Yes	40 (35.7%)	28 (25.9%)	
Immunomodulators	112 (100.0%)	108 (100.0%)	0.7449
No	108 (96.4%)	103 (95.4%)	
Yes	4 (3.6%)	5 (4.6%)	
Biologics	112 (100.0%)	108 (100.0%)	0.6165
No	111 (99.1%)	106 (98.1%)	
Yes	1 (0.9%)	2 (1.9%)	
Sulfasalazine	112 (100.0%)	108 (100.0%)	0.7868
No	62 (55.4%)	57 (52.8%)	
Yes	50 (44.6%)	51 (47.2%)	
Sulfa-free oral 5-ASAs	112 (100.0%)	108 (100.0%)	0.2597
No	35 (31.3%)	42 (38.9%)	
Yes	77 (68.8%)	66 (61.1%)	
Any oral 5-ASAs	112 (100.0%)	108 (100.0%)	0.4765
No	17 (15.2%)	21 (19.4%)	
Yes	95 (84.8%)	87 (80.6%)	
Rectal Therapies	112 (100.0%)	108 (100.0%)	0.1403
No	53 (47.3%)	62 (57.4%)	
Yes	59 (52.7%)	46 (42.6%)	

N = number of patients within specified treatment.
n(%) = number and percentage of patients in category and treatment group.
p-value corresponds to the test of no treatment difference using chi-square test.
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Table 6 Ulcerative Colitis History ITT Analysis After March 2, 2007 --- Protocol 2006444 (Continued)

Ulcerative Colitis History
(Intent-to-treat After March 2, 2007)
(Page 2 of 2)

Parameter Category	2.4 g/day Asacol (400 mg tablet) (N=112) n (%)	4.8 g/day Asacol (800 mg tablet) (N=108) n (%)	p-value
Relapse Frequency	112 (100.0%)	108 (100.0%)	0.3264
Newly diagnosed	26 (23.2%)	24 (22.2%)	
Less than once a year	25 (22.3%)	22 (20.4%)	
Once every 6-12 months	31 (27.7%)	31 (28.7%)	
Once every 6 months	26 (23.2%)	31 (28.7%)	
More than once a month	4 (3.6%)	0 (0.0%)	

N = number of patients within specified treatment.
n(%) = number and percentage of patients in category and treatment group.
p-value corresponds to the test of no treatment difference using chi-square test.
/ASACOL/2006444/FDA_04DEC2007/ANAL/eff_demog.sas; SAS 8.2 05DEC07 14:03 AW2116.

Table 7 Baseline Disease State Characteristics ITT Analysis Before March 2, 2007--- Protocol 2006444

Baseline Disease State Characteristics (Intent-to-treat Before March 2, 2007)			
Parameter Statistic/Category	2.4 g/day Asacol (400 mg tablet) (N=271)	4.8 g/day Asacol (800 mg tablet) (N=281)	p-value
Stool Frequency Score	271 (100.0%)	281 (100.0%)	0.0877
1 (1 to 2 greater than normal)	37 (13.7%)	33 (11.7%)	
2 (3 to 4 greater than normal)	185 (68.3%)	214 (76.2%)	
3 (>= 5 greater than normal)	49 (18.1%)	34 (12.1%)	
Rectal Bleeding Score	271 (100.0%)	281 (100.0%)	0.7737
1 (Streak, less than 1/2 time)	82 (30.3%)	93 (33.1%)	
2 (Obvious, most of time)	186 (68.6%)	185 (65.8%)	
3 (Blood alone)	3 (1.1%)	3 (1.1%)	
Patient's Functional Assessment Score	271 (100.0%)	281 (100.0%)	0.7019
0 (Generally well)	12 (4.4%)	18 (6.4%)	
1 (Fair)	123 (45.4%)	124 (44.1%)	
2 (Poor)	134 (49.4%)	138 (49.1%)	
3 (Terrible)	2 (0.7%)	1 (0.4%)	
Sigmoidoscopy Score	271 (100.0%)	281 (100.0%)	0.5917
1 (Mild)	1 (0.4%)	0 (0.0%)	
2 (Moderate)	257 (94.8%)	268 (95.4%)	
3 (Severe)	13 (4.8%)	13 (4.6%)	
Baseline UCDAI			0.2558
n	271	281	
Mean (SD)	7.8 (0.71)	7.7 (0.68)	
Median	8.0	8.0	
Min,Max	7,9	6,9	
Number of days in Flare	269 (100.0%)	279 (100.0%)	0.9431
0 to 14	34 (12.6%)	38 (13.6%)	
15 to 28	62 (23.0%)	64 (22.9%)	
>28	173 (64.3%)	177 (63.4%)	

N = number of patients within specified treatment.
n(%) = number and percentage of patients in category and treatment group.
Categorical p-values are chi-square test and continuous p-values are one-way ANOVA.
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Table 8 Baseline Disease State Characteristics ITT Analysis After March 2, 2007 --- Protocol 2006444

Baseline Disease State Characteristics (Intent-to-treat After March 2, 2007)			
Parameter Statistic/Category	2.4 g/day Asacol (400 mg tablet) (N=112)	4.8 g/day Asacol (800 mg tablet) (N=108)	p-value
Stool Frequency Score	112 (100.0%)	108 (100.0%)	0.4549
1 (1 to 2 greater than normal)	16 (14.3%)	17 (15.7%)	
2 (3 to 4 greater than normal)	86 (76.8%)	76 (70.4%)	
3 (>= 5 greater than normal)	10 (8.9%)	15 (13.9%)	
Rectal Bleeding Score	112 (100.0%)	108 (100.0%)	0.3513
1 (Streak, less than 1/2 time)	30 (26.8%)	27 (25.0%)	
2 (Obvious, most of time)	80 (71.4%)	81 (75.0%)	
3 (Blood alone)	2 (1.8%)	0 (0.0%)	
Patient's Functional Assessment Score	112 (100.0%)	108 (100.0%)	0.3781
0 (Generally well)	4 (3.6%)	6 (5.6%)	
1 (Fair)	49 (43.8%)	53 (49.1%)	
2 (Poor)	57 (50.9%)	49 (45.4%)	
3 (Terrible)	2 (1.8%)	0 (0.0%)	
Sigmoidoscopy Score	112 (100.0%)	108 (100.0%)	0.2868
1 (Mild)	1 (0.9%)	0 (0.0%)	
2 (Moderate)	107 (95.5%)	100 (92.6%)	
3 (Severe)	4 (3.6%)	8 (7.4%)	
Baseline UCDAI			0.3413
n	112	108	
Mean (SD)	7.7 (0.60)	7.8 (0.68)	
Median	8.0	8.0	
Min,Max	7,9	7,9	
Number of days in Flare	112 (100.0%)	108 (100.0%)	0.2590
0 to 14	17 (15.2%)	11 (10.2%)	
15 to 28	22 (19.6%)	30 (27.8%)	
>28	73 (65.2%)	67 (62.0%)	

N = number of patients within specified treatment.
n(%) = number and percentage of patients in category and treatment group.
Categorical p-values are chi-square test and continuous p-values are one-way ANOVA.
/ASACOL/2006444/FDA_04DEC2007/ANAL/eff_demog.sas; SAS 8.2 05DEC07 14:03 AW2116.

Table 9 Primary Efficacy Analysis ITT and PP Analysis Before March 2, 2007 --- Protocol 2006444

Primary Efficacy Analysis
Non-Inferiority of Treatment Outcome at Week 6: Missing Observations Set to Treatment Failure
(Intent-to-treat Patients Before March 2, 2007)

Treatment Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 271) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 281) n (%)	Total (N = 552) n (%)	2.4 - 4.8 Difference in Success Rates[a]	95% Confidence Interval for 2.4 - 4.8[b]
Success	180 (66.4%)	195 (69.4%)	375 (67.9%)		
Failure	91 (33.6%)	86 (30.6%)	177 (32.1%)		
Total	271	281	552	-3.0	(-10.8, 4.8)

N = number of patients in treatment group with treatment outcome
n (%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome.
[a] Difference between 2.4 g/day and 4.8 g/day
[b] Confidence interval for the difference in success rates between 2.4 g/day compared to 4.8 g/day with no stratification.
/ASACOL/2006444/FDA_04DEC2007/ANAL/mch.sas; SAS 8.2 06DEC07 08:48 AI9318.

Per-Protocol Analysis
Non-Inferiority of Treatment Outcome at Week 6
(Per-Protocol Patients Before March 2, 2007)

Treatment Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 245) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 264) n (%)	Total (N = 509) n (%)	2.4 - 4.8 Difference in Success Rates[a]	95% Confidence Interval for 2.4 - 4.8[b]
Success	178 (72.7%)	193 (73.1%)	371 (72.9%)		
Failure	67 (27.3%)	71 (26.9%)	138 (27.1%)		
Total	245	264	509	-0.5	(-8.2, 7.3)

N = number of patients in treatment group with treatment outcome at Week 6
n (%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome.
[a] Difference between 2.4 g/day and 4.8 g/day
[b] Confidence interval for the difference in success rates between 2.4 g/day compared to 4.8 g/day with no stratification.
/ASACOL/2006444/FDA_04DEC2007/ANAL/mch.sas; SAS 8.2 06DEC07 08:48 AI9318.

Table 10 Primary Efficacy Analysis ITT and PP Analysis After March 2, 2007 --- Protocol 2006444

Primary Efficacy Analysis
Non-Inferiority of Treatment Outcome at Week 6: Missing Observations Set to Treatment Failure
(Intent-to-treat Patients After March 2, 2007)

Treatment Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 112) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 108) n (%)	Total (N = 220) n (%)	2.4 - 4.8 Difference in Success Rates[a]	95% Confidence Interval for 2.4 - 4.8[b]
Success	71 (63.4%)	78 (72.2%)	149 (67.7%)		
Failure	41 (36.6%)	30 (27.8%)	71 (32.3%)		
Total	112	108	220	-8.8	(-21.1, 3.5)

N = number of patients in treatment group with treatment outcome
n (%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome.
[a] Difference between 2.4 g/day and 4.8 g/day
[b] Confidence interval for the difference in success rates between 2.4 g/day compared to 4.8 g/day with no stratification.
/ASACOL/2006444/FDA_04DEC2007/ANAL/mch.sas; SAS 8.2 06DEC07 08:48 AI9318.

Per-Protocol Analysis
Non-Inferiority of Treatment Outcome at Week 6
(Per-Protocol Patients After March 2, 2007)

Treatment Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 103) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 95) n (%)	Total (N = 198) n (%)	2.4 - 4.8 Difference in Success Rates[a]	95% Confidence Interval for 2.4 - 4.8[b]
Success	69 (67.0%)	77 (81.1%)	146 (73.7%)		
Failure	34 (33.0%)	18 (18.9%)	52 (26.3%)		
Total	103	95	198	-14.1	(-26.1, -2.0)

N = number of patients in treatment group with treatment outcome at Week 6
n (%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome.
[a] Difference between 2.4 g/day and 4.8 g/day
[b] Confidence interval for the difference in success rates between 2.4 g/day compared to 4.8 g/day with no stratification.
/ASACOL/2006444/FDA_04DEC2007/ANAL/mch.sas; SAS 8.2 06DEC07 08:48 AI9318.

Table 11 Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6 Before March 2, 2007 --- Protocol 2006444

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6
Excluding Patients With Both Baseline and Visit Scores of Zero
(Intent-to-Treat Patients Before March 2, 2007)

Parameter	Visit	Outcome	2.4 g/day Asacol (400 mg Tablet) n (%)	4.8 g/day Asacol (800 mg Tablet) n (%)	Total n (%)	CMH General Association p-value[a]	4.8 - 2.4 Difference in Improvement Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
PGA	Week 6	I	180 (74.1%)	197 (77.0%)	377 (75.6%)			
		NI	63 (25.9%)	59 (23.0%)	122 (24.4%)			
		Total	243	256	499	0.4452	2.9	(-4.7, 10.4)
Stool Frequency	Week 3	I	166 (65.6%)	197 (74.6%)	363 (70.2%)			
		NI	87 (34.4%)	67 (25.4%)	154 (29.8%)			
		Total	253	264	517	0.0247	9.0	(1.1, 16.9)
	Week 6	I	191 (78.0%)	199 (77.1%)	390 (77.5%)			
		NI	54 (22.0%)	59 (22.9%)	113 (22.5%)			
		Total	245	258	503	0.8355	-0.8	(-8.1, 6.5)
Rectal Bleeding	Week 3	I	194 (76.7%)	197 (74.6%)	391 (75.6%)			
		NI	59 (23.3%)	67 (25.4%)	126 (24.4%)			
		Total	253	264	517	0.5911	-2.1	(-9.5, 5.3)
	Week 6	I	196 (80.0%)	211 (81.8%)	407 (80.9%)			
		NI	49 (20.0%)	47 (18.2%)	96 (19.1%)			
		Total	245	258	503	0.5993	1.8	(-5.1, 8.7)

n(%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome in specified parameter
I = Improved
NI = Not improved
[a] 4.8 g/day compared to 2.4 g/day, stratified by gender using the Cochran-Mantel-Haenszel test.
[b] Difference between 4.8 g/day and 2.4 g/day
[c] Confidence interval for the difference in success rates between 4.8 g/day and 2.4 g/day with no stratification
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Table 11 Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6 Before March 2, 2007 Protocol 2006444 (Continued)

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6
Excluding Patients With Both Baseline and Visit Scores of Zero
(Intent-to-Treat Patients Before March 2, 2007)

Parameter	Visit	Outcome	2.4 g/day Asacol (400 mg Tablet) n (%)	4.8 g/day Asacol (800 mg Tablet) n (%)	Total n (%)	CMH General Association p-value[a]	4.8 - 2.4 Difference in Improvement Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
PFA	Week 3	I	154 (63.1%)	178 (71.2%)	332 (67.2%)			
		NI	90 (36.9%)	72 (28.8%)	162 (32.8%)			
		Total	244	250	494	0.0561	8.1	(-0.2, 16.3)
	Week 6	I	179 (76.2%)	184 (75.1%)	363 (75.6%)			
		NI	56 (23.8%)	61 (24.9%)	117 (24.4%)			
		Total	235	245	480	0.8074	-1.1	(-8.7, 6.6)
Sigmoidoscopy	Week 6	I	76 (31.3%)	67 (26.2%)	143 (28.7%)			
		NI	167 (68.7%)	189 (73.8%)	356 (71.3%)			
		Total	243	256	499	0.2165	-5.1	(-13.0, 2.8)

n(%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome in specified parameter
I = Improved
NI = Not improved
[a] 4.8 g/day compared to 2.4 g/day, stratified by gender using the Cochran-Mantel-Haenszel test.
[b] Difference between 4.8 g/day and 2.4 g/day
[c] Confidence interval for the difference in success rates between 4.8 g/day and 2.4 g/day with no stratification
/ASACOL/2006444/FDA_04DEC2007/ANAL/adv2.sas; SAS 8.2 06DEC07 08:49 AI9318.

Table 12 Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6 After March 2, 2007 Protocol 2006444

Table 7

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6
Excluding Patients With Both Baseline and Visit Scores of Zero
(Intent-to-Treat Patients After March 2, 2007)

(Page 1 of 2)

Parameter	Visit	Outcome	2.4 g/day Asacol (400 mg Tablet) n (%)	4.8 g/day Asacol (800 mg Tablet) n (%)	Total n (%)	CMH General Association p-value[a]	4.8 - 2.4 Difference in Improvement Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
PGA	Week 6	I	72 (70.6%)	79 (85.9%)	151 (77.8%)			
		NI	30 (29.4%)	13 (14.1%)	43 (22.2%)			
		Total	102	92	194	0.0103	15.3	(3.9, 26.6)
Stool Frequency	Week 3	I	71 (67.0%)	82 (81.2%)	153 (73.9%)			
		NI	35 (33.0%)	19 (18.8%)	54 (26.1%)			
		Total	106	101	207	0.0206	14.2	(2.4, 26.0)
	Week 6	I	67 (65.7%)	81 (85.3%)	148 (75.1%)			
		NI	35 (34.3%)	14 (14.7%)	49 (24.9%)			
		Total	102	95	197	0.0015	19.6	(7.9, 31.2)
Rectal Bleeding	Week 3	I	84 (79.2%)	86 (85.1%)	170 (82.1%)			
		NI	22 (20.8%)	15 (14.9%)	37 (17.9%)			
		Total	106	101	207	0.2695	5.9	(-4.5, 16.3)
	Week 6	I	80 (78.4%)	87 (91.6%)	167 (84.8%)			
		NI	22 (21.6%)	8 (8.4%)	30 (15.2%)			
		Total	102	95	197	0.0087	13.1	(3.4, 22.9)

n(%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome in specified parameter
I = Improved
NI = Not improved
[a] 4.8 g/day compared to 2.4 g/day, stratified by gender using the Cochran-Mantel-Haenszel test.
[b] Difference between 4.8 g/day and 2.4 g/day
[c] Confidence interval for the difference in success rates between 4.8 g/day and 2.4 g/day with no stratification
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Table 12 Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6 After March 2, 2007 Protocol 2006444 (Continued)

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6
Excluding Patients With Both Baseline and Visit Scores of Zero
(Intent-to-Treat Patients After March 2, 2007)

Parameter	Visit	Outcome	2.4 g/day Asacol (400 mg Tablet) n (%)	4.8 g/day Asacol (800 mg Tablet) n (%)	Total n (%)	CMH General Association p-value[a]	4.8 - 2.4 Difference in Improvement Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
PFA	Week 3	I	69 (65.7%)	66 (69.5%)	135 (67.5%)			
		NI	36 (34.3%)	29 (30.5%)	65 (32.5%)			
		Total	105	95	200	0.5705	3.8	(-9.2, 16.7)
	Week 6	I	64 (63.4%)	70 (78.7%)	134 (70.5%)			
		NI	37 (36.6%)	19 (21.3%)	56 (29.5%)			
		Total	101	89	190	0.0213	15.3	(2.6, 28.0)
Sigmoidoscopy	Week 6	I	30 (29.4%)	38 (41.3%)	68 (35.1%)			
		NI	72 (70.6%)	54 (58.7%)	126 (64.9%)			
		Total	102	92	194	0.0859	11.9	(-1.5, 25.3)

n(%) = number and percentage (n/Total x 100) of patients in treatment with specified outcome in specified parameter
I = Improved
NI = Not improved
[a] 4.8 g/day compared to 2.4 g/day, stratified by gender using the Cochran-Mantel-Haenszel test.
[b] Difference between 4.8 g/day and 2.4 g/day
[c] Confidence interval for the difference in success rates between 4.8 g/day and 2.4 g/day with no stratification
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Concur with review.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

SECONDARY REVIEW

NDA/Serial Number:	21-830
Drug Name:	Asacol (mesalamine) Delayed Release Tablet, 800 mg.
Indication(s):	Treatment of moderately active ulcerative colitis
Applicant:	P&G Pharmaceuticals
Date(s):	PDUFA goal date August 29, 2005
Review Priority:	Standard
Secondary Reviewer:	Stella Grosser

Keywords: protocol amendment, single study, subgroup analysis

Introduction

Asacol 400 mg is currently approved for the treatment of mildly to moderately active ulcerative colitis at 2.4 grams per day. This is a new strength tablet and new dosing regimen (4.8 g/day). There are two Phase 3 studies, 2000082 and 2000083, conducted in parallel. Both were designed to study patients with mild or moderate disease. The first study failed to show superiority of 4.8 g/day to 2.4 g/day. However, a subgroup analysis of the patients with moderate disease found a difference in the response in favor of Asacol 800 at 4.8 g/day. The second study was changed when most of the intended sample size had been enrolled. A faxed communication from the Agency agreed to this amendment. Superiority of 4.8 g/day was found among the entire moderate population enrolled in the second study.

The primary statistical reviewer is Dr. Milton Fan.

An outline of the studies and statistical issues is given below.

Study 2000083

Study 083 finished first. It enrolled patients with mild and moderate disease, randomized to 4.8 g/day with 800 mg tablets or 2.4 g/day with 400 mg tablets. Here are the results, from Dr. Fan's review.

	2.4 g/day	4.8 g/day	Difference	P-value
Completers (mild and moderate)	77/150 (51%)	76/136 (56%)	5%	0.44
Moderate completers	53/93 (57%)	55/76 (72%)	15%	0.04
All moderate (incomplete=failure)	53/96 (55%)	55/84 (66%)	11%	0.16

Only the subgroup of moderate completers showed a difference at a significance level less than 0.05. However, much of this effect disappears if dropouts are treated as treatment failures (66% vs. 55%; p=0.16). Moreover, more than a dozen subgroups were analyzed without adjustment for multiplicity. Thus I consider the analysis of moderates in study 083 to be exploratory.

Study 2000082

Study 082 initially had the same design as study 83. The protocol for study 082 was amended soon after the completion of study 083, when 96% of the planned enrollment for study 082 had been completed. The study was changed to enroll only patients with

moderate disease. Under the amended protocol, only patients with moderate disease were to be enrolled. Up to 100 additional patients were planned.

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. This amendment was accepted by the FDA.

Here are the results, from Dr. Fan's review.

(completers only)	2.4 g/day	4.8 g/day	Difference	P-value
Mild and moderate, enrolled before amendment	73/156 (47%)	77/148 (52%)	5%	0.36
Moderates enrolled before amendment	52/95 (55%)	58/83 (70%)	15%	0.04
Moderates enrolled after amendment	25/35 (71%)	31/41 (76%)	4%	0.68
All moderates	77/130 (59%)	89/124 (72%)	13%	0.04
All moderates, with analysis stratified by time of enrollment (pre- or post- amendment)				0.046

There is unexplained inconsistency in the results in important subgroups of the moderate patients, namely males vs. females (males had a 50% success rate at 2.4 g/day and 76% at 4.8 while females 67% and 69% respectively) and pre- vs. post-amendment moderate enrollees.

There are several issues which arise in considering study 082.

First, what is the appropriate population on which to base an evaluation of Study 082?

The primary reviewer believes that, based on the ITT principle, all randomized patients, mild and moderate, should be analyzed.

I see no violation of randomization-based inference in excluding, prior to unblinding, a stratum of patients where the strata are based on a baseline characteristic. The analysis of moderates is not post-hoc, since it was specified before the study was analyzed. We have no evidence that the results for patients with moderate disease compared to those with mild were known for Study 082 before the protocol amendment.

Another issue is the appropriate calculation of the level of significance in Study 082. A related question is whether Study 082, as a single study, provides sufficient evidence of efficacy.

The primary reviewer claims the two studies 083 and 082 are "dependent," because the protocol for 082 was changed based on the results of 083, which happened to finish first. I do not understand the precise nature of this dependency, which must be specified if we are to make any p-value adjustment.

Furthermore, the patients already enrolled in 082 at the time of enrollment showed results similar to those of 083 at completion. Had 082 finished first, it is likely that the protocol for 083 would have been amended to extend the study and enroll only patients with moderate disease.

If we had 10 "very failed" studies of a drug and two very successful ones, would we approve the drug or would we have, on average, a failed result, and therefore not approve the drug? That is, would we somehow adjust the p-value for multiple attempts to carry out two successful studies, analogous to the way we adjust for multiplicity in analyses of a single study?

Does the near simultaneity of these two studies matter theoretically or practically and, if so, how?

Can we take into consideration the information in the original NDA for this drug? One of the successful pivotal studies used a high dose of 4.8 g/day, but in a different formulation (400 mg tablets rather than 800 mg tablets) and tested against a placebo comparator for patients with mild or moderate ulcerative colitis. A choice was made to approve only the lower dose despite efficacy of the higher dose.

Conclusions

The fact that the change was made so close to the end of study 082 and fewer than 100 additional patients were enrolled reflects poor planning. But the change is not post hoc in the sense of happening after analysis or breaking of the blind. I see no clear theoretical problems or evidence of misconduct in this study.

However, while I believe study 082 is legitimate from a purely statistical point of view and the p-value correctly calculated, I don't think study 082 is strong enough to stand on its own as a definitive single study. The statistical evidence is not very convincing. The difference between dosing regimens in favor of 4.8 g/day is significant at p= 0.04 (or 0.02 if dropouts are considered failures), less than the 0.05 standard but not particularly small, well above 0.001, for example. There is unexplained inconsistency in the results in important subgroups of the moderate patients, namely males vs. females (males had a 50% success rate at 2.4 g/day and 76% at 4.8 while females 67% and 69% respectively) and pre- vs. post-amendment enrollees. Study 083 provides some supportive evidence,

but that evidence comes from a post-hoc subgroup analysis. The study using 4.8 mg/day Asacol in the original NDA has important differences in design (comparator used, formulation tested).

The distinction between "mild or moderate ulcerative colitis" and "moderate ulcerative colitis" is not sharp in clinical practice and the post-amendment results may reflect misclassification of patients with mild disease as moderate. All other mesalamine products, including Asacol (400 mg tablets), are approved for the treatment of mild-to-moderate ulcerative colitis. Finally, there is no pressing public health need for this product: Asacol is already available and being prescribed at (the unapproved) 4.8 mg/day.

Given the uncertainties in the data and the clinical considerations, I concur with the conclusion of the primary reviewer in recommending another study be carried out in patients with moderately active ulcerative colitis.

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/s/

Stella Grosser
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BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

NDA/Serial Number:	21-830
Drug Name:	Asacol (mesalamine) delayed-release tablets
Indication(s):	Treatment of moderately active ulcerative colitis
Applicant:	P&G Pharmaceuticals, Inc.
Date(s):	Submitted October 22, 2004
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Milton C. Fan, Ph.D. (HFD-715)
Concurring Reviewers:	Stella Grosser, Ph.D. (HFD-715)
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Clinical Team:	Fathia Gibril M.D. (HFD-180)
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Keywords: post hoc analysis, increase in sample size, subgroup analysis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor has submitted two controlled Studies (2000083 and 2000082) comparing efficacy and safety of mesalamine 4.8 g/day (800 mg tablet) versus mesalamine 2.4 g/day (400 mg tablet) in the treatment of patients with moderately active ulcerative colitis.

Both studies were designed to study patients with mild-to-moderate active ulcerative colitis.

Neither of studies 2000083 and 2000082 showed that there was statistically significant difference in the treatment outcome between 2.4 g/day administered as a 400 mg tablet and 4.8 g/day administered as 800 mg tablet in treatment after 6 weeks of treatment in patients with mildly to moderately active ulcerative colitis.

For the subgroup of patients with moderately active ulcerative colitis at baseline, the sponsor's analysis of study 2000083 that showed a significant difference in favor of 4.8 g/day is found to be not valid, for reasons of bias, as explained in this review.

The second pivotal study (2000082) was amended on February 18, 2003 when most of the intended sample size (96%) had been enrolled. Under the amended protocol, only patients with moderate disease at baseline (PGA=2) were to be enrolled and the sponsor changed the sample size and changed the focus to the subgroup of patients with moderate active ulcerative colitis at baseline.

For study 2000082, superiority was seen among the all patients with moderate disease at baseline enrolled in the second study (pre-amendment and post amendment). But, the results were inconsistent with those observed for studies 2000083 for patients with moderate disease at baseline in the reviewer's analyses where patients with missing values were considered failures. However, superiority was not demonstrated for patients enrolled after the amendment. The success rates were much higher than those for patients enrolled before the amendment for patients with moderate disease at baseline (71.4% vs. 52.0% for 2.4 g/day and 75.6% vs. 67.4%). So, it seems to this reviewer, either the patients enrolled after the amendment might be wrong patients or disease at baseline might be misclassified.

Only study 2000082 showed to a slightly better rate of treatment success at week 6 when dosed at 4.8 g/day than when dosed at 2.4 g/day, but the results might not be robust.

So, from a statistical perspective, based on a post-hoc subgroup analysis from a single study (2000082) with nominal p-value of 0.0463 with adjustment for time of enrollment, it is not statistically persuasive. The subgroup analysis should be confirmed in subsequent Phase III trials.

Furthermore, studies 20000082 and 2000083 were conducted in parallel. Study 2000083 was completed first. For study 2000082, the sponsor made amendments consisting of changing

objective of study and primary analysis, increasing sample size, enrolling only patients with moderate disease at baseline, and statistical method after assessing the efficacy results from study 2000083. These two studies became dependent. These changes were not pre-specified, so this study could not be considered to have a valid adapted design as allowed by E9. It should be considered as post hoc adjustment. The p-value might not be interpreted properly. At the time of amendment, the study 2000082 was close to being completed (96.1% enrolled). The sponsor should perform a new clinical study for moderate disease patients instead of trying to salvage study 2000082.

1.2 Brief Overview of Clinical Studies

1.2.1 **Study 2000083**

This study was a double-blind, randomized, multi-site (41 sites), controlled study in newly- and previously-diagnosed patients who were experiencing a flare-up of mildly to moderately active ulcerative colitis. This study was conducted in U.S. and Canada.

Patients were randomized to receive either Mesalamine 2.4 g/day (400 mg tablet) or Mesalamine 4.8 g/day (800 mg tablet) for 6 weeks.

Patients were screened according to inclusion and exclusion criteria within 7 days before receiving study drug. The Baseline visit was within 7 days after the Screen Visit. Visits 1 and 2 were scheduled at 3 and 6 weeks, respectively, from Day 1 of dosing. A visit window of ±3 calendar days was permitted.

The primary efficacy parameter was the proportion of patients who improved from baseline to Week 6. Improvement was defined as either a complete response (remission) or partial response (improvement). A complete response was defined as complete resolution of the following symptoms: stool frequency, rectal bleeding, patient's functional assessment (PFA), sigmoidoscopy finding, and a physician's global assessment (PGA=0). A partial response was defined as improvement from baseline in the PGA, accompanied by improvement in at least 1 other category of symptoms (stool frequency, rectal bleeding, PFA, or sigmoidoscopy score) and no worsening in all remaining categories.

Secondary efficacy endpoints include patient improvement at Week 3, sigmoidoscopic and clinical improvement (stool frequency, rectal bleeding, PGA, and PFA), and quality of life (Inflammatory Bowel Disease Questionnaire) at Weeks 3 and 6.

The intent-to-treat analyses (ITT) were the primary analyses. All randomized patients were included in the ITT analyses.

Patients who completed the study were classified as either treatment success (complete or partial improvement) or treatment failure. Patients who withdrew from the study before Week 6 due to AEs or worsening of symptoms were counted as "treatment failure." For patients who were lost to follow-up during the study, the "last observation carried

forward (LOCF)" method was used to define treatment outcome, i.e., the last known treatment outcome of a patient lost to follow-up would be used to determine the treatment outcome.

The Fisher's exact test was used to determine the overall treatment effect, and the 95% confidence interval for the treatment difference between the 2 treatment groups was provided.

Treatment outcomes for each individual efficacy parameter (stool frequency, rectal bleeding, PFA, sigmoidoscopy score, PGA, and quality-of-life score) at Week 3 and Week 6 was analyzed to compare the treatment effect using the chi-square test.

The association between treatment and treatment outcomes was also investigated by considering the disease characteristic variables (disease extent, length of history of ulcerative colitis, prior steroid use) and demographic variables (age, gender, and race). The Cochran-Mantel-Haenszel (CMH) method using the variables as strata and a log-linear model for categorical data were used to examine the treatment effect.

It was assumed that the true rate of improvement for the 2.4 g/day treatment group was 40% and for the 4.8 g/day group was 60%. To detect a true difference of 20% between these 2 groups with a 2-sided test, type 1 error of 0.05, and power of 90%, it would require 140 patients per group. To account for a 10% dropout/withdrawal rate, a total of approximately 308 patients were planned to be enrolled in the study.

A total of 14 changes to the protocol were implemented during the study. Major changes to the protocol are listed below.

1. Increase the number of study sites.
2. Revised inclusion criteria to allow for a colonoscopy (instead of sigmoidoscopy) at screening to determine extent of ulcerative colitis.
3. Remove exclusion criteria prohibiting H_2 blockers and proton pump inhibitors. Also removed these from prohibited concomitant medications list.
4. Revised age limit criteria to allow order patients into the study.

A total of 301 patients were randomized to treatment groups (154 in 2.4 g/day and 147 in 4.8 g/day).

In the 2.4 g/day (400 mg tablet) group, 133 (86.4%) patients completed the 6-week study, and in the 4.8 g/day (800 mg tablet) group, 123 (83.7%) patients completed the 6-week study.

A total of 15 patients (4 in 2.4 g/day and 11 in 4.8 g/day) were excluded from the sponsor's Intent-to-Treat (ITT) analysis. A total of 33 patients (16 in 2.4 g/day and 17 in 4.8 g/day) were excluded from Per-Protocol analysis.

1.2.2 **Study 2000082**

The study design for this study was similar to that for Study 2000083.

The original objective was to evaluate the safety and effectiveness of Mesalamine 4.8 g/day (800 mg tablet) versus Mesalamine 2.4 g/day (400 mg tablet) in patients with *mildly to moderate* ulcerative colitis.

The sponsor made three amendments dated February 23, 2001, May 24, 2001, and February 19, 2003.

The study was amended to evaluate the safety and effective of Mesalamine 4.8 g/day (800 mg tablet) versus Mesalamine 2.4 g/day (400 mg tablet) in patients with *moderate* ulcerative colitis.

A total of 14 changes to the protocol were implemented during the study. Major changes to the protocol are listed below.

1. Increase the number of study sites.
2. Revised inclusion criteria to allow for a colonoscopy (instead of sigmoidoscopy) at screening to determine extent of ulcerative colitis.
3. Remove exclusion criteria prohibiting H_2 blockers and proton pump inhibitors. Also removed these from prohibited concomitant medications list.
4. Revised age limit criteria from $\leq$65 years to $\leq$75 years to allow order patients into the study.
5. Changed study objective and primary analysis from studying patients with mildly to moderately active ulcerative colitis (PGA=1 or 2) to studying only patients with moderately active ulcer colitis (PGA=2).
6. Increase enrollment by up to 100 additional patients with moderately active ulcerative colitis.

A total of 386 patients were randomized to the two treatment groups at study sites in the U.S. and Canada. Of these, 117 had mild disease at baseline, 268 (139 in 2.4 g/day and 129 in 4.8 g/day) had moderate disease at baseline, and 1 had insufficient data to determine baseline disease severity. This patient was excluded from efficacy analyses and safety analyses in patients with moderate disease.

The primary efficacy analysis was performed on the ITT population in patients with moderate disease at baseline (PGA=2).

1.3 Statistical Issues and Finding

The sponsor has submitted two phase III Studies (2000083 and 2000082). Both studies were designed to study patients with mild-to-moderate active ulcerative colitis. The first study (2000083) failed to show superiority of 4.8 g/day to 2.4 g/day. However, the sponsor's subgroup analysis of the patients with moderate disease at baseline (PGA=2) found a statistically significant difference in the response in favor of mesalamine 4.8 g/day.

It was found that the sponsor's subgroup analysis excluded 11 patients (3 in 2.4 g/day and 8 in 4.8 g/day). More patients in 4.8 g/day group were excluded in the sponsor's analysis (p=0.0738). The sponsor's analysis tended to be biased in favor of 4.8 g/day group. If those 11 patients were included in the analysis as treatment failure, p-value would be 0.173 by Fisher's exact test and 0.1607 by chi-square test. So, the sponsor's finding for patients with PGA=2 at baseline was not robust.

The second study (2000082) was amended on February 18, 2003 when most of the intended sample size (96%) had been enrolled. Under the amended protocol, only patients with moderate disease at baseline (PGA=2) were to be enrolled. A faxed communication dated March 17, 2003 from the Agency agreed to this amendment.

For study 2000082, the sponsor changed the sample size and changed the focus to the subgroup of patients with moderate active ulcerative colitis at baseline. It should be considered as post-hoc adjustment of study.

Superiority was seen among the all patients with moderate disease at baseline enrolled in the second study (pre-amendment and post amendment). But, the results were inconsistent in the reviewer's analyses with those observed for the first study (2000083) for patients with moderate disease at baseline and where patients with missing values were considered failures.

For study 2000082, among the patients enrolled after the amendment, superiority was not demonstrated. The success rates were much higher than those for patients enrolled before the amendment for patients with moderate disease at baseline (71.4% vs. 52.0% for 2.4 g/day and 75.6% vs. 67.4%). So, it seems to this reviewer, either the patients enrolled after the amendment might be wrong patients or disease at baseline might be misclassified.

Furthermore, the sponsor performed the primary efficacy analysis on the ITT population in patients with moderate disease at baseline (PGA=2). The sponsor's efficacy analyses excluded patients who were randomized earlier and had mild disease at baseline (PGA=1). The sponsor's efficacy analyses including only patients with moderate disease at baseline should be considered as post hoc subgroup analyses. Based on ITT principal, the primary efficacy analysis should include all randomized patients regardless of disease severity at baseline.

This reviewer performed an analysis of treatment success at week 6 for all randomized patients ("Reviewer's ITT Population") stratified by time of enrollment (pre- or post amendment). In this analysis, the missing outcomes were set to treatment failure. It was found that there was no treatment difference for treatment success at week 6 for all randomized patients. With adjustment for strata (defined by time of enrollment pre- or post amendment), p-value would be 0.2476 (Cochran-Mantel-Haenszel method).

This sponsor's subgroup analysis is exploratory and hypothesis generating. Subgroup analyses of this kind tend to have high false-positive rates unless the analysis is done at a very low significance level. The p-value resulting from the subgroup analysis cannot be interpreted properly, particularly, when the unadjusted nominal p-value is not far from 0.05.

2. INTRODUCTION

2.1 **Overview**

Mesalamine 400 mg tablets were first approved in 1992 for treatment of mildly to moderately active ulcerative colitis at dose of 2.4 g/day and were also approved for the maintenance of remission of mildly to moderately active ulcerative colitis at a dose of 1.6 g/day in 1997.

In the current NDA submission, the sponsor seeks approval of Mesalamine delayed-release tablets, 800 mg, at a total daily dosage of 4.8 g/day for the treatment of moderately active ulcerative colitis.

The sponsor has submitted two Phase III pivotal studies (2000083 and 2000082) to support the claim. Note that study 2000083 was completed before study 2000082.

These two studies are:

Study 2000083 – A double-blind, randomized, 6-week, parallel-group design clinical trial in patients with mildly to moderately active ulcerative colitis to assess safety and efficacy of Mesalamine 4.8 g/day (800 mg tablet) versus Mesalamine 2.4 g/day (400 mg tablet).

Study 2000082 - A double-blind, randomized, 6-week, parallel-group design clinical trial to assess safety and efficacy of Mesalamine 4.8 g/day (800 mg tablet) versus Mesalamine 2.4 g/day (400 tablet) for the treatment of moderately active ulcerative colitis.

2.2 **Data Sources**

The NDA dated October 22, 2004 was submitted in electronic format to the EDR.

The NDA Amendment #15, responding to FDA's request for the number of patients originally planned for enrollment into the pivotal studies 2000082 and 20000083 and the percent of patients enrolled in each study as of the 18 February 2003 meeting request date, was submitted on July 13, 2005.

3. STATISTICAL EVALUATION

3.1 **Evaluation of Efficacy**

3.1.1 **Study 2000083**

3.1.1.1 **Description of Study**

This study was a double-blind, randomized, multi-site (41 sites), controlled study in newly- and previously-diagnosed patients who were experiencing a flare-up of mildly to moderately active ulcerative colitis. This study was conducted in U.S. and Canada.

Patients were randomly assigned to receive either Mesalamine 2.4 g/day (400 mg tablet) or Mesalamine 4.8 g/day (800 mg tablet) for 6 weeks.

Patients were screened according to inclusion and exclusion criteria within 7 days before receiving study drug. The Baseline visit was within 7 days after the Screen Visit. Visits 1 and 2 were scheduled at 3 and 6 weeks, respectively, from Day 1 of dosing. A visit window of ±3 calendar days was permitted.

The primary efficacy parameter was the proportion of patients who improved from baseline at Week 6. Improvement was defined as either a complete response (remission) or partial response (improvement). A complete response was defined as complete resolution of the following symptoms: stool frequency, rectal bleeding, patient's functional assessment (PFA), sigmoidoscopy finding, and a physician's global assessment (PGA=0). A partial response was defined as improvement from baseline in the PGA, accompanied by improvement in at least 1 other category of symptoms (stool frequency, rectal bleeding, PFA, or sigmoidoscopy score) and no worsening in all remaining categories.

Secondary efficacy endpoints include patient improvement at Week 3, sigmoidoscopic and clinical improvement (stool frequency, rectal bleeding, PGA, and PFA), and quality of life (Inflammatory Bowel Disease Questionnaire) at Weeks 3 and 6.

The intent-to-treat analyses (ITT) were the primary analyses. All randomized patients were included in the ITT analyses.

It was assumed that the true rate of improvement for the 2.4 g/day treatment group was 40% and for the 4.8 g/day group was 60%. To detect a true difference of 20% between these 2 groups with a 2-sided test, type 1 error of 0.05, and power of 90%, it would require 140 patients per group. To account for a 10% dropout/withdrawal rate, a total of approximately 308 patients were planned to be enrolled in the study.

A total of 14 changes to the protocol were implemented during the study. Major changes to the protocol are listed below.

1. Increase the number of study sites.
2. Revised inclusion criteria to allow for a colonoscopy (instead of sigmoidoscopy) at screening to determine extent of ulcerative colitis.
3. Remove exclusion criteria prohibiting H_2 blockers and proton pump inhibitors. Also removed these from prohibited concomitant medications list.
4. Revised age limit criteria to allow older patients into the study.

3.1.1.2 **Sponsor's Analysis**

A total of 301 patients were randomized to treatment groups (154 in 2.4 g/day and 147 in 4.8 g/day).

In the 2.4 g/day (400 mg tablet) group, 133 (86.4%) patients completed the 6-week study, and in the 4.8 g/day (800 mg tablet) group, 123 (83.7%) patients completed the 6-week study.

A total of 15 patients (4 in 2.4 g/day and 11 in 4.8 g/day) were excluded from the sponsor's Intent-to-Treat (ITT) analysis. A total of 33 patients (16 in 2.4 g/day and 17 in 4.8 g/day) were excluded from Per-Protocol analysis.

3.1.1.2.1 **Planned Analysis**

Patients who completed the study were classified as either treatment success (complete or partial improvement) or treatment failure. Patients who withdrew from the study before Week 6 due to AEs or worsening of symptoms were counted as "treatment failure." For patients who were lost to follow-up during the study, the "last observation carried forward (LOCF)" method was used to define treatment outcome, i.e., the last known treatment outcome of a patient lost to follow-up would be used to determine the treatment outcome.

The Fisher's exact test was used to determine the overall treatment effect, and the 95% confidence interval for the treatment difference between the 2 treatment groups was provided.

Treatment outcomes for each individual efficacy parameter (stool frequency, rectal bleeding, PFA, sigmoidoscopy score, PGA, and quality-of-life score) at Week 3 and Week 6 was analyzed using the chi-square test to compare the treatment effect.

The association between treatment and treatment outcomes was also investigated by considering the disease characteristic variables (disease extent, length of history of ulcerative colitis, prior steroid use) and demographic variables (age, gender, and race). The Cochran-Mantel-Haenszel (CMH) method using the variables as strata and a log-linear model for categorical data were used to examine the treatment effect.

3.1.1.2.2 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline for all randomized patients is given in Appendix Table 1.

As seen from Appendix Table 1, no statistically significant differences between the two treatment groups were observed for demographic and baseline characteristics with exception of stool frequency score (p=0.0085)

3.1.1.2.3 **Sponsor's Analysis of Primary Efficacy Variable**

The primary efficacy parameter was the proportion of patients in each treatment group who improved from baseline at Week 6.

Treatment success was defined as improvement from baseline at Week 6. Improvement from baseline was defined as either a complete response (remission) or partial response (improvement) to treatment. A complete response was defined as a PGA score of 0 and complete resolution of the following clinical assessments: stool frequency, rectal bleeding, PFA, and sigmoidoscopy findings. A partial response was defined as improvement from baseline in the PGA score, accompanied by improvement from baseline in at least 1 of the clinical assessments listed above, and no worsening in any of the remaining clinical assessments.

Treatment failure was defined as: 1) PGA score that stayed the same or worsened from baseline (regardless of whether the other clinical assessment resolved), 2) worsening of any clinical assessment at Week 6, or 3) withdrawal from the study due to an AE or lack of treatment effect.

The summary of results of sponsor's analysis of primary efficacy variable is given below.

Summary of Treatment Outcomes at Week 6
(Intent-to-Treat Population)
Study 2000083

	2.4 g/day mesalamine (N=150)		4.8 g/day mesalamine (N=136)		
Treatment Outcome	n	(%)	n	(%)	p-value
Treatment Success	77	(51.3%)	76	(55.9%)	0.4411
Complete success	29	(19.3%)	35	(25.7%)	
Partial success	48	(32.0%)	41	(30.2%)	
Treatment Failure	73	(48.7%)	60	(44.1%)	
Failure (same)	35	(23.3%)	34	(25.0%)	
Failure (worsen)	38	(25.3%)	26	(19.1%)	

Compiled by this reviewer.
P-value was obtained by the chi-square test.

As seen from table above, the difference in treatment outcome at Week 6 between the two treatment groups was not statistically significant.

3.1.1.2.4 **Sponsor's Analyses of Secondary Efficacy Variables**

The secondary efficacy parameters included the proportion of patients who improved from baseline at Week 3, and the percentage of patients whose clinical assessment scores (stool frequency, rectal bleeding, sigmoidoscopy scores, the patient's functional assessment [PFA]), and physician's global assessment (PGA) score improved from baseline at Weeks and 6.

3.1.1.2.4.1 **Treatment Outcomes at Week 3**

The summary of results of sponsor's analysis of treatment outcomes at Week 3 is given below.

Summary of Treatment Outcomes at Week 3
(Intent-to-Treat Population)
Study 2000083

	2.4 g/day mesalamine (N=150)		4.8 g/day mesalamine (N=137)		
Treatment Outcome	n	(%)	n	(%)	p-value
Treatment Success	63	(42.0%)	53	(38.7%)	0.5677
Treatment Failure	87	(58.0%)	84	(61.3%)	

Copied from EoT Table 7.
P-value was obtained by the chi-square test.

As seen from table above, the difference in treatment outcome between the two treatment groups at Week 3 was not statistically significant.

3.1.1.2.4.2 **Other Secondary Efficacy Variables**

The analysis of treatment outcomes for physician's global assessment, stool frequency, rectal bleeding, patient's functional assessment, and sigmoidoscopy at Weeks 3 and 6 is summarized in Appendix Table 2.

As seem from Appendix Table 2, the percentage of patients whose clinical assessment improved from baseline was not statistically different between two treatment groups at Weeks 3 or 6.

3.1.1.3 **Reviewer's Comments and Evaluation**

3.1.1.3.1 **Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable**

3.1.1.3.1.1 **Reviewer's Comments on Sponsor's Intent-to-Treat Analysis**

The sponsor excluded 15 patients (4 in 2.4 g/day and 11 in 4.8 g/day) from its Intent-to-Treat Analysis (ITT) because Week 6 treatment outcomes could not be determined. The sponsor's ITT analysis did not include all randomized patients, so it is not 'true' ITT analysis. More patients in 4.8 g/day group were excluded in the sponsor's ITT analysis (p=0.0644). Thus, the sponsor's ITT analysis may be biased in favor of 4.8 g/day group.

The sponsor also performed sensitivity analysis for primary efficacy endpoint. The worst case and LOCF methods were used. In the worst case, the missing outcomes were set to treatment failure. The results were summarized in Appendix Table 3.

As seen from Appendix Table 3, using either worst case or LOCF method, the difference in treatment outcome between the two treatment groups was not statistically significant with p-values 0.7680 and 0.7638, respectively for worst case and LOCF method.

3.1.1.3.1.2. **Subgroup Analysis**

Subgroup analyses were performed by this reviewer on the number of patients with treatment success at week 6 by age, gender, disease extent, length of disease history, prior treatment, relapse frequency, physician's global assessment score, stool frequency score, rectal bleeding score, patient's functional assessment score, and sigmoidoscopy score.

In these analyses, the missing outcomes were set to treatment failure. The results of subgroup analyses of the number of patients with treatment success are given below.

Number of Patients with Treatment Success at Week 6 by Subgroup
Reviewer's ITT Population
Protocol 2000083

Subgroup	2.4 g/day	4.8 g/day	Difference	95% C. I.
Gender				
Male	32/75 (43%)	38/80 (48%)	5%	(-10.8%, 20.5%)
Female	45/79 (57%)	38/67 (57%)	0%	(-16.4%, 15.9%)
Age				
18 to 64	69/141 (49%)	70/133 (53%)	4%	(-8.1%, 15.5%)
≥65	8/13 (62%)	6/14 (43%)	-19%	(-5.6%, 18.4%)
Disease Extent				
Proctitis	19/25 (76%)	13/29 (45%)	-31%	(-55.8%, -6.5%)
Proctosigmoiditis	20/45 (44%)	22/38 (58%)	14%	(-7.9%, 34.8%)
Left-sided Colitis	18/45 (40%)	22/46 (48%)	8%	(-12.5%, 28.2%)
Pancolitis	20/39 (51%)	19/34 (56%)	5%	(-18.3%, 27.5%)

Length of Disease History				
< 1 year	31/62 (50%)	23/50 (46%)	-4%	(-22.6%, 14.6%)
1 to 5 years	13/25 (52%)	24/40 (60%)	8%	(-16.8%, 32.8%)
>5 to 10 years	11/28 (39%)	12/23 (52%)	13%	(-14.4%, 40.2%)
> 10 years	22/38 (58%)	17/33 (52%)	-6%	(-29.6%, 16.8%)
Prior Treatment				
Steroids	22/51 (43%)	25/43 (58%)	15%	(-5.1%, 35.1%)
Sulfasalazine	29/57 (51%)	22/43 (51%)	0%	(-19.5%, 20.1%)
Sulfa-free oral 5-ASAs	30/61 (49%)	37/70 (53%)	4%	(-13.5%, 20.8%)
Rectal therapy	31/67 (46%)	34/60 (57%)	11%	(-6.9%, 27.7%)
Relapse Frequency				
Newly diagnosed	28/55 (51%)	21/43 (49%)	-2%	(-22.0%, 17.9%)
More than once a month	8/14 (57%)	13/20 (65%)	8%	(-25.4%, 41.2%)
Once every 6 months	7/20 (35%)	8/14 (57%)	22%	(-11.2%, 55.5%)
Once every 6 to 12 months	13/26 (50%)	15/32 (47%)	-3%	(-29.0%, 22.7%)
Less than once a year	21/39 (54%)	19/38 (50%)	-4%	(-26.2%, 18.5%)
Physician's Global Assessment Score				
1	24/58 (41%)	21/63 (33%)	-8%	(-25.3%, 9.2%)
2	53/96 (55%)	55/84 (65%)	10%	(-4.0%, 24.5%)
Stool Frequency Score				
0	11/18 (61%)	7/13 (54%)	-7%	(-42.5%, 28.0%)
1	44/83 (53%)	27/66 (41%)	-12%	(-28.1%, 3.9%)
2	13/29 (45%)	32/53 (60%)	15%	(-6.8%, 37.9%)
3	9/24 (38%)	10/15 (67%)	29%	(-1.6%, 59.9%)
Rectal Bleeding Score				
0	15/35 (43%)	12/26 (46%)	3%	(-21.9%, 28.5%)
1	29/54 (54%)	31/61 (51%)	-3%	(-21.2%, 15.4%)
2	29/58 (50%)	31/55 (56%)	6%	(-12.0%, 24.7%)
3	4/7 (57%)	2/5 (40%)	-17%	(-73.6%, 39.3%)
Patient's Functional Assessment Score				
0	14/37 (38%)	11/29 (38%)	0%	(-23.5%, 23.7%)
1	48/84 (57%)	38/81 (47%)	-10%	(-25.4%, 4.9%)
2	13/31 (42%)	23/32 (72%)	30%	(6.6%, 53.3%)
3	2/2 (100%)	4/5 (80%)	-20%	(-55.1%, 15.1%)
Sigmoidoscopy Score				
1	26/53 (49%)	23/53 (43%)	-6%	(-24.6%, 13.3%)
2	48/90 (53%)	48/83 (58%)	5%	(-10.3%, 19.3%)
3	3/11 (27%)	5/11 (45%)	18%	(-21.3%, 57.7%)

Compiled by this reviewer.

As seen from table above, treatment difference was inconsistent among all subgroups. Interaction between treatment and subgroup was found to be statistically significant at significance level of 0.10 for subgroups of disease extent, stool frequency, and patient's functional assessment score with p-values, 0.0567, 0.0637, and 0.0470 (Breslow-Day method), respectively.

Furthermore, it was revealed that treatment success rate for patients with proctitis in 2.4 g/day group was statistically significantly higher than that for those in 4.8 g/day group. The reverse was observed for patients with patient's functional assessment score of 2.

3.1.1.3.1.3 **Reviewer's Comments on Sponsor's Subgroup Analysis for Patients with Moderate Disease at Baseline (PGA=2)**

The sponsor performed a subgroup analysis in the subgroup of patients who had moderate disease at baseline. The summary of results are given Appendix Table 4.

This subgroup analysis should be considered as supporting and exploratory.

The sponsor stated that for the subgroup of patients who had moderate ulcerative colitis at baseline, the difference in treatment outcomes between the two treatment groups at Week 6 was statistically significant, with the 4.8 g/day group showing a greater improvement from baseline (72.4% vs. 57.0%).

However, p-value obtained by the sponsor using chi-square test was 0.038 (refer to Appendix Table 4). If more conservative method, Fisher's exact test, were used, the p-value would be 0.053. So, the sponsor's finding was method dependent.

3.1.1.3.1.3.1 **Reviewer's ITT Analysis**

The sponsor's ITT analysis excluded 11 patients (3 in 2.4 g/day and 8 in 4.8 g/day). More patients in 4.8 g/day group were excluded in the sponsor's analysis (p=0.0738). The sponsor's analysis tends to be bias in favor of 4.8 g/day group. This reviewer's performed an analysis for all randomized patients ("Reviewer's ITT Population"). In these analyses, the missing outcomes were set to treatment failure. The results of analyses of the number of patients with treatment success at week 6 are given below.

Summary of Treatment Outcomes at Week 6
(Reviewer's Intent-to-Treat Patients with Moderate Disease [PGA=2] at Baseline)
Study 2000083

	2.4 g/day mesalamine (N=96)		4.8 g/day mesalamine (N=84)		
Treatment Outcome	n	(%)	n	(%)	p-value
Treatment Success	53	(55.2%)	55	(65.5%)	0.1607
Treatment Failure	43	(44.8%)	29	(34.5%)	

Compiled by this reviewer.
P-value was obtained by the chi-square test.

As seen from table above, if those 11 patients were included in the analysis as treatment failure, p-value would be 0.173 by Fisher's exact test and 0.1607 by chi-square test. The treatment difference was reduced to 10% from 15% observed from the sponsor's ITT analysis. So, the sponsor's finding for patients with PGA=2 at baseline was not robust.

3.1.1.3.1.3.2 **Imbalance for Stool Frequency Scores at Baseline**

There was imbalance of stool frequency scores at baseline (p=0.0085) for all randomized patients. This reviewer performed a post-hoc analysis of treatment success at week 6 for patients with moderate disease (PGA=2) adjusted for stool frequency scores at baseline using CATMOD (**Cat**egorical data **Mod**eling) method. The resulting p-value adjusted for stool frequency scores at baseline and interaction between dose and stool frequency scores at baseline was 0.2866, greater than 0.0357 given by the sponsor. So, the sponsor's finding for treatment success at week 6 for patients with PGA=2 was not robust.

3.1.1.3.1.3.3 **Subgroup Analysis**

Per Medical officer's request, this reviewer performed subgroup analyses of patients with moderate disease at baseline (PGA=2). The number of patients with treatment success at week 6 by age, gender, disease extent, length of disease history, prior treatment, relapse frequency, physician's global assessment score, stool frequency score, rectal bleeding score, patient's functional assessment score, and sigmoidoscopy score was calculated.

In these analyses, missing outcomes were set to treatment failure. The results of subgroup analyses are given in Appendix Table 5.

As seen from Appendix Table 5, it was revealed that treatment difference was inconsistent for subgroups of gender, age, disease extent, length of disease history, stool frequency score, rectal bleeding score, and patient's functional assessment score. However, treatment success rate in 4.8 g/day group was statistically significantly high than that for those in 2.4 g/day group for male patients, patients with stool frequency score of 2 and patients with patient's functional assessment score of 2.

3.1.2 **Study 2000082**

3.1.2.1 **Description of Study**

This study was a double-blind, randomized, 6-week, parallel-group design clinical trial to assess safety and efficacy of mesalamine 4.8 g/day (800 my tablet) versus mesalamine 2.4 g/day (400 mg tablet) for the treatment of moderately actively ulcerative colitis.

The original objective was to evaluate the safety and effectiveness of mesalamine 4.8 g/day (800 mg tablet) versus mesalamine 2.4 g/day (400 mg tablet) in patients with *mild to moderate* ulcerative colitis.

The study was amended to evaluate the safety and effective of mesalamine 4.8 g/day (800 mg tablet) versus mesalamine 2.4 g/day (400 mg tablet) in patients with *moderate* ulcerative colitis. This amendment of February 18, 2003 was submitted after study 2000083 was completed see Section 3.1.2.3.1.1 for further discussion

A total of 14 changes to the protocol were implemented during the study. Major changes to the protocol are listed below.

1. Increase the number of study sites.
2. Revised inclusion criteria to allow for a colonoscopy (instead of sigmoidoscopy) at screening to determine extent of ulcerative colitis.
3. Remove exclusion criteria prohibiting H_2 blockers and proton pump inhibitors. Also removed these from prohibited concomitant medications list.
4. Revised age limit criteria from ≤65 years to ≤75 years to allow order patients into the study.
5. Changed study objective and primary analysis from study patients with mildly to moderately active ulcerative colitis (PGA=1 or 2) to studying only patients with moderately active ulcer colitis (PGA=2).
6. Increase enrollment by up to 100 additional patients with moderately active ulcerative colitis.
7. Change primary analyses to intent-to-treat patients with moderately active ulcerative colitis.
8. Change method used for primary from 2 x 2 Fisher's Exact Test to Chi-square test.

Note: Major changes 5, 6, 7, and 8 were made after study 2000083 was completed. The chi-squared test is less conservative.

3.1.2.2 **Sponsor's Analysis**

A total of 386 patients were randomized to the two treatment groups at study sites in the U.S. and Canada. Of these, 117 had mild disease at baseline, 268 (139 in 2.4 g/day and 129 in 4.8 g/day) had moderate disease at baseline, and 1 had insufficient data to determine baseline disease severity. This patient was excluded from efficacy analyses and safety analyses in patients with moderate disease.

The primary efficacy analysis was performed on the ITT population in patients with moderate disease at baseline (PGA=2).

3.1.2.2.1 **Planned Analysis**

The planned analysis was same as those described in Section 3.1.1.2.1 for Study 2000083.

3.1.2.2.2 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline for all randomized patients is given in Appendix Table 6.

As seen from Appendix Table 6, no statistically significant differences between the two treatment groups were observed for demographic and baseline characteristics with exception of sigmoidoscopy score (p=0.0816).

3.1.2.2.3 **Sponsor's Analysis of Primary Efficacy Variable**

The primary efficacy parameter was the proportion of patients in each treatment group who improved from baseline to Week 6.

The treatment success was defined as improvement from baseline to Week 6. Improvement from baseline was defined as either a complete response (remission) or partial response (improvement) to treatment. A complete response was defined as a PGA score of 0 and complete resolution of the following clinical assessments: stool frequency, rectal bleeding, PFA, and sigmoidoscopy findings. A partial response was defined as improvement from baseline in the PGA score, accompanied by improvement from baseline in at least 1 of the clinical assessments listed above, and no worsening in any of the remaining clinical assessments.

Treatment failure was defined as: 1) PGA score that stayed the same or worsened from baseline (regardless of whether the other clinical assessment resolved), 2) worsening of any clinical assessment at Week 6, or 3) withdrawal from the study due to an AE or lack of treatment effect.

The summary of results of sponsor's analysis of primary efficacy variable is given below.

Summary of Treatment Outcomes at Week 6
(Intent-to-Treat Patients with Moderate Disease [PGA=2] at Baseline)
Study 2000082

	2.4 g/day mesalamine (N=130)		4.8 g/day mesalamine (N=124)		
Treatment Outcome	n	(%)	n	(%)	p-value
Treatment Success	77	(59.2%)	89	(71.8%)	0.0357
Treatment Failure	53	(40.8%)	35	(28.2%)	

Copied from Table 9.
P-value was obtained by the chi-square test.

As seen from table above, the 4.8 g/day group achieved a statistically significant improvement over the 2.4 g/day group.

3.1.2.2.4 **Sponsor's Analyses of Secondary Efficacy Variables**

The secondary efficacy parameters included the proportion of patients who improved from baseline at Week 3, and the percentage of patients whose clinical assessment scores (stool frequency, rectal bleeding, sigmoidoscopy scores, the patient's functional assessment [PFA]), and physician's global assessment (PGA) score improved from baseline at Weeks and 6.

3.1.2.2.4.1 **Treatment Outcomes at Week 3**

The summary of results of sponsor's analysis of treatment outcomes at Week 3 is given below.

Summary of Treatment Outcomes at Week 3
(Intent-to-Treat Patients with Moderate Disease [PGA=2] at Baseline)
Study 2000082

	2.4 g/day mesalamine (N=130)		4.8 g/day mesalamine (N=124)		
Treatment Outcome	n	(%)	n	(%)	p-value
Treatment Success	67	(51.5%)	76	(61.3%)	0.1173
Treatment Failure	63	(48.50%)	48	(38.7%)	

Copied from EoT Table EoT 7.
P-value was obtained by the chi-square test.

As seen from table above, the difference in treatment outcome between the two treatment groups at Week 3 failed to achieve statistically significance.

3.1.2.2.4.2 **Other Secondary Efficacy Variables**

The summary of analysis of treatment outcomes for physician's global assessment, stool frequency, rectal bleeding, patient's functional assessment, and sigmoidoscopy at Weeks 3 and 6 is in Appendix Table 7.

As seem from Appendix Table 7, the percentage of patients whose clinical assessment improved from baseline was not statistically different between two treatment groups at Weeks 3 or 6.

3.1.2.3 **Reviewer's Comments and Evaluation**

3.1.2.3.1 **Reviewer's Comments on Study Design**

The original objective was to evaluate the safety and effective of mesalamine 4.8 g/day (800 mg tablet) versus mesalamine 2.4 g/day (400 mg tablet) in patients with *mild to moderate* ulcerative colitis.

The sponsor made Amendment 3 on February 19, 2003 at almost the end of enrollment. 296 patients were enrolled according to Sponsor's NDA amendment #15 dated July 13, 2005. But, this reviewer found that actually 304 patients were enrolled (156 patients in 2.4 gm and 148 patients in 4.8 gm).

The objective of study was changed evaluate the safety and effective of mesalamine 4.8 g/day (800 mg tablet) versus mesalamine 2.4 g/day (400 mg tablet) in patients with *moderate* ulcerative colitis. The primary analysis was changed from studying patients with mildly to moderately active ulcerative colitis (PGA=1 or 2) to studying only patients

with moderately active ulcerative colitis (PGA=2). Enrollment was increased by up to 100 additional patients with moderately active ulcerative colitis. The statistical method used for primary analysis was change from 2x2 Fisher's Exact Test to the less conservative Chi-square test. These changes were made to study 2000082 after study 2000083 was completed.

In the sponsor's internal SAP dated May 25, 2004, it stated that under the amended protocol, recruitment was limited to patients with moderately active ulcerative colitis. A power calculation in that internal SAP found that a total of 240 patients with moderate disease (120 patients per group) provides 80% power to detect a true difference of 20% between the 2 groups in patients with moderate ulcerative colitis, using a 2-sided test, type I error of 0.05 (α=0.05). However, the amendment called for an additional 100 patients.

Increasing sample size 100 was arbitrary. A total of 82 patients were actually enrolled after the protocol amendment (39 in 2.4 g/day and 43 in 4.8 g/day).

3.1.2.3.2 **Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable**

3.1.2.3.2.1 **Reviewer's Comments on Sponsor's Intent-to-Treat Analysis**

The sponsor excluded 14 patients (9 in 2.4 g/day and 5 in 4.8 g/day) from its Intent-to-Treat Analysis (ITT) because Week 6 treatment outcomes could not be determined. The sponsor's ITT analysis did not include all randomized patients, so it is not 'true' ITT analysis.

3.1.2.3.2.2 **Reviewer's Comments on Sponsor's Primary Efficacy Analysis**

The sponsor performed the primary efficacy analysis on the ITT population in patients with moderate disease at baseline (PGA=2). The sponsor's efficacy analyses excluded patients who were randomized earlier and had mild disease at baseline (PGA=1). The sponsor's efficacy analyses including only patients with moderate disease at baseline should be considered as post hoc subgroup analyses. Based on ITT principal, the primary efficacy analysis should include all randomized patients regardless of disease severity at baseline.

3.1.2.3.2.3 **Reviewer's Analysis of Treatment Success**

This reviewer performed an analysis of treatment success at week 6 for all randomized patients ("Reviewer's ITT Population") by time of enrollment (pre- or post amendment). In this analysis, the missing outcomes were set to treatment failure. The results are summarized below.

Treatment Success at Week 6
Reviewer's ITT Population
Study 2000082

Time of Enrollment	2.4 g/day mesalamine	4.8 g/day mesalamine	Diff	P-value
Pre-Amendment	73/156 (46.8%)	77/148 (52.0%)	5.2%	0.4219
Post Amendment	25/39 (64.1%)	31/43 (72.1%)	8%	0.4827

Compiled by this reviewer.
P-value was obtained by Fisher's exact test.

As seen from table above, there was no treatment difference for treatment success at week 6 for both strata. With adjustment for strata (defined by time of enrollment pre- or post amendment), p-value would be 0.2476 (Cochran-Mantel-Haenszel method), so, there was no treatment difference for treatment success at week 6 for all randomized patients.

3.1.2.3.2.4 **Subgroup Analysis**

Subgroup analyses were performed on the number of patients with treatment success at week 6 by age, gender, disease extent, length of disease history, prior treatment, relapse frequency, physician's global assessment score, stool frequency score, rectal bleeding score, patient's functional assessment score, and sigmoidoscopy score.

In these analyses, the missing outcomes were set to treatment failure. The results of subgroup analyses of the number of patients with treatment success are given below.

Number of Patients with Treatment Success at Week 6 by Subgroup
Reviewer's ITT Population
Protocol 2000082

Subgroup	2.4 g/day	4.8 g/day	Difference	95% C. I.
Gender				
Male	40/88 (46%)	50/77 (65%)	19%	(4.6%, 34.4%)
Female	58/107 (54%)	58/114 (51%)	-3%	(-16.5%, 9.8%)
Age				
18 to 64	89/178 (50%)	100/175 (57%)	7%	(-3.2%, 17.5%)
≥65	9/17 (53%)	8/16 (50%)	-3%	(-37.1%, 31.2%)
Disease Extent				
Proctitis	17/38 (45%)	20/34 (59%)	14%	(-8.8%, 37.0%)
Proctosigmoiditis	30/62 (48%)	27/50 (54%)	6%	(-13.0%, 24.2%)
Left-sided Colitis	30/53 (57%)	38/68 (56%)	-1%	(-18.6%, 17.1%)
Pancolitis	21/42 (50%)	23/39 (59%)	9%	(-12.6%, 30.6%)
Length of Disease History				
< 1 year	42/75 (56%)	43/72 (60%)	4%	(-12.2%, 19.7%)
1 to 5 years	22/48 (46%)	22/41 (54%)	8%	(-13.0%, 28.6%)
>5 to 10 years	16/31 (52%)	19/36 (53%)	1%	(-22.8%, 25.2%)
> 10 years	18/38 (47%)	24/41 (59%)	12%	(-10.7%, 33.1%)

Prior Treatment				
Steroids	27/61 (44%)	37/59 (63%)	19%	(0.9%, 36.0%)
Sulfasalazine	34/71 (48%)	36/67 (54%)	6%	(-10.8%, 22.5%)
Sulfa-free oral 5-ASAs	34/73 (47%)	45/80 (56%)	9%	(-6.1%, 25.5%)
Rectal therapy	28/66 (42%)	43/69 (62%)	20%	(3.4%, 36.4%)
Relapse Frequency				
Newly diagnosed	37/64 (58%)	37/65 (57%)	-1%	(-18.0%, 16.2%)
More than once a month	12/33 (36%)	12/21 (57%)	21%	(-6.0%, 47.6%)
Once every 6 months	14/31 (45%)	20/37 (54%)	9%	(-14.9%, 32.7%)
Once every 6 to 12 months	15/28 (54%)	21/34 (62%)	8%	(-16.5%, 32.9%)
Less than once a year	19/37 (51%)	18/34 (53%)	2%	(-21.7%, 24.9%)
Physician's Global Assessment Score				
1	21/55 (38%)	19/62 (31%)	-7%	(-24.8%, 9.7%)
2	77/139 (55%)	89/129 (69%)	14%	(2.1%, 25.1%)
Stool Frequency Score				
0	6/17 (35%)	7/23 (30%)	-5%	(-34.3%, 24.6%)
1	45/88 (51%)	44/80 (55%)	4%	(-11.2%, 19.0%)
2	34/59 (58%)	40/62 (65%)	7%	(-10.5%, 24.2%)
3	13/30 (43%)	17/26 (65%)	22%	(-3.4%, 47.5%)
Rectal Bleeding Score				
0	12/37 (32%)	11/32 (34%)	2%	(-20.4%, 24.3%)
1	36/62 (58%)	33/57 (58%)	0%	(-17.9%, 17.6%)
2	46/81 (57%)	59/93 (63%)	6%	(-7.9%, 21.2%)
3	4/14 (29%)	5/9 (56%)	27%	(-13.2%, 67.2%)
Patient's Functional Assessment Score				
0	18/43 (42%)	23/43 (54%)	12%	(-9.3%, 32.6%)
1	54/107 (51%)	58/108 (54%)	3%	(-10.1%, 16.6%)
2	23/39 (59%)	25/38 (66%)	7%	(-14.8%, 28.4%)
3	3/5 (60%)	2/2 (100%)	40%	(-3.0%, 83.0%)
Sigmoidoscopy Score				
1	22/49 (45%)	31/68 (46%)	1%	(-17.6%, 19.0%)
2	70/128 (55%)	69/108 (64%)	9%	(-3.3%, 21.7%)
3	6/18 (28%)	8/15 (53%)	25%	(-13.3%, 53.3%)

Compiled by this reviewer.

As seen from table above, treatment difference was inconsistent for some subgroups. Interaction between treatment and subgroup was found to be statistically significant at significance level of 0.05 for subgroups of gender and physician's global assessment score with p-values, 0.0258 and 0.0485 (Breslow-Day method), respectively.

Furthermore, it was revealed that treatment success rate for the 4.8 g/day group was statistically significantly higher than that for the 2.4 g/day group for males, patients with prior treatment of steroids, patients with prior treatment of rectal therapy, and patients with PGA=2.

3.1.2.3.3 Reviewer's Comments on Sponsor's Analysis for Patients with PGA=2 at Baseline

Statistical method for analyzing the primary endpoint was pre-specified in the protocol as Fisher's exact test. In the statistical plan, it was changed to chi-square test. If Fisher's exact test were used, the p-value would be 0.0476 instead of 0.0357 given by chi-square test. So, sponsor's finding was method dependent.

3.1.2.3.3.1 Analysis of Treatment Response

Treatment outcomes were further classified into one of four treatment responses: complete response, partial response, no response, and worsened. The treatment responses were ordered categories that might not be equally spaced. This reviewer performed a statistical analysis using Cochran-Mantel-Haenszel method for ordered data with modified ridit scores. The result of this analysis is given below.

Summary of Treatment Outcomes at Week 6
Intent-to-Treat Patients with Moderate Disease [PGA=2] at Baseline)
Study 2000082

	2.4 g/day mesalamine (N=130)		4.8 g/day mesalamine (N=124)		
Treatment Outcome	n	(%)	n	(%)	p-value
Complete success	23	(17.7%)	25	(20.2%)	0.0943
Partial success	54	(41.5%)	64	(51.6%)	
Failure (same)	17	(13.1%)	10	(8.1%)	
Failure (worsen)	36	(27.7%)	25	(20.2%)	

Compiled by this reviewer.
P-value was obtained by the CMH method.

As seen from table above, the treatment difference failed to achieve statistical significance.

So, the sponsor's finding for treatment success at week 6 for patients with PGA=2 was not robust.

3.1.2.3.3.2 Imbalance for Sigmoidoscopy Score at Baseline

There was a slight imbalance of sigmoidoscopy scores at baseline (p=0.0816) for all randomized patients. This reviewer performed a post-hoc analysis of treatment success at week 6 for patients with moderate disease (PGA=2) adjusted for sigmoidoscopy scores using Cochran-Mantel-Haenszel method. The result of this analysis is given Appendix Table 8.

As seen from Appendix Table 8, the resulting p-value adjusted for sigmoidoscopy score at baseline was 0.0580, greater than 0.0357 given by the sponsor. So, the sponsor's finding for treatment success at week 6 for patients with PGA=2 was not robust.

3.1.2.3.3.3 **Subgroup Analysis**

Per Medical officer's request, this reviewer performed subgroup analyses on the number of patients with PGA=2. The number of patients with treatment success at week 6 by age, gender, disease extent, length of disease history, prior treatment, relapse frequency, physician's global assessment score, stool frequency score, rectal bleeding score, patient's functional assessment score, and sigmoidoscopy score was calculated.

In these analyses, the missing outcomes were set to treatment failure. The results of subgroup analyses of the number of patients with treatment success are given in Appendix Table 9.

As seen from Appendix Table 9, treatment difference was consistent among all subgroups. Furthermore, it was revealed that treatment success rate for the 4.8 g/day group was statistically significantly higher than that for the 2.4 g/day group for males, patients aged from 18 to 64, patients with prior treatment of steroids, patients with prior treatment of rectal therapy, patients with stool frequency score of 3, patients with rectal bleeding score of 0, and patients with patient's functional assessment score of 0.

3.1.2.3.3.4 **Analysis of Treatment Success by Time of Enrollment (Pre- or Post Amendment)**

This reviewer performed an analysis on the number of patients with PGA=2 with treatment success at week 6 by time of enrollment (pre- or post amendment). The results are summarized below.

Treatment Success at Week 6
(Intent-to-Treat Patients with Moderate Disease [PGA=2] at Baseline)
Study 2000082

Enrollment Time	2.4 g/day mesalamine	4.8 g/day mesalamine	Diff	P-value
Pre-Amendment	52/95 (54.7%)	58/83 (69.9%)	15.2%	0.0381
Post Amendment	25/35 (71.4%)	31/41 (75.6%)	4.2%	0.6799

Compiled by this reviewer.
P-value was obtained by Fisher's exact test.

As seen from table above, the treatment difference reached statistical significance at the time of protocol amendment. There was not statistically significant difference between treatment groups after protocol amendment. The treatment difference after protocol amendment was much smaller than those before protocol amendment (4.2% vs. 15.2 %). It was difficult for this reviewer to interpret this result. In the post protocol amendment stratum where the patients were restricted to have moderate disease (PGA=2) and randomized to 2.4 g/day or 4.8 g/day doses, it was shown to have treatment difference of 4.2%. But, in the post protocol amendment stratum were the patients were restricted to have moderate disease (PGA=2) and was not randomized to 2.4 g/day or 4.8 g/day doses, it was shown to have treatment difference of 15.2%. If 4.8 g/day were more effective than

2.4 g/day, a significant treatment difference or a trend should be shown for enriched patients enrolled post protocol amendment. The inconsistent treatment difference might be due misclassification of disease (PGA=1 vs. PGA=2) at baseline.

Furthermore, with adjustment for strata (defined by time of enrollment: pre- or post amendment), p-value would be 0.0463 (Cochran-Mantel-Haenszel method).

3.1.3 Reviewer's Integrated Summary of Efficacy

The efficacy results from sponsor's analyses for study 2000083 and study 2000082 at the time of amendment are summarized below.

Treatment Success at Week 6
(Intent-to-Treat Patients)

Study	PGA	2.4 g/day mesalamine	4.8 g/day mesalamine	Diff	P-value
2000083	Mild	24/57 (42.1%)	21/60 (35.0%)	-7.1%	0.4298
	Moderate	53/93 (57.0%)	55/76 (72.4%)	15.4%	0.0384
	Total	77/150 (51.3%)	76/136 (55.9%)	4.6%	0.4411
2000082[†]	Mild	21/52 (40.4%)	19/58 (32.8%)	-7.6%	0.4065
	Moderate	52/95 (54.7%)	58/83 (69.9%)	15.2%	0.0381
	Total	73/147 (49.7%)	77/141 (54.6%)	4.9%	0.4006

Compiled by this reviewer.
[†]At the time of amendment.
P-value was obtained by the Chi-square test.

The efficacy results from reviewer analyses (reviewer's ITT population) for study 2000083 and study 2000082 at the time of amendment are summarized below. In these analyses, patients with missing value were considered as failures.

Treatment Success at Week 6
(Reviewer's Intent-to-Treat Patients)

Study	PGA	2.4 g/day mesalamine	4.8 g/day mesalamine	Diff	P-value
2000083	Mild	24/58 (41.4%)	21/63 (33.3%)	-8.1%	0.4298
	Moderate	53/96 (55.2%)	55/84 (65.5%)	10.3%	0.1607
	Total	77/154 (50.0%)	76/147 (51.7%)	1.7%	0.7680
2000082[†]	Mild	21/56 (37.5%)	19/62 (30.6%)	-6.9%	0.4322
	Moderate	52/100 (52.0%)	58/86 (67.4%)	15.4%	0.0327
	Total	73/156 (46.8%)	77/148 (52.0%)	5.2%	0.3618

Compiled by this reviewer.
[†]At the time of amendment.
P-value was obtained by the Chi-square test.

As seen from table above, in the reviewer's analyses where patients with missing value were considered failures, there were inconsistent results between studies for patients with moderate disease at baseline.

The efficacy results from sponsor's analyses for study 2000082 after amendment are summarized below.

Treatment Success at Week 6
(Intent-to-Treat Patients with Moderate Disease [PGA=2] at Baseline)
Post-Amendment
Study 2000082

Study	PGA	2.4 g/day mesalamine	4.8 g/day mesalamine	Diff	P-value
2000082	Moderate	25/35 (71.4%)	31/41 (75.6%)	4.2%	0.6799

Compiled by this reviewer.
P-value was obtained by Fisher's exact test.

As seen from table above, there was no statistically significant difference between treatment groups for patients enrolled after the amendment. The success rates were much higher than those observed for patients enrolled before the amendment for patients with moderate disease at baseline (71.4% vs. 52.0% for 2.4 g/day and 75.6% vs. 67.4% for 4.8 g/day). So, it seems to this reviewer, either the patients enrolled after the amendment might be wrong patients or disease at baseline might be misclassified.

Furthermore, studies 20000082 and 2000083 were conducted in parallel. Study 2000083 was completed first. For study 2000082, the sponsor made amendments consisting of changing objective of study and primary analysis, increasing sample size, enrolling only patients with moderate disease at baseline, and statistical method after assessing the efficacy results from study 2000083. These two studies became dependent. These changes were not pre-specified, so this study could not be considered to have a valid adapted design as allowed by E9. It should be considered as post hoc adjustment. The p-value might not be interpreted properly. At the time of amendment, the study 2000082 was close to being completed (96.1% enrolled). The sponsor should perform a new clinical study for moderate disease patients instead of trying to salvage study 2000082.

3.2 Evaluation of Safety

3.2.1 Study 2000083

A similar percentage of patients experienced AEs between treatment groups. The majority of AEs reported were assessed as mild or moderate in severity and non-serious. More serious AEs were reported in the 2.4 g/day group than in the 4.8 g/day group.

AEs of colitis ulcer and flu synd were reported by more patients in the 2.4 g/day group than in the 4.8 g/day group, and AEs of nausea, flatul, and vomit were reported by more patients in the 4.8 g/day group than in the 2.4 g/day group.

3.2.1 **Study 2000082**

More serious AEs were reported in the 2.4 g/day group than in the 4.8 g/day group. The number and percentage of patients who reported at least one AE were similar between treatment groups for all body systems.

AEs of colitis ulcer and flu synd were reported by more patients in the 2.4 g/day group than in the 4.8 g/day group, and AEs of nausea, flatul, and vomit were reported by more patients in the 4.8 g/day group than in the 2.4 g/day group.

4. FINDING IN SPECIAL/SUBGROUP POPULATION

4.1 **Gender, Race and Age**

No conclusion on race can be drawn due to lack of representation of Black and other races. Similarly, there were very few patients aged 65 or older, no conclusion on age can be drawn.

The number of patients with treatment at week 6 by gender is given below.

Number of Patients with Treatment Success at Week 6 by Subgroup
Reviewer's ITT Population with
Moderate Disease [PGA=2] at Baseline
Protocol 2000083

Subgroup	2.4 g/day	4.8 g/day	Difference	95% C. I.
Gender				
Male	21/44 (48%)	29/40 (73%)	25%	(4.58%, 45.0%)
Female	32/52 (62%)	26/44 (59%)	-3%	(-22.1%, 17.2%)

Protocol 2000082

Subgroup	2.4 g/day	4.8 g/day	Difference	95% C. I.
Gender				
Male	29/62 (47%)	40/54 (74%)	27%	(10.2%, 44.4%)
Female	48/77 (62%)	49/75 (65%)	3%	(-12.3%, 18.3%)

As seen from tables above, treatment difference was statistically significant for males but not for female.

4.2 **Other Special/Subgroup Population**

There was no consistent or important differences among numerous other subgroups examined (see Sections 3.1.1.3.1.3.2 and 3.1.2.3.3.3 for more details).

No conclusion on other special/subgroup population was drawn.

5. SUMMARY AND CONCLUSIONS

5.1 **Statistical Issues and Collective Evidence**

The sponsor has submitted two phase III Studies (2000083 and 2000082). Both studies were designed to study patients with mild-to-moderate active ulcerative colitis.

Efficacy results from the first pivotal study (2000083) showed that the difference in treatment outcome at week 6 between mesalamine 2.4 g/day and 4.8 g/day groups was not statistically significant for patient with mildly to moderately active ulcerative colitis. The treatment difference in treatment success between two treatment groups at Week 3 was not statistically significant. The percentage of patients whose clinical assessment improved from baseline was not statistically significant different between two treatment group at Weeks 3 and 6 for physician's global assessment, stool frequency, rectal bleeding, patient's functional assessment, and sigmoidoscopy.

The sponsor performed a subgroup analysis in patients who had moderate disease at baseline. The sponsor stated that for the subgroup of patients who had moderate ulcerative colitis at baseline, the difference in treatment outcomes between the two treatment groups at Week 6 was statistically significant, with the 4.8 g/day group showing a greater improvement from baseline.

This subgroup analysis should be considered as supporting and exploratory. The p-value obtained by the sponsor using chi-square test was 0.038. If more conservative method, Fisher's exact test, were used, the p-value would be 0.053. So, the sponsor's finding was method dependent.

Furthermore, the sponsor's subgroup analysis excluded 11 patients (3 in 2.4 g/day and 8 in 4.8 g/day). More patients in 4.8 g/day group were excluded in the sponsor's analysis (p=0.074). The sponsor's analysis tends to be bias in favor of 4.8 g/day group. If those 11 patients were included in the analysis as treatment failure, p-value would be 0.17 by Fisher's exact test and 0.16 by chi-square test. So, the sponsor's finding for patients with PGA=2 at baseline was not robust.

The second pivotal study (2000082) was amended on February 18, 2003 when most of the intended sample size (96%) had been enrolled. Under the amended protocol, only patients with moderate disease at baseline (PGA=2) were to be enrolled and the sponsor changed the sample size and changed the focus to the subgroup of patients with moderate active ulcerative colitis at baseline. A faxed communication dated March 17, 2003 from the Agency agreed to this amendment. Since it was not pre-specified, it should be considered as post-hoc adjustment of study.

Superiority was seen among the all patients with moderate disease at baseline enrolled in the second study (pre-amendment and post amendment). But, the results were inconsistent in the reviewer's analyses with those observed for the first study (2000083) for patients with moderate disease at baseline and where patients with missing values were considered failures. However, superiority was not demonstrated for patients

enrolled after the amendment. The success rates were much higher than those for patients enrolled before the amendment for patients with moderate disease at baseline (71.4% vs. 52.0% for 2.4 g/day and 75.6% vs. 67.4% for 4.8 g/day). So, it seems to this reviewer, either the patients enrolled after the amendment might be wrong patients or disease at baseline might be misclassified.

The sponsor performed the primary efficacy analysis on the ITT population in patients with moderate disease at baseline (PGA=2). The sponsor's efficacy analyses excluded patients who were randomized earlier and had mild disease at baseline (PGA=1). The sponsor's efficacy analyses including only patients with moderate disease at baseline should be considered as post hoc subgroup analyses. Based on ITT principal, the primary efficacy analysis should include all randomized patients regardless of disease severity at baseline.

This reviewer performed an analysis of treatment success at week 6 for all randomized patients ("Reviewer's ITT Population") stratified by time of enrollment (pre- or post amendment). In this analysis, the missing outcomes were set to treatment failure. It was found that there was no treatment difference for treatment success at week 6 for all randomized patients. With adjustment for strata (defined by time of enrollment pre- or post amendment), p-value would be 0.2476 (Cochran-Mantel-Haenszel method).

This sponsor's subgroup analysis is exploratory and hypothesis generating. Subgroup analyses of this kind tend to have high false-positive rates unless the analysis is done at a very low significance level. The p-value resulting from the subgroup analysis cannot be interpreted properly, particularly, when the unadjusted nominal p-value is not far from 0.05.

Furthermore, studies 20000082 and 2000083 were conducted in parallel. Study 2000083 was completed first. For study 2000082, the sponsor made amendments consisting of changing objective of study and primary analysis, increasing sample size, enrolling only patients with moderate disease at baseline, and statistical method after assessing the efficacy results from study 2000083. These two studies became dependent. These changes were not pre-specified, so this study could not be considered to have a valid adapted design as allowed by E9. It should be considered as post hoc adjustment. The p-value might not be interpreted properly. At the time of amendment, the study 2000082 was close to being completed (96.1% enrolled). The sponsor should perform a new clinical study for moderate disease patients instead of trying to salvage study 2000082.

5.2 **Conclusions and Recommendations**

The sponsor has submitted two controlled Studies (2000083 and 2000082) comparing efficacy and safety of mesalamine 4.8 g/day (800 mg tablet) versus mesalamine 2.4 g/day (400 mg tablet) in the treatment of patients with moderately active ulcerative colitis.

Both studies were designed to study patients with mild-to-moderate active ulcerative colitis.

Neither of studies 2000083 and 2000082 showed that there was statistically significant difference in the treatment outcome between 2.4 g/day administered at a 400 mg tablet and 4.8 g/day administered at 800 mg tablet in treatment after 6 weeks of treatment in patients with mildly to moderately active ulcerative colitis.

For the subgroup of patients with moderately active ulcerative colitis at baseline, the sponsor's analysis of study 2000083 that showed a significant difference in favor of 4.8 g/day is found to be not valid, for reasons of bias, as explained in this review.

The second pivotal study (2000082) was amended on February 18, 2003 when most of the intended sample size (96%) had been enrolled. Under the amended protocol, only patients with moderate disease at baseline (PGA=2) were to be enrolled and the sponsor changed the sample size and changed the focus to the subgroup of patients with moderate active ulcerative colitis at baseline.

Superiority was seen among the all patients with moderate disease at baseline enrolled in the second study (pre-amendment and post amendment). But, the results were inconsistent in the reviewer's analyses with those observed for the first study (2000083) for patients with moderate disease at baseline and where patients with missing values were considered failures. However, superiority was not demonstrated for patients enrolled after the amendment. The success rates were much higher than those for patients enrolled before the amendment for patients with moderate disease at baseline (71.4% vs. 52.0% for 2.4 g/day and 75.6% vs. 67.4% for 4.8 g/day). So, it seems to this reviewer, either the patients enrolled after the amendment might be wrong patients or disease at baseline might be misclassified.

Only study 2000082 showed to a slightly better rate of treatment success at week 6 when dosed at 4.8 g/day than when dosed at 2.4 g/day, but the results might not be robust.

So, from a statistical perspective, based on a post-hoc subgroup analysis from a single study (2000082) with nominal p-value of 0.0463 with adjustment for time of enrollment, it is not statistically persuasive. The subgroup analysis should be confirmed in subsequent Phase III trials.

Furthermore, studies 20000082 and 2000083 were conducted parallel. Study 2000083 was completed first. For study 2000082, the sponsor made amendments consisting of changing objective of study and primary analysis, increasing sample size, enrolling only patients with moderate disease at baseline, and statistical method after assessing the efficacy results from study 2000083. These two studies became dependent. These changes were not pre-specified, so this study could not be considered to have a valid adapted design as allowed by E9. It should be considered as post hoc adjustment. The p-value might not be interpreted properly. At the time of amendment, the study 2000082 was closed to be completed (96.1% enrolled). The sponsor should perform a new clinical study for moderate disease patients instead of trying to salvaging study 2000082.

6. APPENDIX

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 2000083

	(All Randomized Patients)		
Characteristics	2.4 g/day mesalamine (400 mg Tablet) (N=154)	4.8 g/day mesalamine (800 mg Tablet) (N=147)	Between Treatment p-value
Sex			0.3209
Male	75 (48.7%)	80 (54.4%)	
Female	79 (51.3%)	67 (45.6%)	
Race			
White	122 (79.2%)	116 (78.9%)	
Black	18 (11.7%)	18 (12.2%)	
Asian	3 (1.9%)	2 (1.4%)	
Hispanic	10 (6.5%)	9 (6.1%)	
Other Races	1 (0.6%)	2 (1.4%)	
Age (months)			0.1237
Mean (SD)	43.5 (13.7)	45.9 (13.4)	
Age			0.7426
18 to 64	141 (91.6%)	133 (90.5%)	
≥65	13 (8.4%)	14 (9.5%)	
Height (cm)			0.7051
Mean (SD)	170.4 (10.1)	170.8 (10.5)	
Weight (kg)			0.4054
Mean (SD)	77.6 (16.3)	79.2 (17.0)	
Smoking History			0.4822
Never smoked	78 (50.6%),	69 (46.9%)	
Used to smoke	66 (42.9%)	63 (42.9%)	
Currently smokes	10 (6.5%)	15 (10.2%)	
Disease Extent			0.7824
Proctitis	25 (16.2%)	29 (19.7%)	
Proctosigmoiditis	45 (29.2%)	38 (25.9%)	
Left-sided colitis	45 (29.2%)	46 (31.3%)	
Pancolitis	39 (25.3%)	34 (23.1%)	
Length of Disease History			0.1430
N	153	146	
< 1 year	62 (40.5%)	50 (34.2%)	
1 to 5 years	25 (16.3%)	40 (27.4%)	
>5 to 10 years	28 (18.3%)	23 (15.8%)	
> 10 years	38 (24.8%)	33 (22.6%)	

Compiled by this reviewer. P-values were obtained by this reviewer.
CMH test adjusted for strata was used for sex, age group and race. ANOVA was used for age, height, and weight

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 2000083 (Continued)

Characteristics	(All Randomized Patients) 2.4 g/day mesalamine (400 mg Tablet) (N=154)	4.8 g/day mesalamine (800 mg Tablet) (N=147)	Between Treatment p-value
Prior Treatment			
Steroids	51 (33.1%)	43 (29.3%)	0.4695
Immunomodulators	7 (4.5%)	7 (4.8%)	0.9290
Sulfasalazine	57 (37.0%)	43 (29.3%)	0.1530
Sulfa-free oral 5-ASAs	61 (39.6%)	70 (47.6%)	0.1612
Rectal therapies	67 (43.5%)	60 (40.8%)	0.6366
Intolerant to Sulfasalazine			0.5372
N	57	43	
Yes	8 (14.0%)	8 (18.6%)	
Relapse Frequency			0.3979
Newly diagnosed	55 (35.7%)	43 (29.3%)	
More than once a month	14 (9.1%)	20 (13.6%)	
Once every 6 months	20 (13.0%)	14 (9.5%)	
Once every 6 to 12 months	26 (16.9%)	32 (21.8%)	
Less than once a year	39 (25.3%)	38 (25.9%)	
Physician's Global Assessment Score			0.3582
0 (Quiescent)	0 (0%)	0 (0%)	
1 (Mild activity)	58 (37.7%)	63 (42.9%)	
2 (Moderate activity)	96 (62.3%)	84 (57.1%)	
3 (Severe activity)	0 (0%)	0 (0%)	
Stool Frequency Score			0.0085
0 (Normal frequency)	18 (11.7%)	13 (8.8%)	
1 (1 to 2 greater than normal)	83 (53.9%)	66 (44.9%)	
2 (3 to 4 greater than normal)	29 (18.8%)	53 (36.1%)	
3 (≥ 5 greater than normal)	24 (15.6%)	15 (10.2%)	
Rectal Bleeding Score			0.5713
0 (none)	35 (22.7%)	26 (17.7%)	
1 (Streak, less than ½ times)	54 (35.1%)	61 (41.5%)	
2 (Obvious, most of time)	58 (37.7%)	55 (37.4%)	
3 (Blood alone)	7 (4.5%)	5 (3.4%)	
Patient's Functional Assessment Score			0.5390
0 (Generally well)	37 (24.0%)	29 (19.7%)	
1 (Fair)	84 (54.5%)	81 (55.1%)	
2 (Poor)	31 (20.1%)	32 (21.8%)	
3 (Terrible)	2 (1.3%)	5 (3.4%)	

Compiled by this reviewer. P-values were obtained by this reviewer.
CMH test adjusted for strata was used for sex, age group and race. ANOVA was used for age, height, and weight

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 2000083 (Continued)

Characteristics	(All Randomized Patients) 2.4 g/day mesalamine (400 mg Tablet) (N=154)	4.8 g/day mesalamine (800 mg Tablet) (N=147)	Between Treatment p-value
Sigmoidoscopy Score			0.9415
0 (Normal)	0 (0%)	0 (0%)	
1 (Mild)	53 (34.4%)	53 (36.1%)	
2 (Moderate)	90 (58.4%)	83 (56.5%)	
3 (Severe)	11 (7.1%)	11 (7.5%)	
IBDQ Total Score			0.2369
N	152	146	
Mean (SD)	146.7 (36.6)	141.8 (35.1)	

Compiled by this reviewer. P-values were obtained by this reviewer.
CMH test adjusted for strata was used for sex, age group and race. ANOVA was used for age, height, and weight

Table 2 Treatment Outcomes for Physician's Global Assessment, Stool Frequency, Rectal Bleeding, Patient's Functional Assessment, and Sigmoidoscopy at Weeks 3 and 6 for Study 2000083

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6 (All Randomized Patients)
(Page 1 of 2)

Parameter	Visit	Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 154) n	(%)	4.8 g/day Asacol (800 mg Tablet) (N = 147) n	(%)	Total (N = 301) n	(%)	p-value[a]
Physician's Global Assessment	Week 3	I	66	(49.3%)	56	(44.8%)	122	(47.1%)	
		NI	68	(50.7%)	69	(55.2%)	137	(52.9%)	
		Total	134		125		259		0.4730
	Week 6	I	81	(61.4%)	79	(64.8%)	160	(63.0%)	
		NI	51	(38.6%)	43	(35.2%)	94	(37.0%)	
		Total	132		122		254		0.5761
Stool Frequency	Week 3	I	63	(46.7%)	69	(54.3%)	132	(50.4%)	
		NI	72	(53.3%)	58	(45.7%)	130	(49.6%)	
		Total	135		127		262		0.2150
	Week 6	I	84	(63.2%)	82	(66.7%)	166	(64.8%)	
		NI	49	(36.8%)	41	(33.3%)	90	(35.2%)	
		Total	133		123		256		0.5569
Rectal Bleeding	Week 3	I	65	(48.1%)	75	(59.1%)	140	(53.4%)	
		NI	70	(51.9%)	52	(40.9%)	122	(46.6%)	
		Total	135		127		262		0.0769
	Week 6	I	80	(60.2%)	88	(71.5%)	168	(65.6%)	
		NI	53	(39.8%)	35	(28.5%)	88	(34.4%)	
		Total	133		123		256		0.0551

I = Improved from baseline. Improvement from baseline for each parameter was defined as either a complete response (remission, score = 0) or partial response (improvement) to treatment.
NI = Not improved from baseline. No improvement from baseline was defined as no change or worsening from baseline.
N = number of patients in treatment group
n (%) = number and percentage (n/Total x 100) of patients in treatment group with specified outcome in specified parameter
[a] 4.8 g/day compared to 2.4 g/day using the chi-square test
Corresponding data can be found in Appendix 3.8, Table 1.
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Table 2 Treatment Outcomes for Physician's Global Assessment, Stool Frequency, Rectal Bleeding, Patient's Functional Assessment, and Sigmoidoscopy at Weeks 3 and 6 for Study 2000083 (Continued)

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6 (All Randomized Patients)

(Page 2 of 2)

Parameter	Visit	Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 154) n	(%)	4.8 g/day Asacol (800 mg Tablet) (N = 147) n	(%)	Total (N = 301) n	(%)	p-value[a]
Patient's Functional Assessment	Week 3	I	57	(42.2%)	63	(49.6%)	120	(45.8%)	
		NI	78	(57.8%)	64	(50.4%)	142	(54.2%)	
		Total	135		127		262		0.2306
	Week 6	I	72	(54.1%)	74	(60.7%)	146	(57.3%)	
		NI	61	(45.9%)	48	(39.3%)	109	(42.7%)	
		Total	133		122		255		0.2931
Sigmoidoscopy	Week 3	I	69	(51.5%)	65	(52.0%)	134	(51.7%)	
		NI	65	(48.5%)	60	(48.0%)	125	(48.3%)	
		Total	134		125		259		0.9349
	Week 6	I	88	(66.7%)	90	(73.2%)	178	(69.8%)	
		NI	44	(33.3%)	33	(26.8%)	77	(30.2%)	
		Total	132		123		255		0.2583

I = Improved from baseline. Improvement from baseline for each parameter was defined as either a complete response (remission, score = 0) or partial response (improvement) to treatment.

NI = Not improved from baseline. No improvement from baseline was defined as no change or worsening from baseline.

N = number of patients in treatment group

n (%) = number and percentage (n/Total x 100) of patients in treatment group with specified outcome in specified parameter

[a] 4.8 g/day compared to 2.4 g/day using the chi-square test

Corresponding data can be found in Appendix 3.8, Table 1.

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Table 3 Summary of Treatment Outcomes at Week 6 Study 2000083

Summary of Treatment Outcomes at Week 6:
Missing Observations Set to Treatment Failure
(All Randomized Patients)

Treatment Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 154)		4.8 g/day Asacol (800 mg Tablet) (N = 147)		Total (N = 301)		p-value[a]
	n	(%)	n	(%)	n	(%)	
Treatment Success[b]	77	(50.0%)	76	(51.7%)	153	(50.8%)	--
Treatment Failure[c]	77	(50.0%)	71	(48.3%)	148	(49.2%)	--
Total	154		147		301		0.7680

N = number of patients in treatment group

n (%) = number and percentage (n/Total x 100) of patients in treatment group with specified treatment outcome

[a] 4.8 g/day compared to 2.4 g/day using the chi-square test

[b] Treatment success was defined as improvement from baseline at Week 6. Improvement from baseline was defined as either a complete response (remission) or partial response (improvement) to treatment. A complete response was defined as a PGA score of 0 and complete resolution of the following clinical assessments: stool frequency, rectal bleeding, PFA, and sigmoidoscopy findings. A partial response was defined as improvement from baseline in the PGA score, accompanied by improvement from baseline in at least 1 of the clinical assessments listed above, and no worsening in any of the remaining clinical assessments.

[c] Treatment failure was defined as: 1) PGA score that stayed the same or worsened from baseline (regardless of whether the other clinical assessments resolved), 2) worsening of any clinical assessment at Week 6, or 3) withdrawal from the study due to an AE or lack of treatment effect.

Corresponding data can be found in Appendix 3.8, Table 1.

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Table 3 Summary of Treatment Outcomes at Week 6 Study 2000083 (Continued)

Summary of Treatment Outcomes at Week 6:
Last Observation Carried Forward
(All Randomized Patients)

Treatment Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 154)		4.8 g/day Asacol (800 mg Tablet) (N = 147)		Total (N = 301)		p-value[a]
	n	(%)	n	(%)	n	(%)	
Treatment Success[b]	78	(50.6%)	77	(52.4%)	155	(51.5%)	--
Treatment Failure[c]	76	(49.4%)	70	(47.6%)	146	(48.5%)	--
Total	154		147		301		0.7638

N = number of patients in treatment group

n (%) = number and percentage (n/Total x 100) of patients in treatment group with specified treatment outcome

[a] 4.8 g/day compared to 2.4 g/day using the chi-square test

[b] Treatment success was defined as improvement from baseline at Week 6. Improvement from baseline was defined as either a complete response (remission) or partial response (improvement) to treatment. A complete response was defined as a PGA score of 0 and complete resolution of the following clinical assessments: stool frequency, rectal bleeding, PFA, and sigmoidoscopy findings. A partial response was defined as improvement from baseline in the PGA score, accompanied by improvement from baseline in at least 1 of the clinical assessments listed above, and no worsening in any of the remaining clinical assessments.

[c] Treatment failure was defined as: 1) PGA score that stayed the same or worsened from baseline (regardless of whether the other clinical assessments resolved), 2) worsening of any clinical assessment at Week 6, or 3) withdrawal from the study due to an AE or lack of treatment effect.

Corresponding data can be found in Appendix 3.8, Table 1.

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Table 4 Summary of Treatment Outcomes at Week 6 for Patients with Moderate Disease (PGA=2) at Baseline

Summary of Treatment Outcomes at Week 6
(Intent-to-treat Population with Moderate Disease [PGA = 2] at Baseline)

	2.4 g/day Asacol (400 mg Tablet) (N = 93)		4.8 g/day Asacol (800 mg Tablet) (N = 76)		Total (N = 169)		
Treatment Outcome	n	(%)	n	(%)	n	(%)	p-value[a]
Treatment Success[b]	53	(57.0%)	55	(72.4%)	108	(63.9%)	--
Treatment Failure[c]	40	(43.0%)	21	(27.6%)	61	(36.1%)	--
Total	93		76		169		0.0384

N = number of analyzable patients in treatment group

n (%) = number and percentage (n/Total x 100) of patients in treatment group with specified treatment outcome

[a] 4.8 g/day compared to 2.4 g/day using the chi-square test

[b] Treatment success was defined as improvement from baseline at Week 6. Improvement from baseline was defined as either a complete response (remission) or partial response (improvement) to treatment. A complete response was defined as a PGA score of 0 and complete resolution of the following clinical assessments: stool frequency, rectal bleeding, PFA, and sigmoidoscopy findings. A partial response was defined as improvement from baseline in the PGA score, accompanied by improvement from baseline in at least 1 of the clinical assessments listed above, and no worsening in any of the remaining clinical assessments.

[c] Treatment failure was defined as: 1) PGA score that stayed the same or worsened from baseline (regardless of whether the other clinical assessments resolved), 2) worsening of any clinical assessment at Week 6, or 3) withdrawal from the study due to an AE or lack of treatment effect.

Corresponding data can be found in Appendix 3.8, Table 1.

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Table 5: Number of Patients with Treatment Success at Week 6 by Subgroup for Patients with Moderate Disease [PGA=2] at Baseline --- Protocol 2000083

Number of Patients with Treatment Success at Week 6 by Subgroup
Reviewer's ITT Population with
Moderate Disease [PGA=2] at Baseline
Protocol 2000083

Subgroup	2.4 g/day	4.8 g/day	Difference	95% C. I.
Gender				
Male	21/44 (48%)	29/40 (73%)	25%	(4.58%, 45.0%)
Female	32/52 (62%)	26/44 (59%)	-3%	(-22.1%, 17.2%)
Age				
18 to 64	48/88 (55%)	52/76 (68%)	13%	(-0.9%, 28.6%)
≥65	5/8 (63%)	3/8 (38%)	-25%	(-72.5%, 22.4%)
Disease Extent				
Proctitis	13/15 (87%)	9/11 (82%)	-5%	(-33.4%, 23.7%)
Proctosigmoiditis	13/26 (50%)	15/22 (68%)	18%	(-9.2%, 45.5%)
Left-sided Colitis	14/30 (47%)	19/31 (61%)	14%	(-10.1%, 39.4%)
Pancolitis	13/25 (52%)	12/20 (60%)	8%	(-21.1%, 37.1%)
Length of Disease History				
< 1 year	19/37 (51%)	15/23 (65%)	14%	(-11.4%, 39.1%)
1 to 5 years	10/17 (59%)	19/26 (73%)	14%	(-14.7%, 43.2%)
>5 to 10 years	9/16 (56%)	8/15 (53%)	-3%	(-38.0%, 32.1%)
> 10 years	16/26 (62%)	13/19 (68%)	-6%	(-21.1%, 34.9%)
Prior Treatment				
Steroids	15/33 (45%)	19/30 (63%)	18%	(-6.3%, 42.1%)
Sulfasalazine	22/36 (61%)	16/25 (64%)	3%	(-21.8%, 27.5%)
Sulfa-free oral 5-ASAs	21/36 (58%)	27/43 (63%)	5%	(-17.2%, 26.1%)
Rectal therapy	23/44 (52%)	27/38 (71%)	19%	(-1.9%, 39.4%)
Relapse Frequency				
Newly diagnosed	17/32 (53%)	14/19 (74%)	21%	(-5.7%, 46.9%)
More than once a month	6/9 (67%)	8/12 (67%)	0%	(-40.8%, 40.8%)
Once every 6 months	5/8 (63%)	6/9 (67%)	4%	(-41.4%, 49.7%)
Once every 6 to 12 months	8/17 (47%)	10/16 (63%)	16%	(-18.1%, 49.0%)
Less than once a year	17/30 (57%)	17/28 (61%)	4%	(-21.3%, 29.4%)
Stool Frequency Score				
0	7/8 (68%)	3/5 (60%)	-8%	(-76.2%, 21.2%)
1	26/39 (67%)	12/20 (60%)	-7%	(-32.7%, 19.4%)
2	11/26 (42%)	30/44 (68%)	26%	(2.4%, 49.3%)
3	9/23 (39%)	10/15 (67%)	28%	(-3.6%, 58.6%)
Rectal Bleeding Score				
0	8/15 (53%)	5/7 (71%)	18%	(-23.8%, 60.0%)
1	13/23 (57%)	20/27 (74%)	17%	(-8.6%, 43.7%)
2	28/51 (55%)	28/45 (62%)	7%	(-12.4%, 27.0%)
3	4/7 (57%)	2/5 (40%)	-17%	(-73.6%, 39.3%)
Patient's Functional Assessment Score				

0	9/14 (64%)	8/11 (73%)	9%	(-27.9%, 44.8%)
1	30/51 (59%)	25/41 (61%)	2%	(-18.0%, 22.3%)
2	12/29 (41%)	18/27 (67%)	26%	(24.5%, 26.1%)
3	2/2 (100%)	4/5 (80%)	-20%	(-55.1%, 15.1%)
Sigmoidoscopy Score				
1	7/11 (64%)	9/12 (75%)	11%	(-26.2%, 48.9%)
2	45/74 (61%)	41/61 (67%)	6%	(-9.8%, 22.6%)
3	3/11 (27%)	5/11 (45%)	18%	(-21.3%, 57.7%)

Compiled by this reviewer.

Table 6 Summary of Demographic and Baseline Characteristics --- Protocol 2000082

Characteristics	(All Randomized Patients) 2.4 g/day mesalamine (400 mg Tablet) (N=195)	4.8 g/day mesalamine (800 mg Tablet) (N=191)	Between Treatment p-value
Sex			0.3391
Male	88 (45.1%)	77 (40.3%)	
Female	107 (54.9%)	114 (59.7%)	
Race			
White	150 (76.9%)	142 (74.3%)	
Black	17 (8.7%)	24 (12.6%)	
Asian	2 (1.0%)	2 (1.0%)	
Hispanic	16 (8.2%)	11 5.8%)	
Other Races	2 (1.0%)	3 (1.6%)	
Age (months)			0.9643
Mean (SD)	42.8 (14.0)	42.7 (13.1)	
Age			0.9046
18 to 64	178 (91.3%)	175 (91.6%)	
≥65	17 (8.7%)	16 (8.4%)	
Height (cm)			0.7160
N	194	191	
Mean (SD)	169.0 (13.4)	168.6 (10.5)	
Weight (kg)			0.9208
N	194	191	
Mean (SE)	78.9 (20.1)	78.7 (19.1)	
Smoking History			0.3943
Never smoked	120 (61.5%),	113 (59.2%)	
Used to smoke	54 (27.7%)	63 (33.0%)	
Currently smokes	21 (10.8%)	15 (7.9%)	
Disease Extent			0.3290
Proctitis	38 (19.5%)	34 (17.8%)	
Proctosigmoiditis	62 (31.8%)	50 (26.2%)	
Left-sided colitis	53 (27.2%)	68 (35.6%)	
Pancolitis	42 (21.5%)	39 (20.4%)	
Length of Disease History			0.7799
N	192	190	
< 1 year	75 (39.1%)	72 (37.9%)	
1 to 5 years	48 (25.0%)	41 (21.6%)	
>5 to 10 years	31 (16.2%)	36 (19.0%)	
> 10 years	38 (19.8%)	41 (21.6%)	

Compiled by this reviewer. P-values were obtained by this reviewer.
CMH test adjusted for strata was used for sex, age group and race. ANOVA was used for age, height, and weight

Table 6 Summary of Demographic and Baseline Characteristics --- Protocol 2000082 (Continued)

Characteristics	(All Randomized Patients) 2.4 g/day mesalamine (400 mg Tablet) (N=195)	4.8 g/day mesalamine (800 mg Tablet) (N=191)	Between Treatment p-value
Prior Treatment			
Steroids	61 (31.3%)	59 (30.9%)	0.9337
Immunomodulators	3 (1.5%)	6 (3.1%)	0.2968
Sulfasalazine	71 (36.4%)	67 (35.0%)	0.7849
Sulfa-free oral 5-ASAs	73 (37.4%)	80 (41.9%)	0.3716
Rectal therapies	66 (33.9%)	69 (36.1%)	0.6387
Intolerant to Sulfasalazine			0.8696
N	71	67	
Yes	13 (18.3%)	13 (19.4%)	
Relapse Frequency			0.4196
N	193	191	
Newly diagnosed	64 (33.2%)	65 (34.0%)	
More than once a month	33 (17.1%)	21 (11.0%)	
Once every 6 months	31 (16.1%)	37 (19.4%)	
Once every 6 to 12 months	28 (14.5%)	34 (17.8%)	
Less than once a year	37 (19.2%)	34 (17.8%)	
Physician's Global Assessment Score			0.3806
0 (Quiescent)	0 (0%)	0 (0%)	
1 (Mild activity)	55 (28.4%)	62 (32.5%)	
2 (Moderate activity)	139 (71.7%)	129 (67.5%)	
3 (Severe activity)	0 (0%)	0 (0%)	
Stool Frequency Score			0.6554
0 (Normal frequency)	17 (8.8%)	23 (12.0%)	
1 (1 to 2 greater than normal)	88 (45.4%)	80 (41.9%)	
2 (3 to 4 greater than normal)	59 (30.4%)	60 (32.5%)	
3 (≥ 5 greater than normal)	30 (15.5%)	26 (13.6%)	
Rectal Bleeding Score			0.4819
0 (none)	37(19.1%)	32 (16.8%)	
1 (Streak, less than ½ times)	62 (32.0%)	57 (30.0%)	
2 (Obvious, most of time)	81 (41.8%)	93 (48.7%)	
3 (Blood alone)	14 (7.2%)	9 (4.7%)	
Patient's Functional Assessment Score			0.7339
0 (Generally well)	43 (22.2%)	43 (22.5%)	
1 (Fair)	107 (55.2%)	108 (56.5%)	
2 (Poor)	39 (20.1%)	38 (19.9%)	
3 (Terrible)	5 (2.6%)	2 (1.1%)	

Compiled by this reviewer. P-values were obtained by this reviewer.
CMH test adjusted for strata was used for sex, age group and race. ANOVA was used for age, height, and weight

Table 6 Summary of Demographic and Baseline Characteristics --- Protocol 2000082 (Continued)

Characteristics	(All Randomized Patients) 2.4 g/day mesalamine (400 mg Tablet) (N=195)	4.8 g/day mesalamine (800 mg Tablet) (N=191)	Between Treatment p-value
Sigmoidoscopy Score			0.0816
0 (Normal)	0 (0%)	0 (0%)	
1 (Mild)	49 (25.1%)	68 (35.6%)	
2 (Moderate)	128 (65.6%)	108 (56.5%)	
3 (Severe)	18 (9.2%)	15 (7.9%)	
IBDQ Total Score			0.5496
N	189	189	
Mean (SD)	140.6 (33.7)	142.7 (35.5)	

Compiled by this reviewer. P-values were obtained by this reviewer.
CMH test adjusted for strata was used for sex, age group and race. ANOVA was used for age, height, and weight

Table 7 Treatment Outcomes for Physician's Global Assessment, Stool Frequency, Rectal Bleeding, Patient's Functional Assessment, and Sigmoidoscopy at Weeks 3 and 6 for Study 2000082

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6
Excluding Patients with Both Baseline and Visit Scores of Zero
(ITT Patients with Moderate Disease [PGA = 2] at Baseline)
(Page 1 of 2)

Parameter	Visit	Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 130) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 124) n (%)	Total (N = 254) n (%)	Chi-square p-value[a]	Difference in Success Rates[b]	Confidence Interval (%)[c]
PGA	Week 3	I	70 (61.4%)	82 (70.7%)	152 (66.1%)			
		NI	44 (38.6%)	34 (29.3%)	78 (33.9%)			
		Total	114	116	230	0.1369	9.29	(-2.90, 21.47)
	Week 6	I	83 (73.5%)	94 (83.2%)	177 (78.3%)			
		NI	30 (26.5%)	19 (16.8%)	49 (21.7%)			
		Total	113	113	226	0.0758	9.73	(-0.94, 20.40)
Stool Frequency	Week 3	I	66 (60.6%)	70 (63.6%)	136 (62.1%)			
		NI	43 (39.4%)	40 (36.4%)	83 (37.9%)			
		Total	109	110	219	0.6379	3.09	(-9.76, 15.93)
	Week 6	I	77 (71.3%)	77 (74.0%)	154 (72.6%)			
		NI	31 (28.7%)	27 (26.0%)	58 (27.4%)			
		Total	108	104	212	0.6543	2.74	(-9.25, 14.73)
Rectal Bleeding	Week 3	I	65 (63.7%)	82 (74.5%)	147 (69.3%)			
		NI	37 (36.3%)	28 (25.5%)	65 (30.7%)			
		Total	102	110	212	0.0878	10.82	(-1.56, 23.20)
	Week 6	I	79 (77.5%)	84 (78.5%)	163 (78.0%)			
		NI	23 (22.5%)	23 (21.5%)	46 (22.0%)			
		Total	102	107	209	0.8542	1.05	(-10.19, 12.29)

I = Improved
NI = Not improved
N = number of patients in treatment group with treatment outcome at Week 6
n (%) = number and percentage (n/Total x 100) of patients in treatment group with specified outcome in specified parameter
[a] 4.8 g/day compared to 2.4 g/day
[b] Difference between 4.8 g/day and 2.4 g/day
[c] Confidence interval for the difference in improvement rates between 4.8 g/day and 2.4 g/day
Corresponding data can be found in Appendix 3.8, Table 1.
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Table 7 Treatment Outcomes for Physician's Global Assessment, Stool Frequency, Rectal Bleeding, Patient's Functional Assessment, and Sigmoidoscopy at Weeks 3 and 6 for Study 2000082 (Continued)

Distribution of Treatment Outcomes for Physician's Global Assessment and Individual Symptoms at Weeks 3 and 6
Excluding Patients with Both Baseline and Visit Scores of Zero
(ITT Patients with Moderate Disease [PGA = 2] at Baseline)
(Page 2 of 2)

Parameter	Visit	Outcome	2.4 g/day Asacol (400 mg Tablet) (N = 130) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 124) n (%)	Total (N = 254) n (%)	Chi-square p-value[a]	Difference In Success Rates[b]	Confidence Interval (%)[c]
PFA	Week 3	I	56 (58.9%)	54 (56.8%)	110 (57.9%)			
		NI	39 (41.1%)	41 (43.2%)	80 (42.1%)			
		Total	95	95	190	0.7689	-2.11	(-16.14, 11.93)
	Week 6	I	67 (70.5%)	64 (69.6%)	131 (70.1%)			
		NI	28 (29.5%)	28 (30.4%)	56 (29.9%)			
		Total	95	92	187	0.8859	-0.96	(-14.09, 12.17)
Sigmoidoscopy	Week 3	I	66 (57.9%)	71 (61.2%)	137 (59.6%)			
		NI	48 (42.1%)	45 (38.8%)	93 (40.4%)			
		Total	114	116	230	0.6088	3.31	(-9.37, 15.99)
	Week 6	I	78 (69.0%)	85 (75.2%)	163 (72.1%)			
		NI	35 (31.0%)	28 (24.8%)	63 (27.9%)			
		Total	113	113	226	0.2991	6.19	(-5.47, 17.86)

I = Improved
NI = Not improved
N = number of patients in treatment group with treatment outcome at Week 6
n (%) = number and percentage (n/Total x 100) of patients in treatment group with specified outcome in specified parameter
[a] 4.8 g/day compared to 2.4 g/day
[b] Difference between 4.8 g/day and 2.4 g/day
[c] Confidence interval for the difference in improvement rates between 4.8 g/day and 2.4 g/day
Corresponding data can be found in Appendix 3.8, Table 1.
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Table 8 Summary of Treatment Outcomes at Week 6 by Sigmoidoscopy Score at Baseline for Study 2000082

Treatment Success at Week 6
(Intent-to-Treat Patients with Moderate Disease [PGA=2] at Baseline)
Study 2000082

Sigmoidoscopy score	2.4 g/day mesalamine	4.8 g/day mesalamine	p-value
1	11/14 (78.6%)	17/19 (89.5%)	0.6285
2	61/99 (61.6%)	64/92 (69.6%)	0.2875
3	5/17 (29.4%)	8/13 (61.5%)	0.1376

Complied by this reviewer.
P-value was obtained by Fisher's exact test.

Table 9 Summary of Treatment Success at Week 6 by Subgroup for Patients with PGA=2 at Baseline

Number of Patients with Treatment Success at Week 6 by Subgroup
Reviewer's ITT Population with
Moderate Disease [PGA=2] at Baseline
Protocol 2000082

Subgroup	2.4 g/day	4.8 g/day	Difference	95% C. I.
Gender				
Male	29/62 (47%)	40/54 (74%)	27%	(10.2%, 44.4%)
Female	48/77 (62%)	49/75 (65%)	3%	(-12.3%, 18.3%)
Age				
18 to 64	71/126 (56%)	82/118 (69%)	13%	(1.1%, 25.1%)
≥65	6/13 (46%)	7/11 (64%)	18%	(-21.8%, 56.8%)
Disease Extent				
Procitis	12/20 (60%)	15/21 (71%)	11%	(-17.5%, 40.3%)
Proctosigmoiditis	27/49 (55%)	21/32 (66%)	11%	(-11.0%, 32.1%)
Left-sided Colitis	24/42 (57%)	33/49 (67%)	10%	(-9.7%, 30.1%)
Pancolitis	14/28 (50%)	20/27 (74%)	24%	(-0.8%, 48.9%)
Length of Disease History				
< 1 year	30/54 (56%)	34/49 (69%)	13%	(-4.7%, 32.3%)
1 to 5 years	18/32 (56%)	20/29 (69%)	13%	(-11.4%, 36.8%)
>5 to 10 years	12/22 (55%)	17/25 (68%)	13%	(-14.3%, 41.2%)
> 10 years	17/28 (61%)	18/25 (72%)	11%	(-14.0%, 36.5%)
Prior Treatment				
Steroids	24/47 (51%)	30/38 (79%)	28%	(8.6%, 47.2%)
Sulfasalazine	30/53 (57%)	30/40 (75%)	18%	(-0.5%, 37.3%)
Sulfa-free oral 5-ASAs	29/57 (51%)	36/53 (68%)	17%	(-1.0%, 35.1%)
Rectal therapy	27/50 (54%)	35/48 (73%)	19%	(0.2%, 37.6%)
Relapse Frequency				
Newly diagnosed	26/46 (57%)	29/45 (64%)	7%	(-12.1%, 27.9%)
More than once a month	10/21 (48%)	10/13 (77%)	29%	(-2.0%, 60.6%)
Once every 6 months	14/25 (56%)	18/27 (67%)	11%	(-15.7%, 37.0%)
Once every 6 to 12 months	13/18 (72%)	20/25 (80%)	8%	(-18.2%, 33.7%)
Less than once a year	14/29 (48%)	12/19 (63%)	15%	(-13.4%, 43.2%)
Stool Frequency Score				
0	2/9 (22%)	5/13 (38%)	16%	(-21.7%, 54.2%)
1	29/47 (62%)	27/40 (68%)	6%	(-14.3%, 25.9%)
2	33/54 (61%)	40/52 (77%)	16%	(-1.5%, 33.1%)
3	13/29 (45%)	17/24 (71%)	26%	(0.3%, 51.7%)
Rectal Bleeding Score				
0	6/15 (40%)	6/7 (86%)	46%	(9.8%, 81.6%)
1	22/35 (63%)	26/35 (74%)	11%	(-10.2%, 33.0%)
2	45/75 (60%)	52/78 (67%)	7%	(-8.6%, 21.9%)
3	4/14 (29%)	5/9 (56%)	27%	(-13.2%, 67.2%)
Patient's Functional Assessment Score				

0	9/24 (38%)	17/23 (74%)	36%	(10.0%, 62.8%)
1	44/76 (58%)	46/71 (65%)	7%	(-8.8%, 22.6%)
2	21/34 (62%)	24/33 (73%)	11%	(-11.4%, 33.3%)
3	3/5 (60%)	2/2 (100%)	40%	(-3.0%, 83.0%)
Sigmoidoscopy Score				
1	11/15 (73%)	17/19 (89%)	16%	(-10.2%, 42.4%)
2	61/107 (57%)	64/96 (67%)	10%	(-3.6%, 23.0%)
3	5/17 (29%)	8/14 (57%)	28%	(-6.1%, 61.5%)

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