M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: August 26, 2005

From: Ruyi He, M.D.
Medical Team Leader, GI Team II
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Subject: Medical Team Leader Review (AE Comments), Errata Addendum for the Memorandum dated August 17, 2005
NDA 21-830, Asacol 800 (Mesalamine) Delayed-Release Tablet

The proposed indication: Treatment of moderately active ulcerative colitis

Proposed Dosing Regimen: Two 800mg tablets (1.6g) three times a day for 6 weeks

Applicant: Proctor & Gamble Pharmaceuticals

Priority Designation: Standard

To: NDA 21-830

I. RECOMMENDATIONS:

I recommend that Asacol 800 (Mesalamine) Delayed-Release Tablets be approvable for the treatment of **moderately** active ulcerative colitis (UC) in adult population. The recommended dose is two 800 mg tablets (1.6g) three times a day for a total daily dose of 4.8 grams for a duration of 6 weeks.

To obtain approval of Asacol 800 (Mesalamine) Delayed-Release Tablets for the treatment of **moderately** active ulcerative colitis, the sponsor should conduct at least one additional adequate and well-controlled study to confirm statistically significant and clinically meaningful efficacy of Asacol 800 tablets at a dose of 4.8 g/day. The sponsor should also provide rationale and discussion to explain efficacy benefit with Asacol 800 at 4.8 g/day versus Asacol 400 mg at 2.4 g/day was seen in male patients, but not in female patients.

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II. BACKGROUND:

Ulcerative colitis is a chronic inflammatory bowel disease of unknown etiology affecting the colon and rectum. Lesions associated with the disease are characterized by superficial infiltration of the bowel wall by inflammatory white cells, resulting in erythema, mucosal ulcerations, and crypt abscesses. Clinically, patients can present with bloody diarrhea, anorexia, abdominal pain, fever, and weight loss.

Asacol delayed-release tablets contain mesalamine (5-aminosalicylic acid, also referred to as 5-ASA), an anti-inflammatory drug. Although its mechanism of action is not fully elucidated, the available evidence indicates that mesalamine has a topical anti-inflammatory effect on the colon, where it inhibits prostaglandin and leukotriene synthesis. In the United States, Asacol 400 mg tablets were first approved in 1992 for the treatment of mildly to moderately active ulcerative colitis at a dose of 2.4 g/day (NDA 19-651). Asacol was also approved for the maintenance of remission of mildly to moderately active ulcerative colitis at a dose of 1.6 g/day in 1997 (NDA 19-651/S005).

The sponsor believed that a higher dose of Asacol could safely benefit certain patients with ulcerative colitis who do not benefit fully from 2.4 g/day. Consequently, the sponsor developed the clinical program which is the subject of this submission for the treatment of active ulcerative colitis with 4.8 g/day Asacol. To facilitate patient compliance at higher doses, a higher strength (800 mg) of Asacol delayed-release tablet has been developed to allow patients to take the 4.8 g/day dose of Asacol with six (800 mg) tablets instead of twelve (400 mg) tablets.

Efficacy and safety data were generated from 2 double-blind, randomized, 6-week, parallel-group design Phase III clinical trials (Studies 82 and 83). These studies were designed to compare 2.4 g/day dosing, administered as the currently-marketed 400 mg tablet, to 4.8 g/day dosing, administered as the 800 mg tablet.

III. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. CLINICAL/STATISTICAL:

Efficacy

The pre-specified primary efficacy endpoint for both Phase III studies was defined as treatment outcome (i.e., treatment success or treatment failure) at Week 6 among the sponsor's ITT patients (mild to moderate) who were randomly assigned to a treatment group, who ingested at least 1 dose of study medication, and whose primary efficacy endpoint could be determined. 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, patients' functional assessment (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. The primary endpoint used in these studies was also used in the pivotal clinical trials leading to the approval of Asacol 400 mg tablets in patients with mildly to moderately active disease.

In both individual studies, the 2.4 g/day group and the 4.8 g/day group were comparable with respect to baseline and demographic characteristics, disease history, and baseline disease state characteristics. In addition, the populations were similar between Study 82 and 83. The majority of patients with moderate disease in the studies were Caucasian (77%), and the extents of disease ranged from proctitis to pancolitis. Approximately one-third were newly diagnosed, and more than one-half had been treated previously with some type of 5-ASA. Mild and moderate ulcerative colitis are defined according to the Physician's Global Assessment (PGA) score (1=mild and 2=moderate). Results of the primary efficacy analysis, treatment outcome at Week 6 in the sponsor defined ITT patients are presented in Table 1.

Table 1: Summary of Treatment Success at Week 6 for Studies 82, 83 and Pooled Data (sponsor's ITT Patients with Mild and Moderate Disease at Baseline)

Study	2.4 g/day Asacol (400 mg Tablet) n/N (%)	4.8 g/day Asacol (800 mg Tablet) n/N (%)	p-value[a]	Difference in Success % [b]	Confidence Interval [c]
82					
Total	98/182 (53.8%)	108/182 (59.3%)	0.2903	5.5	(-0.05, 0.16)
Moderate	77/130 (59.2%)	89/124 (71.8%)	0.0357	12.6	(1.0, 24.1)
mild	21/52 (40.4%)	19/58 (32.8%)	0.4065	-7.6	(-25.62, 10.37)
83					
Total	77/150 (51.3%)	76/136 (55.9%)	0.4411	4.6	(-0.07, 0.16)
Moderate	53/93 (57.0%)	55/76 (72.4%)	0.0384	15.4	(1.2, 29.6)
Mild	24/57 (42.1%)	21/60 (35.0%)	0.4298	-7.1	(-0.25, 0.11)
Pooled					
Moderate	130/223 (58.3%)	144/200 (72.0%)	0.0034	13.7	(4.7, 22.7)
Mild	45/109 (41.3%)	40/118 (33.9%)	0.2507	-7.4	(-0.20, 0.05)

n (%) = number and percentage (n/Total x 100) of patients in treatment with success.
[a]4.8 g/day compared to 2.4 g/day, from Chi-square test for 82 and 83, and stratified by protocol using the Cochran-Mantel-Haenszel test for pooled analysis. [b]Difference between 4.8 g/day and 2.4 g/day. [c]95% confidence interval for the difference in success rates between 4.8 g/day and 2.4 g/day with no stratification.

Both studies (82 and 83) were originally designed to study patients with mild to moderate active ulcerative colitis (UC). Neither study showed a statistically significant or clinically meaningful difference in the rate of treatment success between 2.4 g/day administered as 400 mg tablets and 4.8 g/day administered as 800 mg tablets after 6 weeks of treatment in patients with mildly to moderately active ulcerative colitis (53.8% vs. 59.3% and 51.3% vs. 55.9%).

Study 83
Study 83 failed to show superiority of 4.8 g/day to 2.4 g/day in patients with mildly to moderately active disease for the primary endpoint (55.9% vs. 51.3%, p=0.4411, Table 1). However, the sponsor's subgroup analysis of patients with moderate disease at baseline showed a statistically significant difference in response rate in favor of Asacol 4.8 g/day (72.4% vs. 57.0%, p=0.0384). By contrast, the subgroup analysis of patients with mild disease at baseline the rate of treatment success was numerally lower in the 4.8 g/day group than that in the 2.4 g/day group (33.9% vs. 41.3%, p=0.2507).

In the sponsor's ITT subgroup analysis of patients with moderate disease at baseline for Study 83, the sponsor excluded 11 patients (3 in the 2.4 g/day group and 8 in the 4.8 g/day group), because Week 6 treatment outcome could not be determined. 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 biased in favor of 4.8 g/day group. In a sensitivity analysis, where missing observations were set to treatment failure, the 4.8g/day was no longer statistically superior over 2.4 g/day (65.5% vs 55.2%; p=0.1607). The treatment difference was reduced to 10% from 15% observed from the sponsor's ITT analysis. So, the sponsor's finding for patients with moderate disease at baseline was not robust. I agree that the analysis of patients with moderate UC in study 83 is to be exploratory. For details, please see Dr. Milton Fan's Statistical Review.

Study 82
Based on results from Study 83, Study 82 was amended on February 2003 when 96% of patients had been enrolled per protocol. Under the amended protocol, primary efficacy population was changed from a population with mildly to moderately active UC to a population with moderately active UC only. Additional 82 patients with moderate disease at baseline were enrolled in Study 82 after amendment. A faxed communication dated March 17, 2003 from the Division agreed to this amendment. However, according to statistical reviewer, Dr. Milton Fan, because at the time of amendment, the Study 82 was closed to be completed (96% enrolled), the sponsor should perform a new clinical study for moderate disease patients instead of trying to salvaging study 82.

Study 82 showed that in patients with moderately active UC, Asacol 4.8 g/day administered as 800 mg delayed-release tablets provides a significant efficacy benefit

over 2.4 g/day administered as 400 mg delayed-release tablet (71.8% vs. 59.2%, p=0.0357). However, I concur with statisticians' conclusion that Study 82 is not strong enough to stand on its own as a single study in support of the proposed indication. See Reviews from Dr. Milton Fan and Dr. Stella Grosser (Team Leader) for details. There is unexplained inconsistency in the results in important subgroups of the moderate patients, namely males vs. females and pre-amendment vs. post-amendment enrollees. Efficacy benefit at a dose of 4.8 g/day over that at 2.4 g/day was showed only in male patients (76% vs 50%), but not in female patients (69% vs 67%). Similarly, efficacy benefit at a dose of 4.8 g/day over that at 2.4 g/day was seen only in pre-amendment enrollees (69.9% vs. 54.7%), but not in post-amendment enrollees (75.6% vs. 71.4%).

In addition, in patients with mildly active UC, Asacol 800 tablets at a dose of 4.8 g/day did not show additional benefits over Asacol 400mg tablets at a dose of 2.4g/day. Patients with mildly UC had **numerically less response rates** with Asacol 800 at 4.8 g/day dosing compared to Asacol 400 mg tablets at 2.4 g/day dosing (33.9% vs. 41.3%, p=0.2507).

In summary, both studies were designed to study patients with mild-to-moderate active ulcerative colitis. Neither of study showed that there was a statistically significant difference in the treatment success between 2.4 g/day and 4.8 g/day 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, Study 83 indicated that Asacol 4.8 g/day may not be more effective than that at 2.4 g/day, because more patients in the 4.8 g/day group were excluded from the sponsor's ITT analysis (3 in the 2.4 g/day group and 8 in the 4.8 g/day group). For Study 82, Asacol 4.8 g/day provides an additional benefit over 2.4 g/day (71.8% vs. 59.2%, p=0.0357) in patients with moderately active UC at baseline. However, this benefit was driven by male patients (76% vs 50%) and pre-amendment enrollees. In female patients, no benefit has been shown at 4.8 g/day dose over 2.4 g/day dose (69% vs 67%).

For the subgroup of patients with **mildly** active UC at baseline, both studies indicated that the rates of treatment success in the Asacol 4.8 g/day group were numerally lower than that in the 2.4 g/day group (32.8% vs. 40.4% and 33.9% vs. 41.3%). Clearly, Asacol at a dose of 4.8 g/day is not indicated for the patients with mildly active ulcerative colitis at baseline.

Safety

The safety of Asacol 2.4 g/day (400 mg tablet) for the treatment of mildly to moderately active ulcerative colitis and Asacol 1.6 g/day (400 mg tablet) for long-term use in the maintenance of ulcerative colitis remission has been evaluated previously in submissions in 1990 (NDA 19-651, approved 1992) and 1996 (NDA 19-651/S005, approved 1997), respectively.

In this submission, 687 subjects were enrolled into phase 3 studies: 349 were randomized to receive Asacol 2.4 g/day (400 mg tablet) and 338 were randomized to receive 4.8 g/day (800 mg tablet) for 6 weeks. A total of 448 patients were with moderate disease: 235 were received Asacol 2.4 g/day (400 mg tablet) and 213 were received 4.8 g/day (800 mg tablet).

There were no meaningful differences between the 2 treatment groups for the occurrence of treatment-emergent adverse events (AEs) for all randomized patients by treatment group.

Table 2 summarizes commonly occurring AEs (AEs occurring in ≥2% of patients in either treatment group) in all randomized patients by treatment group.

Table 2: Adverse Events Occurring in >=2% of Patients in Either Treatment Group Pooled Data for Studies 82 and 83 (All Randomized Patients)

COSTART Term	2.4 g/day Asacol (N = 349) n (%)	4.8 g/day Asacol (N = 338) n (%)	Total (N = 687) n (%)
OVERALL	132 (37.8%)	129 (38.2%)	261 (38.0%)
HEADACHE	24 (6.9%)	24 (7.1%)	48 (7.0%)
PAIN ABDO	18 (5.2%)	11 (3.3%)	29 (4.2%)
INFECT	10 (2.9%)	14 (4.1%)	24 (3.5%)
DIARRHEA	11 (3.2%)	12 (3.6%)	23 (3.3%)
NAUSEA	7 (2.0%)	14 (4.1%)	21 (3.1%)
FLATUL	9 (2.6%)	8 (2.4%)	17 (2.5%)
COLITIS ULCER	9 (2.6%)	7 (2.1%)	16 (2.3%)
DYSPEPSIA	7 (2.0%)	7 (2.1%)	14 (2.0%)
FLU SYND	10 (2.9%)	4 (1.2%)	14 (2.0%)
RECTAL DIS	8 (2.3%)	5 (1.5%)	13 (1.9%)
COUGH INC	10 (2.9%)	2 (0.6%)	12 (1.7%)
RASH	7 (2.0%)	5 (1.5%)	12 (1.7%)
SINUSITIS	8 (2.3%)	3 (0.9%)	11 (1.6%)
VOMIT	4 (1.1%)	7 (2.1%)	11 (1.6%)
DIZZINESS	7 (2.0%)	3 (0.9%)	10 (1.5%)
RHINITIS	7 (2.0%)	1 (0.3%)	8 (1.2%)

Patients who experienced > one AE within a COSTART term are counted only once within that term.
Data are sorted by decreasing incidence in the Total column.
N = number of patients in treatment group
n (%) = number and percentage (n/N x 100) of patients who reported adverse events within

Across treatments, events reported by 2% or more of all randomized patients (in decreasing frequency) were headache, abdominal pain, infection, diarrhea, nausea, flatulence, ulcerative colitis (exacerbation), dyspepsia, and flu syndrome.

In patients with moderate disease, infection, nausea, vomiting, and headache were reported more frequently by patients receiving 4.8 g/day compared to 2.4 g/day, especially for nausea (4.1% vs 2.0%) and vomiting (2.1% vs 1.1%).

All commonly reported AEs have been observed previously with use of Asacol 400 mg tablets, and are described in the current product label. Review of these events suggested that **incidences of nausea and vomiting were significantly increased with administration of the Asacol 800 tablets at a dose of 4.8 g/day.**

There were no deaths in this clinical development program.

A total of 9 patients (7 in the 2.4 g/day group, 2 in the 4.8 g/day group) experienced SAEs (hospitalizations and/or medically significant events) during this clinical program. The SAEs were primarily involving the digestive system, including ulcerative colitis signs and symptoms (rectal bleeding, diarrhea, abdominal pain) or worsening ulcerative colitis; nausea, vomiting, and epigastric pain; and cholecystitis and pancreatitis. Onset of digestive system SAEs occurred primarily in the first 2 weeks of treatment. Other SAEs reported during the program, and described in the current product label, included single reports of nephritis and pericarditis. The only SAEs not described in the current label occurred in a single patient (2.4 g/day group) who was hospitalized and underwent a hysterectomy for dysfunctional uterine bleeding secondary to pre-existing uterine fibroids and ovarian cyst; the patient completed the study (Patient 37263458). The majority of SAEs were considered moderate or severe in nature; all patients had recovered from the events by the time of their last study contact, except for one patient (2.4 g/day group) who remained under treatment for worsening ulcerative colitis and rectal bleeding (Patient 71003796).

Globally, Asacol has been approved for marketing in at least 46 countries since the first marketing authorization in 1985. Periodic data review and annual Periodic Safety Update Reports, last submitted 19 August 2004, indicate that the post-marketing safety profile remains consistent overall with the clinical trials experience with Asacol, as reflected in the current product label for Asacol 400 mg tablets.

In summary, the overall safety profile of Asacol 4.8 g/day is acceptable. However, the incidences of nausea and vomiting were two times higher in the 4.8 g/day group compared to that in the 2.4 g/day group.

B. DSI/DDMAC/DMETS:

Division of Scientific Investigations conducted the inspection on 4 clinical sites. Four subjects were enrolled despite not meeting all eligibility criteria. There were record keeping deficiencies noted at 2 sites that appear not to affect the overall validity of the data. The data from these 4 sites appear acceptable in support of the relevant indication of the NDA.

Division of Medication Errors and Technical Support, Office of Drug Safety has no objections to the use of the proprietary name, Asacol 800.

C. CHEMISTRY AND MANUFACTURING:

No major chemistry issues were identified. The CMC reviewer, Dr. Ysern, concluded that the information provided is sufficient to support the approval of this NDA. See her review dated on May 17, 2005 for detail.

D. PRE-CLINICAL PHARMACOLOGY/TOXICOLOGY:

No new preclinical toxicology studies were submitted in support of this NDA submission. Preclinical toxicology studies were submitted previously in NDA 19-651 and IND 26,093. The data from these studies were reviewed previously by the agency and incorporated in the current Asacol labeling. No nonclinical safety issues relevant to clinical use were identified. Several sections in the proposed Asacol 800 labeling have been revised. For detail preclinical labeling recommendations, please see Dr. Ronald Honchel's review dated 7/22/05.

E. BIOPHARMACEUTICS:

Three Clinical Pharmacology and Biopharmaceutics studies were submitted in this NDA characterizing the single dose PK and relative bioavailability (study 2000027), multiple dose PK (study 2001025), and food effect (study 2001095) . In addition, steady-state pre-dose concentrations were also evaluated from patients participating in Phase III study 82.

The single dose PK study showed that the mean tmax value of 5-ASA was significantly delayed while mean Cmax and AUC values decreased by 36% and 25%, respectively, with administration of the 800 mg tablets relative to the 400 mg tablets.

The results of the multiple dose PK study demonstrated that significant accumulation of 5-ASA and N-Ac-5-ASA take place with the TID regimen.

The food-effect study showed a significant food-effect on the PK of the 800 mg Asacol tablets. In particular, Cmax of 5-ASA decreased by 47% under fed conditions, while tmax was delayed by 14 hours relative to fasting conditions.

Overall, the submission is ACCEPTABLE from a clinical pharmacology and biopharmaceutics perspective.

F. PEDIATRIC USE:

I recommend that the sponsor's request for a partial waiver for patients < 5 years of age and a deferral for pediatric patients age 5 to 17 years of age be granted.

IV. CONCLUSIONS AND RECOMMENDATIONS:

Both studies were designed to study patients with mildly to moderately active ulcerative colitis. Neither of study showed that there was statistically significant difference in the treatment success between 2.4 g/day and 4.8 g/day 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, Study 83 indicated that Asacol 4.8 g/day may not be more effective than 2.4 g/day, because more patients in the 4.8 g/day group were excluded from the sponsor's ITT analysis (3 in the 2.4 g/day group and 8 in the 4.8 g/day group). For Study 82, Asacol 4.8 g/day provides an additional benefit over 2.4 g/day (71.8% vs. 59.2%, p=0.0357) in patients with moderately active ulcerative colitis at baseline. However, this benefit was driven by male patients (76% vs 50%). In female patients, no benefit has been shown at 4.8 g/day dose over 2.4 g/day dose (69% vs 67%).

For the subgroup of patients with **mildly** active ulcerative colitis at baseline, both studies indicated that the rates of treatment success in the Asacol 4.8 g/day group were numerally lower than that in the 2.4 g/day group (32.8% vs. 40.4% and 33.9% vs. 41.3%). Clearly, Asacol at a dose of 4.8 g/day is not indicated for the patients with mildly active ulcerative colitis at baseline.

The overall safety profile of Asacol 4.8 g/day is acceptable. However, the incidences of nausea and vomiting were two times higher in the 4.8 g/day group compared to that in the 2.4 g/day group.

I recommend that Asacol 800 (Mesalamine) Delayed-Release Tablets be approvable for the treatment of **moderately** active ulcerative colitis in adult population. The recommended dose is two 800 mg tablets (1.6g) three times a day for a total daily dose of 4.8 grams for a duration of 6 weeks.

To obtain approval of Asacol 800 (Mesalamine) Delayed-Release Tablets for the treatment of **moderately** active ulcerative colitis, the sponsor should conduct at least one additional adequate and well-controlled study to confirm statistically significant and clinically meaningful benefit of Asacol 800 tablets at a dose of 4.8 g/day. The sponsor should also provide rationale and discussion to explain efficacy benefit with Asacol 800

at 4.8 g/day versus Asacol 400 mg at 2.4 g/day was seen in male patients, but not in female patients.

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V. LABELING RECOMMENDATIONS:

The labeling review for Asacol 800 is not necessary at this time.

In patients with mildly active ulcerative colitis, Asacol 800 tablets at a dose of 4.8 g/day provided a numerically less response rates compared to Asacol 400 mg tablets at 2.4 g/day. Therefore, I recommend that package insert for current Asacol (400 mg) be updated to include that two phase 3 studies with Asacol 800 tablets indicated that for patients with mildly active ulcerative colitis, Asacol at a dose of 4.8 g/day did not show additional benefits over Asacol at a dose of 2.4g/day.

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/s/

Ruyi He
8/26/2005 05:05:33 PM
MEDICAL OFFICER
A p-value in Table 1 was corrected.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-830
Submission Code	N
Letter Date	October 22, 2004
Stamp Date	October 29, 2004
PDUFA Goal Date	August 29, 2005
Reviewer Name	Fathia Gibril, M.D., M.H.Sc.
Review Completion Date	July 21, 2005
Revised Version Completion Date	August 19, 2005
Established Name	Mesalamine
(Proposed) Trade Name	Asacol® 800
Therapeutic Class	Topical ant-inflammatory
Applicant	Proctor & Gamble
pharmaceuticals	
Priority Designation	Standard
Formulation	Delayed-Release Tablet
Dosing Regimen	1.6 grams TID
Indication	Moderately active ulcerative colitis
Intended Population	Adult subjects 18 and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that Asacol 800 delayed-release tablets at a dose of 4.8 g/day be approvable for the treatment of adult patients with moderately active ulcerative colitis.

To gain approval for the desired indication, the applicant should conduct an additional adequate and well-controlled clinical study to confirm the findings from Study 82. The applicant should adequately address the inconsistency in the efficacy benefit in important subgroups of patients with moderate disease, namely, males versus females.

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1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

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

1.2.2 Required Phase 4 Commitments

Safety and efficacy of the currently approved Asacol 400 mg tablets have not been established in pediatric patients. In accordance with the formal Pediatric Written Request (WR) dated on May 19, 2003, the applicant should conduct two studies: Pharmacokinetics/Safety study (study 1) and Exposure/Response and Safety Study (study 2) of Asacol 400 mg tablets in pediatric patients aged 5-17 years with mildly to moderately active ulcerative colitis. In the WR it was indicated that the results of Study 1 should be reported to the Agency before initiating treatment of patients in Study 2. In addition, reports of the studies that meet the terms of the Written Request must be submitted to the Agency on or before December 31, 2005. In addition, the medical officer's review (Dr. Robert Prizont) dated Feb 20, 2003, indicated that pediatric studies conducted with Asacol 400 mg tablet formulation may be applicable to the Asacol 800 mg tablet formulation as long as bridging pharmacokinetics and pharmacodynamic studies are performed to show comparability between the two formulations.

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests for this NDA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The use of 800 mg Asacol (mesalamine) delayed-release tablets for treatment of moderately active ulcerative colitis (UC) at a dose of 4.8 g/day is the subject of this NDA submission.

Mesalamine (5-aminosalicylic acid, also referred to as 5-ASA) has been available world wide for the treatment of inflammatory bowel disease (IBD), specifically for UC for more than 20 years, and as the active component in sulfasalazine for about 50 years. Although the mechanism of action of mesalamine is not fully elucidated, it is thought to exert topical anti-inflammatory effects on the colonic mucosa through inhibition of prostaglandin and leukotriene synthesis.

In the United States, Asacol® (mesalamine) 400 mg delayed-release tablets were approved in 1992 for treatment of mildly to moderately active UC at a dose of 2.4 g/day for 6 weeks. Asacol 400 mg tablets were also approved in 1997 for the maintenance of remission of mildly to moderately active UC at a dose of 1.6 g/day for 6 months. Globally, Asacol 400 mg tablets have been approved for marketing in at least 46 countries since the first marketing authorization in 1985. In addition, there are various oral as well as rectal mesalamine-containing formulations marketed for treatment of mildly to moderately active UC.

The applicant, Procter & Gamble Pharmaceuticals, submitted a New Drug Application (NDA 21-830) on October 22, 2004, seeking approval for Asacol 800 mg delayed-release tablets at a dose of 4.8 g/day given in three divided doses for the treatment of moderately active UC for a duration of 6 weeks.

- Rationale for the Clinical Development Program

The applicant's decision to study a higher dose (4.8 g/day) of Asacol was originated primarily from one of previously submitted placebo-controlled studies (Study C3, NDA 19-651) suggesting that the higher dose (4.8 g/day) of Asacol was associated with increased efficacy with an adverse event profile comparable to placebo in subjects with mildly to moderately active UC.

In support of the proposed indication, the applicant conducted two phase III safety and efficacy clinical studies with Asacol 800 mg delayed-release tablets in the United States and Canada. To facilitate patient compliance at higher doses, a higher strength (800 mg) of Asacol tablet has been developed.

The two phase III clinical studies were active-controlled, double-blind, randomized, parallel-group, multicenter studies (Study 2000082 and Study 2000083) of 6 weeks duration. Hereinafter, the two studies will be referred as Study 82 and Study 83, respectively.

Both studies were originally designed to compare the efficacy and safety of Asacol 4.8 g/day, administered as the newly formulated 800 mg tablet versus 2.4 g/day, administered as the currently-marketed 400 mg tablet in newly- and previously-diagnosed patients who were experiencing a flare of *mildly to moderately active UC.*

- Change in Clinical Program

In the first of the two studies (Study 83) to complete recruitment, the prospectively defined subgroup analysis of patients with moderately active UC suggests that 4.8 g/day dosing with 800 mg Asacol tablets provides a significant improvement compared to 2.4 g/day dosing, but the treatment difference was not significant in the originally planned efficacy population (mildly to moderately active UC). Subsequently, the protocol was amended to change the primary efficacy population from a population with *mildly to moderately active UC* (physician global assessment [PGA] score of 1 or 2) to a population with *only moderately active UC* (PGA = 2) for Study 82 that was nearing the end of the recruitment period (when 96% of the originally planned enrollment had been completed). Under amended protocol, up to 100 additional patients with moderate disease were to be enrolled. A faxed communication dated March 17, 2003 from the Agency agreed to this amendment. Other than the change in study population for the primary efficacy analysis and sample size increase to Study 82, the design of the 2 studies remained identical.

It is worth mentioning that the determination of disease severity (mild or moderate) as well as treatment success in this clinical program was based on the Physician's Global Assessment (PGA), which took into consideration clinical assessments of rectal bleeding, stool frequency, patient's functional assessment (PFA) and sigmoidoscopic examination. The reader may refer to Appendix 10.3 of this review for information on PGA and individual clinical assessment scores used in this clinical program.

Both studies were comparable in terms of study population (demographic and baseline disease characteristics), methodology as well as safety and efficacy endpoints. As well, the two treatment groups in individual studies were comparable with respect to demographic and baseline disease characteristics. The population was primarily Caucasian (77%), had a mean age 43 years (<10% were age 65 years or older), and included slightly more females (56%) than males (44%). The extent of disease at baseline ranged from proctitis to pancolitis and comparable number of patients presented with proctitis, procto-sigmoiditis, left-sided colitis, and pancolitis.

A total of 687 patients (386 in Study 82 and 301 in a Study 83) were randomly assigned to treatment groups: 349 to 2.4 g/day group and 338 to 4.8 g/day group.

It should be pointed out that the originally planned sample size was 308 for Study 82. According to the information provided by the applicant (amendment # 15, dated July 13, 2005), when the protocol amendment to Study 82 was made, 96% (n=296) of the intended patients had been enrolled. But the Agency statistical reviewer found that 304 patients were enrolled when the amendment was made.

Of the 687 patients randomized, 448 (268 in Study 82 and 180 in Study 83) had moderately active UC, while 238 (117 in Study 82 and 121 in Study) had mildly active UC at baseline, and 1 patient had undetermined severity of disease at baseline. In Study 82, a total of 82 patients were enrolled after the protocol amendment, for the total of 268 patients with moderate disease.

The population for which safety data are available for the Asacol 800 mg formulation is comprised of 338 patients with mildly to moderately active UC in two Phase III studies (Study 82 and Study 83) and 54 healthy subjects with limited exposure during biopharmaceutical studies. Of the 687 subjects enrolled into phase III studies, 349 patients were randomized to receive Asacol 2.4 g/day (400 mg tablet) and 338 patients were randomized to receive 4.8 g/day (800 mg tablet) for 6 weeks. In the primary efficacy population (patients with moderate disease, n = 448), 235 patients received 2.4 g/day (400 mg tablet) and 213 patients received 4.8 g/day (800 mg tablet). For all randomized patients, comparable percentages (85%) of patients completed the 6-week study in the two treatment groups.

Asacol 800 mg tablets are not currently approved for marketing in any country; thus, there is no information with respect to the post-marketing use of this formulation at any dose. However, long-term clinical experience with 4.8 g/day dosing using Asacol 400 mg tables has been previously reviewed (NDA 19-651/S005) and is reflected in the current product label.

1.3.2 Efficacy

Efficacy data are generated from two active-controlled phase III clinical studies (Study 82 and Study 83). Both studies were originally designed to compare Asacol 4.8 g/day, administered as the newly formulated 800 mg tablet to 2.4 g/day, administered as the currently approved 400 mg tablet in subjects with mildly to moderately active UC.

- Primary Endpoint

The primary efficacy endpoint for both studies was treatment outcome (treatment success or treatment failure) at Week 6 in the applicant's intent-to-treat (ITT) population defined as those who were randomly assigned to treatment and ingested at least 1 dose of study medication, and whose primary endpoint could be determined. 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 clinical

assessments (stool frequency, rectal bleeding, PFA, PGA, and sigmoidoscopy). 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, and no worsening in any of the remaining clinical assessments.

The primary endpoint used in these studies was used in the pivotal clinical trials leading to the approval of Asacol 400 mg tablets (2.4 g/day) in mildly to moderately active UC. As documented in the February 8, 1999, end of phase II Meeting Minutes, the Agency encouraged the applicant to use the primary endpoint that mirrors the criteria used in previous Asacol (400 mg tablet) studies.

Reviewer's comment: measurement of disease activity is critical in determining whether new therapies are effective in patients with IBD. However, unlike Crohn's disease, there is no gold standard for measuring disease activity in UC. In Crohn's disease, standard definitions for clinical improvement and clinical remission on standard indices have come into common use, allowing useful comparisons across trials. This has not been the case for UC where no single disease activity index is universally accepted and no generally accepted definition of improvement or remission exist (Higgins PDR et al, Gut 2005).

- Secondary Endpoints

There were multiple secondary endpoints analyzed in the studies including the percentage of patients who improved from baseline at Week 3; and the percentage of patients whose individual clinical assessment scores at Weeks 3 and 6 were improved. It should be noted that appropriate statistical measures to correct for multiple comparisons were not prespecified in the protocol.

- Subgroup Analysis for Primary Endpoint

A number of subgroups (demographics characteristics, disease history, and baseline disease activity) were analyzed without adjustment for multiplicity.

- Dose Selection and Duration of Treatment

Although the applicant's decision to study a higher dose (4.8 g/day) than the approved dose (2.4 g/day) was primarily due to the increased efficacy benefit seen with the higher dose in one of previously submitted placebo-controlled studies (Study C3, NDA 19-651), an additional arm with a middle dose (3.6 g/day) using 400 mg tablets (for dosing flexibility) would have provided useful information. The American Collage of Gastroenterology Guideline recommends a range of mesalamine dosing, i.e. from 2 g/day to 4.8 g/day for the treatment of mildly to moderately active UC (Kornbluth et al. Ulcerative Colitis Practice Guidelines in Adults; A J Gastroenterol 2004; 1371-1385).

The duration of treatment for active UC has not been clearly defined. In general, a 6-week to 8-week duration of treatment is recommended as reflected in the currently marketed mesalamine-containing agents.

Efficacy Results

- Study 83

Study 83 failed to demonstrate superiority of 4.8 g/day over 2.4 g/day in the ITT patients with mildly to moderately active UC (56%, 76/136 vs 51%, 77/150; p=0.44).

In the prespecified subgroup analysis of patients with moderate disease at baseline, 4.8 g/day showed a superior efficacy over 2.4 g/day. In the applicant's ITT analysis, the percentage of patients whose treatment outcome at Week 6 was classified as treatment success was 72% (55/76) in 4.8 g/day group, compared to 57% (53/93) in 2.4 g/day group. A difference that was a statistically significant in favor of 4.8 g/day (p=0. 038). It should be pointed out that the p-value presented here is without adjustment for multiplicity, due to the fact that a number of subgroups were analyzed in this study. In addition, more patients in the 4.8 g/day group than in the 2.4 g/day group (8 vs 3) were excluded in the applicant's ITT analysis, because treatment outcome at Week 6 could not be determined. In fact, when 11 patients were included in the analysis as treatment failure, 4.8 g/day was no longer superior to 2.4 g/day (65%, 55/84 vs 55%, 53/96; p=0.1607).

It is worth noting that in the subgroup with moderate disease at baseline, male subjects tend to respond better with 4.8 g/day than with 2.4 g/day (73%, 29/40 vs 48%, 21/44). By contrast, the treatment success rate was similar between 4.8g/day and 2.4 g/day for females with moderate disease at baseline (59%, 26/44 and 62%, 32/52, respectively).

For the subgroup with mildly active UC at baseline, the treatment success rate with 4.8 g/day was numerically inferior (-7%) compared to 2.4 g/day (35%, 21/60 vs 42%, 24/57).

- Study 82

Based on the results seen from Study 83, the protocol to Study 82 was amended when 96% of the planned enrollment had been completed. Under the amended protocol, the primary efficacy population was changed from a population with mildly to moderately active UC to a population with only moderately active UC, [redacted]. Under amended protocol, up to100 additional patients with moderate disease were to be enrolled. Eighty-two patients with moderate disease at baseline were enrolled after the amendment. b(4)

Similar to the results in Study 83, Study 82 failed to demonstrate a statistically significant difference in the rate of treatment success between 4.8 g/day and 2.4 g/day (59% and 54%, respectively; p=0.29) among subjects with mild to moderate disease at baseline.

For patients with moderate disease at baseline, treatment success was achieved in 72% (89/124) of patients receiving 4.8 g/day, compared to 59% (77/130) receiving 2.4 g/day, a

difference that was a statically significant (p = 0.036) in favor of 4.8 g/day. In this analysis, 14 ITT patients were excluded (9 in 2.4 g/day group, and 5 in 4.8 g/day group), because treatment outcome at Week 6 could not be determined. Nonetheless, the superiority of 4.8 g/day still holds true when 14 patients were included in the analysis as treatment failure (69%, 89/129 vs 55%, 77/139; p=0.022). It is worth noting that despite the relatively higher representation of females (57%) in the study, the data indicated that male subjects with moderate disease at baseline showed a significant improvement with 4.8 g/day than with 2.4 g/day (76%, 40/53 vs 50%, 29/58; 95% CI: 8.2%, 42.8%). By contrast, the treatment success rate was similar between 4.8 g/day and 2.4 g/day for females with moderate disease at baseline (69%, 49/71 and 67%, 48/72, respectively).

The Agency statistical reviewer's post hoc analysis involving pre- vs post-amendment enrollees with moderate disease revealed inconsistent results: among pre-amendment enrollees, treatment success was achieved in 70% (58/83) of patients with 4.8 g/day, compared to 55% (52/95) with 2.4 g/day, a difference that was a statistically significant (p=0.04) in favor of 4.8 g/day. By contrast, among post-amendment enrollees, the rate of treatment success was similar between 4.8 g/day and 2.4 g/day (76%, 31/41 and 71%, 25/35, respectively [p=0.68]).

The reasons for such variability in the aforementioned outcomes are unclear to the medical reviewer. It is possible that this is due to the lack of a gold standard for measuring disease severity in UC. Consequently, it is difficult to assure homogeneity of a study population in a clinical trial, which may hamper an appropriate interpretation of the clinical data. It is also possible that the post-amendment analysis is underpowered due to the small sample size (76 post-amendment enrollees vs 178 pre-amendment enrollees) to detect a meaningful treatment difference. However, in the medical reviewer's opinion, a consideration for evidence of effectiveness should be based on the analysis of all randomized patients. The result from all subjects (pre- and post-amendment enrollees) with moderate disease indicates a significant improvement with 4.8 g/day over 2.4 g/day (p=0.02). Further, I concur with the Statistical Team Leader's (DR. Stella Grosser) conclusion that changing the protocol so close to the end of the study and addition of fewer than 100 patients without justification reflects poor planning. But the change is not post hoc since the study was blinded. Therefore, the medical reviewer does not see the rationale for adjusting the p-value presented in this study as indicated by the primary statistical reviewer (Dr. Fan Milton).

By contrast, for the subgroup with mildly active UC, the response rate was numerically inferior (-7%) with 4.8 g/day dosing compared to 2.4 g/day dosing (33%, 19/58 vs 40%, 21/52; p=0.41), which is consistent with that in Study 83.

It is of interest to note the discrepancy in dose response effect between the population with moderate disease vs mild disease (a higher dose was more effective in moderate disease, while it was less effective in mild disease). Typically, a higher dose would be expected to exhibit similar if not better response rates in subjects with less severe (mild) disease when compared to those with more severe (moderate) disease. This apparent inconsistency has not been addressed by the applicant. Nonetheless, in the data presented, there was no obvious or

identifiable factor/s that could explain the lack of dose response effect in subjects with mild disease. Demographic characteristics, baseline disease state, duration or extent of disease did not appear to have an influence on therapeutic activity, because they were comparable between the two populations. Review of published data did not provide useful information for various reasons: most studies involve non-selected patients (i.e. mild to moderate disease); there is heterogeneity in the choice of outcome measures and use of disease activity index. The use of various mesalamine formulations also makes comparisons across studies difficult. A recent dose-finding European study [redacted] formulation found no significant dose response effect in subjects with mild to moderate disease (non-selected subjects) at doses of 1.5 g, 3 g, or 4.5 g daily, regardless of severity of the disease (Kruis W et al. Clin Gastroenterol Hepatol 2003). However, in contrast to the results seen in the current submission, a subgroup analysis in the aforementioned study revealed that subjects with less severe (mild) disease had numerically better response rates at all dose levels compared to those with more severe (moderate) disease.

b(4)

It is also of interest to note that in Study 82, 2.4 g/day is associated with a decreased efficacy in patients with mild disease at baseline compared to patients with moderate disease at baseline (40%, 21/52 vs 59%, 77/130). Similar results were observed in Study 83 (42%, 24/57 vs 57%, 53/93). However, the imbalance in sample size (more patients with moderate disease) may not allow for appropriate comparison between the subgroups. Although definitive conclusions can not be drawn from the aforementioned observation, it does, however, raise an important question as to whether Asacol is effective in the treatment of mildly active UC. Because in both Asacol dose levels (2.4 g/day and 4.8 g/day) tested in this clinical program, the response rate in a population with mild disease was well below the response rate in a population with moderate disease (40% - 42% vs 57% - 59%).

Across both studies multiple comparisons of secondary endpoints in subjects with moderate disease did not reveal statistically significant differences between treatments, although trends in favor of 4.8 g/day were seen for most variables analyzed.

- Overall Efficacy Conclusions

After a careful consideration of the Agency statistical reviewers' arguments, particularly regarding Study 83, I concluded that there is insufficient evidence of efficacy to support the proposed indication for treatment of moderately active UC.

For subjects with moderate disease at baseline, Study 83 did not provide sufficient evidence of efficacy, not only because the data were driven from the subgroup analysis without adjustment for multiplicity, but also because of a potential bias in favor of 4.8 g/day. More patients from the 4.8 g/day group were excluded from the applicant's analysis (p=0.0738), because treatment outcome at Week 6 could not be determined. In fact, in the sensitivity analysis where missing observations were set to treatment failure, 4.8 g/day was no longer superior to 2.4 g/day. On the other hand, although the efficacy data from Study 82 indicated a significant improvement with 4.8 g/day over 2.4 g/day (p=0.022) in all randomized patients with moderate disease, this study is not robust to stand alone as a single study (p> 0.001) to

support the proposed indication for treatment of subjects with moderate disease. Further, the increased efficacy benefit with 4.8 g/day over 2.4 g/day was seen in male subjects, but not in female subjects.

From the regulatory standpoint, the reviewer concluded that a single clinical study finding of efficacy, unsupported by independent study is not adequate for a conclusion of a substantial evidence of effectiveness. To support the proposed indication, an additional adequate and well-controlled clinical study is required to confirm the findings from Study 82. The applicant should adequately address the inconsistency in the efficacy benefit in important subgroups of patients with moderate disease, namely, males versus females.

Across both studies, among subjects with mild disease at baseline, 4.8 g/day was associated with a relative decrease in efficacy when compared to 2.4 g/day. Thus, Asacol 800 mg tablets at a dose of 4.8 g/day are not indicated for the treatment of patients with mild disease at baseline.

1.3.3 Safety

The population for which safety data are available for the Asacol 800 mg formulation is comprised of 338 patients with mildly to moderately active UC in two Phase III studies (Study 82 and Study 83) and 54 healthy subjects with limited exposure during biopharmaceutical studies. Of the total of 687 subjects enrolled into phase III studies, 349 were randomized to receive Asacol 2.4 g/day (400 mg tablet) and 338 were randomized to receive 4.8 g/day (800 mg tablet) for 6 weeks. In the primary efficacy population (patients with moderate disease, n = 448), 235 patients received 2.4 g/day (400 mg tablet) and 213 patients received 4.8 g/day (800 mg tablet). For all randomized patients, comparable percentages of patients (85%) completed the 6-week study in the two treatment groups.

Asacol 800 mg tablets are not currently approved for marketing in any country; thus, there is no information with respect to the post-marketing use of this formulation at any dose. However, safety profile regarding long-term use of 4.8 g/day, using the Asacol 400 mg tablets has been previously reviewed under NDA 19-651/S005 and is described in the current Asacol label.

- Common Adverse Events (AEs)

Across treatments, events reported by 2% or more of all randomized patients (in decreasing frequency) were headache, abdominal pain, infection, diarrhea, nausea, flatulence, ulcerative colitis (exacerbation), dyspepsia, and flu syndrome. Similar AE results were observed in a population with moderate disease. AEs that were reported more frequently by patients receiving 4.8 g/day vs 2.4 g/day were infection (4% vs. 3%) nausea (4% vs. 2%), and vomiting (2% vs. 1%). Particularly, in female subjects the incidence of nausea (6% vs 1.6%) and vomiting (2.2% vs 0.5%) was 3 to 4 times higher with 4.8 g/day dose compared to 2.4 g/day dose.

- Serious Adverse Events (SAEs)

Nine patients (7 in the 2.4 g/day group, 2 in the 4.8 g/day group) experienced SAEs (hospitalizations and/or medically significant events) during this clinical program. The majority of SAEs were events described in the current product label, primarily involving the digestive system, including ulcerative colitis signs and symptoms (rectal bleeding, diarrhea, abdominal pain) or worsening ulcerative colitis; nausea, vomiting, epigastric pain, cholecystitis and pancreatitis. Onset of SAEs occurred primarily in the first 2 weeks of treatment. Other SAEs reported during the program, and described in the current product label, included single reports of nephritis (2.4 g/day) and pericarditis (4.8 g/day). The only SAEs not described in the current label occurred in a single patient (2.4 g/day group) who was hospitalized and underwent a hysterectomy for dysfunctional uterine bleeding secondary to pre-existing uterine fibroids and ovarian cyst; the patient completed the study (Patient 37263458). The majority of SAEs were considered moderate or severe in nature; all patients had recovered from the events by the time of their last study contact, except for one patient (2.4 g/day group) who remained under treatment for worsening ulcerative (Patient 71003796).

- Dropouts due to Adverse Events

A total of 29 patients were withdrawn from study participation due to AEs during the clinical program: 3.8 % (13/338) in 4.8 g/day group and 4.6% (16/349) in 2.4 g/day group. The distribution and types of AEs resulting in study withdrawal was comparable between treatments for all randomized patients, as well as for patients with moderate disease. The majority of withdrawals due to AEs occurred as a result of events involving digestive system including colitis ulcer, nausea, vomiting, diarrhea and abdominal pain. Onset of events leading to withdrawal occurred in the first 2 weeks of treatment in the majority of patients (13/16 in the 2.4 g/day group and 11/13 in the 4.8 g/day group). All patients had recovered from AEs leading to withdrawal by the time of their last study contact with three exceptions. One patient in the 2.4 g/day group (moderate disease) remained under treatment for worsening UC and 2 patients with moderate disease (one in each treatment group) were experiencing ongoing sequelae of worsened UC symptoms at last follow-up.

- Death

. No deaths occurred in this clinical program.

Safety Conclusion

The two active-controlled clinical trials submitted under current application established an acceptable safety profile for Asacol (800 mg tablet) 4.8 g/day for six weeks in adult subjects with mildly to moderately active UC as well as in the primary efficacy population (subjects with moderate disease). Overall, the safety profile for Asacol (800 mg tablet) 4.8 g/day was comparable to that of Asacol (400 mg tablet) 2.4 g/day. However, the incidence of nauseas and vomiting was 2 to 3 times higher with 4.8 g/day compared to that seen with 2.4 g/day.

Particularly, in female subjects there was an increased incidence of nausea (6% vs 1.6%) and vomiting (2.2% vs 0.5%) with 4.8 g/day vs 2.4 g/day dose.

Asacol 800 mg tablets are not currently approved for marketing in any country; thus, there is no information with respect to the post-marketing use of this formulation at any dose. However, the safety profile regarding long-term use of 4.8 g/day using Asacol 400 mg tables has been previously reviewed under NDA 19-651/S005 and is reflected in the current Asacol label.

1.3.4 Dosing Regimen and Administration

Asacol 800 tablets are indicated for the treatment of moderately active UC. The recommended dosage in adults is two Asacol 800 mg tablets (1.6 g) to be taken 3 times a day for a total daily dose of 4.8 g for a duration of 6 weeks. It appears that the proposed indication is a subset of the currently approved indication, i.e. treatment of patients with mildly to moderately UC with Asacol 2.4 g/day (400 mg tablet).

It is worth noting that in patients with mildly active UC at baseline, Asacol 4.8 g/day provided relatively inferior efficacy outcome compared to that with Asacol 2.4 g/day. In addition, although the overall safety profile was comparable between treatments, there was an increased incidence of nausea and vomiting in subjects receiving 4.8 g/day. Thus, Asacol 800 mg tablets at a dose of 4.8 g/day are not indicated for the treatment of patients with mild disease at baseline.

One Asacol 800 mg tablet is not interchangeable with two Asacol 400 mg tablets, because the relative bioavailability study showed that the mean t_{max} value of 5-ASA was significantly delayed while the mean C_{max} and AUC values decreased by 36% and 25%, respectively, with administration of 800 mg tablet relative to 400 mg tablet.

1.3.5 Drug-Drug Interactions

There are no known drug interactions with Asacol, and no drug-drug interaction studies were performed in this clinical development program.

1.3.6 Special Populations

Safety and effectiveness of Asacol 800 mg tablets in pediatric patients have not been established. The clinical program did not include sufficient numbers of subjects aged 65 and older (<10% were age 65 years or older).

When comparing AE reporting for each sex by treatment group, the AE profile for male patients was comparable between the 2.4 g/day and 4.8 g/day groups, while female patients in the 4.8 g/day group more frequently reported nausea (6.1%), vomiting (2.2%), and diarrhea (3.9%) than female patients in the 2.4 g/day group (1.6%, 0.5%, and 2.2%, respectively).

Pregnant women were excluded from the studies. Reproduction studies in rats and rabbits at oral doses up to 480 mg/kg/day have revealed no evidence of teratogenic effects or fetal toxicity due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women.

Patients with kidney and hepatic impairment were excluded from the study. However, the current Asacol label states that renal impairment, including minimal change nephropathy and acute and chronic interstitial nephritis have been reported in patients taking Asacol tablets as well as other products that contain or are converted to mesalamine.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name: Mesalamine (5-aminosalicylic acid, also referred to as 5-ASA)

Proposed Trade Name: Asacol 800

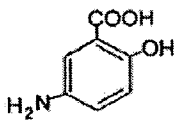
Pharmacological Class: topical anti-inflammatory drug

The exact mechanism of action of mesalamine is unknown. Available evidence suggests that mesalamine exerts topical anti-inflammatory effects on the colonic mucosa through inhibition of prostaglandin and leukotriene synthesis.

Each Asacol 800 mg delayed-release tablet are coated with an acrylic based resin Eudragit S (methacrylic acid copolymer B, NF) which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon. A second enteric coating, which begins to dissolve earlier in the GI tract is added after the Eudragit S coating. This second coat consists of a combination of acrylic based resins, Eudragit S and Eudragit L (methacrylic acid copolymer A, NF).

Mesalamine has the chemical name 5- amino-2-hydroxybenzoic acid.

Structural formula



Molecular Weight: 153.1
Molecular Formula: $C_7H_7NO_3$

Proposed Indication

Asacol 800 tablets are indicated for the treatment of moderately active UC. The recommended dosage in adults is two Asacol 800 mg tablets (1.6 g) to be taken 3 times a day

for a total daily dose of 4.8 g for duration of 6 weeks. The proposed indication is a subset of the currently approved indication, i.e. treatment of patients with mildly to moderately active UC with Asacol 400 mg tablet at a dose of 2.4 g/day.

It is worth noting that in patients with mildly active ulcerative colitis at baseline, Asacol 800 mg tablets at 4.8 g/day provided a relatively inferior efficacy benefit (-7%) compared to Asacol 400 mg tablets at 2.4 g/day. In addition, the higher dose was associated with an increased incidence of nausea and vomiting. Thus, Asacol 800 mg tablets at 4.8 g/day are not indicated for mild disease.

One Asacol 800 mg tablet is not interchangeable with two Asacol 400 mg tablets, because the relative bioavailability study showed that the mean t_{max} value of 5-ASA was significantly delayed, while mean C_{max} and AUC values decreased by 36% and 25%, respectively, with administration of 800 mg tablet relative to 400 mg tablet.

2.2 Currently Available Treatment for Indications

(Literature review)

Ulcerative colitis (UC) is a chronic disease characterized by diffuse mucosal inflammation limited to the colon and rectum. It involves the rectum in the majority of cases and may extend to proximal colon in a continuous fashion. The cardinal symptom during the acute stage is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus. The clinical course is marked by exacerbations and remissions, which may occur spontaneously or in response to the treatment changes or intercurrent illnesses. UC affects approximately 250,000-500,000 individuals in the U.S. with an incidence of 2-7/100,000 population per year. (Loftus EV et al. Gut 2000).The diagnosis of UC is suspected on clinical grounds and supported by the appropriate findings on proctosigmoidoscoy or colonoscopy, biopsy and by negative stool examination for infectious causes.

The pathophysiology of UC is multifactorial and incompletely understood. It appears that the disease results from inappropriate activation of the mucosal immune system, resulting in the inflammatory response (Podolosky DK. N Eng J Med 2002).

Pharmacologic therapy for UC focuses on controlling the immune response, either with systemic agents such as corticosteroids, or topical anti-inflammatory agents such as mesalamine-containing agents. Mesalamine has been available world wide for the treatment of IBD, specifically UC for more than 20 years, and as the active component in sulfasalazine for more than 50 years.

Sulfasalazine has been a major agent in the therapy of mild to moderate disease for more than 50 years (Gilbert JP et al. Dig Dis Sci 2002). In 1977, investigators determined that 5-ASA was the therapeutically active compound in sulfasalazine (Khan AK et al. Lancet 1977). The knowledge that the sulfapyridine moiety was not required for clinical efficacy allowed the

development of other 5-ASA compounds with the aim of maintaining efficacy, but avoiding the common side effects associated with sulfapyridine. Subsequently, sulfa-free 5-ASA has replaced sulfasalazine as first-line therapy for mildly to moderately active UC since its introduction in 1985. Although the exact mechanism of action of mesalamine remains unknown, it is thought to exert topical anti-inflammatory effects on colonic mucosa through inhibition of prostaglandin and leukotriene synthesis.

The goal of treatment in UC is to induce remission during an acute phase and subsequently to maintain remission. Sulfasalazine and 5-ASA is the mainstay of outpatient medical management for patients with mildly to moderately active UC, and are effective in maintaining remission in UC patients. Various formulations of mesalamine have been developed to optimize delivery of this compound to more distal portion of the gastrointestinal (GI) tract. Each product has different mechanisms for release of the active compound in the GI tract.

There is an armamentarium of approved mesalamine-containing various oral formulations for the treatment of mildly to moderately UC including sulfasalazine (5-ASA-pyridine); ASACOL (5-ASA), PENTASA (5-ASA), DIPENTUM (2 molecules of 5-ASA conjugated by an azo-bond), COLAZAL (5-ASA linked to an amino-acid) or in severe UC, corticosteroids.

In addition, mesalamine-containing various topical (rectal) formulations, including suppositories, enemas, and foams, are also available for the direct application of 5-ASA to the rectum in distal UC.

Immunomodulators such as azathioprine, 6-mercaotopurine, cyclosporine or methotrexate has been used off label.

2.3 Availability of Proposed Active Ingredient in the United States

Various oral as well topical (rectal) mesalamine-containing formulations are approved for marketing in the U.S.

2.4 Important Issues With Pharmacologically Related Products

There are no important issues with pharmacological related products.

2.5 Presubmission Regulatory Activity

In the United States, Asacol® (mesalamine) 400 mg delayed-release tablets were approved in 1992 for the treatment of mildly to moderately active *UC* at a dose of 2.4 g/day. Asacol 400 mg tablets were also approved in 1997 for the maintenance of remission of mild to moderate active UC at a dose of 1.6 g/day.

Between 1998 and 2003, representatives from P&GP met and corresponded with the Agency regarding the development program for Asacol 800 mg delayed-release tablets.

- In December 1998, P&GP proposed a development program that was based on data from a previous study (Study C3) along with data from a new single trial of patients with mildly to moderately active UC who are unresponsive to the current registered dose.
- On a correspondence dated February 8, 1999, the Agency could not rule out the possibility of approval based on one additional trial using a p-value < 0.001. The Agency stated that the general expectation is 2 trials, or a single trial with a p-value < 0.001, substantiated by other data such as data from Study C3, would be sufficient for review. In addition, the Agency encouraged the applicant to use a primary endpoint that mirrors the criteria used in the studies that formed the basis of approval of the 2.4 g/day.
- [redacted] b(4)
- On September 1, 2000, the applicant proposed a program consisting of 2 identical double-blind studies evaluating the safety and efficacy of Asacol 4.8 g/day using 800 mg tablets, compared to a 2.4 g/day dose using 400 mg tablets, in patients with mildly to moderately active UC. The Agency agreed that these 2 studies of alternative design were sufficient for review.
- On February 18, 2003, the applicant requested Type A meeting to discuss the need to change the primary study population to be evaluated in the primary efficacy analysis of Study 82. The proposed amendment was to chang the patient population from mildly to moderately active UC to moderately active UC in Study 82. The proposed change was a direct consequence of results obtained in study 83. Subsequently, the applicant submitted a protocol amendment to Study 82 on February 26, 2003.
- On March 4, 2003, the applicant submitted pre-meeting information package along with issues regarding the change to Study 82. In the meeting package (serial 2007; 04 March 2003), the applicant provided the Agency with clinical results from Study 83 and the basis for shifting the focus of the ongoing study from patients with mildly to moderately active UC to patients with moderately active UC. The Agency accepted the proposed modification (faxed communication dated March 17, 2003). In addition, the Agency stated that assuming consistent and statistically significant efficacy outcome are obtained the development strategy could supply the data necessary for the NDA. As a result, the aforementioned modifications were implemented in study 82 prior to unbinding. In addition, the applicant submitted a statistical analysis plan (serial #217) on December 11, 2003.
- On May 19 2003, the Agency submitted to the applicant a formal Pediatric Written Request to study the safety and efficacy of Asacol in pediatric population with mildly to moderately UC, ages 5-17 years.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data evaluated in this review are the two clinical trials conducted by the applicant. These studies were active-controlled, randomized, double blind, parallel group, multicenter studies conducted in the U.S. and Canada.

4.2 Tables of Clinical Studies

Table 1. Listing of Clinical Studies

Type of study	Study identifier and Location	Objectives of the study	Study Design	Test product Dosage regimen	Population	Number Entered/ completed	Duration of Treatment
Safety and efficacy	2000082 Section 5.3.5.1.1	To assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) vs. Asacol 2.4 g/day (400 mg tablet)	Double- blind, randomized, 6-week, parallel group, active control	Two 800 mg tablets and two placebo tablets 3 times daily oral	Mildly to moderately active UC	386/330 2.4 g/day 195/162 4.8 g/day 191/168	6 weeks
Safety and efficacy	2000083 Section 5.3.5.1.2	To assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) vs. Asacol 2.4 g/day (400 mg tablet)	Double- blind, randomized, 6-week, parallel group, active control	Two 800 mg tablets and two placebo tablets 3 times daily oral	Mildly to moderately active UC	301/256 2.4 g/day 154/133 4.8 g/day 147/123	6 weeks

Medical Officer's (MO) comment: It should be noted that the primary population for efficacy assessment in Study 82 was amended to change from subjects with mild to moderate disease to subjects with only moderate disease as described elsewhere.

4.3 Review Strategy

The applicant submitted the current NDA in electronic format to the EDR. In this application, the clinical section included study protocols, efficacy and safety report from 2 phase III clinical studies. The reviewer approached this submission first by focusing upon what the applicant has requested, and what evidence has been submitted in support of the request. The two studies were reviewed separate. In each study, the protocol was examined first, and the study reports were assessed for safety and efficacy. The reviewer's final judgement on safety and efficacy for the proposed indication was based on safety profile of the drug and wether the stated primary objective endpoints were achieved. Further, additional information was sought from published clinical data relevant to the drug product and the medical condition being treated. The reviewer also consulted electronic Physician Desk Reference.

4.4 Data Quality and Integrity

The Division of Scientific Investigation (DSI) has been consulted for this NDA. The two studies in the NDA were conducted in the U.S. and Canada, in multiple centers. Four sites were selected for auditing based on sample size and efficacy results. The DSI report indicates that 4 subjects were enrolled despite not meeting eligibility criteria. There were record keeping deficiencies noted at 2 sites that appear not to affect the overall validity of the data. The DSI concluded that the data from these 4 sites appear acceptable in support of the relevant indication of the NDA.

In addition, the quality and results of the data were discussed and reanalyzed for verification purpose by the Agency's statistical reviewer.

4.5 Compliance with Good Clinical Practices

The applicant documented that all studies were conducted in accordance with the US Code of Federal Regulations for Good Clinical Practices (Title 21, Parts 50, 56, and 312) and in the Declaration of Helsinki, as amended in October 1996 by the 48th General Assembly, Somerset West, Republic of South Africa.

The applicant also indicated that patients were informed by the Investigator or an authorized staff member about the nature of the study prior to the start of the study. Each patient signed a study-specific consent form to serve as a participant in the study. The consent form complied with all applicable regulations governing the protection of human subjects and included the basic elements of informed consent, which are specified in the US CFR (Title 21, CFR 50.20, 50.25 and 50.27) and the ICH Harmonized Tripartite Guideline for GCP.

4.6 Financial Disclosures

P & G certified that they did not enter into any financial agreement with the clinical investigators whereby the value of their compensation could be affected by outcome of the studies.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The single dose administration of Asacol 800 mg delayed-release tablet a relative bioavailability study indicated that, the mean t_{max} value of 5-ASA was significantly delayed while mean C_{max} and AUC values decreased by 36% and 25%, respectively, with administration of the 800 mg tablets relative to the 400 mg tablet.

The results of a multiple dose PK study of the 800 mg tablet indicated that the C_{max} and AUC values of 5-ASA and N-Ac-5-ASA increase significantly with multiple dose administration suggesting that significant accumulation of 5-ASA and N-Ac-5-ASA takes place with the TID regimen.

The results of a population PK analysis in patients with moderately active UC showed that the steady-state plasma concentrations of 5-ASA and N-Ac-5-ASA increased in a dose-related matter.
A significant food-effect was observed on the PK of the 800 mg Asacol tablet. In particular, mean C_{max} of 5-ASA decreased by 47% under fed conditions. In addition, a marked delay in t_{max} was observed under fed conditions with t_{max} increasing by 14 hours relative to fasting conditions.

Overall, the submission was acceptable from Office of Clinical Pharmacology and Biopharmaceutic standpoint.

5.2 Pharmacodynamics

Asacol (mesalamine) is thought to exert its pharmacologic effects topically on the GI tract.

5.3 Exposure-Response Relationships

Asacol 2.4 g/day was previously approved for the treatment of mildly to moderately active UC. The approval was based on the results from two clinical trials (C3 and C14, NDA 19-651). In Study C14 the daily dose was 2.4 g/day, while in Study C3 it was 4.8 g/day. The applicant's decision to study 4.8 g/day of Asacol was originated from Study C3 findings indicating that 4.8 g/day was associated with increased efficacy benefit (also reflected in the current label).

b(4)

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Proposed indication: Asacol 800 tablets are indicated for the treatment of moderately active UC. The recommended dosage in adults is two Asacol 800 mg tablets (1.6 g) to be taken 3 times a day for a total daily dose of 4.8 g for a duration of 6 weeks.

6.1.1 Methods

Efficacy data are generated from two double-blind, randomized, active-controlled, parallel-group, Phase III clinical trials (Study 82 and Study 83) of 6 weeks duration. Both studies were originally designed to compare the efficacy of 4.8 g/day dosing, administered as the newly formulated 800 mg tablet vs 2.4 g/day dosing, administered as the currently-marketed 400 mg tablet in patients with mildly to moderately active UC.

However, the clinical program was amended to change the original efficacy population as a direct consequence of the results from Study 83. The results from study 83 (first study completed) suggested that the response rate between 4.8 g/day and 2.4 g/day was not significantly different in the originally planned efficacy population (mild to moderate disease), but it was significantly different in the prespecified subgroup of patients with moderate disease. Subsequently, the Study 82 protocol was amended (with concurrence from the Agency) to change the primary efficacy population from mild to moderate disease to a population with only moderate disease. [redacted] Under the amended protocol, up to 100 additional patients with moderate disease were to be enrolled. b(4)

However, as described elsewhere, the aforementioned amendment was made when Study 82 was nearing the end of recruitment (intended sample size was 308 with mild to moderate disease). According to the applicant (amendment # 15, dated July 13, 2005), 296 patients were enrolled when amendment was made. But the Agency statistical reviewer found that 304 patients of the intended sample size were already enrolled when the amendment was made. A total of 82 patients were enrolled after the amendment was made.

MO comment: I concur with the Statistical Team Leader's (Dr. Stella Gross) conclusion that changing the protocol close to the end of the study and addition of unjustified number of patients (n=82) reflects poor planing. But the change is not post hoc as suggested by the primary statistical reviewer (Dr. Fan Milton).

6.1.2 General Discussion of Endpoints

- Primary Endpoint

The primary efficacy endpoint for both studies was treatment outcome (treatment success or treatment failure) at Week 6 in the applicant's intent-to-treat (ITT) population defined as those who were randomly assigned to treatment and ingested at least 1 dose of study medication, and whose primary endpoint could be determined. 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 clinical assessments (stool frequency, rectal bleeding, PFA, PGA, and sigmoidoscopy). 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, and no worsening in any of the remaining clinical assessments.

Treatment failure was defined as: 1) a PGA score that stayed the same or worsened from baseline (regardless of whether the other clinical assessments resolved); 2) worsening of any clinical assessments or no improvement from baseline in all clinical assessments at Week 6; or 3) withdrawal from the study due to an AE or lack of treatment effect.

The primary endpoint used in these studies was also used in the pivotal clinical trials leading to the approval of Asacol 400 mg tablets (2.4 g/day) in mildly to moderately active UC. The Agency encouraged the applicant to use the primary endpoint that mirrors the criteria used in the previous Asacol studies.

The primary endpoint was defined on the basis of the Physician's Global Assessment (PGA), which took into consideration clinical assessments of rectal bleeding, stool frequency, patient's functional assessment (PFA) and sigmoidoscopic examination. The reader may refer to Appendix 10.3 of this review for information on PGA scores used in this clinical program.

MO comment: It is worth mentioning that measurement of disease activity is critical in determining whether new therapies are effective. Unlike Crohn's disease, there is no gold standard for measuring disease activity in UC. In Crohn's disease, standard definitions for clinical improvement and clinical remission on standard indices have come into common use, allowing useful comparisons across trials. This has not been the case for UC where no single disease activity index is universally accepted and no generally accepted definition of improvement or remission exist (Higgins PDR et al, Gut 2005).

- Secondary Endpoints

There were multiple secondary endpoints analyzed in the studies including the percentage of patients who improved from baseline at Week 3; and the percentage of patients whose individual clinical assessment scores at Weeks 3 and 6 were improved. It should be pointed out that appropriate statistical measures to correct for multiple comparisons were not prespecified in the protocol.

- Subgroup Analysis for Primary Endpoint

A number of subgroups (demographics characteristics, disease history, and baseline disease activity) were analyzed without adjustment for multiplicity.

6.1.3 Study Design

Of note, since the two studies were conducted under identical protocol, the reviewer summarizes one study protocol only.

Protocol Summary (Study 82)

The study design was double-blind, randomized, multicenter, active-controlled study in newly and previously diagnosed patients who were experiencing a flare of mildly to moderately active ulcerative colitis. Patients were randomly assigned (1:1 ratio) to receive either the approved Asacol 400 mg tablet at 2.4 g/day or the newly formulated Asacol 800 mg tablet at 4.8 g/day for 6 weeks.

MO comment: the design is appropriate for the study. Due to the availability of approved therapies to manage ulcerative colitis, the applicant felt that a positive control is more appropriate than a placebo control. The rationale for choosing active control appears reasonable.

Objective

The original objective for both studies was to compare the safety and efficacy of the two treatment arms in patients with *mildly to moderately active UC*. The protocol for Study 82 was later amended as described under Section 6.1.1 to compare the efficacy of the two treatment arms in patients with *only moderately active UC*, the indication being sought in this application.

Treatments Administered

Treatment 1: Asacol 2.4 g/day (400 mg formulation)
Patients took two 400 mg tablets and 2 placebo tablets (matching the 800 mg formulation) 3 times daily (morning, midday, and evening).

Treatment 2: Asacol 4.8 g/day (800 mg formulation)
Patients took two 800 mg tablets and 2 placebo tablets (matching the 400 mg formulation) 3 times daily (morning, midday, and evening).

MO comment: Although the applicant's decision to study a higher dose (4.8 g/day) than the approved dose (2.4 g/day) was primarily due to the increased efficacy benefit seen with a higher dose in one of previously submitted placebo-controlled studies (Study C3, NDA 19-651), an additional arm with a middle dose (3.6 g/day) using 400 mg tablets (for dosing flexibility) would have provided useful information. The American Collage of Gastroenterology Guideline recommends a range of mesalamine dosing, i.e. from 2 g/day to 4.8 g/day for the treatment of mildly to moderately active UC (Kornbluth et al. Ulcerative Colitis Practice Guidelines in Adults; A J Gastroenterol 2004; 1371-1385).

Study Population

Inclusion Criteria:

- male or female between 18 and 75 years of age, inclusive, at screening;
- a confirmed diagnosis of ulcerative colitis, with the extent varying from proctitis to

pancolitis;
- demonstrated mildly to moderately active disease at study entry, as determined by their PGA score at the Baseline Visit;
- had a clinical assessment of at least 1 for the stool frequency score, the rectal bleeding score, or both, had a sigmoidoscopy score of at least 1, had a PFA score of 0 to 3, and had a PGA score of 1 or 2 at the Baseline visit.

Exclusion Criteria:
- a history of extensive small bowel resection (> ½ the length of the small intestine) causing short bowel syndrome;
- current renal or hepatic disease;
- received corticosteroids within 1 month prior to the Baseline Visit;
- received any other topical rectal therapy during the week prior to the Screening Visit; received immunomodulatory within 3 months prior to the Baseline Visit;
- received any antidiarrheals and/or antispasmodics after the Screening Visit;
- positive stool examination for bacterial pathogens, ova and parasites;
- if female, a positive pregnancy test or lactating.

MO comment: The inclusion/exclusion criteria used in these studies are adequate for the study and they are consistent with the current label for Asacol 400 mg tablets.

Primary Endpoint

The primary efficacy analysis in both studies compared the proportion of patients who improved from baseline at Week 6 using the intent-to-treat (ITT) population. 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 clinical assessments outlined above. 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, and no worsening in any of the remaining clinical assessments

Treatment failure was defined as: 1) a PGA score that stayed the same or worsened from baseline (regardless of whether the other clinical assessments resolved); 2) worsening of any clinical assessments or no improvement from baseline in all clinical assessments at Week 6; or 3) withdrawal from the study due to an AE or lack of treatment effect.

MO comment: It should be noted that unlike Crohn's disease, there is no single uniformly accepted endpoint in UC.

Secondary Endpoints

There were multiple secondary endpoints analyzed in the studies including the percentage of patients who improved from baseline at Week 3; and the percentage of patients whose

individual clinical assessment score (stool frequency, rectal bleeding, PFA, PGA, and sigmoidoscopy) at Weeks 3 and 6 were improved.

MO comment: appropriate statistical measures to correct for multiple comparisons were not pre-specified in the protocol.

Treatment Compliance

Compliance was determined based on returned tablets count and doses missed at Visit 1 and 2. If the returned tablet count for both visits indicated a patient was less than 85% compliant for the study, the patient was considered non-compliant.

Study Procedures

The schedule of patient visits and procedures is summarized in Table 2.

Patients were screened according to inclusion/exclusion criteria within 7 days before receiving study medication. The Baseline visit was within 7 days after the Screening 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 Interactive Voice Response System (IVRS) was used to collect daily information on patients' stool frequency, rectal bleeding, and the PFA.

Table 2 Schedule of Procedures

Procedure	Visit			
	Screening[a]	Baseline	Week 3	Week 6
Informed consent form	X			
Medical/medication history	X	X	X	X
Demographic data	X			
Physical examination[b]	X			X
Clinical laboratory tests[c]	X			X
Serum pregnancy test[d]	X			X
Sigmoidoscopy[e]	X[f]		X	X
Clinical assessments[g]		X	X	X
Quality-of-life questionnaire		X	X	X
Adverse event monitoring	X	X	X	X
Dispense study medication		X	X	
Assess compliance			X	X
Pharmacokinetic blood sample[h]		X	X	X

a Performed within 3 to 7 days before study drug administration
b Included vital signs, body weight, and height measurements (height was taken at screening only)
c Included serum chemistry, hematology, urinalysis, and stool sample (stool sample at screening only, unless previous results were obtained within 1 month prior to screening showing negative results for bacterial pathogens, ova and parasites, and *Clostridium difficile*)
d Required for women of child-bearing potential
e If patients underwent a colonoscopy or sigmoidoscopy (performed by the Investigator) within a week prior to the Screening Visit, the sigmoidoscopy was not performed.
f Sigmoidoscopy or colonoscopy
g Included stool frequency, rectal bleeding, PGA, and PFA
h Analyzed for 5-ASA and N-Ac-5-ASA

Withdrawal from the Study

Patients who were withdrawn from the study for any reason were not allowed to re-enter, and patients who were withdrawn from the study for any reason after study drug administration were not replaced. When possible, exit procedures were completed for all patients withdrawn from the study. Patients withdrawn from the study for medical reasons remained under medical supervision until the Investigator deemed the condition to be resolved or stabilized.

Protocol Amendments

The applicant made 3 amendments dated Feb 23, 2001, May 24, 2001, and Feb 19, 2003. Protocol amendments were implemented during the study. Major changes to the protocol follow:

1. Clarified assessments of sigmoidoscopy, PFA, and PGA in inclusion criteria.
2. Increased the number of study sites.
3. Revised inclusion criteria to allow for a colonoscopy (instead of sigmoidoscopy) at screening to determine extent of ulcerative colitis.
4. Removed exclusion criteria prohibiting H_2 blockers and proton pump inhibitors. Also removed these from prohibited concomitant medications list.
5. Clarified prohibition of corticosteroids as concomitant medications.

6. Revised age limit criteria from ≤ 65 years to ≤ 75 years to allow older patients into the study.
7. 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 ulcerative colitis (PGA = 2).
8. Increased enrollment by up to 100 additional patients with moderately active ulcerative colitis.

Statistical Analysis Plans

Statistical analyses were performed using 2 study populations: the intent-to-treat (ITT) population and the per-protocol (PP) population.

The ITT population was defined as those patients who were randomized and ingest at least 1 dose of study medication **and** whose primary efficacy endpoint could be determined. For patients whose reason for withdrawal was not recorded as lack of treatment effect or AE, the treatment outcome at Week 6 could not be determined; the patients were classified as non-analyzable. These non-analyzable patients were excluded from the ITT analyses.

The PP population was defined as all patients who complete the study, had no major protocol violations, were at least 85% compliant with the dosing regimen and met the baseline disease-related inclusion criteria. Patients who violate major inclusion or exclusion criteria were excluded from the PP analysis.

MO comment: The applicant's definition of ITT population is not acceptable. Based on the ITT principal, the ITT analysis should include all randomized patients regardless of degree of follow-up.

Primary Efficacy Analysis

The primary efficacy analysis compared the percentage of patients in each treatment group who were classified as treatment success at Week 6, using the ITT population.
The null hypothesis and alternative hypothesis were tested for the primary endpoint.
The Chi-square test was used to determine the overall treatment effect, and the 95% confidence intervals for the treatment difference between the 2 treatment groups were provided.

Handling of Missing Data for Primary Efficacy Endpoint

For patients whose treatment outcome at Week 6 was not available for evaluation, two methods were used to define treatment outcome: the "set to treatment failure" method and the "last observation carried forward" method, i.e. for patients whose treatment outcome at Week 3 was available, the efficacy evaluation was carried forward to Week 6. For patients whose efficacy results after baseline were missing, the baseline score was carried forward to Week

6. In the latter case, the treatment outcome for Week 6 was treatment failure (stayed the same compared to baseline).

Secondary Efficacy Endpoints

All statistical tests for secondary efficacy endpoints were conducted at the 2-sided, 5% level of significance.

MO comment: the applicant compared multiple secondary endpoints as described above, however, appropriate statistical steps to correct for multiple comparisons were not prespecified in the protocol.

Subgroup Analyses

Subgroup analyses were conducted on the primary endpoint using ITT population across subgroup variables defined by demographics characteristics, disease history, and baseline disease activity. For each of the subgroup variables, the Cochran-Mantel-Haenszel chi-square test using the subgroup variable as the stratum variable was used to examine the treatment effect adjusted for that stratum variable.

Sample size consideration

It was assumed that the true rate of improvement for the 2.4 g/day group was 40% and for the 4.8 g/day group was 60%. To detect a true difference of 20% between the two groups with 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.

6.1.4 Efficacy Findings

I. RESULTS FROM STUDY 82

Patient Disposition

Study 82 was initiated in February 28, 2001 and completed in April 15, 2004. A total of 386 patients were enrolled in approximately 50 centers in the U.S. and Canada. Of these, 268 had moderate disease, 117 had mild disease, and 1 had insufficient data to determine baseline disease severity and was excluded from efficacy analyses in patients with moderate disease.

Of note, as described elsewhere, on February 18, 2003, the applicant made an amendment to change the primary efficacy population from mild to moderate disease to only moderate disease and to increase sample size by up to 100 additional patients with disease to Study 82 that was nearing the end of the planned enrolment (n=308). According to the applicant (amendment # 15, dated July 13, 2005), a total of 296 patients with mild to moderate disease were enrolled when amendment was made. However, the Agency statistical reviewer found

that 304 patients were enrolled when the amendment was made. Thus, a total of 82 patients were enrolled post-amendment.

Of the total of 268 patients with moderate disease, 139 were assigned to the 2.4 g/day group, and 129 to the 4.8 g/day group (Table 3). In the 2.4 g/day group, 81% of patients completed the 6-week study, while in the 4.8 g/day group 88% of patients completed the 6-week study. Patient distribution was comparable between treatments with the exception of the number of patients who did not complete the study due to lack of treatment effect: more patients in the 2.4 g/day group did not complete the study due to lack of treatment effect (11 vs 5).

Table 3. Patient Disposition (Patients with Moderate Disease at Baseline)

Category	2.4 g/day Asacol (400 mg tablet) (N = 139)		4.8 g/day Asacol (800 mg tablet) (N = 129)		Total (N = 268)	
	n	(%)	n	(%)	n	(%)
Completed Study	113	(81.3)	113	(87.6)	226	(84.3)
Did not complete study:	26	(18.7)	16	(12.4)	42	(15.7)
Protocol violation	2	(1.4)	1	(0.8)	3	(1.1)
Adverse event	4	(2.9)	4	(3.1)	8	(3.0)
Voluntary withdrawal without adverse event	6	(4.3)	5	(3.9)	11	(4.1)
Investigator recommendation	3	(2.2)	1	(0.8)	4	(1.5)
Lack of treatment effect	11	(7.9)	5	(3.9)	16	(6.0)

Ref. Section 5.3.5.1.1, Table 3

Protocol Deviations

There were no significant differences between treatment groups in protocol deviations (Table 4). The most common protocol deviations were patients violating entry criteria and receiving excluded concomitant medications. The most commonly violated entry criterion was failure to test, or testing out-of-window for enteric pathogens. The most common excluded concomitant medications reported were those for treating gastrointestinal conditions and NSAIDs. The most common other deviation was visits that occurred outside the protocol specified window.

Table 4. Protocol Deviations (Patients with Moderate Disease at Baseline)

Deviation	2.4 g/day Asacol (400 mg Tablet) (N = 139)		4.8 g/day Asacol (800 mg Tablet) (N = 129)	
	n	(%)	n	(%)
Violated entry criteria	21	(15.1)	17	(13.2)
Developed withdrawal criteria but were not withdrawn	0	(0.0)	1	(0.8)
Received wrong treatment or incorrect dose	0	(0.0)	2	(1.6)
Received an excluded concomitant medication	7	(5.0)	12	(9.3)
Other violations	24	(17.3)	10	(7.8)

Ref. section 5.3.5.1.1, Table 4

Compliance with Dosing Regimen

According to the definition in the protocol, 120 (86%) patients in the 2.4 g/day group were at least 85% compliant and 117 (91%) patients in the 4.8 g/day group were at least 85% compliant.

Demographic Characteristics

The two treatment groups were comparable with respect to age, height, weight, sex, race, and smoking status (Table 5). The population was primarily Caucasian (76%), had a mean age of 42 years (< 10% were age 65 years or older), and included slightly more females (57%) than males (43%). The mean height and weight was about 170 cm and 78 kg, respectively.

Table 5. Baseline Demographic Characteristics (Patients with Moderate Disease at Baseline).

Parameter	2.4 g/day Asacol (400 mg tablet) (N = 139) n (%)	4.8 g/day Asacol (800 mg tablet) (N = 129) n (%)	p-value[c]
Age (years)[a]	42.3 (1.20)	42.0 (1.17)	0.8760
18-64[b]	126 (90.6%)	118 (91.5%)	
>= 65[b]	13 (9.4%)	11 (8.5%)	
Height (cm)[a]	170.0 (0.95)	167.9 (0.95)	0.1095
Weight (kg)[a]	79.3 (1.76)	77.1 (1.69)	0.3779
Race[b]			0.6979
Caucasian	108 (77.7%)	96 (74.4%)	
Black	11 (7.9%)	14 (10.9%)	
Asian (Indian)	1 (0.7%)	2 (1.6%)	
Asian (Oriental)	1 (0.7%)	3 (2.3%)	
Hispanic	16 (11.5%)	11 (8.5%)	
Multi-racial/other	2 (1.4%)	3 (2.3%)	
Sex[b]			0.6506
Male	62 (44.6%)	54 (41.9%)	
Female	77 (55.4%)	75 (58.1%)	
Smoking History[b]			0.9024
Never Smoked	89 (64.0%)	80 (62.0%)	
Used to Smoke	40 (28.8%)	38 (29.5%)	
Currently Smokes	10 (7.2%)	11 (8.5%)	

a Data shown are mean (standard error).
[b] Data shown are number and percentage (n/N x 100) of patients in demographic category and treatment group (Ref. Section 5.3.5.1.1, Table 6)

Baseline Disease Characteristics

There were no statistically significant differences between treatments with respect to extent of disease, length of disease history, prior treatments, and relapse frequency (Table 6). The extent of the disease ranged from proctitis to pancolitis and comparable number of patients presented with proctitis, left-sided colitis and pancolitis; fewer patients presented with

proctosigmoiditis in the 4.8 g/day group. Approximately one-third were newly diagnosed and more than one-half had been treated previously with some type of 5-ASA.

Table 6. Ulcerative Colitis History (Patients with Moderate Disease at Baseline)

	2.4 g/day (400 mg tablet) (n = 139)		4.8 g/day (800 mg tablet) (n = 129)		p-value
Parameter	n	(%)	n	(%)	
Disease Extent					0.2861
Proctitis	20	(14.4)	21	(16.3)	
Proctosigmoiditis	49	(35.3)	32	(24.8)	
Left-sided colitis	42	(30.2)	49	(38.0)	
Pancolitis	28	(20.1)	27	(20.9)	
Length of Disease History					0.9168
< 1 year	54	(38.8)	49	(38.0)	
1 to 5 years	32	(23.0)	29	(22.5)	
> 5 to 10 years	22	(15.8)	25	(19.4)	
> 10 years	28	(20.1)	25	(19.4)	
Unknown	3	(2.2)	1	(0.8)	
Prior Treatment					
Steroids (oral or IV)	47	(33.8)	38	(29.5)	0.4439
Immunomodulators	3	(2.2)	5	(3.9)	0.4090
Sulfasalazine	53	(38.1)	40	(31.0)	0.2210
Sulfa-free oral 5-ASAs	57	(41.0)	53	(41.1)	0.9896
Any oral 5-ASAs	83	(59.7)	73	(56.6)	0.6045
Rectal Therapies	50	(36.0)	48	(37.2)	0.8335
Intolerant to Sulfasalazine					0.7589
Yes	12	(22.6)	8	(20.0)	
No	41	(77.4)	32	(80.0)	
Total	53		40		
Relapse Frequency					0.3055
Newly Diagnosed	46	(33.1)	45	(34.9)	
More than once a month	21	(15.1)	13	10.1)	
Once every six months	25	(18.0)	27	(20.9)	
Once every six to 12 months	18	(12.9)	25	(19.4)	
Less than once a year	29	(20.9)	19	(14.7)	

Ref. Section 5.3.5.1.1, Table 7

The 2 treatment groups were comparable in terms of baseline disease activity (Table 7). At baseline, the majority of patients with moderate disease reported increased daily stool frequency, about 58% of the patients reported more than 3 stools greater than normal per day. Most patients had rectal bleeding at baseline (about 26% had streaks of blood less than half the time, and about 57% had obvious blood most of the time). In addition, these patients lacked signs of significant systemic toxicity at baseline; about 70% rated their PFA as generally well or fair. At baseline, 13% of the patients had sigmoidoscopy results that were mild, and about 75% had sigmoidoscopy results that were moderate.

Table 7. Baseline Disease Characteristics (Patients with Moderate Disease at Baseline)

	2.4 g/day Asacol (400 mg Tablet) (N = 139)	4.8 g/day Asacol (800 mg Tablet) (N = 129)	p-value
Parameter	n (%)	n (%)	
Stool Frequency Score			0.6988
0 (Normal Frequency)	9 (6.5)	13 (10.1)	
1 (1 to 2 greater than normal)	47 (33.8)	40 (31.0)	
2 (3 to 4 greater than normal)	54 (38.8)	52 (40.3)	
3 (>= 5 greater than normal)	29 (20.9)	24 (18.6)	
Rectal Bleeding Score			0.2973
0 (none)	15 (10.8)	7 (5.4)	
1 (Streak, less than 1/2 time)	35 (25.2)	35 (27.1)	
2 (Obvious, most of time)	75 (54.0)	78 (60.5)	
3 (Blood alone)	14 (10.1)	9 (7.0)	
Patient's Functional Assessment Score			0.7721
0 (Generally well)	24 (17.3)	23 (17.8)	
1 (Fair)	76 (54.7)	71 (55.0)	
2 (Poor)	34 (24.5)	33 (25.6)	
3 (Terrible)	5 (3.6)	2 (1.6)	
Sigmoidoscopy Score			0.6110
0 (Normal)	0 (0.0)	0 (0.0)	
1 (Mild)	15 (10.8)	19 (14.7)	
2 (Moderate)	107 (77.0)	96 (74.4)	
3 (Severe)	17 (12.2)	14 (10.9)	
Number of days in Flare			0.8859
0 to 14	4 (2.9)	3 (2.3)	
15 to 28	18 (12.9)	15 (11.6)	
> 28	112 (80.6)	108 (83.7)	
Unknown	5 (3.6)	3 (2.3)	

Ref. Section 5.3.5.1.1, Table 8

Efficacy Analysis

- **Primary Endpoint**

In the ITT analysis, the primary endpoint, i.e. the percentage of patients whose treatment outcome at Week 6 was classified as treatment success was 72% (20% complete success and 52% partial success) with 4.8 g/day, compared to 59% (18% complete success and 41% partial success) with 2.4 g/day, a difference that was statistically significant (p=0.0357) in favor of 4.8 g/day (Table 8). Similar results were observed in the PP analysis for the primary endpoint (76% vs. 63%; p=0.039) as shown in Table 9.

Table 8. Treatment Outcome at Week 6 (ITT Patients with Moderate Disease at Baseline)

	2.4 g/day Asacol (400 mg tablet) (n = 130)		4.8 g/day Asacol (800 mg tablet) (n = 124)		chi-square p-value	Difference in Success Rates	Confidence Interval (%)
Treatment Outcome	n	(%)	n	(%)			
Treatment Success	77	(59.2)	89	(71.8)	0.0357	12.543	(0.96, 24.12)
Complete	23	(17.7)	25	(20.2)			
Partial	54	(41.5)	64	(51.6)			
Treatment Failure	53	(40.8)	35	(28.2)			

Ref. Section 5.3.5.1.1, Table 9 and EoT Table 4. (Compiled by the Reviewer)

Table 9. Treatment Outcome at Week 6 (PP patients with Moderate Disease at Baseline)

	2.4 g/day Asacol (400 mg Tablet) (N = 112)		4.8 g/day Asacol (800 mg Tablet) (N = 106)		Chi-square p-value	Difference in Success Rate	Confidence Interval (%)
Treatment Outcome	n	(%)	n	(%)			
Treatment Success	70	(62.5)	80	(75.5)	0.0388	13.0	(0.83, 25.12)
Treatment Failure	42	(37.5)	26	(24.5)			

Ref. Section 5.3.5.1.1, EoT Table 17

- **Sensitivity Analysis Primary Endpoint**

A total of 14 patients (9 in the 2.4 g/day group and 5 in the 4.8 g/day group) were excluded from the aforementioned ITT analysis, because Week 6 treatment outcome could not be determined. However, the superiority of 4.8 g/day over 2.4 g/day holds true in a sensitivity analysis where missing observations were set to treatment failure (69% vs. 55%; p=0.0220) and last observation carried forward (69% vs. 56%; p= 0.0297) as summarized in Table 10 and Table 11, respectively.

Table 10. Treatment Outcome at Week 6: missing observations set to treatment failure (Patients with Moderate Disease at Baseline)

	2.4 g/day Asacol (400 mg Tablet) (N = 139)		4.8 g/day Asacol (800 mg Tablet) (N = 129)		Chi-square p-value	Difference in Success Rate	Confidence Interval (%)
Treatment Outcome	n	(%)	n	(%)			
Treatment Success	77	(55.4)	89	(69.0)	0.0220	13.6	(2.11, 25.09)
Treatment Failure	62	(44.6)	40	(31.0)			

Ref. Section 5.3.5.1.1, EoT Table 5

Table 11. Treatment Outcome at Week 6: last observation carried forward (Patients with Moderate Disease)

	2.4 g/day Asacol (400 mg Tablet) (N = 139)		4.8 g/day Asacol (800 mg Tablet) (N = 129)		Chi-square p-value	Difference in Success Rate	Confidence Interval (%)
Treatment Outcome	n	(%)	n	(%)			
Treatment Success	78	(56.1)	89	(69.0)	0.0297	12.9	(1.40, 24.36)
Treatment Failure	61	(43.9)	40	(31.0)			

Ref. Section 5.3.5.1.1, EoT Table 6

- **Additional Analysis by Time of Enrollment**

The Agency statistical reviewer performed a post hoc primary efficacy analysis in patients with moderate disease at baseline by time of enrollment (pre- or post-amendment). As shown in the statistical reviewer's Table below, among pre-amendment enrollees, the treatment difference reached a statistical significance in favor of 4.8 g/day (70% vs 55%; p=0.038). By contrast, among post-amendment enrollees, the response rate was not significantly different between the 4.8 g/day group and 2.4 g/day group (76% and 71%, respectively; p=0.679).

MO comment: The reasons for such variability in the outcomes are unclear to this reviewer. It is possible that this is due to the lack of a gold standard for measuring disease severity in UC. Consequently, it is difficult to assure homogeneity of a study population in a clinical trial, which may hamper an appropriate interpretation of the clinical data. It is also possible that the post-amendment analysis is underpowered due to the small sample size (76 vs 178) to detect a meaningful treatment difference.

Statistical Reviewer's Table. Treatment success at Week 6

Enrollment time	2.4 g/day	4.8 g/day	Difference	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

- **Secondary Endpoints**

By Week 3, the disease severity had improved from baseline in 52% of the patients in 2.4 g/day group, compared to 61% in 4.8 g/day group (Table 12). While the treatment difference of 9.8% at Week 3 in favor of 4.8 g/day was not statistically significant (p = 0.117), the difference in treatment success showed further divergence at the Week 6 (primary endpoint), becoming a statistically significant difference (12.5%) between treatments (Table 8).

Table 12. Treatment Outcome at Week 3 (Patients with Moderate Disease at Baseline)

	2.4 g/day Asacol (400 mg Tablet) (N = 130)		4.8 g/day Asacol (800 mg Tablet) (N = 124)		Chi-square p-value	Difference in Success Rate	Confidence Interval (%)
Treatment Outcome	n	(%)	n	(%)			
Treatment Success	67	(51.5)	76	(61.3)	0.1173	9.75	(-2.39, 21.89)
Treatment Failure	63	(48.5)	48	(38.7)			

Ref. Section 5.3.5.1.1, Table EoT 7

Analyses of individual clinical assessment score at Week 3 and Week 6 showed numerical trends favoring 4.8 g/day over 2.4 g/day with the exception of PFA (Table 13).

Table 13. Treatment Outcome at Weeks 3 and 6 (Patients with Moderate Disease at Baseline)

			2.4 g/day (400 mg Tablet) (N = 130)		4.8 g/day (800 mg Tablet) (N = 124)		p-value	*Difference	Confidence Interval (%)
Parameter	Visit	Outcome	n	(%)	n	(%)			
PGA	Week 3	I	70	(61.4)	82	(70.7)	0.1369	**9.29**	(-2.90, 21.47)
		NI	44	(38.6)	34	(29.3)			
		Total	114		116				
	Week 6	I	83	(73.5)	94	(83.2)	0.0758	**9.73**	(-0.94, 20.40)
		NI	30	(26.5)	19	(16.8)			
		Total	113		113				
Stool Frequency	Week 3	I	66	(60.6)	70	(63.6)	0.6379	**3.09**	(-9.76, 15.93)
		NI	43	(39.4)	40	(36.4)			
		Total	109		110				
	Week 6	I	77	(71.3)	77	(74.0)	0.6543	**2.74**	(-9.25, 14.73)
		NI	31	(28.7)	27	(26.0)			
		Total	108		104				
Rectal Bleeding	Week 3	I	65	(63.7)	82	(74.5)	0.0878	**10.82**	(-1.56, 23.20)
		NI	37	(36.3)	28	(25.5)			
		Total	102		110				
	Week 6	I	79	(77.5)	84	(78.5)	0.8542	**1.05**	(-10.19, 12.29)
		NI	23	(22.5)	23	(21.5)			
		Total	102		107				
PFA	Week 3	I	56	(58.9)	54	(56.8)	0.7689	-2.11	(-16.14, 11.93)
		NI	39	41.1	41	43.2			
		Total	95		95				
	Week 6	I	67	70.5	64	69.6	0.8859	-0.96	(-14.09, 12.17)
		NI	28	29.5	28	30.4			
		Total	95		92				
Sigmoidoscopy	Week 3	I	66	57.9	71	61.2	0.6088	**3.31**	(-9.37, 15.99)
		NI	48	42.1	45	38.8			
		Total	114		116				
	Week 6	I	78	69.0	85	75.2	0.2991	**6.19**	(-5.47, 17.86)
		NI	35	31.0	28	24.8			
		Total	113		113				

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.

Ref. Section5.3.5.1.1, EoT Table 8 * Difference in treatment success rate 4.8 g/day vs 2.4 g/day

- **Subgroup Analysis**

In general, prespecified analyses of subgroups showed a treatment effect favoring 4.8 g/day dosing over 2.4 g/day across the subgroups examined (Table 14). Of particular importance, in the subgroup analysis for extent of disease, the consistency across all extents of disease indicated that 4.8 g/day dosing provides increased efficacy benefit regardless of disease extent. Furthermore, the rate of treatment success is significantly higher with 4.8 g/day over 2.4 g/day for males and for patients with prior treatment with steroid or sulfasalazine.

Table 14. Treatment success at Week 6 by subgroup (Patients with Moderate Disease at Baseline)

	2.4 g/day (400 mg tablet) (N = 130)	4.8 g/day (800 mg tablet) (N = 124)	*Difference	95% C.I
Age Group				
18 to 64 years	71/117 (60.7%)	82/114 (71.9%)	**11%**	(-0.9%, 23.3%)
>=65 years	6/13 (46.2%)	7/10 (70.0%)	**24%**	(-15.4%, 63.1%)
Gender				
Male	29/ 58 (50%)	40/53 (76%)	**26%**	**(8.2%, 42.8%)**
Female	48/72 (67%)	49/71 (69%)	**2%**	(-13.0%, 17.7%)
Disease Extent				
Proctitis	12/20 (60%)	15/20 (75%)	**15%**	(-13.7%, 43.7%)
Proctosigmoiditis	27/45 (60%)	21/30 (70%)	**10%**	(-11.8%, 31.8%)
Left-sided colitis	24/40 (60%)	33/47 (70%)	**10%**	(-9.8%, 30.3%)
Pancolitis	14/25 (56%)	20/27 (74%)	**18%**	(-7.5%, 43.6%)
Length of disease history				
<1 year	30/51 (59%)	34/48 (71%)	**12%**	(-6.6%, 30.7%)
1 to 5 years	18/30 (60%)	20/29 (69%)	**9%**	(-15.3%, 33.3%)
>5 to 10 years	12/22 (55%)	17/24 (71%)	**16%**	(-11.4%, 43.9%)
>10 years	17/26 (65%)	18/23 (78%)	**13%**	(-12.0%, 37.8%)
Prior treatment				
Steroid	24/44 (55%)	30/36 (83%)	**28%**	**(9.7%, 47.9%)**
Sulfasalazine	30/50 (60%)	30/37 (81%)	**21%**	**(2.5%, 39.6%)**
Sulfa-free oral 5-ASA	29/54 (54%)	36/51 (71%)	**17%**	(-1.4%, 35.1%)
Rectal therapy	27/47 (57%)	36/46 (76%)	**19%**	(-1.2%, 37.4%)
Stool Frequency Score				
1	29/46 (63%)	27/40 (68%)	**5%**	(-15.7%, 24.6%)
2	33/49 (67%)	40/49 (82%)	**15%**	(-2.7%, 31.3%)
3	13/27 (48%)	17/22 (77%)	**29%**	(3.4%, 54.9%)
Rectal bleeding score				
1	22/23 (67%)	26/33 (79%)	**12%**	(-9.2%, 33.4%)
2	45/72 (63%)	52/76 (68%)	**5%**	(-9.4%, 21.2 %)
3	4/11 (36%)	5/8 (74%)	**27%**	(-17.8%, 70.1%)
PFA score				
1	44/69 (64%)	46/69 (67%)	**3%**	(-13.0%, 18.8%)
2	21/33 (64%)	24/30 (89%)	**16%**	(-5.4%, 38.1%)
3	3/5 (60%)	2/2 (100%)	**40%**	(-3.0%, 83.0%)
Sigmoidoscopy score				
1	11/14 (79%)	17/19 (90%)	**11%**	(-14.6%, 36.5%)
2	61/99 (62%)	64/92 (70%)	**8%**	(-5.5%, 21.4%)
3	5/17 (29%)	8/13 (62%)	**33%**	(-2.1%, 66.3%)

(Compiled by the Agency's statistical reviewer)
* Difference in treatment success rate 4.8 g/day vs 2.4 g/day

Results in Subjects with Mild to Moderate Disease at Baseline

Demographic and Baseline Disease Characteristics

The two treatment groups were comparable with respect to age, sex, height, weight and race (Table 15). The population was primarily Caucasian (76%), had a mean age of 42 years (< 10% were age 65 years or older), and included slightly more females (55% - 60%) than males (40% - 45%). The mean height and weight was about 169 cm and 78 kg, respectively.

Table 15. Baseline Demographic Characteristics (Patients with Mild to Moderate Disease at Baseline)

	2.4 g/day Asacol (400 mg tablet) (N = 195)	4.8 g/day Asacol (800 mg tablet) (N = 191)	p-value
Parameter	n (%)	n (%)	
Age (years)[a]	42.8 (1.00)	42.7 (0.94)	0.9643
18-64	178 (91.3)	175 (91.6)	
>= 65	17 (8.7)	16 (8.4)	
Sex			0.3391
Male	88 (45.1)	77 (40.3)	
Female	107 (54.9)	114 (59.7)	
Height (cm)[a]	169.0 (0.96)	168.6 (0.76)	0.7160
Weight (kg)[a]	78.9 (1.45)	78.7 (1.38)	0.9208
Race			0.4624
Caucasian	150 (76.9)	142 (74.3)	
Black	17 (8.7)	24 (12.6)	
Asian (Indian)	3 (1.5)	2 (1.0)	
Asian (Oriental)	1 (0.5)	4 (2.1)	
Hispanic	21 (10.8)	15 (7.9)	

[a]Data shown are mean (standard error).
Ref. Section 5.3.5.1.1, Appendix 5, Table 18

As shown in Table 16, there was no significant difference between treatments with respect to history of UC. The extent of disease ranged from proctitis to pancolitis and comparable number of patients presented with proctitis, procto-sigmoiditis, left-side colitis and pancolitis.

Table 16. Ulcerative colitis history (Patients with Mild to Moderate Disease at Baseline)

	2.4 g/day Asacol (400 mg tablet) (N = 195)	4.8 g/day Asacol (800 mg tablet) (N = 191)	p-value
Parameter	n (%)	n (%)	
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
< 1 year	75 (38.5%)	72 (37.7%)	
1 to 5 years	48 (24.6%)	41 (21.5%)	
>5 to 10 years	31 (15.9%)	36 (18.8%)	
> 10 years	38 (19.5%)	41 (21.5%)	
Unknown	3 (1.5%)	1 (0.5%)	

Ref. Section 5.3.5.1.1, Appendix 5.

The 2 treatment groups were also comparable in terms of baseline disease activity (Table17). At baseline, the majority of patients had moderate disease (PGA score = 2) and the majority reported increased daily stool frequency. Most patients had rectal bleeding at baseline (about 30% had streaks of blood less than half the time, and about 48% had obvious blood most of the time). In addition, these patients lacked signs of significant systemic toxicity at baseline; about 77% rated their PFA as generally well or fair. At baseline, about 60% of the patients had sigmoidoscopy results that were moderate.

Table 17. Baseline Disease Characteristics (Patients with Mild to Moderate Disease at Baseline)

Parameter	2.4 g/day Asacol (400 mg Tablet) (N = 195) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 191) n (%)	p-value
Physician's Global Assessment Score			0.3806
0 (Quiescent)	0 (0.0%)	0 (0.0%)	
1 (Mild Activity)	55 (28.2%)	62 (32.5%)	
2 (Moderate Activity)	139 (71.3%)	129 (67.5%)	
3 (Severe Activity)	0 (0.0%)	0 (0.0%)	
Stool Frequency Score			0.6554
0 (Normal Frequency)	17 (8.7%)	23 (12.0%)	
1 (1 to 2 greater than normal)	88 (45.1%)	80 (41.9%)	
2 (3 to 4 greater than normal)	59 (30.3%)	62 (32.5%)	
3 (>= 5 greater than normal)	30 (15.4%)	26 (13.6%)	
Rectal Bleeding Score			0.4819
0 (none)	37 (19.0%)	32 (16.8%)	
1 (Streak, less than 1/2 time)	62 (31.8%)	57 (29.8%)	
2 (Obvious, most of time)	81 (41.5%)	93 (48.7%)	
3 (Blood alone)	14 (7.2%)	9 (4.7%)	
Patient's Functional Assessment Score			0.7339
0 (Generally well)	43 (22.1%)	43 (22.5%)	
1 (Fair)	107 (54.9%)	108 (56.5%)	
2 (Poor)	39 (20.0%)	38 (19.9%)	
3 (Terrible)	5 (2.6%)	2 (1.0%)	
Sigmoidoscopy Score			0.0816
0 (Normal)	0 (0.0%)	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%)	
Number of days in Flare			0.7548
0 to 14	10 (5.1%)	7 (3.7%)	
15 to 28	24 (12.3%)	25 (13.1%)	
> 28	154 (79.0%)	156 (81.7%)	
Unknown	7 (3.6%)	3 (1.6%)	

Ref. Section 5.3.5.1.1, Appendix 5. Table 20

Efficacy Analyses in Patients with in Mild to Moderate Disease at Baseline

- **Primary Endpoint**

In the ITT analysis, the percentage of patients with mild to moderate disease whose treatment outcome at Week 6 was classified as treatment success was 59% in the 4.8 g/day group, compared to 54% in the 2.4 g/day group, a difference that was not statistically significant (p=0.2903) (Table 18).

Table 18. Treatment Outcome at Week 6 (Patients with Mild to Moderate Disease at Baseline)

	2.4 g/day (N = 182)		4.8 g/day (N = 182)	Difference In success rate	p-value	Confidence Interval (%)
Treatment Outcome	n	(%)	n (%)			
Treatment Success	98	(53.8)	108 (59.3)	5.49	0.2903	(-4.67, 15.66)
Treatment Failure	84	(46.2)	74 (40.7)			

Ref. Section 5.3.5.1.1, Appendix 5, Table 22

- **Secondary Endpoint**

By Week 3, the severity of the disease had improved in 45% of patients in 4.8 g/day group, compared to 42% in 2.4 g/day group, a difference that was not statistically significant (p=0.5257) Table 19.

Table 19. Treatment Outcome at Week 3 (Patients with Mild to Moderate Disease at Baseline)

Treatment Outcome	2.4 g/day Asacol (400 mg tablet) (N = 182) n (%)	4.8 g/day Asacol (800 mg tablet) (N = 182) n (%)	Difference	p-value	C.I (%)
Treatment Success	76 (41.8)	82 (45.1)	3.30	0.5257	(-6.88, 13.47)
Treatment Failure	106 (58.2)	100 (54.9)			

Ref. Section5.3.5.1.1, Appendix 5, Table 22

Results in a Subset of Patients with Mild Disease at Baseline

Demographic and Baseline Disease Characteristics

The two treatment groups were comparable with respect to age, sex, height, weight and race (Table 20). The population was primarily Caucasian (74%), had a mean age of 43 years (< 10% were age 65 years or older), and included slightly more females (53% - 63%) than males (37% - 47%).

Table 20. Baseline Demographic Characteristics (Patients with Mild Disease at Baseline)

	2.4 g/day Asacol (400 mg tablet) (N = 55)	4.8 g/day Asacol (800 mg tablet) (N = 62)	p-value
Parameter	n (%)	n (%)	
Age (years)[a]	43.7 (1.81)	44.2 (1.58)	0.8404
18-64	51 (92.7)	57 (91.9)	
≥ 65	4 (7.3)	5 (8.1)	
Sex			0.2655
Male	26 (47.3)	23 (37.1)	
Female	29 (52.7)	39 (62.9)	
Height (cm)[a]	166.6 (2.39)	170.1 (1.25)	0.1755
Weight (kg)[a]	78.0 (2.50)	82.0 (2.38)	0.2438
Race			0.5603
Caucasian	41 (74.5)	46 (74.2%)	
Black	6 (10.9)	10 (16.1%)	
Asian (Indian)	2 (3.6)	0 (0.0%)	
Asian (Oriental)	0 (0.0)	1 (1.6)	
Hispanic	5 (9.1)	4 (6.5)	

[a] Data shown are mean (standard error)

Ref. Section 5.3.5.1.1, Appendix 5, Table 30

As shown in Table 21, there were no significant differences between treatments with respect to history of UC. The extent of disease ranged from proctitis to pancolitis and comparable number of patients presented with procto-sigmoiditis and pancolitis, fewer patients presented with left-side colitis in the 2.4 g/day group and with proctitis in the 4.8 g/day group.

Table 21. Ulcerative Colitis History (Patients with Mild Disease at Baseline)

Parameter	2.4 g/day Asacol (400 mg tablet) (N = 55) n (%)	4.8 g/day Asacol (800 mg tablet) (N = 62) n (%)	p-value
Disease Extent			0.2451
Proctitis	18 (32.7%)	13 (21.0%)	
Proctosigmoiditis	13 (23.6%)	18 (29.0%)	
Left-sided colitis	10 (18.2%)	19 (30.6%)	
Pancolitis	14 (25.5%)	12 (19.4%)	
Length of Disease History			0.5500
< 1 year	21 (38.2%)	23 (37.1%)	
1 to 5 years	16 (29.1%)	12 (19.4%)	
> 5 to 10 years	8 (14.5%)	11 (17.7%)	
> 10 years	10 (18.2%)	16 (25.8%)	

Ref. Section 5.3.5.1.1, Appendix 5, Table 31

- **Analysis of Primary Endpoint by Subgroup with Mild Disease at Baseline**

Among subjects with mild disease at baseline, 4.8 g/day showed a relative decrease in efficacy compared to 2.4 g/day (Table 23). In the ITT analysis, the percentage of patients with mild disease at baseline whose treatment outcome at Week 6 was classified as treatment success was 40% with 2.4 g/day, compared to 33% with 4.8 g/day. While the difference was not statistically significant (p=0.4065), it was numerically higher in favor of 2.4 g/day.

Table 23. Treatment Outcome at Week 6 (Patients with Mild Disease at Baseline)

	2.4 g/day (400 mg tablet) (N = 52)		4.8 g/day (800 mg tablet) (N = 58)		p-value	*Difference in Success Rate	Confidence Interval (%)
Treatment Outcome	n	(%)	n	(%)			
Treatment Success	21	(40.4)	19	(32.8)	0.4065	-7.6	(-25.62, 10.37)
Treatment Failure	31	(59.6)	39	(67.2)			

* Difference in treatment success rate 4.8 g/day vs 2.4 g/day
Ref. Section 5.3.5.1.1, Appendix 5, Table 33

II. RESULTS FROM STUDY 83

Patient Disposition (Mild to Moderate Disease at Baseline)

Study 83 was initiated on February 9, 2001 and completed on November 19, 2002. A total of 301 patients (180 with moderate disease and 121 with mild disease) with mildly to moderately active UC were randomized to the treatment groups at 41 study sites in the U.S. and Canada: 154 to the 2.4 g/day group and 147 to the 4.8 g/day group. In the 2.4 g/day group, 133 (86.4%) patients completed the 6-week study, and in the 4.8 g/day group, 123 (83.7%) patients completed the 6-week study (Table 24).

Table 24. Patient Disposition (Patients with Mild to Moderate Disease at Baseline)

Category	2.4 g/day Asacol (400 mg Tablet) (N = 154)		4.8 g/day Asacol (800 mg Tablet) (N = 147)		Total (N = 301)	
	n	(%)	n	(%)	n	(%)
Completed study	133	(86.4)	123	(83.7)	256	(85.0)
Did not complete study						
Protocol deviation	1	(0.6)	4	(2.7)	5	(1.7)
Adverse event	8	(5.2)	5	(3.4)	13	(4.3)
Voluntary withdrawal without adverse event	2	(1.3)	6	(4.1)	8	(2.7)
Investigator recommendation	2	(1.3)	2	(1.4)	4	(1.3)
Lack of treatment effect	8	(5.2)	7	(4.8)	15	(5.0)

Ref. Section 5.3.5.1.2, Table 2

Protocol Deviations

The distribution and type of protocol violation were comparable between treatments with the exception of use of excluded concomitant medications: more patients in 2.4 g/day group received an excluded concomitant medication than those in 4.8 g/day group (13 vs 7) Table 25. The most common excluded concomitant medications reported were those used for gastrointestinal conditions and NSAIDs. The most common deviations of protocol entry criteria were patients receiving excluded pre-study medications, positive stool examinations, and pregnancy tests not being performed. The most common other deviation was visits that occurred outside the protocol-specified window. One patient (#20393610) in the 4.8 g/day group experienced an ectopic pregnancy that resulted in her withdrawal from the study. The patient narrative is described under section 7.1.13 of this review.

Table 25. Protocol Deviations (Patients with Mild to Moderate Disease at Baseline)

	2.4 g/day (400 mg Tablet) (N = 154)		4.8 g/day (800 mg Tablet) (N = 147)	
Deviation	n	(%)	n	(%)
Violated entry criteria	16	(10.4%)	17	(11.6%)
Received wrong treatment or incorrect dose	1	(0.6%)	0	(0.0%)
Received an excluded concomitant medication	13	(8.4%)	7	(4.8%)
Other deviations	8	(5.2%)	10	(6.8%)

Ref. Section 5.3.5.1.2, Table 3

Compliance with Dosing Regimen

One hundred forty (91%) patients in the 2.4 g/day group were at least 85% compliant and 130 (88%) patients in the 4.8 g/day group were at least 85% compliant according to the definition in the protocol.

Demographic and Baseline Disease Characteristics (Mild to Moderate Disease)

The 2 treatment groups were comparable with respect to baseline demographic characteristics (Table 26). The population was primarily Caucasian (79%), had a mean age of 44 years (<10% were age 65 years or older), and included similar number of males and female.

Table 26. Demographic characteristics (Patients with Mild to Moderate Disease at Baseline)

Characteristics	2.4 g/day (400 mg Tablet) (n=154)	4.8 g/day (800 mg Tablet) (n=147)	p-value (Chi-square test)
Age (years)[a]	43.5 (1.10)	45.9 (1.10)	0.1237
18 to 64	141 (91.6%)	133 (90.5%)	
≥ 65	13 (8.4%)	14 (9.5%)	
Height (cm)[a]	170.4 (0.82)	170.8 (0.87)	0.7051
Weight (kg)[a]	77.6 (1.31)	79.2 (1.40)	0.4054
Race			0.9873
Caucasian	122 (79.2%)	116 (78.9%)	
Black	18 (11.7%)	18 (12.2%)	
Asian (Indian)	2 (1.3%)	2 (1.4%)	
Asian (Oriental)	1 (0.6%)	0 (0.0%)	
Hispanic	10 (6.5%)	9 (6.1%)	
Sex			0.3209
Male	75 (48.7%)	80 (54.4%)	
Female	79 (51.3%)	67 (45.6%)	
Smoking History			0.4822
Never smoked	78 (50.6%)	69 (46.9%)	
Used to smoke	66 (42.8)	63 (42.8)	
Currently smoking	10 (6.4)	15 (10.2)	

[a] Data shown are mean (standard error).

Ref. Section 5.3.5.1.2, Table 5

The 2 treatment groups were comparable in terms of history of ulcerative colitis (Table 27). Similar numbers of patients presented with procto-sigmoiditis, left sided colitis, panclolitis and proctitis. Approximately one-third were newly diagnosed, one-third had been previously treated with steroid and more than one-half had been treated previously with some type of 5-ASA.

Table 27. Ulcerative colitis history (Patients with Mild to Moderate Disease at Baseline)

	2.4 g/day (400 mg Tablet) (n= 154)		4.8 g/day (800 mg Tablet) (n= 147)		p-value
Ulcerative Colitis History	n	(%)	n	(%)	
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
< 1 year	62	(40.3%)	50	(34.0%)	
1 to 5 years	25	(16.2%)	40	(27.2%)	
> 5 to 10 years	28	(18.2%)	23	(15.6%)	
> 10 years	38	(24.7%)	33	(22.4%)	
Unknown	1	(0.6%)	1	(0.7%)	
Prior Treatment					
Steroids (oral or IV)	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
Yes	8	(14.0%)	8	(18.6%)	
No	49	(86.0%)	35	(81.4%)	
Total	57		43		
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%)	

Ref. Section 5.3.5.1.2, Table 6

As summarized in Table the 28, treatment groups were comparable with respect to baseline disease activity except for stool frequency scores. At baseline, more than one-half had moderate disease (PGA score of 2) and the majority of patients reported increased daily stool frequency. Most patients had rectal bleeding at baseline (more than one-third had streaks of blood less than half the time, and one-third had obvious blood most of the time). In addition, these patients lacked signs of significant systemic toxicity at baseline; about 77% rated their PFA as generally well or fair. At baseline, about one-third of these patients had sigmoidoscopy results that were mild, and more than one-half had sigmoidoscopy results that were moderate.

Table 28. Baseline Disease State (Patients with Mild to Moderate Disease at Baseline)

	2.4 g/day (400 mg Tablet) (n= 154)		4.8 g/day (800 mg Tablet) (n= 147)		p-value
Disease State Characteristic	n	(%)	n	(%)	
Physician's Global Assessment Score (**PGA**)					0.3582
0 (Quiescent)	0	(0.0)	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	(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 1/2 time)	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 (**PFA**)					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)	
Sigmoidoscopy Score					0.9415
0 (Normal)	0	(0.0)	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)	

[a] Data are presented as mean (standard deviation)

Ref. Section 5.3.5.1.2, Table 7

Efficacy Analysis

- **Primary Endpoint**

In the ITT population with mild to moderate disease, the percentage of patients whose treatment outcome at Week 6 was classified as treatment success was 56% in the 4.8 g/day group, compared to 51% in the 2.4 g/day group, a difference that was not statistically significant (p=0.44) (Table 29).

Table 29. Treatment outcome at Week 6 (Patients with Moderate to Mild Disease at Baseline)

	2.4 g/day (n=150)	4.8 g/day (n=136)	p-value
Treatment outcome	n (%)	n (%)	
Treatment success	77 (51.3)	76 (55.5)	0.441
Treatment failure	73 (48.7)	60 (44.1)	

Ref. Section 5.3.5.1.1, Table 8

- **Sensitivity Analysis**

A total of 15 patients (4 in the 2.4 g/day group and 11 in the 4.8 g/day group) were excluded from the primary ITT analyses, because Week 6 treatment outcome could not be determined. The sensitivity analysis where missing observations were set to treatment failure showed similar results (50% vs. 51%; p=0.768) Table 30.

Table 30. Treatment outcome at Week 6: missing observations set to treatment failure (Patients with Mild to Moderate Disease at Baseline)

	2.4 g/day (n=154)	4.8 g/day (n=147)	p-value
Treatment outcome	n (%)	n (%)	
Treatment success	77 (50.0)	76 (51.7)	0.7680
Treatment failure	77 (50.0)	71 48.3)	

Ref. Section 5.3.5.1. EoT Table 3

- **Secondary Endpoints**

By Week 3, the disease severity had improved from baseline in 42% of the patients in the 2.4 g/day group, compared to 39 % in the 4.8 g/day group (p=0.567) Table 31.

Table 31. Treatment outcome at Week 3 (Patients with Mild to Moderate Disease at Baseline)

	2.4 g/day (400 mg Tablet) (n=150)	4.8 g/day (800 mg Tablet) (n=136)	p-value
Treatment outcome	n (%)	n (%)	
Treatment success	63 (42.0%)	53 (38.7)	0.5677
Treatment failure	87 (58.0)	84 (61.3)	

Ref. Section 5.3.5.1.2, Table 9.

For other secondary efficacy variables (stool frequency, rectal bleeding, PFA, PGA, and sigmoidoscopy) analyzed, the proportion of patients with successful treatment outcome at Week 3 and Week 6 was comparable between treatments (Table 32).

Table 32 Treatment outcome at Weeks 3 and 6 (Patients with Mild to Moderate disease)

Parameter			2.4 g/day (400 mg Tablet) (n= 154)		4.8 g/day (800 mg Tablet) (n = 147)		p-value
	Visit	Outcome	n	(%)	n	(%)	
PGA	Week 3	I	66	(49.3)	56	(44.8)	
		NI	68	(50.7)	69	(55.2)	
		Total	134		125		0.4730
	Week 6	I	81	(61.4)	79	(64.8)	
		NI	51	(38.6)	43	(35.2)	
		Total	132		122		0.5761
Stool Frequency	Week 3	I	63	(46.7)	69	(54.3)	
		NI	72	(53.3)	58	(45.7)	
		Total	135		127		0.2150
	Week 6	I	84	(63.2)	82	(66.7)	
		NI	49	(36.8)	41	(33.3)	
		Total	133		123		0.5569
Rectal Bleeding	Week 3	I	65	(48.1)	75	(59.1)	
		NI	70	(51.9)	52	(40.9)	
		Total	135		127		0.0769
	Week 6	I	80	(60.2)	88	(71.5)	
		NI	53	(39.8)	35	(28.5)	
		Total					
PFA	Week 3	I	57	(42.2)	63	(49.6)	
		NI	78	(57.8)	64	(50.4)	
		Total	135		127		0.2306
	Week 6	I	72	(54.1)	74	(60.7)	
		NI	61	(45.9)	48	(39.3)	
		Total	133		122		0.2931
Sigmoidoscopy	Week 3	I	69	(51.5)	65	(52.0)	
		NI	65	(48.5)	60	(48.0)	
		Total	134		125		0.9349
	Week 6	I	88	(66.7)	90	(73.2)	
		NI	44	(33.3)	33	(26.8)	

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.

Ref. Section 5. 3.5.1.2, Tables 9 and 10

- **Subgroups Analyses**

In a pre-specified analysis of a subgroup with moderate disease at baseline, 4.8 g/day dosing provided superior efficacy over 2.4 g/day dosing (Table 33). In the applicant's ITT population with moderate disease, the percentage of patients whose outcome at Week 6 was classified as treatment success was 72% with 4.8 g/day, compared to 57% with 2.4 g/day, a difference that was statistically significant in favor of 4.8 g/day (p=0.0348). However, in this analysis, 11 patients (3 in the 2.4 g/day and 8 in the 4.8 g/day) were excluded, because Week 6 treatment outcome could not be determined. In the subsequent sensitivity analysis where missing observations were set to treatment failure, 4.8 g/day was no longer superior to 2.4 g/day (65.5% vs 55.2%; p=0.1607) (Table 34).

Table 33. Treatment Outcome at Week 6 (Patients with Moderate Disease at Baseline)

	2.4 g/day Asacol (400 mg Tablet) (n=93)	4.8 g/day Asacol (800 mg Tablet) (n=76)	Difference in success rate	p-value
Treatment outcome	n (%)	n (%)		
Treatment success	53 (57.0%)	55 (72.4%)	15.4	0.0348
Treatment failure	40 (43.0)	21 (27.6)		

Ref. Section 5. 3.5.1.2, Table 11

Table 34. Treatment Outcome at Week 6: missing observations set to treatment failure (Patients with Moderate Disease at Baseline)

	2.4 g/day Asacol (400 mg Tablet) (n=96)	4.8 g/day Asacol (800 mg Tablet) (n=84)	Difference	p-value
Treatment outcome	n (%)	n (%)		
Treatment Success	53 (55.2)	55 (65.5)	10.3	0.1607
Treatment Failure	43(44.8)	29 (34.5)		

- **Analyses of Other Subgroups**

Subgroup analyses (age, gender, disease extent, length of disease history, prior treatment and baseline disease activity) were also performed in patients with moderate. In these analyses, the missing outcomes were set to treatment failure. As shown in Table 35, most subgroup variables showed treatment effect favoring 4.8 g/day over 2.4 g/day. While the treatment differences were statistically significant in favor of 4.8 g/day for male subjects, stool frequency score of 2 and a PFA score of 2.

Table 35. Treatment Success at Week 6 by Subgroup (Patients with Moderate Disease at baseline)

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				
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				
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%)
PFA score				
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 the Agency's statistical Reviewer)

- **Secondary Endpoints in a Subgroup with Moderate Disease at Baseline**

By Week 3, the disease severity had improved from baseline in 62% of the patients with 4.8 g/day, compared to 53% with 2.4 g/day (Table 36), while the treatment difference was not statistically significant, the trend favors 4.8 g/day dosing.

Table 36. Treatment outcome at Week 3 (Patients with Moderate Disease at Baseline)

	2.4 g/day (400 mg Tablet) (N = 93)	4.8 g/day (800 mg Tablet) (N = 76)	p-value	Difference in Success Rates	Confidence Interval
Treatment Outcome	n (%)	n (%)			
Treatment Success	50 (53.8%)	46 (62.2%)	0.2769	8.4	(-6.6, 23.4)
Treatment Failure	43 (46.2%)	28 (37.8%)			
Patients not analyzable at Week 6 or at Week 3 were excluded from this analysis.					

Ref. Section 2.7.3, Appendix 5, E-Table 3

At Weeks 3 and 6, all individual clinical assessment scores except PFA directionally favored 4.8 g/day dosing over 2.4 g/day dosing in patients with moderate disease, although the differences were not statistically significant (Table 37).

Table 37. Treatment outcomes at Weeks 3 and 6 (Subgroup with Moderate Disease at Baseline)

			2.4 g/day (n=96)		4.8 g/day (n=84)		p-value	**Difference**
Parameter	Visit	Outcome	n	(%)	n	(%)		
PGA	Week 3	**I**	53	(67.1)	49	(73.1)	0.4276	**6**
		NI	26	(32.9)	18	(26.9)		
		Total	79		67			
	Week 6	**I**	56	(72.7)	58	(87.9)	0.0247	**15.2**
		NI	21	(27.3)	8	(12.1)		
		Total	77		66			
Stool Frequency	Week 3	**I**	42	(53.2)	43	(62.3)	0.2612	**9.1**
		NI	37	(46.8)	26	(37.7)		
		Total	79		69			
	Week 6	**I**	50	(64.1)	50	(74.6)	0.1720	**10.5**
		NI	28	(35.9)	17	(25.4)		
		Total	78		67			
Rectal Bleeding	Week 3	**I**	45	(57.0)	47	(68.1)	0.1628	**11.1**
		NI	34	(43.0)	22	(31.9)		
		Total	79		69			
	Week 6	**I**	51	(65.4)	53	(79.1)	0.0674	**13.7**
		NI	27	(34.6)	14	(20.9)		
		Total	78		67			
PFA	Week 3	**I**	44	(55.7)	38	(55.1)	0.9393	-0.6
		NI	35	(44.3)	31	(44.9)		
		Total	79		69			
	Week 6	**I**	47	(60.3)	44	(66.7)	0.4268	**6.4**
		NI	31	(39.7)	22	(33.3)		
		Total	78		66			
Sigmoidoscopy	Week 3	**I**	45	(57.0)	40	(59.7)	0.7380	**2.7**
		NI	34	(43.0)	27	(40.3)		
		Total	79		67			
	Week 6	**I**	51	(66.2)	56	(83.6)	0.0175	**17.4**
		NI	26	(33.8)	11	(16.4)		
		Total	77		67			

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.

Ref. Section 5. 3.5.1.2, Appendix 5, Table 64

- Analysis of Primary Endpoint in a Subgroup with Mild Disease at Baseline

Among subjects with mild disease at baseline, 4.8 g/day showed a relatively inferior efficacy results compared to 2.4 g/day. In the ITT analysis, the percentage of patients with mild disease at baseline, whose treatment outcome at Week 6 was classified as treatment success was 42% with 2.4 g/day, compared to 35% with 4.8 g/day. While the difference was not statistically significant (p=0.4298), it was numerically higher in favor of 2.4 g/day (Table38).

Table 38. Treatment Outcome at Week 6 (Patients with Mild Disease at Baseline)

	2.4 g/day Asacol (400 mg Tablet) (n = 57)		4.8 g/day Asacol (800 mg Tablet) (n = 60)		*Difference In success arte	p-value
Treatment Outcome	n	(%)	n	(%)		
Treatment Success	24	(42.1)	21	(35.0)	-7	0.4298
Treatment Failure	33	(57.9)	39	(65.0)		

Ref. Section 5. 3.5.1.2, EoT Table 8.
* Difference in treatment success rate 4.8 g/day vs 2.4 g/day

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

Efficacy data are generated from two, double-blind, randomized and active-controlled phase III multi-center clinical studies (Study 82 and Study 83) of 6 weeks duration. Both studies were originally designed to compare Asacol 4.8 g/day, administered as the newly formulated 800 mg tablet to 2.4 g/day, administered as the currently approved 400 mg tablet in subjects with mild to moderate disease at baseline.

It is worth reiterating that in this clinical program, the determination of disease severity and definition of treatment success were based on the Physician's Global Assessment (PGA), which took into consideration clinical assessments of rectal bleeding, stool frequency, patient's functional assessment (PFA) and sigmoidoscopic examination. The reader may refer to Appendix 10.3 of this review for information on PGA scores used in this clinical program.

Reviewer's comment: measurement of disease activity is critical in determining whether new therapies are effective in patients with IBD. However, unlike Crohn's disease, there is no gold standard for measuring disease activity in UC. In Crohn's disease, standard definitions for clinical improvement and clinical remission on standard indices have come into common use, allowing useful comparisons across trials. This has not been the case for UC where no single disease activity index is universally accepted and no generally accepted definition of improvement or remission exist (Higgins PDR et al, Gut 2005).

Efficacy Results

- Study 83

This study failed to demonstrate superiority of 4.8 g/day over 2.4 g/day in ITT patients with mildly to moderately active UC (56%, 76/136 vs 51%, 77/150; p=0.44).

In the prespecified subgroup analysis of patients with moderate disease at baseline, 4.8 g/day showed a superior efficacy over 2.4 g/day. In the applicant's ITT analysis, the primary endpoint, the percentage of patients whose treatment outcome at Week 6 was classified as treatment success was 72% (55/76) in 4.8 g/day group, compared to 57% (53/93) in 2.4 g/day group. A difference that was a statistically significant in favor of 4.8 g/day (p=0. 038). It should be pointed out that the p-value presented here is without adjustment for multiple subgroups analyzed. In addition, more patients in the 4.8 g/day group than in the 2.4 g/day group (8 vs 3) were excluded in the applicant's analysis, because treatment outcome at Week 6 could not be determined. In fact, when 11 patients were included in the analysis as treatment failure, 4.8 g/day was no longer superior to 2.4 g/day (65%, 55/84 vs 55%, 53/96; p=0.1607).

It is worth noting that in the subgroup with moderate disease at baseline, male subjects tend to respond better with 4.8 g/day than with 2.4 g/day (73%, 29/40 vs 48%, 21/44), but the response rate was similar between treatments for females with moderate disease at baseline (59%, 26/44 vs 62%, 32/52).

For the subgroup with mildly active UC at baseline, the response rate with 4.8 g/day was numerically inferior (-7%) compared to 2.4 g/day (35%, 21/60 vs 42%, 24/57).

- Study 82

Based on the results seen from Study 83, the protocol to Study 82 was amended when 96% of the planned enrollment had been completed. Under the amended protocol, the primary efficacy population was changed from a population with mildly to moderately active UC to a population with only moderately active UC . Under amended protocol, up to100 additional patients with moderate disease were to be enrolled. Eighty-two patients with moderate disease at baseline were enrolled after the amendment. b(4)

Similar to the results in Study 83, Study 82 failed to demonstrate a statistically significant difference in the rate of treatment success between 4.8 g/day and 2.4 g/day (59% and 54%, respectively; p=0.29) among subjects with mild to moderate disease at baseline.

For patients with moderate disease at baseline, treatment success was achieved in 72% (89/124) of patients receiving 4.8 g/day, compared to 59% (77/130) receiving 2.4 g/day, a difference that was a statically significant (p = 0.036) in favor of 4.8 g/day. In this analysis, 14 ITT patients were excluded (9 in 2.4 g/day group, and 5 in 4.8 g/day group), because treatment outcome at Week 6 could not be determined. Nonetheless, the superiority of 4.8 g/day still holds true when 14 patients were included in the analysis as treatment failure

(69%, 89/129 vs 55%, 77/139; p=0.022). It is worth noting that despite the relatively higher representation of females (57%) in the study, the data indicated that male subjects with moderate disease at baseline showed a significant improvement with 4.8 g/day than with 2.4 g/day (76%, 40/53 vs 50%, 29/58; 95% CI: 8.2%, 42.8%). By contrast, the response rate was similar between the higher and lower dose for females with moderate disease at baseline (69%, 49/71 and 67%, 48/72, respectively).

The Agency statistical reviewer's post hoc analysis involving pre- vs post-amendment enrollees with moderate disease revealed inconsistent results: among pre-amendment enrollees, treatment success was achieved in 70% (58/83) of patients with 4.8 g/day, compared to 55% (52/95) with 2.4 g/day, a difference that was a statistically significant (p=0.04) in favor of 4.8 g/day. By contrast, among post-amendment enrollees, the response rate between 4.8 g/day and 2.4 g/day was similar (76%, 31/41 and 71%, 25/35, respectively [p=0.68]).

The reasons for such variability in the aforementioned outcomes are unclear to the medical reviewer. It is possible that this is due to the lack of a gold standard for measuring disease severity in UC. Consequently, it is difficult to assure homogeneity of a study population in a clinical trial, which may hamper an appropriate interpretation of the clinical data. It is also possible that the post-amendment analysis is underpowered due to the small sample size (76 in pre-amendment vs 178 in post-amendment) to detect a meaningful treatment difference.

However, in the medical reviewer's opinion, a consideration for evidence of effectiveness should be based on the analysis of all randomized patients. The result from all subjects (pre- and post-amendment enrollees) with moderate disease indicates a significant improvement with 4.8 g/day over 2.4 g/day. Further, I concur with the Statistical Team Leader's (DR. Stella Grosser) conclusion that the fact that the change that was made so close to the end of the study and fewer than 100 addition patients were enrolled, with no justification for that number, reflects poor planning, but the change is not post hoc as the study was blinded. Therefore, the medical reviewer does not see the rationale for adjusting the p-value presented in this study as indicated by the primary statistical reviewer (Dr. Fan Milton).

For the subgroup with mildly active UC, the response rate was numerically inferior (-7%) with 4.8 g/day dosing compared to 2.4 g/day dosing (33%, 19/58 vs 40%, 21/52; p=0.41), which is consistent with that in Study 83.

It is of interest to note the discrepancy in dose response effect between the population with moderate disease vs mild disease (a higher dose was more effective in moderate disease, while it was less effective in mild disease). Typically, a higher dose would be expected to exhibit similar if not better response rates in subjects with less severe (mild) disease when compared to those with more severe (moderate) disease. This apparent inconsistency has not been addressed by the applicant. Nonetheless, in the data presented, there was no obvious or identifiable factor/s that could explain the lack of dose response effect in subjects with mild disease. Demographic characteristics, baseline disease state, duration or extent of disease did not appear to have an influence on therapeutic activity, because they were comparable

between the two populations. Review of published data did not provide useful information for various reasons: most studies involve non-selected patients (i.e. mild to moderate disease); there is heterogeneity in the choice of outcome measures and use of disease activity index. The use of various mesalamine formulations also makes comparisons across studies difficult. A recent dose-finding European study found no significant dose response effect in subjects with mild to moderate disease (non-selected subjects) at doses of 1.5 g, 3 g, or 4.5 g daily, regardless of severity of the disease (Kruis W et al. Clin Gastroenterol Hepatol 2003). However, in contrast to the results seen in the current submission, a subgroup analysis in the aforementioned study revealed that subjects with less severe (mild) disease had numerically better response rates at all dose levels compared to those with more severe (moderate) disease.

b(4)

It is also of interest to note that in Study 82, 2.4 g/day is associated with a decreased efficacy benefit in patients with mild disease at baseline compared to patients with moderate disease at baseline (40%, 21/52 vs 59%, 77/130). Similar results were observed in Study 83 (42%, 24/57 vs 57%, 53/93). However, in both studies there is an imbalance in sample size between the groups (more patients with moderate disease). Although definitive conclusions can not be drawn from the aforementioned observation, it does, however, raise an important question as to whether Asacol is effective in the treatment of mildly active UC. Because in both Asacol dose levels (2.4 g/day and 4.8 g/day) tested in this clinical program, the response rate in a population with mild disease was well below the response rate in a population with moderate disease (40% - 42% vs 57% - 59%).

Across both studies multiple comparisons of secondary endpoints in subjects with moderate disease did not reveal statistically significant differences between treatments, although trends in favor of 4.8 g/day were seen for most variables analyzed.

- Overall Efficacy Conclusions

After a careful consideration of the Agency statistical reviewers' arguments, particularly regarding Study 83, I concluded that there is insufficient evidence of efficacy to support the proposed indication i.e. treatment of moderately active UC.

For subjects with moderate disease at baseline, Study 83 did not provide sufficient evidence of effectiveness, not only because the data were driven from the subgroup analysis without adjustment for multiplicity, but also because of a potential bias in favor of 4.8 g/day. More patients from the 4.8 g/day group were excluded from the applicant's analysis (p=0.0738), because treatment outcome at Wee6 could not e determined. In fact, in the sensitivity analysis where missing observations were set to treatment failure, 4.8 g/day was no longer superior to 2.4 g/day. On the other hand, the efficacy data from Study 82 indicated a significant improvement with 4.8 g/day over 2.4 g/day (p=0.022) in all randomized patients with moderate disease. However, Study 82 is not robust enough to stand alone as a single study (p> 0.001) to support the proposed indication for the treatment of moderate disease. Further, the increased efficacy benefit with 4.8 g/day over 2.4 g/day was seen in male subjects, but not in female subjects with moderate disease.

From the regulatory standpoint, the reviewer concluded that a single clinical study finding of efficacy, unsupported by independent study is not adequate for a conclusion of a substantial evidence of effectiveness. To support the proposed indication, an additional adequate and well-controlled clinical study is required to confirm the findings from Study 82. The applicant should adequately address the inconsistency in the efficacy benefit in important subgroups of patients with moderate disease, namely, males versus females.

Across both studies, 4.8 g/day was associated with a relative decrease in efficacy when compared to 2.4 g/day in subjects with mild disease at baseline. Thus, Asacol 800 mg tablets at a dose of 4.8 g/day are not indicated for the treatment of patients with mild disease at baseline.

7 INTEGRATED REVIEW OF SAFETY

The two active-controlled clinical trials submitted under current application established an acceptable safety profile for Asacol (800 mg tablet) 4.8 g/day for six weeks in adult subjects with mildly to moderately active UC as well as in the primary efficacy population (subjects with moderate disease). Overall, the safety profile for Asacol (800 mg tablet) 4.8 g/day was comparable to that of Asacol (400 mg tablet) 2.4 g/day. However, the incidence of nauseas and vomiting was 2 to 3 times higher with 4.8g/day compared to 2.4 g/day. Particularly, in female subjects the incidence of nausea (6% vs 1.6%) and vomiting (2.2% vs 0.5%) was 3 to 4 times higher with 4.8 g/day vs 2.4 g/day.

Asacol 800 mg tablets are not currently approved for marketing in any country; thus, there is no information with respect to the post-marketing use of this formulation at any dose. However, safety profile regarding long-term use of 4.8 g/day, using the Asacol 400 mg tablets has been previously reviewed under NDA 19-651/S005 and is described in the current Asacol label.

The Integrated Summary of Safety submitted to NDA 19-651/S005 included safety data from 14 clinical studies conducted with Asacol (400 mg tablet) for varying indications. Of these 14 studies, the majority of patient exposure to doses of 4.8 g/day or greater occurred in 3 studies: C3 (6-week placebo-controlled study), and C12 and C13 (long-term, open-label, compassionate use studies). In these compassionate use studies, the Asacol dose was permitted to vary over time, at the Investigator's discretion, based on the individual patient's response. Maximum recorded daily doses during the studies were 6.4 g/day in Study C12, and 7.2 g/day in Study C13. According to the data submitted by the applicant in response to the Agency's information request (amendment # 14, dated July 11, 2005) a total of 903 patients were exposed to an average daily dose of 4.8 g/day or higher and approximately 405 patients were exposed for > 6 month, while 247 of them were exposed for > 1 year.

The aforementioned exposure information complements the exposure from current application, in which 338 patients were randomized to receive Asacol (800 mg tablet) 4.8 g/day for six weeks for treatment of active UC.

7.1 Methods and Findings

The population for which safety data are available for the Asacol 800 mg formulation is comprised of 338 patients with mildly to moderately active UC in two Phase III, double-blind, randomized, multicenter studies (Study 82 and Study 83) submitted under current application.

Of the total of 687 subjects enrolled in the two studies, 349 patients were randomized to receive Asacol 2.4 g/day (400 mg tablet) and 338 patients were randomized to receive 4.8 g/day (800 mg tablet) for 6 weeks. In the primary efficacy population (patients with moderate disease [n = 448]), 235 patients received 2.4 g/day (400 mg tablet) and 213 patients received 4.8 g/day (800 mg tablet). For all randomized patients, 85 % of patients completed the 6-week study and 25% did not (S-Table 1). The distribution of patients who did or did not complete the study was comparable between treatments with the exception of patients who did not complete the study due to lack treatment effect: more patients in 2.4 g/day did not complete the study due to lack of treatment effect (19 patients vs 12 patients).

In addition to UC patients in Studies 82 and 83, 54 healthy subjects were exposed to the 800 mg tablet during formulation development in three studies: Studies 2000027 (20 subjects exposed to a single 800 mg dose), 2001025 (16 subjects exposed to 7 days of 2 x 800 mg [1.6 g] three times daily [4.8 g/day]), and 2001095 (18 subjects exposed to 2 single 800 mg doses in a crossover fashion, fed and fasted) (S-Table 11). Safety data (adverse events, vital signs, and clinical laboratory evaluations) from these studies in healthy subjects did not suggest any new concerns with respect to the safety profile of Asacol 4.8 g/day (800 mg tablet) compared to the current product label for Asacol 2.4 g/day (400 mg tablet).

S-Table 1. Patient Disposition Pooled Data Studies 82 and 83 (All Randomized Patients)

Category	2.4 g/day Asacol (400 mg Tablet) (N = 349)	4.8 g/day Asacol (800 mg Tablet) (N = 338)	Total (N = 687)
	n (%)	n (%)	n (%)
Completed study	295 (84.5%)	291 (86.1%)	586 (85.3%)
Did not complete study:			
Protocol violation	3 (0.9%)	5 (1.5%)	8 (1.2%)
Adverse event	16 (4.6%)	13 (3.8%)	29 (4.2%)
Voluntary withdrawal without AEs	11 (3.2%)	13 (3.8%)	24 (3.5%)
Investigator recommendation	5 (1.4%)	4 (1.2%)	9 (1.3%)
Lack of treatment Effect	19 (5.4%)	12 (3.6%)	31 (4.5%)

Ref. Section 2.7.4, S-Table 1

Analysis of Adverse Events by Organ System

Of the total of 687 randomized patients in both studies, 38% (261/687) reported a total of 520 AEs: 37.8 % (132/349) reported 278 AEs in the 2.4 g/day group, and 38% (129/338) reported 242 AEs in the 4.8 g/day group (S-Table 2). In all populations studied the Body as a Whole and the Digestive System comprise the most frequently reported COSTART body systems.

For all randomized patients in the 4.8 g/day group, 66% (159/242) reports involved these two body systems; the remaining 34% (83/242) reports were distributed among 9 other body systems.

Of the 159 reports in the 4.8 g/day group involving the Body as a Whole and Digestive systems, 149 (96%) involved events described in the current Asacol label. The 10 unlisted reports included accidental injury (3 reports), allergic reaction (2 reports), and cellulitis, neoplasm, hernia, periodontal abscess, and thirst (1 report each). In the 9 other reported body systems, 69% (57/83) reports in the 4.8 g/day group involved events described in the current Asacol label. In these other body systems, the 26 unlisted reports were primarily single patient reports. Only two of these unlisted events (hypesthesia and vaginitis) were reported by two patients each in the 4.8 g/day group.

S-Table 2.
Frequency of AEs by Body System, Pooled data for Studies 82 and 83
(All Randomized Patients)

Body System COSTART Term	2.4 g/day (400 mg Tablet) (N = 349)		4.8 g/day (800 mg Tablet) (N = 338)	
	n (%)	nAE	n (%)	nAE
OVERALL	**132 (37.8%)**	**278**	**129 (38.2%)**	**242**
Body as a Whole				
ALLERG REACT	1 (0.3%)	1	2 (0.6%)	2
ASTHENIA	4 (1.1%)	5	5 (1.5%)	5
CELLULITIS	1 (0.3%)	1	1 (0.3%)	1
CHILLS	0 (0.0%)	0	1 (0.3%)	1
FEVER	5 (1.4%)	5	5 (1.5%)	5
FLU SYND	10 (2.9%)	10	4 (1.2%)	4
HEADACHE	24 (6.9%)	28	24 (7.1%)	26
HERNIA	0 (0.0%)	0	1 (0.3%)	1
INFECT	5 (1.4%)	6	5 (1.5%)	5
INFECT VIRAL	1 (0.3%)	1	0 (0.0%)	0
INJURY ACCID	3 (0.9%)	3	3 (0.9%)	3
NEOPL	1 (0.3%)	1	1 (0.3%)	1
PAIN	4 (1.1%)	4	2 (0.6%)	2
PAIN ABDO	18 (5.2%)	19	11 (3.3%)	11
PAIN BACK	5 (1.4%)	5	3 (0.9%)	3
PAIN CHEST	2 (0.6%)	2	3 (0.9%)	3
PAIN FLANK	1 (0.3%)	2	0 (0.0%)	0
PAIN NECK	2 (0.6%)	2	3 (0.9%)	3
Cardiovascular System				
ARTERIOSCLEROSIS	1 (0.3%)	2	0 (0.0%)	0
HYPERTENS	1 (0.3%)	1	1 (0.3%)	1
MIGRAINE	1 (0.3%)	1	0 (0.0%)	0
PALPITAT	0 (0.0%)	0	1 (0.3%)	1
PERICARDITIS	0 (0.0%)	0	1 (0.3%)	1
TACHYCARDIA	0 (0.0%)	0	1 (0.3%)	1
VASODILAT	1 (0.3%)	1	0 (0.0%)	0
Digestive System				
ABSCESS PERIODONT	1 (0.3%)	1	1 (0.3%)	1
ANOREXIA	0 (0.0%)	0	1 (0.3%)	1
CHOLECYST	2 (0.6%)	2	0 (0.0%)	0
COLITIS ULCER	9 (2.6%)	9	7 (2.1%)	7
CONSTIP	3 (0.9%)	3	1 (0.3%)	1
DIARRHEA	11 (3.2%)	11	12 (3.6%)	12
DRY MOUTH	0 (0.0%)	0	1 (0.3%)	1
DYSPEPSIA	7 (2.0%)	7	7 (2.1%)	8
FLATUL	9 (2.6%)	9	8 (2.4%)	8

N = number of patients in treatment group
n (%) = number and percentage (n/N x 100) of patients who reported adverse events in treatment group, body system, and COSTART term
nAE = number of adverse events reported by patients in treatment group, body system, and COSTART term

Ref. Section 2.7.4, S-Table 6

S-Table 2 (cont)
Frequency of AEs by Body System, Pooled Data for Studies 82 and 83
(All Randomized Patients)

Body System COSTART Term	2.4 g/day (400 mg Tablet) (N = 349)		4.8 g/day (800 mg Tablet) (N = 338)	
Digestive System	n (%)	nAE	n (%)	nAE
GASTROENTERITIS	2 (0.6%)	2	2 (0.6%)	2
GI DIS	2 (0.6%)	2	0 (0.0%)	0
HEM GI	1 (0.3%)	1	0 (0.0%)	0
HEM RECTAL	1 (0.3%)	1	3 (0.9%)	4
HERPES SIMPLEX	1 (0.3%)	1	0 (0.0%)	0
JAUNDICE	0 (0.0%)	0	1 (0.3%)	1
LIVER FUNC ABNORM	0 (0.0%)	0	2 (0.6%)	2
MELENA	0 (0.0%)	0	1 (0.3%)	1
NAUSEA	7 (2.0%)	7	14 (4.1%)	15
NAUSEA VOMIT	3 (0.9%)	6	1 (0.3%)	1
PANCREATITIS	1 (0.3%)	1	0 (0.0%)	0
PROCTITIS	0 (0.0%)	0	4 (1.2%)	4
RECTAL DIS	8 (2.3%)	8	5 (1.5%)	5
STOMATITIS	1 (0.3%)	1	0 (0.0%)	0
THIRST	0 (0.0%)	0	1 (0.3%)	1
VOMIT	4 (1.1%)	4	7 (2.1%)	8
Hemic and Lymphatic System				
ANEMIA HYPOCHROM	0 (0.0%)	0	1 (0.3%)	1
LEUKOCYTOSIS	0 (0.0%)	0	1 (0.3%)	1
SPLENOMEGALY	1 (0.3%)	1	0 (0.0%)	0
THROMBOCYTHEM	1 (0.3%)	1	1 (0.3%)	1
Metabolic and Nutritional Disorders				
EDEMA PERIPH	1 (0.3%)	1	2 (0.6%)	2
GLUCOSE TOLER DEC	0 (0.0%)	0	1 (0.3%)	1
GOUT	1 (0.3%)	1	0 (0.0%)	0
HEALING ABNORM	1 (0.3%)	2	0 (0.0%)	0
HYPERGLYCEM	1 (0.3%)	1	0 (0.0%)	0
HYPOGLYCEM	1 (0.3%)	1	0 (0.0%)	0
HYPOKALEM	0 (0.0%)	0	1 (0.3%)	1
PHOSPHATASE ALK INC	0 (0.0%)	0	2 (0.6%)	2
SGOT INC	1 (0.3%)	1	2 (0.6%)	2
SGPT INC	2 (0.6%)	2	1 (0.3%)	1
WEIGHT DEC	2 (0.6%)	2	0 (0.0%)	0

S-Table 2 (cont)
Frequency of AEs by Body System, Pooled Data for Studies 82 and 83
(All Randomized Patients)

Body System COSTART Term	2.4 g/day (400 mg Tablet) (N = 349)		4.8 g/day (800 mg Tablet) (N = 338)	
Musculo-skeletal System	n (%)	nAE	n (%)	nAE
ARTHRALGIA	3 (0.9%)	3	2 (0.6%)	2
ARTHRITIS	0 (0.0%)	0	1 (0.3%)	1
ARTHROSIS	0 (0.0%)	0	1 (0.3%)	1
MYALGIA	2 (0.6%)	2	2 (0.6%)	4
PAIN BONE	1 (0.3%)	1	0 (0.0%)	0
TENDON DIS	0 (0.0%)	0	1 (0.3%)	1
Nervous System				
AMNESIA	0 (0.0%)	0	1 (0.3%)	1
ANXIETY	1 (0.3%)	1	1 (0.3%)	1
DEPRESSION	1 (0.3%)	1	0 (0.0%)	0
DIZZINESS	7 (2.0%)	7	3 (0.9%)	3
EMOTION LABIL	0 (0.0%)	0	1 (0.3%)	1
HYPERTONIA	0 (0.0%)	0	1 (0.3%)	1
HYPESTHESIA	0 (0.0%)	0	2 (0.6%)	2
INSOMNIA	2 (0.6%)	4	2 (0.6%)	2
NERVOUSNESS	0 (0.0%)	0	1 (0.3%)	1
PARESTHESIA	1 (0.3%)	1	0 (0.0%)	0
SLEEP DIS	0 (0.0%)	0	1 (0.3%)	1
SOMNOLENCE	2 (0.6%)	2	0 (0.0%)	0
TWITCH	0 (0.0%)	0	1 (0.3%)	1
Respiratory System				
ASTHMA	1 (0.3%)	1	0 (0.0%)	0
BRONCHITIS	2 (0.6%)	2	4 (1.2%)	4
COUGH INC	10 (2.9%)	10	2 (0.6%)	2
DYSPNEA	3 (0.9%)	3	0 (0.0%)	0
EPISTAXIS	0 (0.0%)	0	1 (0.3%)	1
INFECT	5 (1.4%)	5	9 (2.7%)	9
LUNG DIS	2 (0.6%)	2	1 (0.3%)	1
PHARYNGITIS	3 (0.9%)	3	3 (0.9%)	3
PNEUMONIA	0 (0.0%)	0	1 (0.3%)	1
RHINITIS	7 (2.0%)	7	1 (0.3%)	1
SINUSITIS	8 (2.3%)	8	3 (0.9%)	3

S-Table 2 (cont)
Frequency of AEs by Body System, Pooled Data for Studies 82 and 83
(All Randomized Patients)

Body System COSTART Term	2.4 g/day (400 mg Tablet) (N = 349)		4.8 g/day (800 mg Tablet) (N = 338)	
	n (%)	nAE	n (%)	nAE
Skin and Appendages				
DERM CONTACT	1 (0.3%)	1	0 (0.0%)	0
ECZEMA	0 (0.0%)	0	1 (0.3%)	1
NAIL DIS	0 (0.0%)	0	1 (0.3%)	1
NEOPL SKIN	0 (0.0%)	0	1 (0.3%)	1
NODULE SUBCUTAN	0 (0.0%)	0	1 (0.3%)	1
PHOTOSENSITIVITY	2 (0.6%)	2	0 (0.0%)	0
PRURITUS	3 (0.9%)	3	1 (0.3%)	1
RASH	7 (2.0%)	7	5 (1.5%)	5
RASH MAC PAP	1 (0.3%)	1	0 (0.0%)	0
SWEAT	2 (0.6%)	2	1 (0.3%)	1
Special Senses				
OTITIS MED	1 (0.3%)	1	0 (0.0%)	0
TASTE PERVERS	0 (0.0%)	0	1 (0.3%)	1
Urogenital System				
CYST	1 (0.3%)	1	0 (0.0%)	0
DYSURIA	1 (0.3%)	1	1 (0.3%)	1
HEMATURIA	0 (0.0%)	0	1 (0.3%)	1
INFECT URIN TRACT	1 (0.3%)	1	1 (0.3%)	1
KIDNEY CALCULUS	0 (0.0%)	0	1 (0.3%)	1
NEPHRITIS	1 (0.3%)	1	0 (0.0%)	0
PROSTAT DIS	1 (0.3%)	1	0 (0.0%)	0
URIN FREQUENCY	0 (0.0%)	0	1 (0.3%)	1
URIN IMPAIRED	1 (0.3%)	1	0 (0.0%)	0
UTER FIBROID ENLARGE	1 (0.3%)	1	0 (0.0%)	0
VAGINITIS	2 (0.6%)	2	2 (0.6%)	2

7.1.1 Deaths

No deaths occurred in this clinical program.

7.1.2 Other Serious Adverse Events

Nine patients (7 in the 2.4 g/day group, 2 in the 4.8 g/day group) experienced SAEs (hospitalizations and/or medically significant events) during this clinical program. The majority of SAEs were events described in the current product label, primarily involving the digestive system, including ulcerative colitis signs and symptoms (rectal bleeding, diarrhea, abdominal pain) or worsening ulcerative colitis; nausea, vomiting, epigastric pain (4.8 g/day), cholecystitis and pancreatitis. Onset of digestive system SAEs occurred primarily in

the first 2 weeks of treatment. Other SAEs reported during the program, and described in the current product label, included single reports of nephritis (2.4 g/day) and pericarditis (4.8 g/day). The only SAEs not described in the current label occurred in a single patient (2.4 g/day group) who was hospitalized and underwent a hysterectomy for dysfunctional uterine bleeding secondary to pre-existing uterine fibroids and ovarian cyst; the patient completed the study (Patient 37263458). The majority of SAEs were considered moderate or severe in nature; all patients had recovered from the events by the time of their last study contact, except for one patient (2.4 g/day group) who remained under treatment for worsening ulcerative (Patient 71003796).

In addition to the 9 patients reporting SAEs during this clinical program, one other patient in the 4.8 g/day group experienced an SAE temporally related to clinical study participation. This patient (Patient 74824378), who had moderate disease at baseline, was withdrawn from the study due to lack of treatment effect, with worsening of disease after approximately one week of treatment. Following withdrawal from the study, the patient was treated with prescription Asacol and prednisone (doses unknown), and was hospitalized one week later due to refractory ulcerative colitis.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A total of 29 patients (13 in the 4.8 g/day group, 16 in the 2.4 g/day group) were withdrawn from study participation due to AEs during the clinical program (S-Table 3). The distribution and types of AEs resulting in study withdrawal was comparable between treatments for all randomized patients, as well as for patients with moderate disease. Onset of events leading to withdrawal occurred in the first 2 weeks of treatment in the majority of patients (13/16 in the 2.4 g/day group and 11/13 in the 4.8 g/day group). All patients had recovered from AEs leading to withdrawal by the time of their last study contact with three exceptions. One patient in the 2.4 g/day group (moderate disease) remained under treatment for worsening UC and 2 patients with moderate disease (one in each treatment group) were experiencing ongoing sequelae of worsened UC symptoms at last follow-up. The majority of withdrawals due to an AE occurred as a result of events described in the current product label and primarily involved the digestive system.

7.1.3.2 Adverse events associated with dropouts

The percentage of patients who withdrew due to an AE was comparable between treatment groups for all randomized patients (4.6% in the 2.4 g/day group, 3.8% in the 4.8 g/day group) S-Table 3. The majority of withdrawals due to AEs occurred as a result of events involving digestive system including colitis ulcer, nausea, vomiting, diarrhea and abdominal pain and they were reported more frequently in the 2.4 g/day group. It should be noted that the number of AEs does not equal the number of patients withdrawn due to an AE, since some patients had more than 1 AE causing discontinuation.

S-Table 3
Adverse Events led to withdrawal, Pooled data for Study 82 and Study 83
(Compiled by the Reviewer from S-Table 5, Section 2.7.4)

AEs led to dropouts	2.4 g/day (400 mg tablet) (n=349)	4.8 g/day (800 mg tablet) (n= 338)
Total patients withdrew due to AEs	16 (4.6%)	13 (3.8%)
Colitis ulcer	6	4
Nausea/vomiting	5	5
Diarrhea	5	2
Abdominal pain	5	2
Headache	1	3
Fever	1	1
Myalgia	1	1
Arthralgia	0	2
Dyspnea/lung disease	1	1
Others[1]	2	2

[1] Others include: chest pain (n=1) and pancreatitis (n=1) in 2.4 g/day group; gastroenteritis (n=1) and dizziness (n=1) in 4.8 g/day group.

7.1.4 Common Adverse Events

7.1.4.1 Eliciting adverse events data in the development program

Primary safety parameters measured in this clinical program were Investigator-reported AEs as well as those volunteered by the patient, and clinical laboratory evaluations. When an AE was suspected, all relevant evaluations were carried out and appropriate treatment provided. Patients who experienced any clinically significant AE remained under medical supervision until the Investigator and the Sponsor's Medical Monitor deemed the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up. Additional follow-up was performed as necessary, recorded in the patient's source documents, and forwarded to the Sponsor. AEs were monitored during all scheduled visits: screening, baseline, Week 3 and Week 6. Clinical laboratory assessments were performed at screening and at Week 6 visits. Each AE was evaluated for duration, severity, seriousness, and causal relationship to the drugs.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

As in previous studies of the Asacol 400 mg tablets, the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART 5th edition) system was used to code reported AE verbatim. In the reviewer's opinion AE categorization and preferred terms used in the clinical program is acceptable.

7.1.4.3 Incidence of Common Adverse Events

Across treatments, events reported by 2% or more of all randomized patients (in decreasing frequency) were headache, abdominal pain, infection, diarrhea, nausea, flatulence, ulcerative colitis (exacerbation), dyspepsia, and flu syndrome (S-Table 4). AEs that were reported slightly more frequently by patients receiving 4.8 g/day vs 2.4 g/day were infection (4% vs. 3%) nausea (4% vs. 2%), and vomiting (2% vs. 1%); however, the numbers of patients involved were few. Similar AE results were observed in a population with moderate disease (S-Table 5). All commonly reported AEs have been observed previously with use of Asacol 400 mg tablets, and are described in the current product label.

7.1.4.4 Common Adverse Event Table

S-Table 4
Adverse Events Occurring in ≥ 2% of Patients
Pooled Data for Studies 82 and 83
(All Randomized Patients with mild-moderate disease)

Adverse Event	2.4 g/day (400 mg Tablet) (N = 349)	4.8 g/day (800 mg Tablet) (N = 338)	Total (N = 687)
COSTART Term	n (%)	n (%)	n (%)
OVERALL	132 (37.8%)	129 (38.2%)	261 (38.0%)
HEADACHE	24 (6.9%)	24 (7.1%)	48 (7.0%)
PAIN ABDO	18 (5.2%)	11 (3.3%)	29 (4.2%)
INFECT	10 (2.9%)	14 (4.1%)	24 (3.5%)
DIARRHEA	11 (3.2%)	12 (3.6%)	23 (3.3%)
NAUSEA	7 (2.0%)	14 (4.1%)	21 (3.1%)
FLATUL	9 (2.6%)	8 (2.4%)	17 (2.5%)
COLITIS ULCER	9 (2.6%)	7 (2.1%)	16 (2.3%)
DYSPEPSIA	7 (2.0%)	7 (2.1%)	14 (2.0%)
FLU SYND	10 (2.9%)	4 (1.2%)	14 (2.0%)
RECTAL DIS	8 (2.3%)	5 (1.5%)	13 (1.9%)
COUGH INC	10 (2.9%)	2 (0.6%)	12 (1.7%)
RASH	7 (2.0%)	5 (1.5%)	12 (1.7%)
SINUSITIS	8 (2.3%)	3 (0.9%)	11 (1.6%)
VOMIT	4 (1.1%)	7 (2.1%)	11 (1.6%)
DIZZINESS	7 (2.0%)	3 (0.9%)	10 (1.5%)
RHINITIS	7 (2.0%)	1 (0.3%)	8 (1.2%)

Patients who experienced more than one AE within a COSTART term are counted only once within that term.
Data are sorted by decreasing incidence in the Total column.
N = number of patients in treatment group
n (%) = number and percentage (n/N x 100) of patients who reported adverse events within specified treatment group and COSTART term

Ref. Section 2.7.4, S-Table 3

Appears This Way
On Original

S-Table 5
Adverse Events Occurring in ≥ 2% of Patients
Pooled Data for Studies 82 and 83
(All Patients with Moderate Disease)

Adverse Event*	**2.4 g/day (400 mg tablet) N = 235**	**4.8 g/day (800 mg tablet) N = 213**
COSTART Term	n (%)	N (%)
HEADACHE	14 (6.0%)	16 (7.5%)
ABDOMINAL PAIN	12 (5.1%)	9 (4.2%)
DIARRHEA	9 (3.8%)	8 (3.8%)
NAUSEA	4 (1.7%)	8 (3.8%)
RESPIRATORY INFECTION	4 (1.7%)	7 (3.3%)
COLITIS EXACERBATION	6 (2.6%)	6 (2.8%)
DYSPEPSIA	5 (2.1%)	6 (2.8%)
VOMITING	2 (0.9%)	6 (2.8%)
FLATULENCE	7 (3.0%)	5 (2.3%)
RECTAL DISORDER	6 (2.6%)	4 (1.9%)
FLU SYNDROME	8 (3.4%)	3 (1.4%)
RASH	5 (2.1%)	3 (1.4%)
INCREASED COUGH	9 (3.8%)	1 (0.5%)
SINUSITIS	5 (2.1%)	1 (0.5%)
RHINITIS	7 (3.0%)	0 (0.0%)

*Adverse events in are listed by decreasing frequency in the 4.8 g/day treatment group.

7.1.4.5 Identifying common and drug-related adverse events

In both treatment groups, events assessed as possibly or probably related to study drug administration in 1% or more of patients included headache, nausea, abdominal pain, diarrhea, UC exacerbations, and flatulence. These events have also been observed previously with use of Asacol 400 mg tablets, and are described in the current product label.

7.1.5 Less Common Adverse Events

The important less common AEs are addressed under section 7.1.3.

7.1.6 Laboratory Findings

7.1.6.1 Overview of laboratory testing in the development program

Routine clinical laboratory evaluations were performed for all patients at the Screening Visit (baseline value) and after Week 6 of treatment. The mean change from baseline by treatment group was calculated for all serum chemistry and hematology parameters, using data from patients who had both Screening and Week 6 values.

7.1.6.2 Standard analyses and explorations of laboratory data

The mean change from baseline by treatment group was calculated for all serum chemistry and hematology parameters, using data from patients who had both Screening and Week 6 values

7.1.6.3 Analyses focused on measures of central tendencies

In all randomized patients and in patients with moderate disease, total bilirubin at Week 6 showed a greater increase from baseline in the 4.8 g/day group compared to the 2.4 g/day group, and in patients with moderate disease, platelets showed a greater decrease from baseline in the 4.8 g/day group compared to the 2.4 g/day group. However, group mean results for these parameters at Week 6 were not clinically different between treatments for any population. Further, group mean results at Screening and at Week 6 were not clinically different between treatments for any parameter for any population evaluated.

7.1.6.4 Marked outliers and dropouts for laboratory abnormalities

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

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

In this clinical program, vital signs (blood pressure, heart rate, respiration rate and temperature) were assessed at the screening visit and at Week 6 of treatment. Mean change from baseline was calculated for all vital signs parameters using data from patients who had screening and Week 6 values.

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

Examination of the vital signs data from two phase III active-controlled studies revealed no adverse event signal.

7.1.7.3 Marked outliers and dropouts for vital sign abnormalities

There were no marked outliers or dropouts due to vital signs abnormalities in this clinical program.

7.1.7.4 Analyses focused on measures of central tendencies

There were no notable differences from baseline at Week 6 for any parameter of vital signs in treatment groups (S-Table 6).

S-Table 6
Mean Vital Signs Results, Pooled Data for Studies 82 and 83
(Patients with Moderate Disease with Both Screening and Week 6 Values)

Treatment Group		Screening		Week 6		Change from Baseline		% Change from Baseline	
Parameter	n	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)
2.4 g/day (400 mg tablet) (N = 235)									
Systolic Blood Pressure	190	122.1	(1.1)	121.6	(1.1)	-0.5	(0.8)	0.0	(0.7)
Diastolic Blood Pressure	190	75.0	(0.7)	76.3	(0.6)	1.3	(0.6)	2.5	(0.9)
Heart Rate	190	74.8	(0.8)	74.5	(0.8)	-0.3	(0.7)	0.6	(1.0)
Respiration Rate	188	16.9	(0.2)	17.0	(0.2)	0.2	(0.2)	1.8	(1.0)
Temperature	187	36.9	(0.0)	36.9	(0.0)	-0.0	(0.0)	-0.0	(0.1)
4.8 g/day (800 mg tablet) (N = 213)									
Systolic Blood Pressure	180	122.0	(1.1)	120.9	(1.2)	-1.0	(1.0)	-0.4	(0.8)
Diastolic Blood Pressure	180	75.6	(0.7)	75.4	(0.7)	-0.2	(0.7)	0.5	(1.0)
Heart Rate	180	74.5	(0.7)	74.1	(0.7)	-0.4	(0.8)	0.5	(1.0)
Respiration Rate	179	16.6	(0.2)	16.7	(0.2)	0.2	(0.2)	2.2	(1.2)
Temperature	178	36.9	(0.0)	36.9	(0.0)	-0.0	(0.0)	-0.1	(0.1)
n = number of patients in treatment group with test results at both Screening and Week 6 visits (SE) = standard error of the mean									

Ref. Section 2.7.4.7.3 S-Table 27

7.1.8 Electrocardiograms (ECGs)

The applicant did not provide any clinical or adverse event data regarding ECGs in this application.

7.1.9 Immunogenicity

The applicant did not provide any clinical or adverse event data regarding Immunogenicity in this application.

7.1.10 Human Carcinogenicity

The applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application. Results from preclinical carcinogenicity studies have been previously reviewed and are reflected in the current Asacol product label.

7.1.11 Special Safety Studies

The applicant did not provide a special safety study in this submission. Long-term safety studies were submitted and reviewed under NDA19-651/S005.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

There is no clinical information with respect to the potential for withdrawal or rebound effects with use of the Asacol 800 mg tablet formulation at a dose of 4.8 g/day in patients with active UC. Additionally, there is no new information with respect to the potential for these effects associated with the active ingredient, mesalamine.

There is no clinical information with respect to the potential for abuse of the Asacol 800 mg tablet formulation at a dose of 4.8 g/day in patients with active UC. Additionally, there is no new information with respect to the potential for abuse associated with the active ingredient, mesalamine.

7.1.13 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. Reproduction studies in rats and rabbits at oral doses up to 480 mg/kg/day have revealed no evidence of teratogenic effects or fetal toxicity due to mesalamine.

Two pregnancies were reported in patients during the clinical development program: 1 ectopic pregnancy requiring therapeutic termination (4.8 g/day, moderate disease), and 1 resulting in spontaneous abortion secondary to a blighted ovum at approximately 12 weeks gestation (2.4 g/day group, mild disease).

Patient 20393610 was a 40-year-old Caucasian female who experienced an ectopic pregnancy resulting in withdrawal from the study. She had a history of UC since 1993, with relapse frequency more than once a month. The onset of her most recent flare was [redacted] (left-sided colitis by colonoscopy). Prior treatment for UC included steroids, oral sulfa-free 5-ASAs, and rectal therapies. She received Asacol 1.6 g/day from 1 December 2001 to 16 January 2002. b(6)

The patient received 4.8 g/day Asacol from 17 January 2002 to 9 February 2002. The patient had a negative serum pregnancy test at screening [redacted] and agreed to use acceptable contraceptive methods during the study. She began taking study drug on 17 January 2002, and was seen for Visit 1 , at which time she informed the Investigator that she was pregnant). The pregnancy was reported to be ectopic, and the patient received intramuscular methotrexate 80 mg as an abortifacient . Study drug was discontinued on 9 February 2002, and the patient was withdrawn from the study due to protocol violation (pregnancy). A serum pregnancy test was still positive; no further information was received regarding the outcome of this pregnancy. b(6)

The patient also had a history of mitral valve prolapse (1985), fertility treatments, and fallopian tube removal (2000). She had an allergy to sulfa drugs (nausea) and reported no concomitant medication usage during the study.

Patient 51052094 was a 28 year-old Black female who completed study medication administration and at study Visit 2 was found to have a positive pregnancy test; the outcome of the pregnancy was a spontaneous abortion at approximately 12 weeks gestation, secondary to a blighted ovum. The patient received Asacol 2.4 g/day (400 mg tablet) from 22 June 2001 to 07August 2001.

The patient had a negative urine pregnancy test, and reported use of Ortho Cyclen (ethinyl estradiol/norgestimate) 1 tablet orally daily since 01-Feb-2001 for contraception. The patient began taking blinded study drug on 22-Jun-2001; at study Visit 1 (Week 3), she was counseled regarding compliance with study medication use. The per-protocol serum pregnancy test done at study completion was positive; a confirmatory repeat done b(6)
was also positive. The Investigator broke the study blind for the patient's treatment, and she was referred to her obstetrician for management of the pregnancy. The patient was primigravida; date of last menstrual period was and she indicated she had discontinued her oral contraception on 20-Jul-2001. On the patient experienced a spontaneous abortion, secondary to a blighted ovum. The Investigator indicated that the patient had recovered from the pregnancy, and that the spontaneous abortion was not considered related to study drug administration.

Medical History: Ulcerative colitis (newly diagnosed , with symptom onset [left-sided colitis by colonoscopy]; baseline PGA score 1 [mild disease]; no prior treatment); history of cigarette use, stopped Jan-2001; history of left knee torn ligament with arthroscopic surgery , mild headaches (Jan-1999), urinary tract infection (Jun-1999), sinusitis , gastroesophageal reflux disease (diagnosed b(6)
currently active), nausea and vomiting (Feb/Mar-2001, currently active), vaginal candidiasis (Mar-2001), and allergic rhinitis (onset date not reported). Concomitant Medications: Ortho Cyclen (ethinyl estradiol/norgestimate) 1 tablet orally daily, from 01-Feb-2001 to 20-Jul-2001, for contraception.

7.1.14 Assessment of Effect on Growth

Not applicable

7.1.15 Overdose Experience

There is no clinical experience with overdose of the 800 mg tablet formulation, and no new information with respect to the toxicity of the active ingredient, mesalamine. According to the document submitted, there are no documented reports of serious human toxicity following overdose with mesalamine. In dogs, single doses of 6 grams of delayed-release Asacol (400 mg tablets) resulted in renal papillary necrosis but were not fatal. This was approximately 6.2 times the recommended human dose (based on a dose of 4.8 g/day in a 50

kg person). Single oral doses of mesalamine suspension in mice and rats of 5000 mg/kg and 4595 mg/kg, respectively, or 3000 mg/kg in cynomolgus monkeys, caused significant lethality.

7.1.16 Postmarketing Experience

Asacol 800 mg tablets are not currently approved for marketing in any country; thus, there is no information with respect to the post-marketing use of this formulation at any dose.

7.2 Adequacy of Patient Exposure and Safety Assessments

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

The population for which safety data are available for the Asacol 800 mg formulation is comprised of 338 patients with mildly to moderately active UC in two Phase III studies (Study 82 and Study 83) and 54 healthy subjects with limited exposure during biopharmaceutical studies (S-Table 7). The two phase III studies were double-blind, randomized, multiple-site, active-controlled studies in newly and previously diagnosed patients who were experiencing a flare of mildly to moderately active ulcerative colitis. 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 screened according to inclusion/exclusion criteria within 7 days before receiving study medication.

Of the total of 687 subjects enrolled in two phase III studies, 349 patients were randomized to receive Asacol 2.4 g/day and 338 patients were randomized to receive 4.8 g/day for 6 weeks. In the primary efficacy population (patients with moderate disease, n = 448), 235 patients received 2.4 g/day and 213 patients received 4.8 g/day. For all randomized patients, comparable percentages of patients in the treatment groups completed the study (86%).

In addition to UC patients in Studies 82 and 83, 54 healthy subjects were exposed to the 800 mg tablet during formulation development in three studies: Studies 2000027 (20 subjects exposed to a single 800 mg dose), 2001025 (16 subjects exposed to 7 days of 2 x 800 mg [1.6 g] three times daily [4.8 g/day]), and 2001095 (18 subjects exposed to 2 single 800 mg doses in a crossover fashion, fed and fasted). Safety data (adverse events, vital signs, and clinical laboratory evaluations) from these studies in healthy subjects did not suggest any new concerns with respect to the safety profile of Asacol 4.8 g/day (800 mg tablet) compared to the current product label for Asacol 2.4 g/day (400 mg tablet).

7.2.1.1 Study type and design/patient enumeration

S-Table 7. Listing of Clinical Studies

Type of study	Study identifier	Location of Study report	Objectives of the study	Study Design	Test product Dosage regimen	Population	Number entered/ completed	Duration of Treatment
Safety and efficacy	2000082	Section 5.3.5.1.1	To assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) vs. Asacol 2.4 g/day (400 mg tablet)	Double blind, randomized, 6-week, parallel group, active control	Two 800 mg tablets and two placebo tablets 3 times daily oral	Mildly to moderately active UC	386/330 2.4 g/day 195/162 4.8 g/day 191/168	6 weeks
Safety and efficacy	2000083	Section 5.3.5.1.2	To assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) vs. Asacol 2.4 g/day (400 mg tablet)	Double blind, randomized, 6-week, parallel group, active control	Two 800 mg tablets and two placebo tablets 3 times daily oral	Mildly to moderately active UC	301/265 2.4 g/day 154/133 4.8 g/day 147/123	6 weeks
Human PK	2001025	5.3.3.1.1	To characterize PK of 5-ASA and N-Ac-5-ASA	Open-label, multiple-dose study of the 800 mg tablet administered at 4.8 g/day for 6 days	Two 800 mg tablets tid for 6 days oral	Healthy subjects	16/16	1 week
Biopharm	2000027	5.3.1.2.1	To characterize PK of 5-ASA and N-Ac-5-ASA	Open-label, single dose, 4-period randomized cross over	800 mg and two 400 mg, single dose, oral	Healthy subjects	20/20	Single dose
Biopharm	2001095	5.3.1.1.1	To characterize the effect of a high-fat meal	Open-label single dose, 2-period, randomized cross over	800 mg single dose oral	Healthy subjects	18/16	Single dose

7.2.1.2 Demographics

In both clinical trials baseline demographic characteristics were comparable between treatment groups (S-Tables 8 and 9). The population was primarily Caucasian (77%), had a mean age of 43 years (<10% were age 65 years or older), and included slightly more females (53%) than males (47%).

S-Table 8
Baseline Demographic Characteristics
All Randomized Patients (Study 82)

Characteristic	2.4 g/day Asacol (400 mg tablet) (N = 195)	4.8 g/day Asacol (800 mg tablet) (N = 191)	p-value
Age (years)[a]	42.8 (1.00)	42.7 (0.94)	0.9643
18-64	178 (91.3%)	175 (91.6%)	
≥65	17 (8.7%)	16 (8.4%)	
Sex			0.3391
Male	88 (45.1%)	77 (40.3%)	
Female	107 (54.9%)	114 59.7%)	
Height (cm)[a]	169.0 (0.96)	168.6 (0.76)	0.7160
Weight (kg)[a]	78.9 (1.45)	78.7 (1.38)	0.9208
Race			0.4624
Caucasian	150 (76.9%)	142 (74.3%)	
Black	17 (8.7%)	24 (12.6%)	
Asian (Indian)	3 (1.5%)	2 (1.0%)	
Asian (Oriental)	1 (0.5%)	4 (2.1%)	
Hispanic	21 (10.8%)	15 (7.9%)	

[a] Data shown are mean (standard error).

Re. Section 5.3.5.1.1, Appendix 5, Table 18.

S-Table 9
Baseline Demographic Characteristics
All Randomized Patients (Study 83)

Characteristic	2.4 g/day Asacol (400 mg Tablet) (N = 154)		4.8 g/day Asacol (800 mg Tablet) (N = 147)		p-value
Age (years)[a]	43.5	(1.10)	45.9	(1.10)	0.1237
18 to 64	141	(91.6%)	133	(90.5%)	
≥ 65	13	(8.4%)	14	(9.5%)	
Sex					0.3209
Male	75	(48.7%)	80	(54.4%)	
Female	79	(51.3%)	67	(45.6%)	
Height (cm)[a]	170.4	(0.82)	170.8	(0.87)	0.7051
Weight (kg)[a]	77.6	(1.31)	79.2	(1.40)	0.4054
Race					0.9873
Caucasian	122	(79.2%)	116	(78.9%)	
Black	18	(11.7%)	18	(12.2%)	
Asian (Indian)	2	(1.3%)	2	(1.4%)	
Asian (Oriental)	1	(0.6%)	0	(0.0%)	
Hispanic	10	(6.5%)	9	(6.1%)	
Multi-racial/other	1	(0.6%)	2	(1.4%)	

[a] Data shown are mean (standard error).

Ref. Section 5. 3.5.1.2, Table 5

7.2.1.3 Extent of exposure (dose/duration)

S-Table 10 displays the extent of exposure to study drug for all randomized patients by treatment group. In each of these groups, the expected dose-related increase in grams per patient was observed.

S-Table 10
Extent of Exposure
Pooled data for Studies 82 and 83 (All randomized Patients)

Category	2.4 g/day Asacol (400 mg Tablet) (N = 349)	4.8 g/day Asacol (800 mg Tablet) (N = 338)
Number of patients with known exposure	347	336
Total patient-days of exposure[a]	13467	13170
Mean (SE) patient-days of exposure[b]	39.4 (0.53)	39.3 (0.56)
Total grams of exposure[c]	31691.2	61280.4
Mean (SE) grams exposure per patient[d]	91.3 (1.30)	182.9 (2.69)

N = number of patients in treatment group
(SE) = standard error of the mean
a =Defined as sum of days of exposure for all patients in treatment group
b =Defined as average patient-days of exposure across all patients with known exposure
c= Defined as sum of grams of exposure for all patients in treatment group (individual exposure based on actual tablet counts) excluding patient #27884427.
d =Defined as the average grams of exposure across all patients with known exposure excluding patient #27884427.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

All safety information for Asacol 800 mg tablets at a dose 4.8 g/day was obtained from the current submission. Asacol 800 mg tablets are not currently approved for marketing in any country; thus, there is no information with respect to the post-marketing use of this formulation at any dose. However, safety profile regarding long-term use of 4.8 g/day using Asacol 400 mg tablets has been previously reviewed under NDA 19-651/S005 and is described in the current Asacol label.

The Integrated Summary of Safety submitted to NDA 19-651/S005 included safety data from 14 clinical studies conducted with Asacol (400 mg tablet) for varying indications. Of these 14 studies, the majority of patient exposure to doses of 4.8 g/day or greater occurred in 3 studies: C3 (6-week placebo-controlled study), and C12 and C13 (long-term, open-label, compassionate use studies). In these compassionate use studies, the Asacol dose was

permitted to vary over time, at the Investigator's discretion, based on the individual patient's response. Maximum recorded daily doses during the studies were 6.4 g/day in Study C12, and 7.2 g/day in Study C13. According to the data submitted by the applicant in response to the Agency's information request (amendment # 14, dated July 11, 2005), a total of 903 patients were exposed to an average daily dose of 4.8 g/day or higher. Of these, 405 patients were exposed for > 6 month, and 247 of them were exposed for > 1 year (S-Table 11).

S-Table 11. Number of Patients Exposed to 4.8 g/day or Higher by Time

Time (months)	Study C3 N =38	Study C12 + C13 N=865
	n (%)	n (%)
<3	38 (100%)	302 (35%)
>3-6	--	158 (18.3%)
>6-9	--	91 (10.5%)
>9-12	--	67 (7.75%)
>12	--	247 (28.55%)

Ref. Table 1, amendment # 14 (dated July 11, 2005)

The applicant concluded that the overall safety profile for Asacol, across all doses, durations, and indications studied, was similar to that previously observed with Asacol used in short-term treatment of UC and that the most frequently reported adverse events were comparable in nature to frequently reported adverse events in the short-term, placebo-controlled studies in active disease. Additionally, increased duration of Asacol therapy was not associated with an increased frequency of AEs. A slight dose-related effect was observed for some commonly reported adverse events (asthenia, fever, flu syndrome, pain, abdominal pain, back pain, flatulence, gastrointestinal bleeding, arthralgia, and rhinitis), many of which are also commonly reported symptoms in inflammatory bowel disease. This relationship was not observed in placebo-controlled trials, and it was unclear in these studies whether the effect was due to more severe disease, higher Asacol doses, or a combination of both factors.

The exposure information described above complements the exposure from current application, where 338 patients were randomized to receive Asacol (800 mg tablet) 4.8 g/day for six weeks for treatment of active UC.

7.2.2.2 Postmarketing experience

Asacol 800 mg tablets are not currently approved for marketing in any country; thus, there is no information with respect to the post-marketing use of this formulation at any dose.

7.2.2.3 Literature

The applicant provided limited number of articles electronically with this application. The reviewer performed additional literature search utilizing the Agency's on line database as well as resources and used them in describing various sections of this review.

7.2.3 Adequacy of Overall Clinical Experience

The study design and the protocol defined endpoints were acceptable. The trials were limited in their lack of sufficient geriatric population and racial subsets.

7.2.4 Adequacy of Routine Clinical Testing

The protocol defined clinical testing and safety assessments were adequate.

7.2.5 Assessment of Quality and Completeness of Data

The data necessary to conduct safety review were included in the NDA. Overall, the applicant's quality of assessment was acceptable.

Asacol 800 mg tablets are not currently approved for marketing in any country; thus, there is no information with respect to the post-marketing use of this formulation at any dose. However, safety profile regarding the long-term use of 4.8 g/day, using the Asacol 400 mg tablets has been previously reviewed under NDA 19-651/S005. This exposure information complements the exposure from current application, where 338 patients were randomized to receive Asacol (800 mg tablet) 4.8 g/day for six weeks for treatment of moderately active UC.

7.2.6 Additional Submissions, Including Safety Update

The safety update provides available blinded safety information from Study 2004112, which was initiated in Europe and the United States in January 2005.

The following report summarizes safety update for the Asacol 800 delayed-release tablet used in study 2004112, for the period from first patient enrollment (28 February 2005) to May 16, 2005. The Data presented are cumulative for this review period, and all data are preliminary.

This double-blind, active-control study was designed to assess the efficacy and safety of a new product, RDP58, in the treatment of moderately active UC in patients concomitantly receiving mesalamine 2.4 g/day, compared to monotherapy with mesalamine 4.8 g/day only. As of the data lock point (25 April 2005), 64 patients had been enrolled in the study in a 1:1 randomization. One SAE was reported, an exacerbation of UC resulting in hospitalization; the patient recovered.

Additional late-breaking information (preliminary data) were also reviewed in the database for the period 26 April 2005 to 16 May 2005. A total of 69 additional patients had been enrolled (total study enrollment 133), with 3 additional non-serious adverse event reported (continuous diarrhea; abdominal pain and rash on hands; and hematuria [1 patient each]). One additional SAE was reported, hospitalization due to exacerbation of UC resulting in study withdrawal.

The applicant concluded that there have been no death and no serious unexpected AEs in Study 2004112. The data currently available from this study do not suggest any new concerns regarding the use of Asacol 800 mg tablets in patients with moderately active UC.

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

In both clinical trials, events most assessed as possibly or probably related to study drug administration in 1% or more of all patients included headache, nausea, abdominal pain, diarrhea, ulcerative colitis exacerbations, and flatulence. These events have all been observed previously with use of Asacol 400 mg tablets, and are described in the current product label.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Of the total of 687 patients randomized in both studies, 38% (261/687) reported a total of 520 AEs: 37.8 % (132/349) reported 278 AEs in the in the 2.4 g/day group and 38% (129/338) reported 242 AEs in the 4.8 g/day group. The distribution of patients for all parameter assessed was similar between the two treatment groups (S-Table 12).

S-Table 12
Summary of Adverse Events
Pooled Data for Studies 82 and 83
(All Randomized Patients)

Category	2.4 g/day Asacol (400 mg Tablet) (N = 349) n (%)	4.8 g/day Asacol (800 mg Tablet) (N = 338) n (%)	Total (N = 687) n (%)
Number (%) of patients with AEs[a]	132 (37.8%)	129 (38.2%)	261 (38.0%)
Number (%) of patients with serious AEs	7 (2.0%)	2 (0.6%)	9 (1.3%)
Number (%) of patients withdrawn due to AEs	16 (4.6%)	13 (3.8%)	29 (4.2%)
Number (%) of deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of AEs reported	278	242	520
Number of AEs assessed as[b]:			
Mild	169 (60.8%)	128 (52.9%)	297 (57.1%)
Moderate	87 (31.3%)	94 (38.8%)	181 (34.8%)
Severe	22 (7.9%)	20 (8.3%)	42 (8.1%)
Number (%) of AEs assessed as[b]:			
Doubtfuly related to study drug	203 (73.0%)	167 (69.0%)	370 (71.2%)
Possibly related to study drug	63 (22.7%)	60 (24.8%)	123 (23.7%)
Probably related to study drug	12 (4.3%)	15 (6.2%)	27 (5.2%)
Number of serious AEs reported	16	3	19
Mean number of AEs per patient[c]	0.8	0.7	0.8
Mean number of AEs among patients with AEs[d]	2.1	1.9	2.0
Mean number of AEs per patient month of exposure[e]	0.62	0.55	0.58

N = number of patients in treatment group
n (%) = number and percentage (n/N x 100) of patients in category and treatment group
[a] Patients who experienced one or more AEs in the category were counted only once.
[b] Percentage based on number of AEs reported
[c] Number of AEs reported/N
[d] Number of AEs reported/Number of patients with AEs
[e] Based on a 30-day month
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Ref. Section 2.7.4.7.3 S-Table 28

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Overall, the type and incidence of adverse events were similar between treatments (2.4 g/day vs 4.8 g/day). AEs that were reported slightly more frequently by patients receiving 4.8 g/day vs 2.4 g/day were infection (4% vs. 3%) nausea (4% vs. 2%), and vomiting (2% vs. 1%).

7.4.2.2 Explorations for drug-demographic interactions

Demographic characteristics at baseline were similar between the two treatment groups. The population was primarily Caucasian (77%), had a mean age of 43 years, and included slightly more females (53%) than males (47%).

Age
Less than 10% of the patient population in this clinical program was 65 years of age or older. Events reported by these patients were few in number and highly variable in nature. There is no clinical experience in patients younger than 18 years of age.

Sex
When comparing AE reporting for each sex by treatment group, the AE profile for male patients was comparable between the 2.4g/day and 4.8 g/day groups, while female patients in the 4.8 g/day group more frequently reported nausea (6.1%), vomiting (2.2%), and diarrhea (3.9%) than female patients in the 2.4 g/day group (1.6%, 0.5%, and 2.2%, respectively).

Race
Seventy seven percent of the patient population in this clinical development program was Caucasian, 11% was Black, and other races comprised another 12%. There were no notable differences between the 2 treatment groups for any race.

7.4.2.3 Explorations for drug-disease interactions

AEs by duration of disease and treatment group for all randomized patients present the same information for patients with moderate disease. One-third of all randomized patients were newly diagnosed with ulcerative colitis. There were no clinically relevant differences in reporting rates between treatments for either population.

7.4.2.4 Explorations for drug-drug interactions

There are no known drug interactions with Asacol, and no drug-drug interaction studies were performed in this clinical development program. For Studies 82 and 83, prohibited concomitant medications were prospectively defined on the basis of potential for confounding efficacy assessment only. In these studies, examination of the safety data for the patients receiving concomitant proton pump inhibitors or histamine-2 receptor antagonists in

both treatment groups did not identify additional concerns beyond those described in the current Asacol label.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Asacol 800 mg delayed-release tablet is indicated for the treatment of moderately active UC. The recommended dosage in adults is two Asacol 800 mg tablets (1.6 g) to be taken 3 times a day for a total daily dose of 4.8 g for duration of 6 weeks. It appears that the proposed indication is for a subset of the currently approved indication, i.e. treatment of patients with mildly to moderately UC with Asacol 400 mg tablet at a dose of 2.4 g/day.

It is worth noting that in patients with mildly active ulcerative colitis at baseline, Asacol 4.8 g/day provided a relatively inferior efficacy (-7%) compared to Asacol 2.4 g/day. In addition, although the overall safety profile was comparable between Asacol 4.8 g/day and 2.4 g/day, there was an overall increased incidence of nausea (4% vs 2%) and vomiting (2% vs 1%) in subjects receiving 4.8 g/day compared to 2.4 g/day. Thus, the relative decrease in efficacy combined with the relative increase in incidence of adverse events with 4.8 g/day compared to 2.4 g/day, favors the currently approved Asacol (400 mg tablet) 2.4 g/day for subjects with mild disease.

One Asacol 800 mg tablet is not interchangeable with two Asacol 400 mg tablets, because the relative bioavailability study showed that the mean t_{max} value of 5-ASA was significantly delayed, while mean C_{max} and AUC values decreased by 36% and 25%, respectively, with administration of 800 mg tablet relative to 400 mg tablet.

8.2 Drug-Drug Interactions

There are no known drug interactions with Asacol, and no drug-drug interaction studies were performed in this clinical development program.

8.3 Special Populations

Safety and effectiveness of Asacol 800 mg tablets in pediatric patients have not been established.

The clinical program did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently than younger subjects.

Reproduction studies in rats and rabbits at oral doses up to 480 mg/kg/day have revealed no evidence of teratogenic effects or fetal toxicity due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women.

Patients with kidney and hepatic impairment were excluded from the study. However, the current Asacol label states that renal impairment, including minimal change nephropathy and acute and chronic interstitial nephritis, has been reported in patients taking Asacol tablets as well as other products that contain or are converted to mesalamine. Caution should be exercised when using Asacol in patients with known renal dysfunction or history of renal disease. It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol tablets and periodically while on Asacol therapy.

8.4 Pediatrics

On May 20, 2003, the applicant received a Pediatric Written Request stipulating that reports from studies to evaluate appropriate dosing and safety of Asacol in children must be submitted to the Agency on or before December 31, 2005. Subsequent to the Agency's request for submission of pediatric drug development plans (letter dated 01/21/2005), the applicant submitted an amendment to NDA 21-830 (amendment #10, dated May 9, 2005) that outlines a plan for pediatric drug development. The submitted study plans will be addressed in a separate review.

8.5 Advisory Committee Meeting

There was no Advisory Committee meeting required for this NDA.

8.6 Literature Review

The applicant provided few articles electronically with this application. The reviewer performed additional literature search utilizing the Agency's on line database as well as resources and used them in describing various sections of this review.

8.7 Postmarketing Risk Management Plan

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

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

Conclusions on safety and efficacy of Asacol (mesalamine) 800 delayed-release tablets are drawn from two active-controlled, randomized, double-blind, multicenter phase III clinical studies (Study 82 and 83) of 6 weeks duration. Both studies were originally designed to compare Asacol 4.8 g/day, administered as the newly formulated 800 mg tablet to Asacol 2.4 g/day, administered as the approved 400 mg tablet in patients with mildly to moderately active UC.

Both studies failed to demonstrate superiority of 4.8 g/day over 2.4 g day after 6 weeks of treatment in patients with *mildly to moderately active UC at baseline.*

In both studies, 4.8 g/day revealed a numerically inferior response rate (-7%) compared to 2.4 g/day in subjects with *mildly active UC at baseline.*

For subjects with *moderately active UC* at baseline (the proposed indication), 4.8 g/day was superior to 2.4 g/day (p=0.02) in Study 82, but not in Study 83 (p=0.16). Further, the superior efficacy of 4.8 g/day in Study 82 was driven by Male subjects. However, Study 82 is not robust enough (p>0.001) to stand alone as a single study to support the proposed indication for treatment of subjects with moderately active disease.

From the regulatory standpoint, the reviewer concluded that a single clinical study finding of efficacy, unsupported by independent study is not adequate for a conclusion of a substantial evidence of effectiveness. To support the proposed indication, an additional adequate and well-controlled clinical study is required to confirm the findings from Study 82. The applicant should adequately address the inconsistency in the efficacy benefit in important subgroups of patients such as males and females.

The clinical program established an acceptable safety profile for Asacol (800 mg tablet) 4.8 g/day for six weeks in adult subjects with mildly to moderately active UC as well as in the primary efficacy population (subjects with moderate disease). The overall incidence of adverse events was comparable to that seen with 2.4 g/day. However, in all patients randomized, events reported more frequently in the 4.8 g/day group than in the 2.4 g/day group include nausea (4% vs 2%) and vomiting (2% vs 1%). In particular, female patients in the 4.8 g/day group more frequently reported nauseas (6.1% vs 1.6%), vomiting (2.2% vs 0.5%) and diarrhea (3.9% vs 2.2%) compared to females in the 2.4 g/day.

Asacol 800 mg tablets are not currently approved for marketing in any country; thus, there is no information with respect to the post-marketing use of this formulation at any dose. However, safety profile regarding long-term use of 4.8 g/day using Asacol 400 mg tablets has been previously reviewed under NDA 19-651/S005 and is reflected in the current Asacol label.

Asacol 800 mg tablets at a dose of 4.8 g/day are not indicated for the treatment of patients with *mild disease*, because Asacol 4.8 g/day administered as 800 mg tablets is associated with a relatively decreased efficacy benefit and relatively increased incidence of adverse events (nausea and vomiting) when compared to the approved Asacol 2.4 g/day administered as 400 mg tablets.

9.2 Recommendation on Regulatory Action

From the regulatory standpoint, I recommend that Asacol 800 delayed-release tablets at a dose of 4.8 g/day be approvable for the treatment of adult patients with *moderately active ulcerative colitis.*

To gain approval for the desired indication, the applicant should conduct an additional adequate and well-controlled clinical study to confirm the findings from Study 82. The applicant should adequately address the inconsistency in the efficacy benefit in important subgroups of patients with moderate disease, namely, males versus females.

b(4)

9.3 Recommendation on Postmarketing Actions.

9.3.1 Risk Management Activity

There are no applicable activities related to risk management for this NDA.

9.3.2 Required Phase 4 Commitments

In accordance with the formal Pediatric Written Request dated on May 19, 2003, the applicant should conduct two studies: Pharmacokinetics and Safety study (study 1) and Exposure/Response and Safety Study (study 2) of Asacol in pediatric patients aged 5-17 years with mildly to moderately active ulcerative colitis. The results of Study 1 should be reported to the Agency before initiating treatment of patients in Study 2. In addition, reports of the studies that meet the terms of the Written Request must be submitted to the Agency on or before December 31, 2005. In addition, the medical officer's review (Dr. Robert Prizont) dated Feb 20, 2003, indicated that pediatric studies conducted with Asacol 400 mg tablet formulation may be applicable to the Asacol 800 mg tablet formulation as long as bridging PK and PD studies are performed to show comparability between the two formulations.

9.3.3 Other Phase 4 Requests

There are no phase 4 requests for this NDA.

9.4 Labeling Review

The proposed labeling will need to be changed as dictated by the results of the additional study.

9.5 Comments to Applicant

The reviewer has no additional comments to the applicant.

10 APPENDICES

10.1 List of Abbreviations and Definition of Terms

AE	Adverse event
5-ASA 5-	Aminosalicylic acid
BUN	Blood urea nitrogen
C. difficile	Clostridium difficile
CFR	Code of Federal Regulations
CQA	Clinical Quality Assurance
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract Research Organization
GCP	Good Clinical Practices
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IVRS	Interactive voice response system
N-Ac-5-ASA	N-Acetyl-5-aminosalicylic acid
NSAID	Nonsteroidal anti-inflammatory drug
P&GP	Procter & Gamble Pharmaceuticals, Inc.
PFA	Patient's functional assessment
PGA	Physician's global assessment
UC	Ulcerative colitis

10.2 Criteria for Markedly Abnormal Clinical Laboratory Values

Table Criteria for Markedly Abnormal Clinical Laboratory Values (Section 5.3.5.1.1, Appendix 3.11, Table 2)

		Percent Change
Laboratory Test	Limits	From Baseline
Glutamate oxaloacetate transaminase (SGOT) AST	≥ 3X ULN	> 30% ↑
Glutamate pyruvate transaminase (SGPT) ALT	≥ 3X ULN	> 30% ↑
Gamma glutamyltransferase (GGT)	≥ 3X ULN	> 30% ↑
Total bilirubin	≥ 2.0 MG/DL	> 50% ↑
Alkaline phosphatase	≥ 3X ULN	> 20% ↑
Lactate dehydrogenase (LDH)	≥ 3X ULN	> 30% ↑
Glucose: Fasting	> 140 MG/DL	> 15% ↑/↓
Non-fasting (random)	> 200 MG/DL	
Fasting and Non-fasting	< 50 MG/DL	
Uric acid: Male	≥ 10.5 MG/DL	> 20% ↑
Female	≥ 8.5 MG/DL	> 20% ↑
Creatinine	≥ 2.0 MG/DL	> 25% ↑
Blood urea nitrogen (BUN)	≥ 30 MG/DL	> 30% ↑
Bicarbonate (HCO3-) - as carbon dioxide	> 1.25X ULN < 0.75X LLN	> 25% ↑/↓
Phosphorus (as phosphate)	> 1.25X ULN < 0.75X LLN	> 25% ↑/↓
Calcium	> 1.1X ULN < 0.9X LLN	> 10% ↑/↓
Sodium	> 1.05X ULN < 0.95X LLN	> 5% ↑/↓
Potassium	> 1.25X ULN < 0.75X LLN	> 25% ↑/↓
Chloride	> 1.05X ULN < 0.95X LLN	> 5% ↑/↓
Creatine Phosphokinase (CPK)	≥ 5X ULN	> 30% ↑
Hematocrit: Male	≤ 37%	> 30% ↓
Female	≤ 32%	
Hemoglobin: Male	< 11.5 G/DL	> 30% ↓
Female	< 9.5 G/DL	
WBC	< 2.8 x 10^9/L > 16.0 x 10^9/L	> 25% ↑/↓
Neutrophils: Percent	< 15%	
Eosinophils	> 10%	> 50% ↑
Platelets	< 75 10^9/L > 700 10^9/L	> 30% ↑/↓
Values are markedly abnormal if they are outside the limits and in excess of the allowed absolute or percent change from baseline.		

10.3 Disease Activity Scoring Methods

PHYSICIAN'S GLOBAL ASSESSMENT (PGA)

0 = Quiescent disease activity
0 = Stool frequency
0 = Rectal Bleeding
0 = PFA
0 = Sigmoidoscopy findings

1 = Mild disease activity (mostly 1's)
0 or 1 = Stool frequency
0 or 1 = Rectal bleeding
0 or 1 = PFA
0 or 1 = Sigmoidoscopy findings

2 = Moderate disease activity (mostly 2's)
1 or 2 = Stool frequency
1 or 2 = Rectal bleeding
1 or 2 = PFA
1 or 2 = Sigmoidoscopy findings

3 = Severe disease activity (mostly 3's)
2 or 3 = Stool frequency
2 or 3 = Rectal bleeding
2 or 3 = PFA
2 or 3 = Sigmoidoscopy findings

PHYSICIAN'S JUDGMENT -- in the case of equal scoring (i.e., 50% one score and 50% another score)

SIGMOIDOSCOPY ASSESSMENT SCORE*

0 = NORMAL (intact vascular pattern, no friability or granularity)

1 = MILD (erythema; diminished or absent vascular markings; mild granularity; friability)

2 = MODERATE (marked erythema, granularity; absent vascular markings; bleeds with minimal trauma; no ulcerations)

3 = SEVERE (spontaneous bleeding, ulcerations)

* If a colonoscopy was performed within the week prior to the Screening Visit by the same Investigator, the Sigmoidoscopy Assessment Score will be based on the first 60 cm from the anal verge.

STOOL FREQUENCY

0 = Normal stool frequency per day

1 = 1-2 stools greater than normal per day

2 = 3-4 stools greater than normal per day

3 = 5 or more stools greater than normal per day

RECTAL BLEEDING

0 = No blood seen

1 = Streaks of blood with stool less than half of the time

2 = Obvious blood with stool most of the time

3 = Blood alone passed

PATIENT'S FUNCTIONAL ASSESSMENT (PFA)

0 = Generally well

1 = Fair

2 = Poor

3 = Terrible

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MEDICAL OFFICER