

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 019651/S005**

**MEDICAL REVIEW(S)**

**Pages: 1 through 25**

*McNeil*

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER REVIEW

JUN - 4 1997

NDA: 19-651/SE1-005

Sponsor: Procter & Gamble Pharmaceuticals

Drug: Asacol® (mesalamine) Delayed-Release Tablets

Indication: Maintenance of Remission of Ulcerative Colitis

Date Received by DGCDP (HFD-180): June 6, 1996 and April 16, 1997

Date Received by Medical Officer: June 10, 1996 and April 22, 1997

User Fee Due Date: June 5, 1997

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Date Finalized: May 31, 1997

Medical Officer: Dr. Robert Prizont, MD

I. The following submitted volumes and requested in-house documents were reviewed:

(a) Submitted P&G Volumes 1, 7 (two volumes), 43, 44, 48, 51, 119, 120, 131, 155, 156. P&G Responses to DGCDP Queries in Vol. 1/7.

(b) Transcripts of the Thirty-Second Meeting of the FDA Gastrointestinal Drugs Advisory Committee. Volume II, held on Friday, September 11, 1987, Conference Room D&E, Parklawn Building.

(c) Medical Officer Review on Asacol for Therapy of induction of Ulcerative Colitis Remission, and Maintenance of Remission, Dr. William H Bachrach, February 1987. Medical Officer Review of Asacol for Treatment of Mildly to Moderate Active Ulcerative Colitis, Dr. Kathy Robie-Suh, November 1990. Volume 1/4, HFD-180.

(e) Statistical Review by Dr. W Chen, Division of Biometrics, April 1997.

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## A. INTRODUCTION AND BACKGROUND.

1. *5-ASA Formulation and Approved Indication.* Asacol<sup>®</sup> delayed-release tablets contain 400 mg of mesalamine, or 5-amino-salicylate (5-ASA), an anti-inflammatory drug. Each Asacol<sup>®</sup> delayed-release tablet is coated with an acrylic based resin, Eudragit S, *"which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti inflammatory action in the colon"*.

Asacol<sup>®</sup> delayed release tablets for oral administration was approved in January 31, 1992, for the *"treatment of mildly to moderately active ulcerative colitis: The usual dosage in adults is two 400mg tablets to be taken three times a day for a total daily dose of 2.4 grams for a duration of 6 weeks"*.

Approval of Asacol for treatment of mildly or moderately active ulcerative colitis was supported by the results of two adequate and well-controlled clinical trials. In one study, ulcerative colitis (UC) patients with active disease, placed on **2.4 grams of Asacol for 6 weeks**, had a significantly higher occurrence of sigmoidoscopic improvement than placebo patients ( $p = 0.048$ ). In the other study, UC patients with active disease, given **4.8 grams of Asacol for 6 weeks**, had a significantly higher rate of sigmoidoscopic improvement than placebo patients ( $p < 0.001$ ),

2. *Brief History of 5-ASA.* For the last 40 years, sulfasalazine oral tablets (Sulfasalazine<sup>®</sup> marketed by Lederle, or, Azulfidine<sup>®</sup> marketed by Pharmacia) administered alone or in combination with steroids, has been the conventional therapy for ulcerative colitis patients<sup>1,2</sup>. **In acute UC, daily doses of sulfasalazine tablets, 3-4 grams, control symptoms and revert the typical diffuse sigmoidoscopic appearance of rectal and colonic lesions, i.e. friability and inflammation. After the symptomatology and acute colonic inflammation subsides, oral daily doses of 1-2 grams of sulfasalazine, help to maintain and prolong the remission in ulcerative colitis treated patients.**

3. *Benefit of Asacol Use as Maintenance.* On Page 278, Vol. 1, Procter & Gamble states that the introduction of Asacol in the prescription drug market, as an additional treatment of UC in remission, would be valuable to physicians for two principal reasons:

- *"(a) Current labeled use of Asacol for the treatment of mildly to moderately active UC requires that patients who achieve remission after a 6-week,*

**2.4 g/d Asacol regimen be switched to one of only two available mesalamine-based therapies labeled for use in maintenance of UC in remission [sulfasalazine or Dipentum® (olsalazine)]. Approval of Asacol for UC maintenance would obviate the requirement that a patient be switched to a different mesalamine-based product with a distinct side-effect profile after successfully being brought into remission with Asacol. Additionally, in patients taking Asacol to maintain remission, a subsequent relapse with return of mild to moderate symptoms of active UC could be managed by increasing the Asacol dose to a level recommended for treatment of active disease.**

**(b) The side effects of Asacol are limited to those associated with free mesalamine. Both sulfasalazine and olsalazine may cause additional side effects related to their unique chemical structures. The sulfapyridine component of sulfasalazine, which is absorbed into the systemic circulation, can cause dose-related side effects (nausea, anorexia, malaise, headache) in patients described as 'slow acetylators' as well as non-dose-related hypersensitivity or idiosyncratic reactions typical of other sulfa-containing drugs<sup>4</sup>. Sulfasalazine can also cause infertility in a high percentage of male patients<sup>5,6</sup>. The olsalazine molecule, composed of two molecules of mesalamine joined by a diazo bond, is a secretagogue which can cause secretory diarrhea distinguishable from diarrhea associated with UC by its high water content and lack of blood. Overall, about 17% of patients receiving olsalazine in clinical studies reported diarrhea sometime during therapy and 6% withdrew for treatment for this reason.**

**The availability of Asacol for maintenance of UC remission would provide an additional first line therapeutic choice as well as valuable alternative mesalamine treatment for many patients with symptoms of intolerance to sulfasalazine or olsalazine".**

**Relevant References Cited from Proctor & Gamble Submitted Literature,**

- 1. Lennard-Jones JE et al. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as outpatient treatment for ulcerative colitis. Gut, 1:217-222, 1960.**
- 2. Baron JH et al. Sulphasalazine and salisylazosulphadimidine in ulcerative colitis. Lancet, 1:1094-1096, 1962.**
- 3. Azad Khan AK, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet, 2:892-895, 1977.**

4. *Das KM et al Adverse reactions during salizylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. NEJM, 289:491-195, 1973.*
5. *Levi AJ et al. Male infertility due to sulphasalazine. Lancet, 2:275-278, 1979.*
6. *Toth A. Reversible toxic effect of salisylazosulphapyridine on semen quality. Fert Steril., 31:5438-540, 1979*

## **B. PROPOSED INDICATION AND DOSAGE.**

- In Attachment A, Pages 243 and 250, Volume 1, the sponsor proposes the following changes (highlighted here), in the (a) **INDICATIONS** and (b) **DOSAGE**:

*(a) Asacol tablets are indicated for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis.*

*(b) For the treatment of mildly to moderately active ulcerative colitis: The total dosage in adults is two 400-mg tablets to be taken three times a day for a total daily dose of 2.4 grams for a duration of 6 weeks.*

*"For the maintenance of remission of ulcerative colitis: The usual dosage in adults is one 400-mg tablet to be taken two times a day for a total daily dose of 0.8 grams. In some patients, a higher daily dose of 1.6 grams, or four 400-mg tablets in divided doses may be required".*

## **C. PREVIOUS ULCERATIVE COLITIS STUDIES SUBMITTED BY P&G ON MAINTENANCE Rx WITH ASACOL; CHRONOLOGY OF REGULATORY DECISIONS.**

P & G has been seeking approval for Asacol® as maintenance therapy in ulcerative colitis patients since 1986. In the next informative paragraphs, I will briefly mention the chronology of relevant written reviews, official regulatory letters, and meetings held about submitted studies of Asacol®, and, the sequence of proposed trial designs recommended to P&G, so as to properly assess the efficacy of mesalamine as maintenance therapy for ulcerative colitis patients in remission.

- **September 12, 1986.** First P&G submission of NDA 19-651. On Page 28 of his clinical review, the late Dr. William H. Bachrach, (medical officer)

concludes that: ***"The data submitted in this NDA do not provide substantial evidence that Asacol is effective in the treatment or prophylaxis of ulcerative colitis, or that Asacol is safer than sulfasalazine for this indication"*** (February 27, 1987). Dr. Bachrach recommendation was to ***"advise the sponsor that at least one additional large placebo-controlled trial is required to permit a regulatory decision for marketing of this drug in the USA"***.

- **September 11, 1987.** NDA 19-651 is presented and discussed at the 32th Gastrointestinal Drugs Advisory Committee Meeting; Committee Chairman was Dr. David Ransohoff, members were Drs. S. Szabo, B. Fleshler, J.H. Butt, M. Shapiro, J.L. Thistle, L.F. Burmeister, M.D. Gershon, J.H. Lewis. The committee vote was ***"4-3 against"*** approval of Asacol for either sought indication, i.e., treatment of acute UC or maintenance of remission in treated UC patients (see Dr. S. Fredd counting of votes, Page 199, Transcripts of Proceedings of the September 11, 1987 GI Advisory Committee Meeting). Several committee members considered the possibility of approval of mesalamine in patients intolerant to sulfasalazine. Only one of the nine committee members voted for the unconditional approval of Asacol for both indications (Dr. J.H. Butt).
- **October 30, 1987.** Date of the non-approvable letter from the Director of Drug Research and Review to P&G, in reference to the NDA 19-651. It states that ***"it failed to provide substantial evidence consisting of adequate and well controlled studies, to demonstrate that Asacol tablets will be safe and effective for either the induction of remission or the maintenance of remission in patients with mild or moderate ulcerative colitis as either first line therapy or in patients intolerant to sulfasalazine"***. As regards to the specific data needed for Asacol approval as maintenance therapy, Dr. Robert Temple stated that the data submitted for the maintenance claim, i.e., C.1, C.2 and C.6 trials had insufficient power, and ***recommended to P&G that "The maintenance claim can be supported by a randomized withdrawal study in patients with mild to moderate ulcerative colitis on a stable dose of sulfasalazine or mesalamine, but not on steroids. The patients should be stratified by maintenance dose and randomized to placebo or a dose of mesalamine equivalent to that which had maintained remission in the particular patient"***.
- **November 25, 1987 and December 7, 1987.**

December letter, the sponsor informed that the protocol was amended on the dosage of the active compound. The planned doses of 5-ASA will be 0.8 g/day and 1.6 g/day, as recommended by the Director of the DGCDP (Pages 27-29, Vol. 1, this submission).

- **January 22, 1996.** Meeting between P & G and the DGCDP, requested by the firm to discuss *"the available data to support a maintenance of remission claim, and included in their May 17, 1995 pre-meeting package, the final report of Study 87086-86" (a multicenter, withdrawal, placebo-controlled UC maintenance trial with two doses of mesalamine)*. Representing the DGCDP were the DGCDP Director, Dr. S. Fredd,, medical officers Dr. Hugo Gallo<sup>z</sup> Torres and Dr. J. Senior, and statistician Dr. M. Huque. The Minutes of this meeting, submitted in Pages 44-48, Vol. 1. reported that *"Dr. Fredd reminded the firm of the regulatory requirement for more than a single adequate and well controlled study for approval of a maintenance of remission indication, and stated the available option for meeting this requirement. One is to conduct a second study. Another is to glean information from Studies C.1, C.2 and C.6 which can provide pivotal support. If such information isn't available, the firm must make the case that due to the robustness of the results in Study 87086, a single study is sufficient for approval. If the firm chooses the latter option, Dr. Fredd said that the application would be filed and reviewed, but could not state unequivocally that it could be approved based on a single study....Dr. Fredd acknowledged that applications have been approved on the basis of a single study, adding that he is not wedded to the absolute requirement for 2 studies; a single study may be sufficient if there is a dose response, the results are robust, and the study is internally replicated"*.

#### **D. THE SUBMITTED PIVOTAL CONTROLLED STUDIES.**

- P&G submitted two sources of data to support the claim of Asacol for maintenance of remission in patients with quiescent UC, these data are:
  1. A large multicenter, randomized, placebo-controlled trial (Study 87806).
  2. A pooled analysis of four "positive-controlled studies" of Asacol vs. sulfasalazine (C1 + C2 + C6 + C15).

**1. The Pivotal Study 87086. Titled "A Multi-Center, Double-Blind, Randomized Withdrawal Study to Compare the Efficacy of Asacol versus Placebo in the Maintenance of Remission in Subjects with Ulcerative Colitis".**

**I. Protocol.**

- **Note from the Reviewer.** P & G submitted an amended version of the original protocol. The apparent final date of the submitted amended protocol is listed in footnote numbers as July 1990, Pages 12-19, Volume 44. The actual study had already started over 2 years prior to this amended protocol version, in May 1988, under the design established in the original protocol,

When deemed necessary, I will comment on pertinent specific amendments, either during this summary, or in my final comments of the presented data.

a. **Study Population.** "At least 180 subjects . . . at least 70 subjects will be assigned to each of the three treatment groups". This sample size was revised before the start of the trial, 4/18/88, with an additional increase of "10 subjects/study group, for a total of 210 subjects".

b. **Centers.** The original version of the protocol planned for the enlistment of 3-5 centers. On 2/9/89, the sponsor amended this section of the protocol because only "57/210 subjects had been enrolled" in the first 10 months of the trial. According to the sponsor, "Dr. Fredd (FDA) recommended adding additional sites in an effort to attain our subject goal" (Page 28, Vol. 44).

c. **Inclusion Criteria.** Patients with "historically" confirmed diagnosis of ulcerative colitis in remission, as revealed by a proctosigmoidoscopy of grade 0, having  $\leq 5$  bloodless stools per day, "on any oral product containing 5-ASA, for 1 to 12 months", with the dose constant for at least 1 month prior to enrollment. Eligible patients must be "steroid independent" for at least 1 month prior to the study and if female, have a negative pregnancy test or, be willing to practice contraception. Eligible patients must be willing to keep a daily diary during the study.

d. **Exclusion Criteria.** Patients with a history of allergy or intolerance to aspirin, 5-ASA or other salicylates, or having received topical rectal therapy during 1 month prior to study entry, or of extensive small bowel resection causing short bowel syndrome. Excluded will also be nursing mothers or patients with a BUN or serum creatinine of 1.5 times the upper limit of normal (uln) or liver enzymes  $> 2$  times the uln.

*e. Schedule for Patient Visits, Proctosigmoidoscopy and Lab Assessments.*

The schedule include a prestudy assessment to ensure the patient meets the inclusion criteria, is provided with the blinded medication and is informed of sequence of procedures, benefits, risks involved in using the experimental therapy. The protocol defines this patient visit as **VISIT 1**.

According to the protocol, three more study visits will be scheduled, i.e., one month after the first assessment = **VISIT 2**, three months after the first assessment = **VISIT 3**, and six months after the first assessment = **VISIT 4**.

All Patient VISITS include proctosigmoidoscopy, drug compliance and lab tests.

The following protocol chart, included on Page 7 of the original protocol, lists schedule visits.

	Prestudy	Double-Blind Treatment Period		
		Months		
		1	3	6
History	X			
Physical Examination	X	X	X	X
CBC	X	X	X	X
Serum Chemistry	X	X	X	X
Special Evaluation of Blood	X			X*
Complete Urinalysis	X	X	X	X
Special Evaluation of Urine	X			X*
Pregnancy Test	X	X	X	X
Stool Examination/ Microbiology		*	*	*
Proctosigmoidoscopy	X	X	X	X
Drug Compliance		X	X	X

\*To be performed only on subjects suspected of having a relapse.

\*To be performed at 6 months or at time of withdrawal from study.

*f. Dosing. The original version of the protocol established that eligible UC patients in remission will be randomized to placebo, 1.2 g/day or 2.4/day of Asacol. This section was revised before the start of the trial, 12/1/87, to change the two doses of Asacol from 1.2 g/day and 2.4 g/day to 0.8 g/day and 1.6 g/day.*

*g. Definition of Treatment Failures. According to the submitted protocol, the following will be considered treatment failures:*

*"a. Relapse, defined as a proctosigmoidoscopy score  $\geq 1$  as related to ulcerative colitis;*

*b. Significant adverse reaction (whether or not felt to be drug related) or intolerance to study medication".*

*h. Proctosigmoidoscopy.* According to the protocol, endoscopic assessment of inflammation in the rectum and sigmoid due to ulcerative colitis, will be scored as follows:

**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).

*i. Efficacy Analysis.* The protocol states that *"comparison of efficacy of Asacol versus placebo in maintaining remission in subjects with ulcerative colitis will be accomplished by analyzing the main efficacy parameter of interest: the proportion of subjects in each treatment group who relapse during the course of the study. There will be different comparisons of each Asacol treated group with the placebo group"*.

The original version of the protocol established an *"interim analysis on the first 3 months of data from all subjects"*. It stated that *"The sponsor will keep track of the number of subjects who relapse within the first 3 months of therapy for each treatment group and, when the last subject entered completes the 3-month visit, the data will be analyzed"*.

The sponsor revised this section of the protocol before commencing the trial, on 3/18/88, i.e., *"removal of the 3-month interim analysis"*.

*ii. Descriptive of Pivotal Study 87086.* Included in Volume 43.

- My descriptive of this placebo-controlled multicenter trial is a brief summary of the relevant results provided by the sponsor,

*1. Duration of the Trial.* This trial lasted 4 years and 4 months; from May 1988 until September 1992 (page 8).

*2. Centers.* There were 18 centers enlisted in the trial; 17 centers enrolled patients, one center chose to discontinue participation prior to entering any patients.

3. *Study Population.* According to the *Synopsis* section, Page 6, Vol. 43, and the data included in the results section, "there were 264 patients enrolled in this study with 189 patients eligible for the completed-patient analysis".

On Page 44, Vol. 43, P & G states that "Blinded review of the number of non-analyzable study patients (conducted on February 1, 1991) indicated that the 10% dropout rate anticipated during the original sample size determination was a significant underestimate of the number of non-analyzable patients to date. The actual dropout rate (30%) was then used to determine the number of additional patients needed to achieve a sufficient enrollment for study completion. The calculated increase from 210 to 261 study patients

The sponsor listed the *Patient Enrollment and Study Completion by Investigator* in Table 4.

The sponsor's Table 4, Page 44, Vol. 43, with listing of *Patient Enrollment by Investigator* is included as Appendix 1 of this review.

4. *Patient Disposition.* In the following P&G Table 5, Page 45, Vol. 43, the sponsor "presents the number of patients who completed the study per protocol (completed patients) and the number of patients discontinued from the study for unrelated to efficacy or adverse events (non-completed patients).

Table 5  
Patient Accountability

	Placebo N = 87	Asacol 0.8 g/day N = 90	Asacol 1.6 g/day N = 87	Total N = 264
<b>Completed</b>	61	68	58	187
Completed - success	25	40*	38	103
Completed - failure/relapse	34	24	18	76
Completed - failure - Adverse Events	4	4	2	10
<b>Non-Completed:</b>	24	22	23	25
Entry Criteria Violations	12	10	12	34
Post-Study Entry Protocol Violations	12	12	11	41
<b>Entry Criteria Violations:</b>	12	10	12	34
Baseline therapy	8	7	10	25
Not in remission per proctosigmoidoscopy	3	0	0	3
Diagnosis of UC unconfirmed	1	2	2	5
Elevated liver enzymes	0	1	0	1
<b>Post-Study Entry Protocol Violations:</b>	12	12	11	41
Lost to follow-up	2	2	1	5
Voluntary withdrawal	1	0	4	5
Intercurrent illness (surgery)	0	0	1	1
Concomitant medications	3	1	6	10
Non-compliance with study medication	4	9	4	17
Non-compliance with proctosigmoidoscopy	1	0	0	1
Non-compliance with study visits	1	0	1	2

N = number of patients.

\* In the Asacol 0.8g/d treatment group there are 41 completed patients with proctosigmoidoscopy scores of "0" at the month 6 visit (i.e. treatment success). However, patient # 34090219 had a proctosigmoidoscopy score of "1" at the 3 month visit and was thus determined a treatment failure.

Supporting data can be found in Appendix 5, Table 25 and in Appendix 8, Table 17.

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Under Table 5, the sponsor included an explanatory paragraph with reference to three patients who received topical steroids, but completed the trial. This paragraph states that *“Three patients were prescribed topical rectal therapies during their participation in this study, despite the protocol guidelines regarding concomitant medication use. Patient #16330214 (0.8 g/day Asacol) was diagnosed with pruritus ani and was prescribed Proctofoam (1-2 application prn, duration unknown). Patient #18800218 (0.8 g/day Asacol) was prescribed Anusol-HC for hemorrhoids (1 suppository/day, for 6 days). Patient #19430213 (1.6 g/day Asacol) was prescribed Anusol to treat hemorrhoids (2 suppositories/day for 4 days). Due to the nature of the concomitant illness and short duration of medication use, these patients were not excluded from study participation”.*

The next sponsor Table 6, Page 46, Vol. 43, displays the time of discontinuation of patients by study visit and reason for discontinuation..

**Table 6**  
**Time of Discontinuation of Patients by Study Visit and Reason<sup>a</sup>**

Study Month	Reason for Discontinuation <sup>b</sup>	Placebo N = 87 n (%)	Asacol 0.8 g/day N = 90 n (%)	Asacol 1.6 g/day N = 87 n (%)
MTH 0.0 to < MTH 1.0	Voluntary withdrawal	0 (0%)	0 (0%)	2 (2.3%)
	Not in remission per proctosigmoidoscopy	1 (1.1%)	0 (0%)	0 (0%)
	Elevated liver enzymes	0 (0%)	1 (1.1%)	0 (0%)
MTH 1.0 to < MTH 3.0	Voluntary withdrawal	1 (1.1%)	0 (0%)	1 (1.1%)
	Non-compliance with study medication	0 (0%)	2 (2.2%)	0 (0%)
	Lost to follow-up	2 (2.3%)	1 (1.1%)	1 (1.1%)
	Baseline therapy	1 (1.1%)	1 (1.1%)	2 (2.3%)
	Not in remission per proctosigmoidoscopy	1 (1.1%)	0 (0%)	0 (0%)
MTH 3.0 to < MTH 6.0	Voluntary withdrawal	0 (0%)	0 (0%)	1 (1.1%)
	Non-compliance with study medication	0 (0%)	2 (2.2%)	1 (1.1%)
	Lost to follow-up	0 (0%)	1 (1.1%)	0 (0%)
	Baseline therapy	1 (1.1%)	1 (1.1%)	0 (0%)
	Not in remission per proctosigmoidoscopy	1 (1.1%)	0 (0%)	0 (0%)
	Concomitant medications	0 (0%)	0 (0%)	1 (1.1%)
MTH 6.0	Non-compliance with study medication	4 (4.6%)	5 (5.6%)	3 (3.4%)
	Baseline therapy	6 (6.9%)	5 (5.6%)	6 (6.9%)
	Concomitant medications	3 (3.4%)	1 (1.1%)	5 (5.7%)
	Diagnosis of UC unconfirmed	1 (1.1%)	2 (2.2%)	2 (2.3%)
	Intercurrent illness	0 (0%)	0 (0%)	1 (1.1%)
	Non-compliance with proctosigmoidoscopy	1 (1.1%)	0 (0%)	0 (0%)
	Non-compliance with study visits	1 (1.1%)	0 (0%)	1 (1.1%)

N = number of patients in each treatment group. n = number of patients in each discontinuation group. % = n/N.

<sup>a</sup> "Reasons for Discontinuation" column for each time period lists only reasons that caused patients to discontinue study participation during that period.

<sup>b</sup> See Table 2, pg 11 for a listing of the accountability categories used in the CRFs and in the evaluations.

Supporting data can be found in Patient Information Displays (PIDs) and in Appendix 8, Tables 16 and 17.

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The sponsor states that *“A relatively large proportion of patients discontinued the study at Month 6 for reason Other”.*

5. *Demographics.* According to the text and tables provided by the sponsor (Tables 7 and 9, Vol. 43) there were no differences in patient age between the placebo and the two 5-ASA doses, either in the all-patients comparison or in the completed patient analysis. There were differences in the proportion of *All Patients males* enrolled the Placebo patients = 54(62%) or 5-ASA 0.8 g = 55 (61%) and Asacol 1.6 g = 37(43%). The same difference, but in reverse, was observed in the proportion of females enrolled in the three treatment groups. A similar difference in males and females between treatment groups was seen in the completed patient population.

Table 8 lists the history of UC, the length of disease, prestudy medication and stool frequency in the *All Patients* group. Table 8, Page 49, Vol. 43, is shown below.

**Table 8**  
**Baseline Characteristics - All Patients**

	Placebo N = 87 n (%)	Asacol 0.8 g/day N = 90 n (%)	Asacol 1.6 g/day N = 87 n (%)
<b>Length of History of Ulcerative Colitis (years):</b>			
< 1	9 (10.3%)	13 (14.4%)	13 (14.9%)
1 - 5	23 (26.4%)	23 (25.6%)	22 (25.3%)
> 5 - 10	22 (25.3%)	22 (24.4%)	23 (26.4%)
> 10	33 (37.9%)	31 (34.4%)	29 (33.3%)
unknown	0	1 (1.1%)	0
<b>Extent of Disease:</b>			
proctitis	→ 13 (14.9%)	→ 10 (11.1%)	→ 16 (18.4%)
proctosigmoiditis	→ 20 (23.0%)	→ 28 (31.1%)	→ 15 (17.2%)
left-sided	13 (14.9%)	18 (20.0%)	17 (19.5%)
pancolitis	24 (27.6%)	26 (28.9%)	23 (26.4%)
unknown	→ 17 (19.5%)	→ 8 (8.9%)	16 (18.4%)
<b>Prestudy Medication for Ulcerative Colitis:</b>			
sulfasalazine	48 (55.2%)	→ 58 (64.4%)	54 (62.1%)
any oral 5-ASA product	37 (42.5%)	31 (34.4%)	32 (36.8%)
other	2 (2.3%)	1 (1.1%)	1 (1.1%)
<b>Stool Frequency:</b>			
one per day	27 (31.0%)	→ 41 (45.6%)	30 (34.5%)
two per day	37 (42.5%)	31 (34.4%)	40 (46.0%)
three per day	14 (16.1%)	12 (13.3%)	10 (11.5%)
four or more per day	9 (10.3%)	6 (6.6%)	7 (8.0%)
mean number per day (SEM)	2.08 (0.109)	1.83 (0.103)	1.95 (0.102)

N = number of patients in treatment group. n = number of patients in baseline characteristic category. % = n/N.  
Supporting data can be found in PIDs; Appendix 5, Tables 1.3.1 and 2.1.1, Appendix 7, Tables 2.1.1, 2.2.1, 2.3.1, and in Appendix 8, Tables 1.1 and 1.2.

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6. *Drug Compliance.* The sponsor states that according to the study protocol, non-compliance with study drug is defined "as missing more than 15% of the study medication over the length of treatment or more than 50% of the study medication for 4 consecutive days (for reasons other than intolerance or adverse events)". Twenty-one study participants were determined to be non-compliant with study treatment on the basis of these criteria. "Sixteen patients were discontinued from the trial because of dosing non-compliance, five were discontinued for dosing non-compliance and other protocol violations".

*The Submitted List of Non-Compliant Patients, Page 56, Volume 43, is Included as Appendix 2 of this review.*

7. *Patient Outcome.* According to the sponsor's *All Patients* analysis, shown in Table 17, fewer patients treated with Asacol 0.8 g/day were treatment failures than the proportion of treatment failures in the Placebo group, this difference was statistically significant at  $p=0.05$  by Fisher's exact test. An even smaller proportion of treatment failures than that observed in placebo or low Asacol dose was seen in UC patients treated with the high Asacol 1.6 g/day dose.

The sponsor's *All Patients* outcome, Table 17, Page 61, Vol. 43, is shown below.

**Table 17**  
**Patient Outcome - All Patients**

	Placebo n (%)	Asacol 0.8 g/day n (%)	Asacol 1.6 g/day n (%)
Treatment Success	42 (48.3%)	57 (63.3%)*	61 (70.1%)#
Treatment Failure	45 (51.7%)	33 (36.7%)	26 (29.9%)
N	87	90	87

N = total number of patients in each treatment group. n = number of patients in each patient outcome category. % = n/N.  
 \*  $p = 0.050$ , compared with Placebo (Fisher's exact test, 2-tail).  
 #  $p = 0.005$ , compared with Placebo (Fisher's exact test, 2-tail).  
 Supporting data can be found in Appendix 5, Table 26.1.1; Appendix 7, Table 3.1.1.

A higher statistical significance in the difference between the proportion of treatment failures in the placebo group and the Asacol dose groups was seen in the comparison of *Completed Patient* populations.

*Completed Patient* outcomes, Table 13, Page 57, Vol. 43, is shown next.

**Table 13**  
**Patient Outcome - Completed Patients**

Patient Outcome	Placebo n (%)	Asacol 0.8 g/day n (%)	Asacol 1.6 g/day n (%)
Treatment Success	25 (39.7%)	40 (58.8%)*	38 (65.5%)#
Treatment Failure	38 (60.3%)	28 (41.2%)	20 (34.5%)
N	63	68	58

N = total number of patients in each treatment group. n = total number of patients in each patient outcome category. % = n/N.  
 \*  $p = 0.036$ , compared with Placebo (Fisher's exact test, 2-tail).  
 #  $p = 0.006$ , compared with Placebo (Fisher's exact test, 2-tail).  
 Supporting data can be found in Appendix 5, Table 26.1.2 and Appendix 7, Table 3.1.2.

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8. *Effect of Amended Scoring System on Patient Outcome.* On 4/2/90, approximately 2 years after the start of the trial, the sponsor amended the entry requirement of normality for the main efficacy endpoint of proctosigmoidoscopy. The amendment, submitted in Page 29, Vol. 44, modifies the entry criteria by defining a proctosigmoidoscopy with a "grade 0" as normal or with features of mild mucosal inflammation, i.e. 1+ edema, 1+ hyperemia, 1+ erythema, 1+ granularity (but no friability).

On Page 52, Vol. 43, P&G explains the following: *"Since the amendment was implemented after the study start date, all patients were evaluated according to the amended scoring system regardless of when they entered into the study. To clearly understand the possible impact of this amendment on the study, the case report forms of all 264 enrolled patients were reviewed prior to unblinding the study data. The purpose of the review was to identify the patients whose proctosigmoidoscopic scores and thus potentially their outcome rating would be affected by retroactive application of the protocol amendment. There were no cases of patients enrolled after the amendment for whom the investigator failed to correctly apply the amended proctosigmoidoscopic scoring system. Also, none of the patients who had been entered into the study under the original scoring system were at later visits evaluated by the amended scoring system"*.

P&Gs CRF review revealed that the proctosigmoidoscopic ratings of 8 patients (3% of the total study population), who were enrolled and evaluated prior to the amendment, were changed after the implementation of the amended scoring system. Outcome changes were made in 6 Asacol 1.6 g patients. All of these Asacol patients were changed from failure to success in the *Intent-To-Treat* analysis; three of these Asacol patients were declared ineligible for the *Completed Patients* analysis. The outcome of two Placebo patients were also changed, in the *Intent-To-Treat* population one Placebo was changed from success to failure whereas the other was changed from failure to success. One of these placebo patients was declared ineligible for the *Completed Patients* analysis. These outcome changes were illustrated by the sponsor in the following P&G Table, included in Page 63, Vol. 43.

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EFFECT OF PROTOCOL AMENDMENT #091 ON THE PRIMARY AND INTENT-TO-TREAT EFFICACY ANALYSES					
Patient #	Treatment group	Original scoring system*		Amended scoring system*	
		Primary analysis	Intent-to-treat analysis	Primary analysis	Intent-to-treat analysis
First group of 3 patients					
15050210	Asacol 1.6 g/day	Failure	Failure	Indigible	Success
16330209	Asacol 1.6 g/day	Indigible	Failure	Indigible	Success
28100212	Placebo	Failure	Failure	Indigible	Success
Second group of 3 patients					
15580214	Placebo	Failure	Failure	Failure	Failure
15580215	Asacol 1.6 g/day	Failure	Failure	Success	Success
35120210	Asacol 1.6 g/day	Failure	Failure	Success	Success
Final 2 patients					
28100213	Asacol 1.6 g/day	Failure	Failure	Success	Success
35120209	Asacol 1.6 g/day	Failure	Failure	Success	Success

\* Possible treatment outcome: Indigible or Eligible (could be treatment success or treatment failure).

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9. *Time to Relapse.* In its comment on the time of relapse in the *All Patients* population, the sponsor notes that "The Placebo and Asacol 0.8 g/day groups did not differ significantly as determined by the log rank test ( $p = 0.074$ ); however, the Placebo and Asacol 1.6 g/day groups did differ significantly with respect to their rates of time to relapse (survival analysis) as determined by the log rank test ( $p = 0.008$ )". The time of relapse in the Completed Patients population favored significantly both Asacol doses over Placebo.

The following P&G Table 22 was taken from Page 65, Vol. 43.

Table 22  
Time to Relapse Results: All Patients.

Time to Relapse (weeks)	Placebo N = 87 n (%)	Asacol 0.8 g/day N = 90 n (%) <sup>a</sup>	Asacol 1.6 g/day N = 87 n (%) <sup>#</sup>
0 - 4	6 (6.9%)	5 (5.6%)	6 (6.9%)
5 - 8	10 (11.5%)	8 (8.9%)	6 (6.9%)
9 - 12	6 (6.9%)	3 (3.3%)	3 (3.4%)
13 - 16	5 (5.7%)	3 (3.3%)	0 (0%)
17 - 20	3 (3.4%)	3 (3.3%)	2 (2.3%)
21 - 24	1 (1.1%)	3 (3.3%)	1 (1.1%)
> 24	6 (6.9%)	4 (4.4%)	6 (6.9%)
Censored <sup>¶</sup>	50 (57.5%)	61 (67.8%)	63 (72.4%)

N = total number of patients who relapsed. n = number of patients who relapsed at specific time. (%) = n/N.  
<sup>a</sup>  $p = 0.074$ , compared with Placebo (log rank test).  
<sup>#</sup>  $p = 0.008$ , compared with Placebo (log rank test).  
<sup>¶</sup> Censored patients were those who did not relapse during study treatment and those who discontinued study participation prematurely because of an adverse event.  
 Supporting data can be found in Appendix 5, Table 27.1 and Appendix 7, Table 4.1.

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**iii. Reviewer Comments.**

**1. About P&G Efficacy Results.** The six month efficacy results for proctosigmoidoscopic relapses, as presented by the sponsor, show superiority of Asacol over placebo in the maintenance of UC remission.

According to the data submitted by P&G in Tables 13 and 17 and presented in my *Descriptive of Patient Outcome*, the superiority of Asacol 1.6 g/day over placebo was highly significant in both, the Completed Patients analysis and Intent-To-Treat analysis. *In contrast, the 19% superiority of Asacol 0.8 g/day over Placebo was very significant in the Completed Patients analysis, i.e.,  $p=0.036$ , but it fell to a minimum significance, i.e.,  $p=0.05$ , in the Intent-To-Treat comparison.*

**2. Enrollment of Patients in Relapse.** As stated in the prospective protocol, the primary requisite for a patient inclusion into this trial was the total absence of rectal mucosal inflammation by proctosigmoidoscopy (score 0 = normal). As stated in my *Descriptive*, subsection *Effect of Amended Scoring System on Patient Outcome*, the sponsor changed this primary efficacy criteria two years into the trial, on April 3, 1997.

Between the starting of the trial, in May 1988, and prior to the change in the primary endoscopy endpoint, on April 1990, the sponsor had enrolled three patients with endoscopic features of rectal mucosal inflammation. Apparently, no other patients with features of mucosal inflammation were enrolled after the amendment of endoscopy at entry.

The only three patients enrolled in UC relapse, i.e., rectal inflammation, were all Placebo patients; all three patients were declared Treatment Failures.

The following MO Reviewer Table 1 summarizes the data and outcome of these three Placebo patients.

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**MO Reviewer Table 1**

**Study 87086. Patients Enrolled With Endoscopic Features of UC Relapse**

Center/Patient Date of Enrollment	Drug	Proctosigmoidoscopy	Outcome *
1505/15050205 Enrolled 10/31/'88	Placebo	<i>Entry: Grade 1; Mild Inflammation</i>	<i>Discontinued; Treatment Failure:</i>
1978/19780208 Enrolled 10/3/'88	Placebo	<i>Entry: Grade 2; Moderate Inflammation, i.e., friability.</i>  <i>Month 1 Visit: Grade 1, Mild Inflammation i.e., no friability.</i>	<i>Discontinued on Month 3 Visit as Treatment Failure</i>
3409/34090232 Enrolled 1/31/'90	Placebo	<i>Entry: Grade 1; Mild Inflammation</i>  <i>Month 1 Visit: Grade 2; Moderate Inflammation.</i>	<i>Treatment Failure</i>

\* Data Taken from Appendix 8, Table 2.2, Vol. 48., and Appendix 8, Table 18, Vol. 51.

The data shown in MO Reviewer Table 1 reveal an imbalance in the number of patients with endoscopic features of UC relapse at entry. The imbalance in the proportion of endoscopic relapses at entry, i.e., 3 PI vs 0 Asacol 0.8 g/day and 1.6 g/day, is unfavorable to the placebo group. Further, Patient 0208 was enrolled with a Grade 2 rectal inflammation and improved, while on placebo, to Grade 1 rectal inflammation. This improvement may have qualified as a success, e.g., decrease in one grade of inflammation.

In order to fully assess the impact of these imbalances upon the primary efficacy results, I requested to the GI Group Statistician Leader, Division of Biometrics (Dr. M. Huque), to perform a sensitivity comparison in the *All Treated Patient Population*, with exclusion of one, two, or all three ineligible placebo patients. The following MO Reviewer Table 2 illustrates the results of this sensitivity analysis. As noticeable in this MO Reviewer table, efficacy in the adjusted placebo population

was compared against efficacy in the 5-ASA 0.8 g/day dose. The comparison with the 5-ASA g/day dose was preferred for two main reasons: (a) 0.8 g/day was the maintenance dose proposed by the sponsor in the submitted label, and (b) as stated in my *Descriptive*, this proposed 0.8 g/day dose exhibited only marginal efficacy superiority over placebo, i.e.,  $p=0.05$ , in the sponsor's *All Treated Patient* or *Intent-To Treat* analysis (ITT, Table 17).

## MO Reviewer Table 2

## Efficacy In The All Treated Patients Entered In Remission By Normal Endoscopy

Sponsor's ITT and Adjusted All Treated Patients	Number of Relapses/Total Patients (%)		Two Sided p-Values
	Placebo	5-ASA 0.8 g	(a) Fishers Exact Test (b) Chi Square Test
Sponsor's Intent-To-Treat	45/87 (52%)	33/90 (37%)	(a) $p=0.05$
<i>Minus 1 Ineligible Placebo</i>	44/86 (51%)	33/90 (37%)	(a) $p=0.068$ * (b) $p=0.053$ *
<i>Minus 2 Ineligible Placebo</i>	43/85 (<51%)	33/90 (37%)	(a) $p=0.069$ * (b) $p=0.064$ *
<i>Minus 3 Ineligible Placebo; - All Patients Entered in Remission Comparison -</i>	42/84 (50%)	33/90 (37%)	(a) $p=0.092$ * (b) $p=0.077$ *

\* Indicates the difference is not statistically significant.

The results of the sensitivity analysis displayed in MO Reviewer Table 2 reveal a lack of statistically significant superiority by the Asacol low dose over Placebo if either one, two, or all three ineligible Placebo patients are excluded from the analysis. The results of this sensitivity analysis weakens considerably a claim of superiority for the 0.8 g/day Asacol dose, since it suggest that the initial apparent superiority with this low Asacol dose was contingent to the inclusion of ineligible placebo patients, entered with proctosigmoidoscopy scores of mucosal inflammation, i.e., endoscopy scores consistent with ulcerative colitis in relapse.

**3. Inconsistencies.** According to P&G Table 23, (see my *Descriptive*, subsection 9. Time to Relapse), the number of relapses which occurred in the Placebo, Asacol 0.8 g and Asacol 1.6 g treatment groups was 37, 29 and 24, respectively. The number of patients withdrawn due to adverse events was 4, 4, and 2, respectively. Therefore, the number of treatment failures in the *All Treated Patients* for the Placebo, 5-ASA 0.8 g and 5-ASA should be 41, 33, and 26, respectively, (e.g., relapses + withdrawn due to AE).

In P&G Table 17 (see my *Descriptive*, subsection 7. *Patient Outcome*), the number of treatment failures included in the sponsor's *All Treated Patient* analysis is 45 for Placebo, 33 for Asacol 0.8 and 26 for Asacol 1.6, respectively.

The patient numbers of these four placebo treatment failures and the reason for inclusion in the sponsor's ITT is unknown to this reviewer. A written request for the identification of these additional placebo treatment failures, as well as reason for inclusion as treatment failures, has been forwarded to the sponsor in a DGCDP letter dated March 31, 1997.

**The March 31, 1997 letter with requests from the DGCDP to the sponsor is included as Appendix 3 of this review.**

**4. Completed Patients vs. Intent-To-Treat.** The patient population included in the sponsor's main analysis of efficacy was the completed patient population. Though this main analysis was included in the study protocol, a comparison of the Intent-To-Treat patient population is now more of relevance because of the following reasons:

(a) As stated in the study Protocol of December 1, 1987 (see *I. Protocol*, subsection a. *Study Population*) the prospectively planned sample size had a total of 180 patients. Four months later but prior to the beginning of the trial, this prospective planned sample size was amended and increased to 210 patients. In August 26, 1991, three years and four months into the trial, the sponsor amended the sample size up to 261 patients. As observed in my *Descriptive*, subsection 3. *Study Population*, this 1996 NDA stated that 264 patients were enrolled in this trial.

On Page 9, Vol. 43, the sponsor states that "*Patients were given study medication for the entire 6-month treatment period at their prestudy screening. After the results of the prestudy screening had been evaluated, patients eligible to participate in the study were instructed to begin taking their study medication. In six cases (Pts. 15580211, 18800219, 19780203, 19780206, 34090209, 34090216) study medication and the corresponding patient number were given to patients who were found to be ineligible for study entry. These patients did not take study medication, and*

*their study medication was returned unopened to the sponsor".* These six, apparently randomized patients, were not included in any patient tabulation list submitted with this NDA. My review indicates that there were largely placebo assignments. A request for clarification about reasons for ineligibility of these six excluded patients was part of the DGCDP letter sent to the sponsor on March 31, 1997 (see Appendix 3, this review). The probable total randomized patient population enrolled in this trial was actually up to 270 patients (*from the 180 patients planned in the prospective protocol*). An Intent-To-Treat (ITT) comparison with inclusion of all randomized patients (RP) becomes now of relevance, for it might well further change the difference in primary efficacy between the low dose Asacol and the placebo control.

(b) The sponsor's main efficacy analysis with completed patients was based on the aforementioned planned population of 180 patients. As I explained in the previous paragraph (a), the actual randomized patient population enrolled in this trial was 50% higher than planned. Further, the prospective total patient size planning estimated a 10% dropout rate. The actual average total dropout rate of the *All Patient* population was over 2½ higher, i.e., 28% (PI = 28%; 5-ASA 0.8g = 24%, 5-ASA 1.6g = 33%). An ITT of all RP is relevant to assess the impact of this high rate of patient dropout, which occurred during the trial (*in fact, to have a complete picture of the dropout impact we would need to add the six randomized patients who were discontinued before their starting of the study medication*).

5. *The Issue of Amending Outcomes* (see my *Descriptive* of this study 87086, subsection 8, "*Effect of Amended Scoring System on Patient Outcome*"). As described, the outcome of 8 patients were changed in compliance with an amendment of the primary endpoint endoscopy scores incorporated in the protocol two years after initiation of the trial.

Two of these patients were placebo patients. The outcome of one placebo patient was changed from success to failure whereas the outcome of the other placebo patient was changed from failure to success. The change in the two placebo patients, per se, should have no substantial impact on the original placebo efficacy, for the one placebo failure was neutralized by another placebo success.

In contrast, *the outcome of the six 5-ASA 1.6g patients, all changed from the originally declared treatment failures into treatment success*, might have possibly altered the original Asacol efficacy. These outcome changes favor the Asacol 1.6 g/day treatment.

The sponsor did not submit any comparative analysis of primary efficacy based on the original endoscopy outcome scores.

I requested the statistician reviewer to calculate the differences in outcome between placebo and Asacol 1.6 using the original placebo and high 5-ASA outcomes.

The following MO Reviewer Table 3 illustrates this point.

**MO Reviewer Table 3**

**ITT Efficacy Results Using Original and Amended Outcomes**

Patient Population	Placebo	Asacol 1.6 g/day
<i>Original Outcomes</i>	41/87 (47%)	55/87 (63%)
	<i>p = 0.033</i>	
Amended Outcomes	42/87 (48%)	61/87 (70%)
	<i>p = 0.005</i>	

As seen in MO Reviewer Table 3, as compared to the amended version, the original Asacol 1.6 patient population revealed a 7% lower efficacy rate, and, the difference with the original placebo efficacy was decreased to 13%.

It should be noted that the placebo patient population in the original version still included three ineligible placebo patients enrolled in UC relapse (*see Reviewer Comments, subsection 2*). The comparison of original outcomes, based on an *all patients in remission at entry as established by the original protocol at the time of enrollment*, markedly decreases the difference between placebo and 5-ASA 1.6. This is illustrated in the following MO Reviewer Table 4.

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## MO Reviewer Table 4

## Comparison of Original Outcomes in the ITT Population of Patients in Remission

Patient Population	Placebo	Asacol 1.6 g/day
Original Outcomes with All Patients in Remission (excludes 3 placebo patients enrolled while in relapse, as established by the protocol at the time of patient enrollment)	41/84 (49%) <i>p</i> = 0.065 (Fisher Exact)* <i>p</i> = 0.058 (Chi Square)*	55/87 (63%)

\* Indicates comparison between placebo and Asacol is not statistically significant.

MO Reviewer Table 4 shows that the comparison of efficacy between placebo and Asacol 1.6 with inclusion of patients in remission and using the original outcomes reveals a difference between success rates of 14% which is only numerical and not longer statistically significant.

**2. Pivotal Results from Combined Trials C1 + C2 + C6 + C15.** As stated in the opening of this review's section C. *Submitted Controlled Pivotal Studies*, P&G submitted, as additional pivotal data to support the indication of Asacol in the maintenance of UC remission, the results of pooled data from four small controlled studies. In these studies, the efficacy of Asacol (5-ASA) in maintaining UC remission was compared to that of sulfasalazine (SAS), the only drug approved for the maintenance indication. These four small controlled trials were each named by P&G as C1, C2, C6, C15, respectively.

- In the following paragraphs, I will very briefly summarize the design and descriptive of these four trials, then show the sponsor's results of the pooled analysis, and complete this section of the review with my comments.

**1. Study C1.** Initiated in November 1981; completed in March 1982.

According to the sponsor's text, NDA 19-651, Vol. 7, 1986 submission, this was a randomized, "double-dummy, double-blind" 16 week study. All patients were in a "state of remission from ulcerative colitis or proctitis, i.e., they claimed to be passing fewer than three stools/day without blood or mucus, confirmed by sigmoidoscopy on admission to the trial. Admission sigmoidoscopy findings were