

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019651/S005

MEDICAL REVIEW(S)

Pages: 26 through 50

verified by a pathological assessment, as occasionally sigmoidoscopy grades are high compared to pathology ratings and the patient's own symptoms ratings".

Prior to the study, patients were taking stable maintenance tablets of sulfasalazine at "a minimal dose of 2g daily". The sponsor states that after randomization, the dose given to patients was based on the patient's usual dose of sulfasalazine. According to the sponsor, the Asacol dose was based on the weight equivalence of 400 mg 5-ASA = 1g SAS, so all patients received at least 3 Asacol tablets "with an increase of 1 tablet for each gram of SAS above the entry dose of 2g".

The mean dose for 5-ASA was 1.4 g/d ; the mean dose for SAS was 2.4 g/d

A total of 72 UC patients were randomized to the trial, 36 in each treatment group. One patient in SAS had Crohn's disease and was withdrawn from the trial. The ITT population does include this patient.

There were some differences in the demographics: F/M ratio was 22/14 for 5-ASA; and 14/22 for SAS. There 15 Asacol patients with left sided colitis vs 8 SAS, but in contrast, only 4 Asacol patients had total colitis vs. 9 total colitis in SAS patients. Both treatments had similar number of proctitis (17-18).

The following table, taken from Page 0759, Vol 7, details the proportion of withdrawals, number and proportion of relapses and number and proportion of maintained without relapse.

	<u>Maintenance of Remission/Relapse Data</u>			
	<u>Total Maintained</u>	<u>Total Relapsed</u>	<u>Withdrawals Because of Adverse Event</u>	<u>Other Withdrawals From Study</u>
Asacol	22 (61%)	9 (25%)	0	5 (14%)
Sulphasalazine	27 (75%)	6 (17%)	0	3 (8%)

ii. *Study C2.* Initiated in February 1982; completed in January 1983.

Similar to C1, this was a "randomized, double-blind, double-dummy, two parallel group". The duration of this study was extended to 6 months. The dose of Asacol was doubled. The actual mean dosage taken from Page 369, Vol. 51, was the following:

MEAN	<u>Asacol</u>	<u>Salazopyrin</u>
DOSAGE:	2.78 g/day in divided doses	2.25 g/day in divided

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The primary endpoint maintenance of remission as evidenced by sigmoidoscopy 1 or 2 (equivalent to grade 0 or 1) at the end of the study.

The following were number of patients enrolled and demographics, taken from Page 369, Vol. 51.

	<u>Asacol</u>	<u>Salazopyrin</u>
Total Patients/Sex	35 (21 males, 14 females)	32 (15 males, 17 females)
Mean Age	49 years (range	43 years (range
Mean Disease Duration	8.9 years (range	7.2 years (range
Extent of Disease	Proctitis 19, left-sided 6, total colon 10	Proctitis 16, left-sided 10, total colon 6

An issue of relevance is noted by the sponsor on Page 110, Vol. 119:

"It should be noted that 51 of the patients who participated in C2 had previously participated in C1. Twenty-seven of the patients who received sulfasalazine in C1 were enrolled in study C2 and crossed over to the Asacol treatment group. Twenty-two of the patients who received Asacol in C1 were crossed over to receive sulfasalazine in C2. One patient received Asacol in both C1 and C2 and one patient received Asacol in both C1 and C2".

The results of this trial, shown next, were taken from Page 370, Vol. 51.

<u>Asacol</u>	<u>Salazopyrin</u>
23 patients (66%) were maintained, completing the study, 7 patients (20%) relapsed, 5 patients (14%) withdrew (4-non-compliance, 1-ventricular tachycardia)	19 patients (59%) were maintained, completing the study, 5 patients (16%) relapsed, 8 patients (25%) withdrew (4-because of side effects, 3-non-compliance, 1-pregnancy)

iii. Study C6. Initiated in May 1984; completed in June 1987.

Randomized, double-blind, double-dummy, two-parallel group, 12 month study. The mean dosage, shown below, was taken from Page 371, Vol. 51.

<u>Asacol</u>	<u>Salazopyrin</u>
0.9 g/day in divided doses (range	2.3 g/day in divided doses (range This was equivalent to a mean 5-aminosalicylic acid dose of 0.9 g/day (range

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Primary efficacy was relapse of UC symptomatology and 1 grade increase in sigmoidoscopic inflammation,

This trial enrolled 100 patients, 50 in 5-ASA and 50 in SAS, there were no imbalances in the characteristics or UC clinical history of enrolled patients. The following are the efficacy results, as submitted in Page 372, Vol. 51.

Asacol

30 patients (60%) were maintained, completing the study,
17 patients (34%) relapsed,
3 patients (6%) withdrew (2-defaulted, 1-did not meet inclusion criteria)

Salazopyrin

27 patients (54%) were maintained, completing the study,
17 patients (34%) relapsed,
6 patients (12%) withdrew (3-defaulted, 2-non-compliance, 1-severe ulcerative stomatitis of uncertain drug relationship)

iv. Study C15. Initiated in June 1985, completed in December 1988.

Randomized, double-blind, double-dummy, 1 year study.

Enrolled patients were in remission for at least one month "*defined as < 3 stools a day without blood*".

Primary endpoint was defined as "*number and severity of relapses*" manifested by symptomatology and confirmed by "*a single grade deterioration in the sigmoidoscopic score*".

Mean Dosage: Asacol 0.8 g/day; SAS 2 g/day

This study enrolled a total of 35 patients; 18 in 5-ASA, and 27 in SAS. The demographics did not reveal major differences.

P&G notes that "*this study was terminated early because of difficulties in recruiting patients*". The following results were submitted in Page 375, Vol. 51.

Asacol

6 Patients (33%) were maintained, completing the study,
7 patients (39%) relapsed,
5 patients (28%) withdrew

Salazopyrin

14 Patients (52%) were maintained, completing the study,
10 patients (37%) relapsed,
3 patients (11%) withdrew

v. P&G Remission Rates of Asacol and SAS in Pooled Studies.

According to the sponsor, remission rates for each drug in each of the studies and the 95% confidence interval of the difference in success rates was calculated. This methodology was then applied by the sponsor to the pooled data from the four studies, i.e., differences in remission rates between Asacol and SAS in the larger pooled patient population and the margin of comparability in efficacy as estimated by the 95% confidence interval.

The sponsor used three scenarios to evaluate the impact of the 51 patients crossed-over from C1 to C2. The following describes this three scenarios:

Scenario 1. Assumes that the 51 patients were "independent in each study and were included in both C1 and C2; this analysis has 283 patients.

Scenario 2. Counts the 51 patients only once. The 51 patients were included only in C1. There were a total of 232 included in this analysis.

Scenario 3. Excludes the 51 patients from all results. This scenario includes, therefore, a total of 181 patients.

The following P&G Tables 14a and 14b, taken from Page 119, Vol. 119, shows the pooled remission rates in the ITT and completed patient population.

Table 14a:			
Pooled Remission Rates (adjusted for study): Completed Patients			
Scenario	Overall Remission Rate (95% confidence interval)		Difference in Remission Rates (95% confidence interval)
	Asacol	Sulfa	Asacol - Sulfa
1	0.62 (0.54, 0.71)	0.70 (0.62, 0.78)	-0.08 (-0.2, 0.04)
2	0.59 (0.50, 0.69)	0.69 (0.61, 0.78)	-0.10 (-0.23, 0.03)
3	0.53 (0.42, 0.63)	0.63 (0.52, 0.74)	-0.10 (-0.25, 0.05)

Note: The overall remission rate is a weighted average of the remission rates for each study. Similarly, the difference in remission rates is a weighted average of the differences in remission rates for each study.

Table 14b:			
Pooled Remission Rates (adjusted for study): Intent-to-Treat Patients			
Scenario	Overall Remission Rate (95% confidence interval)		Difference in Remission Rates (95% confidence interval)
	Asacol	Sulfa	Asacol - Sulfa
1	0.54 (0.46, 0.62)	0.58 (0.50, 0.66)	-0.04 (-0.18, 0.07)
2	0.52 (0.43, 0.62)	0.57 (0.49, 0.66)	-0.05 (-0.18, 0.07)
3	0.44 (0.35, 0.54)	0.52 (0.42, 0.62)	-0.08 (-0.2, 0.08)

Note: The overall remission rate is a weighted average of the remission rates for each study. Similarly, the difference in remission rates is a weighted average of the differences in remission rates for each study.

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In the next Table 15a, Page 120, Vol. 51, the sponsor displays the pooled overall remission rates adjusted for comparable doses of Asacol and SAS.

Table 15a:
Pooled Remission Rates by Dose Levels: Completed Patients

Scenario	Dose Level ¹	Asacol			Sulfasalazine			Difference in Remission Rate Asacol - Sulfasalazine
		Success (n)	Total (N)	Remission Rate (n/N)	Success (n)	Total (N)	Remission Rate (n/N)	
1	1	48	83	0.58	82	116	0.71	-0.13
	2	23	29	0.79	2	6	0.4	0.39
	3	4	0	0.44	-	0	-	-
	Overall ² (95%CI) ³			0.64 (0.55, 0.72)			0.69 (0.61, 0.78)	-0.06 (-0.22, 0.06)
2	1	48	83	0.58	80	96	0.70	-0.13
	2	10	13	0.77	1	4	0.25	0.52
	3	0	2	0	-	0	-	-
	Overall ² (95%CI) ³			0.61 (0.52, 0.71)			0.68 (0.60, 0.77)	-0.08 (-0.21, 0.06)
3	1	34	66	0.52	49	77	0.64	-0.12
	2	6	8	0.75	0	1	0	-
	3	0	2	0	-	0	-	-
	Overall ² (95%CI) ³			0.55 (0.44, 0.66)			0.64 (0.53, 0.74)	-0.12 (-0.28, 0.04)

¹ Dose level 1: 0.8-1.2 g/d for Asacol, 1-3 g/d for sulfasalazine
2: 1.8-2.4 g/d for Asacol, >3-6 g/d for sulfasalazine
3: >2.4 g/d for Asacol, >6 g/d for sulfasalazine
² The overall remission rate is a weighted average of the remission rates for each dose level. Similarly, the difference in remission rates is a weighted average of the differences in remission rates for each study.
³ CI: Confidence Interval

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P&G concludes by stating that *“The pooled efficacy estimates for Asacol ranged , while the pooled efficacy estimates for sulfasalazine ranged (depending of the scenario for treating the data from the 51 ‘crossover’ patients). While the pooled efficacy rates for sulfasalazine were higher than Asacol (approximately depending on the scenario) none of these differences were statistically significant. The association between treatment outcome and Asacol dose was of borderline statistical significance. Patients receiving had an observed higher success rate than the other two dose groups. However, the small numbers in the dose group and the >2.4 g/d dose preclude meaningful interpretation of these results”.*

vi. Reviewer Comments.

1. Asacol vs. SAS, Efficacy Comparability. The pooled efficacy results of the four small controlled studies, shown by the sponsor in Tables 14A and 14B, revealed that the efficacy of the Asacol treatment in maintaining UC remission was not equivalent to the efficacy demonstrated by the parallel administration of the approved sulfasalazine therapy. As observed in the 95% confidence intervals, the difference in efficacy between Asacol and SAS was always favorable to SAS, and,

the confidence intervals spread well beyond the allotted $\pm 10\%$ range. The inferior efficacy of Asacol, as compared to SAS, is more relevant in the data shown in Table 15a, in which remission rates for Asacol and SAS are adjusted with comparable weight doses. At the dose of Asacol proposed for maintenance of UC in remission, i.e. 0.8 g/day, up to an Asacol dose of 2.4 g/day, mesalamine was always inferior to SAS in any of the sponsor's scenarios, and the unfavorable negative confidence interval spread was $> 10\%$.

A criticism could be made about the stringency in the use of a $95\% \pm 10\%$ confidence interval to assess equivalence in active-active parallel drug trials. This criticism has more validity in these trials with ulcerative colitis patients, in which small variations in extent of disease, concomitant medications, misinterpretation of endoscopic features may play confounding roles. In order to decrease the rigorosity of the described methodology, I requested to the statistician reviewer the assess the remission rated in the pooled trials by applying a more liberal $90\% \pm 20\%$ confidence interval. Table 4.2.3, taken from Dr. W. Chen review shows the differences between 5-ASA and SAS in maintenance of remission; in this scenario the 51 crossed over patients are included only once, in the C1 trial.

Table 4.2.3 (Reviewer's)
90% Confidence intervals for differences in success rates using completed patients*

Scenario 1

	P-Value Differences (Asacol - Sulfasalazine)	Lower Bound	Upper Bound
Study C.1	-0.146 (19/31 - 22/29)	-0.34	0.049
Study C.2	-0.033 (4/5 - 5/6)	-0.42	0.35
Study C.6	-0.005 (29/47 - 28/45)	-0.172	0.16
Study C.15	-0.282 (6/15 - 15/22)	-0.55	-0.017
Pooled Results	-0.10	-0.21	0.01

The data shown in the statistician table, demonstrates again a lack of equivalence between Asacol and SAS in the maintenance of UC remission. The large shift to the lower bound, whether in individual trials or in the pooled result, reveals that in these parallel trials, Asacol was consistently inferior to SAS in the maintenance of remission. As such, this submitted pooled efficacy data does not support the claim of Asacol as maintenance therapy for ulcerative colitis patients in remission.

3. Safety of Controlled Studies.

1. Safety of Study 87806.

- *P&G Descriptive.* The following is my brief summary of the submitted safety

(a) *Overview of Adverse Events.* The sponsor states that out of the 264 patients exposed to therapy, 242 (92%) reported at least one adverse event. The following P&G Table 27, Page 70, Vol. 43 illustrates this overview.

Table 27
Summary of Adverse Events - All Patients

	Placebo	Asacol 0.8 g/day	Asacol 1.6 g/day
Number of patients exposed to treatment ^a	87	90	87
Number of patients reporting at least one event	78	80	84
Number of events reported	489	495	506
Total patient-weeks on treatment	1457	1807	1755
Mean patient-weeks on treatment	16.75	20.08	20.17
Percentage of patients reporting at least one event	89.7%	88.9%	96.6%
Number of patients withdrawing due to adverse event	4	4	2
Percentage of patients withdrawing due to adverse event	4.6%	4.4%	2.3%

^a Used as a denominator to compute percentage.
Supporting data can be found in Appendix 5, Tables 23.1, 22.1, and 22.2; Appendix 6; Appendix 8, Table 14.

The sponsor states that the treatments were equally distributed in proportion of adverse events. The sponsor notes that the analysis of adverse events included all randomized patients.

In Table 28, Pages 72-73, the sponsor lists the occurrence of adverse events in all patients in decreasing order of occurrence.

Table 28, Pages 72-73, is included as Appendix 4 of this review.

According to the sponsor, there were no differences in the proportion of adverse events when tabulated by age or sex.

The following Table 31, Page 75, Vol. 43, illustrates the adverse events by sex.

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Table 31
Adverse Events by Sex - All Patients

Sex	Placebo n/N (%)	Asacol 0.8 g/day n/N (%)	Asacol 1.6 g/day n/N (%)
Male	46/54 (85.2%)	45/55 (81.8%)	36/37 (97.3%)
Female	32/33 (97.0%)	35/35 (100%)	48/50 (96.0%)

N = total number of patients of each sex exposed to treatment.
n = number of patients with one or more adverse events. (%) = n/N.
Supporting data can be found in Appendix 5, Table 28.3.

(b) *Serious Adverse Events.* The following P&G Table 34, Page 80, Vol. 43, lists the number of serious adverse events.

Table 34
Serious Adverse Events - All Patients

Treatment Group	Patient Number	Age (years)	Sex	Verbatim Description	COSTART
Placebo	28100218	64	Female	Severe chest pain Hypertension Shortness of breath	Pain chest Hypertens Dyspnea
Asacol 0.8 g/day	19430210	68	Male	Questionable transient ischemic attack Questionable migraine	Ischemia cerebr Migraine
Asacol 1.6 g/day	15580203	24	Female	Miscarriage	Abortion

Supporting data can be found in Appendix 8, Table 13.

Briefly, the narrative of these patients removed because of serious adverse events states the following:

The Placebo patient was a 68 y female with hx of UC. She entered the study end of August 1990 and received the Placebo until February 18, 1991. She had back surgery and a hx of mitral valve prolapse. Meds included Imodium, Tylenol + Codeine, morphine (for back and shoulder pain), Librium, Tranxene for anxiety, quinine for leg cramps and Seldane for nasal congestion. After two months in the study, the patient was hospitalized for chest pain, hypertension and shortness of breath. An EKG showed an abnormal ST segment suggestive of ischemia and abnormal voltage suggestive of left ventricular hypertrophy.

The Asacol 0.8 patient was a 68 y male with hx of UC; he was in the study from August 13, 1990 until February 4, 1991. His past medical history includes migraines, prostate resection and hearing loss. On September 2, 1990, he had a 30-45 minute episode of blurred vision, confusion and loss of memory. CT scan of the head was normal and the patient was started on

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coumarin for a transient ischemic attack. On January 29, 1991 he had a similar episode of short duration, was seen by a neurologist who considered these episodes "consistent with migraine" rather to ischemic attacks. "The investigator commented that this patient had a past hx of migraines".

The Asacol 1.6 patient was a 24 y oriental female with UC who entered the study on August 22, 1988 and received the drug until February 16, 1989. Past hx included anemia and DU. Concomitant meds. included Motrin and Midol (for menstrual cramps), Bactrim for UTI and Zantac for DU. On October 11, 1988, it was discovered that the patient was pregnant by a HCG positive pregnancy test. "On November 2, 1988, she spontaneously miscarried". The investigator felt the event was unrelated to the study medication. The method of birth control at the time of pregnancy was reported as a diaphragm and spermicidal jelly.

(c) *Withdrawals due to Adverse Events.* As mentioned in my Comments of study 87086, issue 5, 10 patients who developed adverse events were withdrawn from the study and declared treatment failures. Four of the patients had been treated with placebo, four with Asacol 0.8 g/day and two with Asacol 1.6 g/day. The following P&G Table 35, Page 81, Vol. 43, "presents pertinent demographic information, the number of weeks on therapy at withdrawal, and the adverse events the patient was experiencing at the time of withdrawal. None of these adverse events that led to discontinuation were considered serious".

Table 35
Adverse Events Necessitating Withdrawal From Study - All Patients

Treatment Group	Patient Number	Age (years)	Sex	Wks. on Therapy at Withdrawal	Verbatim Description	COSTART
Placebo	16330243	24	Male	2.7	Skin rash Skin hypersensitivity	Rash Allergy react
	32520210	39	Male	1.7	Myalgias lower extremities Paresthesias lower extremities Nightmares	Myalgia Paresthesia Dream abnormal
	34090203	35	Male	13.0	Hair loss	Alopecia
	34090239	51	Female	0.6	"Terrible" headache Inability to sleep Numbness left leg and arm, face Weakness left leg and arm, face Drags left foot Backache	Headache Insomnia Paresthesia Myasthenia Foot drop Pain back
Asacol 0.8 g/day	15580201	50	Female	17.9	Headache	Headache
	16330210	44	Male	5.3	Itching	Pruritus
	19430203	66	Male	5.0	Probable rheumatoid arthritis Pain in fingers, shoulder, leg, arm	Arthritis rheumat Pain
	36810204	34	Male	8.4	Decreased sex drive	Libido dec
Asacol 1.6 g/day	19430212	66	Female	17.4	Anxiety state	Anxiety
	28100210	60	Female	22.4	Sore mouth Tired	Stomatitis Asthenia

Supporting data can be found in Appendix 8, Table 14 and 16, and Appendix 6.

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(d) *Patients with Recorded UC Symptomatology Without Significant Proctosigmoidoscopy Changes.* The sponsor included in the Safety section, Pages 84-87, Vol. 43, the narrative of eight patients who had recorded UC symptomatology without significant proctosigmoidoscopy changes. Three patients (1 from Placebo and 2 Asacol 1.6 g/day) were classified as voluntary withdrawals; of the remaining 5 patients, 2 were uncooperative due to lack of adherence to study procedures (both from the Asacol 0.8 g/day), 1 patient was a concomitant medication violator (from the Asacol 0.8 g/day group) 1 patient was lost-to-follow-up (from the Placebo group) and 1 patient violated inclusion criteria (from the Asacol 1.6 g/day group).

Narratives of patients listed in issues (c) and (d), Pages 83-87, Vol. 43, are included as Appendix 5 of this review.

ii. *Safety of Studies Included in the Pooled Analysis (C1 + C2 + C6 + C15).*

- This is this reviewer's descriptive summary from P&G narratives, Pages 180-182, Vol. 120.

These Asacol-SAS trials had a total of 137 patients to Asacol administration. P&G states that due to the small sample sizes of the four Asacol treatment groups (0.8 or 1.2 g/day, 1.5, 2.0 or 2.4 g/day, 2.6 or 3.2 g/day and 4.0 or 4.4 g/day) "conclusions regarding the relationship between adverse event frequency and increasing Asacol doses are difficult to assess". The doses more frequently used were from 0.8 g/day to 2.4 g/day. "Body as a whole" was the system with more subjects experiencing at least one AE.; headache, back pain, asthenia, chills and fever. The descending order of frequency continued with the Digestive (diarrhea, dyspepsia) CNS, i.e., anxiety, insomnia, depression and dizziness.

Table H.4.2.2.3.1, Page 214, Vol. 120, exemplifies these AEs.

TABLE H.4.2.2.3.1
FREQUENCY OF ADVERSE EVENTS
BY BODY SYSTEM, COCART AND DAILY DOSE
PLACEBO-CONTROLLED MAINTENANCE STUDY (87066)

BODY SYSTEM	ASACOL DAILY DOSE				Total n (%)
	PLACEBO (N=87) n (%)	0.8g (N=90) n (%)	1.6g (N=87) n (%)		
BODY AS A WHOLE	67 (77.0%)	65 (72.2%)	68 (78.2%)		200 (75.0%)
CARDIOVASCULAR SYSTEM	5 (5.7%)	13 (14.4%)	4 (4.6%)	←	22 (8.3%)
DIGESTIVE SYSTEM	64 (73.6%)	54 (60.0%)	65 (74.7%)		183 (69.3%)
HEMIC AND LYMPHATIC SYSTEM	2 (2.3%)	5 (5.6%)	2 (2.3%)		9 (3.4%)
METABOLIC AND NUTRITIONAL DISORDERS	1 (1.1%)	7 (7.8%)	5 (5.7%)		13 (4.9%)
MUSCULO-SKELETAL SYSTEM	16 (18.4%)	14 (15.6%)	15 (17.2%)		45 (17.0%)
NERVOUS SYSTEM	20 (23.0%)	22 (24.4%)	23 (26.4%)		65 (24.6%)
RESPIRATORY SYSTEM	41 (47.1%)	49 (54.4%)	46 (52.9%)		136 (51.5%)
SKIN AND APPENDAGES	19 (21.8%)	9 (10.0%)	6 (6.9%)		34 (12.9%)
SPECIAL SENSES	6 (6.9%)	11 (12.2%)	11 (12.6%)		28 (10.6%)
UROGENITAL SYSTEM	7 (8.0%)	9 (10.0%)	19 (21.8%)	←	35 (13.3%)

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These four trials included a total of 144 subjects who were exposed to SAS. SAS doses ranged from [redacted] The most commonly used SAS doses ranged from [redacted] Digestive (dyspepsia, nausea, anorexia), Body as a Whole (headache, asthenia, pain), CNS (anxiety, insomnia, vertigo, depression) were the three most common system more frequently claimed as cause of AEs.

The following P&G Table H.4.2.2.3.2, Page 235, Vol. 120, illustrates these AEs.

TABLE H.4.2.2.3.2
FREQUENCY OF ADVERSE EVENTS
BY BODY SYSTEM, COSTART AND DAILY DOSE
POSITIVE-CONTROLLED MAINTENANCE STUDIES (SULFASALAZINE DATA) *

BODY SYSTEM	SULFASALAZINE DAILY DOSE					TOTAL (N=144) n (%)
	1.0g (N=2) n (%)	1.5 or 2.0g (N=110) n (%)	2.5 or 3.0g (N=26) n (%)	3.5 or 4.0g (N=4) n (%)	> 4.0g (N=2) n (%)	
BODY AS A WHOLE	0 (0.00)	31 (28.20)	9 (34.60)	0 (0.00)	1 (50.00)	41 (28.50)
CARDIOVASCULAR SYSTEM	0 (0.00)	1 (0.90)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.70)
DIGESTIVE SYSTEM	0 (0.00)	29 (25.50)	6 (23.10)	0 (0.00)	1 (50.00)	46 (31.90)
METABOLIC AND NUTRITIONAL DISORDERS	0 (0.00)	1 (0.90)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.70)
MUSCULO-SKELETAL SYSTEM	0 (0.00)	3 (2.70)	0 (0.00)	0 (0.00)	0 (0.00)	3 (2.10)
NERVOUS SYSTEM	0 (0.00)	20 (17.30)	6 (23.10)	0 (0.00)	0 (0.00)	36 (25.00)
SKIN AND APPENDAGES	0 (0.00)	7 (6.40)	0 (0.00)	0 (0.00)	0 (0.00)	7 (4.90)
SPECIAL SENSES	0 (0.00)	4 (3.60)	1 (3.80)	0 (0.00)	0 (0.00)	5 (3.50)
UROGENITAL SYSTEM	0 (0.00)	0 (0.00)	1 (3.80)	0 (0.00)	0 (0.00)	1 (0.70)

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iii. Reviewer Comments.

1. Overall Assessment. The overall proportion and types of AEs reported in the large pivotal placebo-controlled multicenter study and combined C1 + C2 + C6 + C15 trials, revealed an acceptable margin of safety with almost every administered Asacol doses and particularly with the proposed 0.8 g/day 5-ASA dose.

The following is a specific observation on safety.

(a) Asacol. Pregnancy and Miscarriage. The large placebo-controlled multicenter study reported one spontaneous abortion in a 24 y oriental female administered Asacol 1.6 g/dose. My review of the INTEGRATED SUMMARY OF SAFETY INFORMATION, Section 10.2. Pregnant Subjects, Vol. 131, revealed that 40 women had 43 pregnancies "while participating in Asacol clinical trials: 2 subjects in the Maintenance study, 5 subjects in the C12 Compassionate-Use study, and 33 in the C13 Compassionate-Use study. Nineteen chose to discontinue Asacol during the pregnancy, 12 subjects chose to remain on Asacol during their pregnancy, 5 subjects elected to terminate their pregnancy while remaining on Asacol, 3 subjects experienced a miscarriage or spontaneous abortion while on Asacol, and 1 subject experienced an ectopic pregnancy".

This reviewer deems the observed spontaneous abortion rate of 7% (3/43) in patients administered Asacol, to be within acceptable limits and not outside the observed rate of spontaneous abortions reported in the general population.

Selected Literature on Spontaneous Abortion and Asacol.

1. Weerakiet S et al. Spontaneous abortion rate. *J Med Ass Thai*, 79:249-252, 1996
2. Tadese E. Return of fertility after an IUD removal for planned pregnancy: a six year prospective study. *East Afr. Med. J.*, 73:169-171, 1996
3. Trallori G et al. 5-Aminosalicylic acid in pregnancy: clinical report. *Ital. J. Gastroenterol.*, 26:75-78, 1994.
4. Habal et al. Oral 5-aminosalicylic acid for inflammatory bowel disease in pregnancy: safety and clinical course. *Gastroenterol.*, 105:1057-1060, 1993.

E. P&G RESPONSES TO INFORMATION REQUESTED ON MARCH 31, 1997 (See Appendix 3 of this Review).

- The following subsections will include the question number, a brief summary of the requested information, a brief summary descriptive of the sponsor's response, and my comments.

1. QUESTION. Six patients "were declared ineligible for the trial but were given patient number assignments and study medication". They were not included in the Intent-To-Treat (ITT) analysis. The sponsor was requested to provide the following: a) Reason each patient was declared ineligible; b) If these patients were randomized, indicate the treatment group in which they were assigned and include them in an ITT efficacy analysis. Use baseline endoscopy endpoint readings, carrying them forward to the subsequent three visits. i.e. Last Observation Carried Forward (LOCF); c) Please, provide original CRFs of each of these patients with inclusion of baseline endoscopy.

I. P&G RESPONSE. In its response, P&G stated that these patients were assigned a "subject number (which also assigns their randomization number) (but) then, did not participate in the study. Two of the six patients were qualified to participate in the study, but elected not to participate before taking study medication. The remaining four patients were disqualified from study participation due to protocol violations and documentation suggests that they did not take drug". P&G notes that it holds documentation supporting the claim that 5 of the subjects did not take any study medication. For the remaining patients, P&G states that documentation is available to verify "the patient was instructed not to take medication and to return the drug".

The sponsor provided the following table (response 1a).

Subject Number	Assigned Treatment	Reason for not participating.	Source of information
15580211	Placebo	Subject qualified for study and then voluntarily withdrew before taking any drug. The investigator stated that "The patient returned study medication per mail with a letter stating she was not going to participate in research project. Also stated that her doctor suggested she not participate due to increase flare-ups of CUC".	Case Report Forms/Clinical Supplies Record
18800219	Placebo	Subject's pre-study lab results resulted in disqualification. The patient did not take any drug.	Monitor's Contact Report/Clinical Supplies Record
19780203	Asacol 0.8mg	Subject was a screening failure who was assigned a study number, but never received drug.	Monitor's Contact Report/Clinical Supplies Record
19780206	Placebo	Subject was a screening failure who was assigned a study number, but never received drug.	Monitor's Contact Report/Clinical Supplies Record
34090209	Placebo	Subject disqualified due to elevated pre-study alkaline phosphatase and bilirubin values. Medication had been dispensed in advance due to the distance the subject lived from the center. Subject was instructed to return drug.	Monitors' Contact Report
34090216	Placebo	Subject qualified for the study, then prior to taking study medication, flared severely requiring a resection. The subject did not take any drug. Medication had been dispensed in advance due to the distance the subject lived from the center. Subject was instructed to return drug. Drug was returned.	Monitor's Contact Report/Clinical Supplies Record

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P&G responded to our request of an ITT analysis with inclusion of these six randomized patients, submitting the following Table 1 (response 1b). In this table, the efficacy outcome of the 5 randomized Placebo patients are included in 5 different scenarios. from all of 5 Placebo (PBO) outcomes as treatment failures (TF) to all 5 Placebo as treatment successes (TS), with a mix scenario of 1-4 PBO either TF or TS.

Table 1

P-value for the 12 scenarios that compare treatment outcome assuming the 6 subjects participated in the study.

Number of subjects in the Placebo group were treatment failure	Number of subject in the Asacol 0.8g/day was treatment failure	p-value Placebo vs Asacol 0.8g/day	p-value Placebo vs Asacol 1.6g/day
5	1	0.026	0.0014
4	1	0.038	0.0023
3	1	0.054	0.0038
2	1	0.074	0.0060
1	1	0.102	0.0093
0	1	0.136	0.0099
5	0	0.018	0.0014
4	0	0.026	0.0023
3	0	0.037	0.0038
2	0	0.053	0.0060
1	0	0.074	0.0093
0	0	0.101	0.0099

ii. REVIEWER COMMENTS of Response to Question 1. They are the following:

(a) As stated by the sponsor, all of these patients were randomized to this study and all were given experimental medication.

As also stated by the sponsor, two patients did meet the screening requirements and did qualify for the study. These were Placebo (PBO) patient 1558021 and Placebo patient 3409216.

P&G submitted the CRF of one of the placebo patients, Placebo 15580211. According to the CRF, the baseline proctosigmoidoscopy showed UC in remission. This was the last endoscopic assessment of this placebo patient. Our request instructed to include all randomized but-untreated patients who did have baseline endoscopy by "*Carrying the Last Observation (last endoscopy) Forward (LOCF)*", up to the final study observation. Accordingly, I will consider this patient in endoscopic remission (success) in the final outcome of efficacy comparisons.

Placebo 34090216 was the other UC patient who qualified for the trial, was randomized and provided with study drugs. According to the brief narrative submitted by P&G, this patient "*flared severely*" prior to taking study drug and required a "*resection*". Though this narrative was not accompanied by this patient's CRF or other appropriate medical documentation, I will accept the explanation offered by the sponsor and consider this case as a Placebo treatment failure.

Any scenarios with inclusion of these 5 Placebo randomized patients would include no less than 1 Treatment Success, and no less than 1 Treatment Failure, at least in the clinical judgement of this medical officer.

(b) The scenarios shown by P&G in Table 1 reveal the fragility of the proposed Asacol 0.8 g/day dose. Addition of just 1 Placebo treatment success to the placebo patient who had the baseline endoscopy "in remission", i.e., 2PBO TS/3PL TF, renders the difference between Asacol 0.8 and PBO not significant.

In contrast, the displayed scenarios in Table 1 show strength in the superiority of Asacol 1.6 over PBO, i.e. 4PBO TS vs Asacol 1.6, still results in a very significant difference favorable to the Asacol high dose.

(c) The Intention-To-Treat population used in the above scenarios included six Asacol 1.6 patients in whom the outcome was amended to treatment success by P&G, after all of them had been originally declared as treatment failures (see my *Descriptive Section of this Study 87086, subsection 8. Effect of Amended Scoring*

System on Patient Outcome). In the following scenario I will further assess the strength of the high Asacol dose by including 4 of the 5 PBO randomized but-untreated patients as TSs' and changing back, in each consecutive comparison, the amended outcome for each of the six Asacol 1.6 patients, to the original treatment failure outcome. This ITT efficacy comparison of ALL randomized patients is illustrated in my next MO Reviewer Table 5.

MO Reviewer Table 5

All Randomized Comparison Including Four Out of The Five Randomized But-Untreated PBO Patients as Treatment Successes (TS), and, Changing Amended Asacol 1.6 Patient Outcomes From TS to The Original Treatment Failures (TF)

Number of the Six 5-ASA 1.6 Patients Changed From the Amended TS to the Original TF Outcome	Placebo TS/Total (%)	Asacol 1.6 g TS/Total (%)	Two Sided p-Values by Chi-Square*
No Changes In Amended 5-ASA 1.6 g TS Outcomes	46/92 (50%)	61/87 (70%)	<0.01
One Amended 5-ASA 1.6 g TS Changed to the Original TF	46/92 (50%)	60/87 (69%)	0.010
Two Amended 5-ASA 1.6 g TSs Changed to the Original TFs	46/92 (50%)	59/87 (68%)	0.016
Three Amended 5-ASA 1.6 g TSs Changed to the Original TFs	46/92 (50%)	58/87 (67%)	0.024
Four Amended 5-ASA 1.6 g TSs Changed to the Original TFs	46/92 (50%)	57/87 (66%)	0.036
Five Amended 5-ASA 1.6 g TSs Changed to the Original TFs	46/92 (50%)	56/87 (64%)	0.053
Six Amended 5-ASA 1.6 g TSs Changed to the Original TFs	46/92 (50%)	55/87 (63%)	0.076

* Statistical probabilities were computer calculated by Dr. M. Huque, Group Leader, Division of Biometrics, CDER/FDA, using STAT-Xact software program..

- **Observation.** MO Reviewer Table 5 illustrates the comparison of a possible worst scenario for the Asacol 1.6 g/day, in which 4 out of the 5 PBO patients who were

randomized, but untreated, are included as TSs, and the 6 patients on Asacol 1.6 who had amended outcomes are consecutively changed from TSs to TFs. The strength of the Asacol 1.6 superiority is evident; it would require 5/6 (83%) of the amended Asacol 1.6 outcomes changed from TSs to TFs for the high Asacol dose to render the statistically significant superiority over the PBO treatment group.

2. **QUESTION.** This querie states that in P&Gs Table 22, Vol. 43, the number of relapses in all PBO treated patients, i.e., 37 relapses, is different from the number of PBO relapses included in the Intention-To-Treat analysis shown by P&G in Table 17, i.e., 41 relapses, Counting the 4 PBO patients withdrawn due to AEs, the *total* number of PBO relapses would be 41 (in Table 22), but, 45 in the ITT analysis (Table 17). The sponsor was asked to explain the *"reason for the four additional treatment failures in the PBO group"*, and, *if the four additional TFs were incorrectly included in the ITT analysis, to redo the ITT analysis, excluding these four PBO patients.*

1. **P&G RESPONSE.** The sponsor states that the definition of "censored" subjects in the footnote of Table 22 should have also included *"and those patients who had a non-normal baseline proctosigmoidoscopy score and/or had a non-observable time to endoscopic relapse"*. The sponsor further states that there were 4 censored subjects who had an abnormal baseline proctosigmoidoscopy and/or had non-observable time to endoscopic relapse. The four subjects included in the latter category received at least one dose of the study drug, but discontinued from the study due to protocol violations. Therefore, these subjects were included in the ITT analysis. P&G included a short narrative of these four subjects. The following is a brief summary of these narratives:

Subject #15050205 had a proctosigmoidoscopy score of "1" at the pre-study visit. *"The investigator enrolled and discontinued the subject from the study on the same day"*. The investigator commented that *"Pt placed on protocol (in error) before colonoscopy report reviewed-stopped study med after 1 tab & resumed open label Asacol"*.

Subject #18800211 had a proctosigmoidoscopy score of "0" at the pre-study visit. According to the sponsor's narrative, *"the subject had a flare of disease the night before starting study medication; took one day of study medication (4 tabs) and decided to discontinue study therapy"*. P&G notes that *"the investigator was unaware of the flare of UC"*.

Subject #19780208 had a proctosigmoidoscopy score of "2" at the pre-study visit. The investigator commented that *"While he does not have a complete mucosal remission specifically he (the patient) considers himself to*

be in remission". One month later the investigator discontinued the subject from the study. At this final visit, the proctosigmoidoscopy score was "1".

Subject #34090232 had a proctosigmoidoscopy score of "1" at baseline visit. The investigator commented on the baseline endoscopy showed *"very slight friability in midsigmoid, however, patient is in remission"*.

After app. one month of study medication, the proctosigmoidoscopy score was "2". She was discontinued from the study and classified as a protocol violation.

- The following analyses exclude the 4 subjects from the ITT treatment outcome. Included in these ITT are a total of 260 patients (4 excluded), i.e., 83 for Placebo, 90 for Asacol 0.8 g/day, and 87 for Asacol 1.6 g/day.

P&G states that *"There was no significant difference in the treatment outcome between the Placebo and Asacol 0.8 g/day groups (p-value = 0.124) by the Fisher's Exact test. Forty-two out of the 83 PBO subjects (51%) were treatment success while 63% of the subjects in the Asacol 0.8/day group were treatment success"*.

P&G states that *"The treatment outcome between the Placebo and Asacol 1.6/day groups was significantly different (p-value = 0.012); 70% of the subjects in the Asacol 1.6 g/day were treatment success and 51% of the Placebo group were treatment success"*.

ii. REVIEWER COMMENTS of Response to Question 2. I have addressed this issue, i.e., placebo patients entered with proctosigmoidoscopic features consistent with active UC, in the *Reviewer Comments* Section for Study 87086, subsection 2, titled *Enrollment of Patients in Relapse*. As stated, the imbalance in enrollment of active UC patients, i.e., 3 PBO, 0 Asacol 0.8 g/day, 0 Asacol 1.6 g/day, is unfavorable to PBO, for all of these PBO were declared as TFs in the sponsor's ITT. A fourth PBO patient, #18800211, withdrew from the trial one day after being enrolled with an endoscopic score of "0", but was declared a TF because he, apparently, had a symptomatic flare up.

- As illustrated in my MO Reviewer Table 2, a sensitivity analysis with exclusion of just one of these ineligible PBO patients, renders the sponsor's ITT efficacy comparison between the Asacol 0.8 g/day group and the PBO group not statistically significant (two sided $p = 0.068$). My sensitivity analysis clearly illustrates the fragility of the Asacol low dose efficacy.
- Contrasting the feeble efficacy displayed by the low Asacol dose is the apparent robustness exhibited by the high Asacol dose. As shown by the sponsor, the very significant efficacy superiority of the Asacol high dose over

PBO remains unaltered even after exclusion of all of these four PBO TFs (p = 0.012).

3. **QUESTION.** We noted numerous unscheduled endoscopies conducted through the study; may of them occurred after the final 6-month visit. The sponsor was asked the following:

a. *“For both the ITT and the primary efficacy analysis data set, tabulate the frequency distribution for each treatment group by the prospectively established scheduled visits”. Also, perform an analysis of group comparability based on frequency of scheduled visits. Define scheduled visits as follows: Visit 2 = Weeks 3-5; Visit 3 = Weeks 11-13; Visit 4 = Weeks 23-25. Provide treatment comparison of relapses in endoscopies performed at these visit windows.*

b. For all patients relapsed within the endoscopy windows, provide list of patient numbers, drug assignments, and endoscopy grade at relapse.

1. **P&G RESPONSE.** The sponsor states that *“According to the study protocol, patients were scheduled for endoscopy at baseline, Month 1, Month 3, and Month 6 (final visit). If subjects felt they were experiencing worsening of the disease or an adverse event, subjects were instructed to contact the investigator to schedule an extra visit an any time during the study. This is the reason they were numerous unscheduled endoscopy examinations”.*

- The sponsor illustrated the frequency distribution for each treatment group by the defined scheduled visits, and the p-value for group comparability comparisons in the following Table 2 (PBO vs Asacol 0.8 g/day) and Table 3 (PBO vs 1.6 g/day).

Table 2
Number of patients that had scheduled endoscopy within the defined visit windows for the Placebo and Asacol 0.8g/day groups and p-value for comparing group comparability

ITT		Placebo n (%=n/N)	Asacol 0.8g/day n (%=n/N)	Total N	p-value
	Visit 2	77 (47.2)	86 (52.8)	163	0.481
	Visit 3	55 (44.7)	68 (55.3)	123	0.241
	Visit 4	44 (44.4)	55 (55.6)	99	0.269
Primary					
(completed patients)	Visit 2	54 (45)	66 (55)	120	0.273
	Visit 3	38 (42.7)	51 (57.3)	89	0.168
	Visit 4	29 (40.3)	43 (59.7)	72	0.099

Table 3
Number of patients that had scheduled endoscopy within the defined visit windows for the Placebo and Asacol 1.6g/day groups and p-value for comparing group comparability

ITT		Placebo n (%=n/N)	Asacol 1.6g/day n (%=n/N)	Total N	p-value
	Visit 2	77 (49.4)	79 (50.6)	156	0.873
	Visit 3	55 (45.5)	66 (54.5)	121	0.317
	Visit 4	44 (43.8)	57 (56.4)	101	0.196
Primary					
(completed patients)	Visit 2	54 (50.5)	53 (49.5)	107	0.923
	Visit 3	38 (48.3)	44 (53.7)	82	0.508
	Visit 4	29 (42.6)	39 (57.4)	68	0.225

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- In the following Tables 4 and 5, the sponsor displays the number of patients that had relapses within the defined visit windows and the p-value for treatment comparison between PBO and Asacol doses.

Table 4

Number of patients that had relapses within the defined visit windows and the p-value for treatment comparison between Placebo and Asacol 0.8g/day groups

ITT		Placebo			Asacol 0.8g/day			p-value
		n	N	%(n/N)	n	N	%(n/N)	
	Visit 2	12	77	15.6	9	86	10.5	0.358
	Visit 3	7	55	12.7	4	68	5.9	0.216
	Visit 4	8	44	18.2	4	55	7.3	0.126
Primary								
(completed patients)	Visit 2	10	54	18.5	8	66	12.1	0.442
	Visit 3	6	38	15.8	3	51	5.9	0.163
	Visit 4	6	29	20.7	3	43	7.0	0.144

n = # of relapses

N = # of subjects that had a scheduled endoscopy within the visit window

Table 5

Number of patients that had relapses within the defined visit windows and the p-value for treatment comparison between Placebo and Asacol 1.6g/day groups

ITT		Placebo			Asacol 1.6g/day			p-value
		n	N	%(n/N)	n	N	%(n/N)	
	Visit 2	12	77	15.6	5	79	6.3	0.075
	Visit 3	7	55	12.7	0	66	0.0	0.003
	Visit 4	8	44	18.2	7	57	12.3	0.416
Primary								
(completed patients)	Visit 2	10	54	18.5	5	53	9.4	0.265
	Visit 3	6	38	15.8	0	44	0.0	0.008
	Visit 4	6	29	20.7	3	39	7.7	0.156

n = # of relapses

N = # of subjects that had a scheduled endoscopy within the visit window

- The sponsor concludes the following: "There was no significant difference in the number of relapses between the PBO and Asacol 0.8 g/day for any visit based on the ITT. The number of relapses in the Asacol 1.6 g/day group was significantly lower than that of the PBO group for Visit 3 (p = 0.003) but not for Visits 2 and 4".

ii. REVIEWER COMMENTS of P&G Response to Question 3.

(a) As shown in the data submitted by the sponsor, there was a large proportion of patients who underwent unscheduled proctosigmoidoscopic examinations outside the established Visit 2, Visit 3 and final Visit 4 windows. Thus, approximately 56% PBO patients and app. of Asacol 1.6 patients were endoscoped outside the prospectively established visits.

(b) A number of reasons related to the particular clinical course of this inflammatory bowel disease and to the design of this trial would have mandated a rather strict adherence to prospectively established time endpoints. First, UC is characterized by relapses and remissions. Frequent endoscopic examinations at random times increases the chance of finding an endoscopic relapse or a remission, depending on the particular clinical course of a particular UC patient. Second, there is, in some UC patients, an observable dissociation between symptomatology and endoscopic features of UC. Increasing the number of unscheduled endoscopic observations based on the presence, or not, of symptomatology, may consequently result in uneven proportion of endoscopic examinations between the treatment groups. This latter would be the case if one of the treatment groups has lower effectiveness on symptomatology but is somehow effective on mucosal healing. Vice versa, lack of UC symptomatology does not necessarily assure mucosal remission on endoscopy. This phenomenon has been well established in maintenance trials of experimental drugs used to maintain remission in treated peptic ulcer disease and gastroesophageal reflux disease, two other chronic GI disorders also characterized by recurrences and remissions. Third, this trial was not prospectively designed to capture UC symptomatology. Hence, interpretation of what constitutes "a symptomatic flare up" had not been defined in advance in the protocol and was entirely left to the individual judgement of participating centers. This was acknowledged by the group of investigators who participated in this trial in a publication reported last year, (The Mesalamine Group. An Oral Preparation of Mesalamine as Long-Term Maintenance Therapy for Ulcerative Colitis: A Randomized Placebo-Controlled Trial. *Ann. Intern. Med.*, 124:204-211, 1996).

This unusually high proportion of unscheduled endoscopies casts some doubts about the adequacy of this trial.

(c) Two relevant conclusions are gathered from the results of scheduled and unscheduled endoscopies: 1. The efficacy of the low Asacol dose of 0.8 g/day was not superior to PBO in any of the performed endoscopic time-points. 2. The efficacy of the high Asacol dose of 1.6 g/day was superior to PBO, as illustrated by the statistician reviewer in a "success" comparison of unscheduled endoscopies in (see Table 3.1 Page 9, ADDENDUM, Statistician's Review). The strength in

efficacy of the high Asacol dose was even demonstrated in *scheduled* Visits 2 and 3, in spite of small sample size comparisons. *This show of strength in the scheduled and unscheduled endoscopies by the high Asacol dose, together with its favorable efficacy results in an all randomized ITT illustrated in my MO Reviewer Table 5, overrides the inconsistencies in adequacy encountered during this experimental trial, at least for this medical reviewer.*

F. SUMMARY AND CONCLUSIONS OF THE ORIGINALLY SUBMITTED DATA.

1. Summary of Safety from the Pivotal Supporting Trials.

i. Based on the number and types of AEs observed, the safety margin is acceptable for any of the Asacol doses and for the six month period studied.

2. Summary of Efficacy of Pivotal Trial #87086:

i. This was a multicenter, randomized, placebo-controlled trial designed to demonstrate the safety and efficacy of two doses of Asacol, a low dose of 0.8/day, and a high dose of 1.6 g/day, in the maintenance of remission of UC patients. The protocol planned for an enrollment of 180 UC patients in UC remission. Primary efficacy was established as the proportion of patients in remission (treatment success) or rectocolonic relapse (treatment failure) as defined by rectosigmoidoscopic examination. Duration of study treatment was 6 months (last Visit and endoscopy) with two scheduled endoscopies at 1 month (Visit 2 after baseline) and 3 months (Visit 3 after baseline).

ii.. The prospectively planned patient population, i.e. 180 UC patients, was amended twice during the trial and resulted in at least a 50% higher total recruitment than the patient sample size prospectively planned, i.e., All Treated patients = 264. The actual randomized total patient population was 270 patients. Apparently, the many changes in total patient population was due to the large patient dropout rate, i.e., almost three times higher than prospectively planned (> 28%).

iii. The Completed Patient population was 189 patients and the sponsor's Intention-To-Treat analysis was 264 patients. Six patients, 5 PBO and 1 Asacol 0.8 g/day, were randomized but returned study drugs and were not originally included in any of the sponsor's primary efficacy analyses.

iv. The continuous changing patient sample size and unexpected high dropout rate and some imbalances in ineligible randomized patients, makes less relevant the sponsor's proposed *completed patient population* for comparison of primary efficacy. Hence, the relevant patient comparison for primary efficacy is that of the *All-Treated Patients (Sponsor's ITT)*. In the sponsor's ITT, the difference in Treatment Success (TS) between PBO and Asacol 0.8 g/day was 15% favorable to the low 5-ASA dose ($p=0.05$), while the difference between PBO and Asacol 1.6 g/day was 22% favorable to the high 5-ASA dose ($p=0.005$).

v. My examination of the sponsor's ITT revealed that the low Asacol 0.8 dose superiority was driven by three ineligible PBO patients who were enrolled while in endoscopic UC relapse (vs 0 in Asacol 0.8). Exclusion of 1, 2, or 3 of these endoscopically ineligible placebo renders the Asacol 0.8 vs PBO difference not statistically significant (-1 PBO exclusion $p=0.068$, -2 or -3 PBO exclusion $p=0.069$ and $p=0.094$, respectively).

vi. The highly significant superiority over PBO exhibited by the high Asacol dose (1.6 g/day) in the ITT included six Asacol 1.6 patients in whom the final outcome was amended by the sponsor. The sponsor's changes reversed the original outcomes from TF to TS. These changes were, therefore, highly favorable to the sponsor's drug. Inclusion in the ITT population of Asacol 1.6 patients with all the original Treatment Failures (TF) outcomes reduced somehow the superiority of the high dose Asacol but still preserved its highly statistical significance. The strength of the Asacol high dose over PBO was further demonstrated in an All Randomized efficacy comparison in which 5 PBO patients, randomized but untreated, were entered as Treatment Success, and 4 of the amended Asacol 1.6 g/day patients were reverted to the original Treatment Failures; the 16% difference between the high dose vs PBO remained statistically significant ($p=0.036$, see MO Reviewer Table 5).

3. Efficacy Summary of the Pivotal 5-ASA vs SAS Pooled Results.

vii. P&G submitted the pooled results of 4 maintenance trials in which the efficacy of Asacol was compared to that of the approved drug SAS. The trials lasted from 4 months to one year; the doses of Asacol from 0.8 g/day to >2.4 g/day. A combined total of 283 patients were enrolled. This combined total included 51 patients included in two successive trials to alternate treatments (C1 + C2). The combined total patient population is reduced to 200 patients if this 51 patients are only counted in the C1 trial. The pooled efficacy results of the four small controlled trials, *revealed that*

the efficacy of Asacol in maintaining UC remission was not equivalent to the efficacy of the approved SAS. Efficacy, i.e., success, was 59/98 (59%) for Asacol and 70/102 (69%) for sulfasalazine. The difference in success between Asacol minus SAS, using a 90% confidence interval, was 21% favorable to SAS.

3. This Reviewer Conclusion. *Based on the summarized results, this reviewer concludes the following:*

(a) Of the two submitted pivotal data, only one single supporting trial, i.e., the multicenter placebo-controlled trial, supports the claim for Asacol as maintenance therapy for UC patients in remission. Adjusted results do not support the claim for a low Asacol 0.8 g/day dose as maintenance treatment.. The results of the pivotal multicenter trial do support the claim of the high Asacol 1.6 g/day dose as maintenance therapy for patients in UC remission.

G. RECOMMENDATIONS FOR REGULATORY ACTIONS.

They are the following:

- *The submitted results failed to show replication to the Asacol efficacy evidenced in the placebo study. However, this single multicenter placebo-controlled trial (#87806) did show robustness in primary efficacy with the high Asacol dose. Based on my review, I do not recommend approval of the sponsor's proposed low Asacol 0.8 g/day dose. Instead, I do recommend approval of the high Asacol 1.6 g/day as maintenance therapy for patients in UC remission. The ILabel should inform that Asacol safety and efficacy as maintenance treatment beyond the studied 6 months has not been established, and that the Clinical Trial which served as supporting data did not include ulcerative colitis patients younger than 18 years of age.*

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Robert Prizont, M.D.

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APPENDIX 1. Study 87086.
Patient Enrollment by Investigator

Table 4
Patient Enrollment and Study Completion by Investigator

Investigator (Inv. #)	Placebo N = 87 Enrolled (Completed)	Asacol 0.8 g/day N = 90 Enrolled (Completed)	Asacol 1.6 g/day N = 87 Enrolled (Completed)	Total N = 264 Enrolled (Completed)
Hanauer (1505)	10 (8)	10 (7)	10 (4)	30 (19)
Mayle (1558)	8 (7)	10 (9)	10 (5)	28 (21)
Robinson (1633)	16 (11)	14 (10)	14 (11)	44 (32)
DeMicco (1880)	6 (4)	6 (3)	7 (2)	19 (9)
Butt (1943)	5 (4)	4 (4)	5 (5)	14 (13)
McHattie (1978)	3 (2)	2 (1)	3 (3)	8 (6)
Elson (2810)	7 (4)	7 (7)	7 (5)	21 (16)
Wolf (2917)	0 (0)	1 (0)	0 (0)	1 (0)
Sninsky (3252)	4 (3)	3 (3)	3 (3)	10 (9)
Bozdech (3279)	3 (3)	4 (4)	3 (3)	10 (10)
Powers (3409)	14 (11)	17 (10)	16 (9)	47 (30)
Pruitt (3512)	4 (1)	5 (4)	4 (3)	13 (8)
Gurney (3664)	2 (2)	2 (2)	1 (1)	5 (5)
Safdi (3665)	2 (2)	2 (2)	3 (3)	7 (7)
Fixelle (3681)	1 (0)	2 (1)	1 (1)	4 (2)
Smoots (3687)	1 (0)	0 (0)	0 (0)	1 (0)
Levin (3688)	1 (1)	1 (1)	0 (0)	2 (2)
McCarty (3711)	0 (0)	0 (0)	0 (0)	0 (0)

N = number of patients enrolled.

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

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