

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 019651/S005**

**STATISTICAL REVIEW(S)**

*McNeil*

# Statistical Review - Carcinogenicity Studies

**NDA:** 19 - 651/SE1 - 005

**Date:** 3/31/97



**Applicant:** Proctor and Gamble Pharmaceuticals

**Name of Drug:** ASACOL (Mesalamine) Delayed-Release Tablets

## Documents Reviewed:

1. Original NDA volumes 18 to 39 with date referred June 24, 1996.
2. Original data submitted through CANDAs by the sponsor.
3. Corrected data on a floppy diskette supplied by the sponsor on November 14, 1996.

**I. Background:** In this NDA submission two-year carcinogenicity studies in two rodent species, one in Swiss mice and one in Sprague-Dawley rats, were included. These two studies were intended to assess the carcinogenic potential of Asacol in the diet of Swiss mice and Sprague-Dawley rats when administered orally using some selected dose levels. Dr. K. Zhang, HFD-180, who is the reviewing pharmacologist, requested the Division of Biometrics to perform the statistical review and evaluation of this study.

## II. The mouse study

### IIa. Design

Two separate experiments, one in male and one in female mice, were conducted over a period of 24 months. In each of the studies there were three treated groups known as low, medium, and high, and one control group. For each sex, two hundred fifty Swiss mice (approximately 35 days of age) were randomly divided into equal groups of 50 animals each to form the treatment groups and the control group. The dose levels for the treated groups were 200, 1000, and 2000 mg/kg/day for the low, medium, and high dose groups, respectively. The control group received untreated food. The dose of 2000 mg/kg/day was selected as the high dose (expected to be the maximum tolerated dose), since higher doses 6000 mg/kg/day were lethal to mice. The low dose of 200 mg/kg/day is twice the expected highest human dosage. The purpose of this study was to fully evaluate any deviations from the normal or spontaneous lifetime incidence of neoplasms in mice due to drug effect.

Mice were checked at least once daily for moribundity and mortality. Clinical examinations were recorded once weekly. The mice were palpated for abnormal masses at least once monthly. All notebook raw data for clinical signs and palpable masses were entered into the computerized data-collection system. The incidence, size and location of visible or palpable masses were recorded.

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All main study animals found dead or killed during the study were necropsied. The cause of death was determined from the macroscopic and histomorphologic findings. At the conclusion of the dosing phase, surviving animals were euthanized and necropsied from each group on each day.

#### Iib. Sponsor's analysis

##### Survival data analysis:

The sponsor presented mortality data for the main study animals as well as survival curves for both male and female mice. It was concluded that dietary administration of 5-ASA to only male mice at targeted doses of 200, 1000, or 2000 mg/kg/day appeared to decrease survival times when they were compared to those in the control group.

##### Tumor data analysis:

The sponsor analyzed incidental and fatal tumors separately. Tumors observed in an incidental context were analyzed by the prevalence method described in Peto et al. (1980). The logistic regression method was also used as a secondary confirmatory analysis of the prevalence method. Exact permutation p-values were calculated for each tumor using the Statxact and Logxact statistical software. Tumors observed in a fatal context were analyzed by the life table (death rate) method of Haseman. When a tumor occurs in both an incidental and fatal context, the results of the previously described tests were combined into a third test for overall assessment of treatment effect. All statistical tests for tumorigenic effects were one-tailed for dose related increase, separately for males and females.

The sponsor concluded that only in female mice, the trend test for the tumor type, Spleen/Histiocytic Sarcoma, yielded a p-value equal to 0.042 which was not considered significant. Finally the sponsor emphasized that the drug 5-ASA was not carcinogenic to male or female mice.

#### Iic. Reviewer's analysis

The reviewer independently performed analyses on the survival and tumor data. This reviewer compared the intercurrent mortality rates using the survival analysis methods described by Cox (Regression models and life tables. Journal of the Royal Statistical Society, B, 34, 187-220, 1972), and Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52 203-223, 1965). In addition, this reviewer did the trend tests on tumor incidence rates using the method described by Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980) and the method of exact permutation trend test. The data used in this reviewer's analysis were provided

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by the sponsor on a floppy diskette.

Intercurrent mortality data analysis:

Table 1 shows the intercurrent mortality data of the mouse study. Figure 1a and 1b present the plots of Kaplan-Meier estimates of the survival distributions of the treatment groups for male and female mice, respectively. The homogeneity of survival distributions for four treatment groups (Control, Low, Medium, and High) was tested separately for male and female mice using the Cox test and the Generalized Wilcoxon test. The tests show that only for male mice, the departure from trend for the four survival curves is statistically significant at 0.05 level ( $p=0.154$  in the Cox test and  $p=0.0172$  in the Generalized Wilcoxon test). Figure 1a confirmed the behavior of the departure from trend for the four survival curves. In this figure, one noticed that the survival distributions of the three treated groups (low dose, medium dose, and high dose) were not statistically significant. However, the survival distribution of the control group was stochastically larger than those of the other three treated groups. Table 2A and Table 2B provide additional details of the p-values for the linear trend and the pairwise tests, respectively.

Tumor incidence rate analysis:

The sponsor classified the tumor types as 1) 'cause of death', 2) 'not cause of death', and 3) 'undetermined'. Following Peto et al.(1980), the reviewer applied the 'death rate method' to the first tumor type and the 'prevalence' method to the second and the third tumor types to test the positive linear trend in tumor rates. For tumor types occurring in both categories (fatal and non-fatal) a combined test was performed. All tests were done using the method of exact permutation trend test. The scores used in the reviewer's analyses were 0, 200, 1000, and 2000 for the control, low, medium, and high dose groups, respectively. The time intervals used were 0-52, 53-78, 79-92, 93-104 weeks, interim sacrifice, and terminal sacrifice for both sexes.

The incidence rates of tumor types with p-values less than .05 are listed in Table 2.1 (below):

**Table 2.1 (Reviewer) Tumor Incidence Rates with P-values Less Than 0.05**

Female Mice			C	L	M	H	
Organ Name /Tumor Name	MSFLG	0	200	1000	2000		Exact P-Value
Spleen Histiocytic Sarcoma	M	0	0	1	2		0.0442

Multiple testing adjustment: A rule proposed by Haseman could be used to adjust the effect of multiple testings. A similar rule proposed by the Division of Biometrics, CDER/FDA was used in this review. This rule states that in order to keep the overall false-positive rate at the nominal level of approximately ten percent, tumor types with a spontaneous tumor rate of no more than one

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percent should be tested at .025 level, otherwise the level should be set at .005.

On the basis of the Division's p-value adjustment rule, the trend test for the tumor type, Spleen/Histiocytic Sarcoma, in female mice was not significant. The incidence rates of all tumor types tested for linear trend are given in Table 3.

#### IId Evaluation of validity of the design of the mouse study:

The reviewer's analysis results show that in the mouse study there is no statistically significant positive dose-response relationship in any tumor type tested. However, before drawing the conclusion that the drug is not carcinogenic in mouse, it is important to look into the following two issues as having been pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor ?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics II/OEB/CDER, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure.

In addition, Chu, Cueto and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health, Vol. 8, pp 251-280, 1981), suggested that " To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

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It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy.

- i) " A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
- ii) " The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- iii) " In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the Swiss mice carcinogenicity study, in the light of the above guidelines.

The following are summary survival data of mice in the high dose group.

	<u>End of 52</u> <u>weeks</u>	<u>End of 78</u> <u>weeks</u>	<u>End of 92</u> <u>Weeks</u>	<u>End of 104</u> <u>weeks</u>
Male	92%	76%	60%	42%
Female	88%	72%	48%	28%

From the above summary survival data, and the survival criteria mentioned above, it can be concluded that there were enough mice exposed for sufficient amount of time to the drug.

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The following are summary data of body weight gains of the mouse study.

<u>Sex</u>	<u>Group</u>	<u>Mean body weight(gms)</u>			<u>Percentage of Control</u>
		<u>Day 0 of study</u>	<u>End of study</u>	<u>Weight gain</u>	
Male	Control	31.66	40.03	8.37	108.60
	Low				
	Medium	32.0	41.09	9.09	
	High				

<u>Sex</u>	<u>Group</u>	<u>Mean body weight(gms)</u>			<u>Percentage of Control</u>
		<u>Day 0 of study</u>	<u>End of study</u>	<u>Weight gain</u>	
Female	Control	24.04	34.24	10.2	93.43
	Low				
	Medium	23.22	32.75	9.53	
	High				

Therefore, relative to the control, male mouse had a decrement of weight gain in the high dose group equal to 16.73% whereas female rats had an average increment of weight in the high dose group equal to 15.29%, respectively.

The mortality rates at the end of the experiment are as follows:

<u>Sex</u>	<u>Control</u>	<u>High dose</u>
Male	38.0%	58.0%
Female	64.0%	72.0%

From the above table we see that both for male and for female mouse, the mortality rates of the high dose group are higher than those of the control. From the body weight gain data and mortality data, it might be concluded that the high dose level is close to the MTD. However before concluding that the MTD was achieved other clinical signs and histopathological effects must also be taken into consideration.

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### III. The rat study

IIIa. Design: Originally, rats were randomly assigned to a control (0 dose) and four treated groups. Sixty Sprague-Dawley rats (35 days old) of either sex were assigned in each treated group and the control group. The treated groups were given Asacol 60, 120, 360 and 480 mg/kg/day. The purpose of this study was to fully evaluate any deviations from the normal or spontaneous lifetime incidence of neoplasms in rats due to drug effect.

All main study animals found dead or killed during the study were necropsied. At the conclusion of the dosing phase, surviving animals were euthanatized and necropsied so that approximately an equal number of animals were necropsied from each group each day. Due to greater than anticipated mortality among males, surviving male rats were euthanatized approximately 3 weeks prior to the original termination date. Surviving females were killed following 24 months of treatment.

Individual body weight and food consumption were recorded once weekly during the first three months and then every other week for the remainder of the study using a computerized data-collection system.

Rats were checked at least once daily for moribundity and mortality. Clinical examinations were recorded once weekly. The rats were palpated for abnormal masses at least monthly. Based on all pathology observations, cause of death or morbidity was determined for each rat when possible and tumors were classified as incidental or fatal based on this determination.

### IIIb. Sponsor's analysis

#### Survival data analysis:

The sponsor presented survival curves for both male and female rats. It appears that dietary administration of 5-ASA at targeted doses of 0, 60, 120, 360 or 480mg/kg/day have homogeneous survival curves.

#### Tumor data analysis:

The sponsor analyzed incident and fatal tumors separately. Tumors observed in an incidental context were analyzed by the prevalence method described in Peto et al. (1980). The logistic regression method was also used as a secondary or confirmatory analysis of the prevalence method. Exact permutation p-values were calculated for tumor using the Statxact and LogXact statistical software. Tumors observed in a fatal context were analyzed by the life table (death rate) method of Haseman. When a tumor occurs in both an incidental and fatal context, the results of the previously described tests were combined into a third test for overall assessment of treatment

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effect. All statistical test for tumorigenic effects were one-tailed for a dose related increase, separately for males or females.

The sponsor has reported that there was no evidence of an effect of treatment on the incidence of neoplastic findings in this study. There were no tumors observed in this study in which treatment resulted in a strong dose related trend, i.e., significant at  $p < 0.025$ . A single tumor type in one organ in one sex (histiocytic sarcoma/fibrous histiocytoma in liver of male rats) yielded a p-value between 0.025 and 0.05 by exact permutation test (0,0,0,1,2 for control, 60, 120,360, and 480 mg/kg/day, respectively:  $p=0.034$ ). This was not considered a biologically or statistically significant result.

### IIIc. Reviewer's analysis

This reviewer compared the intercurrent mortality rates using the survival analysis methods described by Cox (1972), and Gehan (1965). In addition, this reviewer did the trend tests on tumor incidence rates using the method described by Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. The data used in this reviewer's analysis were provided by the sponsor on a floppy diskette.

#### Intercurrent mortality data analysis:

Table 4 shows the intercurrent mortality data of the rat study. Figure 2a and 2b present the plots of Kaplan-Meier estimates of the survival distributions of the treatment groups for male and female rats, respectively. The homogeneity of survival distributions of five groups (Old Control, New Control, New-Low Dose, Old-Low Dose, Old-Medium Dose) was tested separately for male and female rats using the Cox test and the Generalized Wilcoxon test. The tests show that the survival curves for the five groups are homogeneous. Also there is no significant linear trend for both male and female rats. Tables 5A and 5B provide details of the p-values for the linear trend and the pairwise tests, respectively.

#### Tumor incidence rates analysis:

The sponsor classified the tumor types as 1) 'cause of death', 2) 'not cause of death', and 3) 'undetermined'. Following Peto et al.(1980), the reviewer applied the 'death rate method' to the first tumor type and the 'prevalence' method to the second and the third tumor types to test the positive linear trend in tumor rates. For tumor types occurring in both categories (fatal and non-fatal) a combined test was performed. All tests were done using the method of exact permutation trend test. The scores used in the reviewer's analyses were 0, 60, 120, 360 and 480 for both sexes. The time intervals used were 0 - 52, 53 - 78, 79-92, 93-104 weeks, and terminal sacrifice for both sexes.

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The incidence rates of the tumor types with p-values less than 0.05 are listed in Table 3.1(below).

**Table 3.1 (Reviewer) Tumor Incidence rates with P-value less than 0.05**

MALE RATS									Exact
Organ Name	Tumor Name	MSFLG	C	L	M1	M2	H		P-Value
Liver	Histiocytic Sarcoma/ Fibrous Histiocytoma	S	0	0	0	1	2		0.0331

Multiple testing adjustment: A rule proposed by Haseman could be used to adjust the effect of multiple testings. A similar rule proposed by the Division of Biometrics, CDER/FDA was used in this review. This rule states that in order to keep the overall false-positive rate at the nominal level of approximately ten percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .025 level, otherwise the level should be set at .005.

On the basis of Division's p-value adjustment rule, the trend test for the tumor type Liver Histiocytic Sarcoma/ Fibrous Histiocytoma was not significant. Table 6 provides details of p values on the linear trend tests for the tested tumor types .

#### III.d. Evaluation of validity of the design of the rat study

This reviewer's analysis does not indicate any tumor type is of significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic in rats, it is important to look into the following two issues as pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives. Vol. 58, pp 385-392. 1984). The two issues are:

- (i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor ?
- (ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals ?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology,

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Vol. 5, pp 66-78, 1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics II/OEB/CDER, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number of animals under an adequate exposure.

In addition, Chu, Cueto, and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health. Vol. 8, pp 251-280, 1981), suggested that " To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and the number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto, and Ward (1981), the following criteria are mentioned for dose adequacy.

- i) " A dose is considered adequate if there is a detectable loss in weight gain of up to 10 % in a dosed group relative to the controls."
- ii) " The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- iii) " In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the Sprague-Dawley rat carcinogenicity study, in the light of the above guidelines.

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The following are summary survival data of rats in the old-medium dose (highest dose used in the rat study) group.

Survival rates for the old-medium dose group

Sex	End of 52 weeks	End of 78 weeks	End of 92 weeks	End of Study weeks (104)
Male	96.7%	73.3%	41.7%	21.7%
Female	100.0%	76.7%	56.7%	35.0%

From the above summary data, and the survival criteria mentioned above, it may be concluded that there were enough rats exposed for sufficient amount of time to the drug.

The following are summary data of body weight gains of the rat study.

Body weight gains for five dose groups

Sex	Group	Mean body weight(gms)			Percentage of Control
		Beginning of study	End of study	Weight gain	
Male	Control	248.7	692.8	444.1	
	60	247.0	746.2	499.2	112.4
	120	248.0	741.2	493.2	111.06
	360	244.4	716.2	471.8	106.23
	480	249.4	752.5	503.1	113.28

Body weight gains for five dose groups

Sex	Group	Mean body weight(gms)			Percentage of Control
		Beginning of study	End of study	Weight gain	
Female	Control	178.2	571.8	393.6	
	60	180.1	632.0	451.9	114.81
	120	179.0	546.7	367.7	93.42
	360	179.7	599.4	419.7	106.63
	480	180.1	593.4	413.3	105.00

Therefore, relative to the control, male and female rats had average increment of weight gain in the high dose group equal to 13.23% and 5.0%, respectively.

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The mortality rates at the end of the experiment are as follows:

Sex	Control	High dose
Male	80.0%	78.3%
Female	68.3%	65.0%

From the above table we see that both for male and for female rats, the mortality rate of the high dose group is slightly lower than that of the control.

Thus, from the mortality and body weight gain data it might be concluded that the high dose level might be close to MTD. However, before concluding that the high dose is close to MTD other clinical signs and histopathological effects must also be taken into consideration.

## V. Summary

### a) The mouse study

For the intercurrent mortality data analysis, the tests show that only for male mice, the survival curves are statistically significant at 0.05 level ( $p=0.0291$  in the Cox test and  $p=0.0305$  in the Generalized Wilcoxon test). From Figure 1a, it appeared that the survival distribution of the control group is stochastically larger than those of the other three treated groups.

For tumor incidence rate analysis, on the basis of Division's p-value adjustment rule, no tumor type was found to have linear positive significant trend.

Using the criteria for evaluating the validity of experimental designs of negative studies proposed by experts in the field, it might be concluded that the high dose level is close to the MTD. However, before concluding that the high dose is close to MTD other clinical signs and histopathological effects shall also be taken into consideration.

### b) The rat study

For the intercurrent mortality data analysis, the tests show that for both male and female mice, the survival curves are not statistically significant at 0.05 level ( $p=0.9021$  in the Cox test for male

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mice and  $p=0.2485$  in the Cox's test for female mice).

For tumor incidence rate analysis, on the basis of Division's p-value adjustment rule, no tumor type was found to have linear positive significant trend.

Using the criteria for evaluating the validity of experimental designs of negative studies proposed by experts in the field, the high dose level might be close to MTD. However, before concluding that the high dose is close to MTD other clinical signs and histopathological effects shall also be taken into consideration.

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M. Mushfiqur Rashid, Ph.D.  
Mathematical Statistician

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Concur: Dr. Huque  
Dr. Smith

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Archival : NDA: 19 - 651/SE1 - 005 ASACOL (Mesalamine) Delayed-Release Tablets  
HFD-180/Dr. Fred  
HFD-180/Dr. Choudary  
HFD-180/Dr. Zhang  
HFD-720/Dr. Smith  
HFD-720/Dr. Huque  
HFD-720/Dr. Rashid  
HFD-720/Dr. Chen  
HFD-720/Chron Co  
HFD-720/File Co

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Table 1Intercurrent Mortality Rates In The Mouse Study

Time(wks)	Control	Dose		
		Low	Medium	High
<b>Male</b>				
0-52	1/50 (2.0%)		5/50 (10.0%)	
53-78	5/49 (12.0 %)		7/45 (24.0 %)	
79-92	6/44 (24.0 %)		5/38 (34.0%)	
93-104	7/38 (38.0 %)		11/33 (56.0 %)	
TERM. SAC.	31/50 (62.0 %)		22/50 (44.0 %)	
<b>Female</b>				
0-52	3/50 (6.0 %)		0/50 (0.0 %)	
53-78	10/47 (26.0 %)		10/50 (20.0 %)	
79-92	7/37 (40.0%)		6/40 (32.0 %)	
93-104	12/30 (64.0 %)		12/34 (56.0%)	
TERM. SAC.	18/50(36.0 %)		22/50 (44.0 %)	

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**Table 2A****P-values of tests for linear trend in mortality in the mouse study****Test of homogeneity**

<b>Sex</b>	<b>Test</b>	<b>P-value</b>
<b>Male</b>	Cox	.0291
	Wilcoxon	.0305
<b>Female</b>	Cox	.2485
	Wilcoxon	.1918

**Test of linear trend**

<b>Sex</b>	<b>Test</b>	<b>P-value</b>
<b>Male</b>	Cox	.4153
	Wilcoxon	.3750
<b>Female</b>	Cox	.3141
	Wilcoxon	.2301

Table 2B

P-values of pairwise test for the differences in mortality between treated groups in mouse study

Male Mouse							
ANALYSIS GROUP	EXACT ONE	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W	
	TAIL TEST			EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ PROB .0024**	7.8683 .0050**	POS	8.4526 .0036**	8.4213 .0037**	9.0782 .0026**	9.0468 .0026**
0 VS. 2	CHISQ PROB .0543	2.5692 .1090	POS	3.0733 .0796	3.0678 .0799	3.7540 .0527	3.7477 .0529
0 VS. 3	CHISQ PROB .0543	2.5692 .1090	POS	3.2292 .0723	3.2225 .0726	4.0837 .0433*	4.0759 .0435*
1 VS. 2	CHISQ PROB .1515	1.0611 .3030	NEG	.9857 .3208	.9847 .3210	1.1340 .2869	1.1331 .2871
1 VS. 3	CHISQ PROB .1515	1.0611 .3030	NEG	.8941 .3444	.8931 .3447	.8982 .3433	.8974 .3435
2 VS. 3	CHISQ PROB .5798	.0000 1.0000	POS	.0121 .9125	.0121 .9126	.0330 .8558	.0330 .8558

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Female Mouse							
ANALYSIS GROUP	EXACT ONE	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W ANALYSIS	
	TAIL TEST			EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ PROB .5000	.0000 1.0000	POS	.0155 .9008	.0155 .9009	.0034 .9537	.0034 .9537
0 VS. 2	CHISQ PROB .2703	.3750 .5403	NEG	.5721 .4494	.5716 .4496	.8740 .3498	.8734 .3500
0 VS. 3	CHISQ PROB .2603	.4136 .5201	POS	.9887 .3201	.9854 .3209	1.3922 .2380	1.3894 .2385
1 VS. 2	CHISQ PROB .2062	.6726 .4122	NEG	.7486 .3869	.7468 .3875	.7300 .3929	.7290 .3932
1 VS. 3	CHISQ PROB .3329	.1870 .6654	POS	.8245 .3639	.8229 .3643	1.6295 .2018	1.6272 .2021
2 VS. 3	CHISQ PROB .0721	2.1267 .1447	POS	3.4776 .0622	3.4583 .0629	4.4861 .0342*	4.4698 .0345*

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Table 3

Tumor Rates of the Tested Tumor Types for Positive Linear Trend

Male Mouse Organ Name	Tumor Name	MSFLG	P-Value	Exact			
				C	L	M	H
ADRENAL GLAND(S)	CORTICAL-CELL ADENOMA [B]	S	0.0939	3	0	3	4
ADRENAL GLAND(S)	LYMPHOMA [M]	S	0.6223	2	2	1	2
ADRENAL GLAND(S)	MEDULLARY-CELL ADENOMA/PHEOCHROMOCYTOMA	S	0.1092	1	1	0	3
AORTA	LYMPHOMA [M]	S	0.7308	2	1	1	1
BONE	LYMPHOMA [M]	S	0.8074	2	1	0	1
BONE MARROW	GRANULOCYTIC LEUKEMIA [M]	M	0.2597	0	1	0	1
BONE MARROW	LYMPHOMA [M]	S	0.6570	2	2	0	2
BRAIN	LYMPHOMA [M]	S	0.8577	3	1	1	1
CECUM	LYMPHOMA [M]	S	0.9980	2	1	0	0
COLON	LYMPHOMA [M]	S	0.9972	3	2	0	0
DUODENUM	LYMPHOMA [M]	S	0.9895	1	1	0	0
EPIDIDYMIS(DES)	LYMPHOMA [M]	S	0.6610	2	2	0	2
ESOPHAGUS	LYMPHOMA [M]	S	0.9039	2	0	1	0
EYE(S)	LYMPHOMA [M]	S	0.5269	2	1	1	2
GALLBLADDER	LYMPHOMA [M]	S	0.9348	1	1	0	0
HARDERIAN GLAND(S)	ADENOMA/ADENOCARCINOMA	S	0.7075	4	4	0	3
HARDERIAN GLAND(S)	LYMPHOMA [M]	S	0.7700	2	1	1	1
HEART	LYMPHOMA [M]	S	0.7579	3	0	1	1
ILEUM	LYMPHOMA [M]	S	0.7462	2	1	1	1
JEJUNUM	LYMPHOMA [M]	S	0.7958	1	0	1	0
JOINT(S)	LYMPHOMA [M]	S	0.7545	2	1	1	1
KIDNEY(S)	LYMPHOMA [M]	M	0.6419	4	2	1	3
LACRIMAL GLAND(S)	LYMPHOMA [M]	S	0.8552	3	1	1	1
LIVER	HEMANGIOMA/HEMANGIOSARCOMA	M	0.3143	1	0	3	1
LIVER	HEPATOCELLULAR ADENOMA/CARCINOMA	M	0.6882	9	3	8	4
LIVER	HISTIOCYTIC SARCOMA [M]	M	0.3570	1	2	0	2
LIVER	LYMPHOMA [M]	M	0.5777	2	2	1	2
LUNG	Bronchiolar-alveolar ADENOMA/ADENOCARCINOMA	M	0.8710	15	6	9	7
LUNG	LYMPHOMA [M]	S	0.7395	3	2	1	2
LUNG	MESOTHELIOMA [M]	S	0.4938	0	0	1	0
LYMPH NODE(S)	LYMPHOMA [M]	S	0.6114	0	1	1	0
MEDI.LYMPH NODE(S)	LYMPHOMA [M]	M	0.5023	1	0	0	1
MESE.LYMPH NODE(S)	LYMPHOMA [M]	M	0.7212	2	2	3	1
NASAL CAV/TURB. (S)	LYMPHOMA [M]	S	0.5269	2	1	1	2
PANCREAS	LYMPHOMA [M]	S	0.7471	3	2	1	2
PITUITARY	ADENOMA/CARCINOMA	S	0.4719	1	0	0	1
PITUITARY	LYMPHOMA [M]	S	0.9895	1	1	0	0
PREP/CLIT GLAND(S)	LYMPHOMA [M]	S	0.6045	1	1	1	1
PROSTATE	LYMPHOMA [M]	S	0.7389	3	2	1	2
SALIVARY GLAND(S)	LYMPHOMA [M]	S	0.9429	4	2	1	1
SCIATIC NERVE	LYMPHOMA [M]	S	0.6045	1	1	1	1
SEMINAL VESICLE(S)	LYMPHOMA [M]	S	0.6223	2	2	1	2
SKELETAL MUSCLE	LYMPHOMA [M]	S	0.3600	3	2	1	4
SKIN/SUBCUTIS	HEMANGIOMA/HEMANGIOSARCOMA	S	0.8715	2	0	1	0
SKIN/SUBCUTIS	LIPOMA [B]	S	0.2333	0	0	0	1
SKIN/SUBCUTI	LYMPHOMA [M]	S	0.6045	1	1	1	1
SKIN/SUBCUTIS	PAPILLOMA [B]	S	0.2432	0	0	0	1
SPINAL CORD	LYMPHOMA [M]	S	0.6579	3	1	1	2
SPLEEN	HEMANGIOSARCOMA [M]	M	0.6076	1	2	0	1
SPLEEN	HISTIOCYTIC SARCOMA [M]	M	0.7670	0	2	0	0
SPLEEN	LYMPHOMA [M]	S	0.7255	3	2	1	2
STOMACH	CARCINOMA [M]	S	1.0000	2	0	0	0
STOMACH	LYMPHOMA [M]	S	0.7389	3	2	1	2
STOMACH	SQUAMOUS CELL CARCINOMA [M]	S	1.0000	1	0	0	0
STEM LYMPH NODE(S)	LYMPHOMA [M]	S	0.8324	2	2	1	1
TESTIS ES	INTERSTITIAL CELL ADENOMA	S	0.8830	4	0	0	1
TESTIS ES	LYMPHOMA [M]	S	0.5729	2	1	0	2
THYMUS	LYMPHOMA [M]	S	0.4024	3	1	1	3
THYROID GLAND	LYMPHOMA [M]	S	0.8906	2	0	1	0
TONGUE	LYMPHOMA [M]	S	0.7958	1	0	1	0
TRACHEA	LYMPHOMA [M]	S	0.8767	1	1	1	0
URINARY BLADDER	LYMPHOMA [M]	S	0.9042	4	1	1	1
LYMBA GLAND(S)	LYMPHOMA [M]	S	0.9835	3	2	1	0

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Table 3

Female Mouse Organ Name	Tumor Name	MSFLG	Exact P-Value	C	L	M	H
ADRENAL GLAND(S)	LYMPHOMA [M]	S	0.8646	4	4	4	2
ADRENAL GLAND(S)	MEDULLARY-CELL ADENOMA PHEOCHROMOCYTOMA	S	0.7369	1	0	1	0
ADRENAL GLAND(S)	Subcapsular-cell ADENOMA [B]	S	0.7429	0	1	0	0
AORTA	LYMPHOMA [M]	S	0.2928	4	2	1	5
BONE	CHONDROSARCOMA [M]	S	0.5143	0	0	1	0
BONE	LYMPHOMA [M]	S	0.5143	0	0	1	0
BONE MARROW	LYMPHOMA [M]	S	0.9544	2	2	2	0
BRAIN	LYMPHOMA [M]	S	0.5261	2	0	3	1
CECUM	LYMPHOMA [M]	S	0.5100	2	1	0	2
COLON	LYMPHOMA [M]	S	0.6590	2	2	3	1
DUODENUM	LYMPHOMA [M]	S	0.4810	1	1	2	1
ESOPHAGUS	LYMPHOMA [M]	S	0.4857	0	0	2	0
EYE(S)	LYMPHOMA [M]	S	0.9505	3	1	2	0
GALLBLADDER	Focal PAPILLOMA [B]	S	0.5143	0	0	1	0
GALLBLADDE	LYMPHOMA [M]	S	0.8035	2	2	4	0
HARDERIAN GLAND(S)	DENOMA/ADENOCARCINOMA	S	0.2674	3	0	1	3
HARDERIAN GLAND(S)	LYMPHOMA [M]	S	0.4927	1	3	3	2
HEART	LYMPHOMA [M]	S	0.1702	2	1	4	3
ILEUM	LYMPHOMA [M]	S	0.4614	2	1	1	2
JEJUNUM	LYMPHOMA [M]	S	0.6902	2	1	1	1
JOINT(S)	LYMPHOMA [M]	S	0.2543	0	1	1	1
KIDNEY(S)	LYMPHOMA [M]	S	0.6559	6	6	7	5
KIDNEY(S)	Perirenal LYMPHOMA [M]	S	1.0000	1	0	0	0
LACRIMAL GLAND(S)	LYMPHOMA [M]	S	0.2355	2	1	4	3
LIVER	HEMANGIOMA/HEMANGIOSARCOMA	S	0.5143	0	0	1	0
LIVER	HEPATOCELLULAR ADENOMA CARCINOMA	S	0.6308	1	2	0	1
LIVER	HISTIOCYTIC SARCOMA [M]	S	0.6829	2	2	2	1
LIVER	LYMPHOMA [M]	M	0.7196	3	3	3	2
LUNG Bronchiolar-alveolar	ADENOMA/ADENOCARCINOMA	S	0.3506	11	2	5	8
LUNG	LYMPHOMA [M]	S	0.7661	6	5	4	4
LYMPH NODE(S)	LYMPHOMA	S	0.7902	2	1	0	1
MAMMARY GLAND(S)	ADENOMA/ADENOCARCINOMA	M	0.6997	3	0	1	1
MAMMARY GLAND(S)	LYMPHOMA [M]	S	0.1768	1	2	3	3
MEDIASTINAL LYMPH NODE(S)	LYMPHOMA [M]	M	0.5842	0	1	1	0
MESENTERIC LYMPH NODE(S)	LYMPHOMA [M]	M	0.3571	4	4	6	5
NASAL CAVITY/TURBINATE(S)	LYMPHOMA [M]	S	0.8529	1	1	2	0
OVARY(IES)	LUTEOMA/GRANULOSA-THECA CELL TUMOR	S	0.9367	1	1	0	0
OVARY(IES)	LYMPHOMA [M]	S	0.6814	5	3	2	4
OVARY(IES)	MYXOMA [B]	S	0.4583	0	0	1	0
OVARY(IES)	TERATOMA [B]	S	0.7429	0	1	0	0
OVARY(IES)	Tubular/NOS ADENOMA [B]	M	0.5944	0	1	1	0
PANCREAS	LYMPHOMA [M]	S	0.4528	4	3	6	4
PARATHYROID GLAND(S)	LYMPHOMA [M]	S	1.0000	1	0	0	0
PITUITARY	ADENOMA/CARCINO	M	0.8035	3	1	1	1
PITUITARY	LYMPHOMA [M]	S	0.9874	2	2	0	0
PREPUTIAL/CLIT GLAND(S)	LYMPHOMA [M]	S	0.1416	0	0	4	1
SALIVARY GLAND(S)	Local ADENOMA [B]	S	0.5143	0	0	1	0
SALIVARY GLAND(S)	LYMPHOMA [M]	S	0.6590	3	2	3	2
SCIATIC NERVE	LYMPHOMA [M]	S	0.2591	2	0	3	2
SKELETAL MUSCLE	LYMPHOMA [M]	S	0.6796	3	3	4	2
SKIN/SUBCUTIS	ADENOCARCINOMA [M]	S	0.5143	0	0	1	0
SKIN/SUBCUTIS	ASOSQUAMOUS CARCINOMA SQUAMOUS CELL CARCINOM	S	0.1688	0	0	1	1
SKIN/SUBCUTIS	FIBROSARCOMA [M]	M	0.2578	0	1	0	1
SKIN/SUBCUTIS	LYMPHOMA [M]	S	0.1721	0	0	2	1
SPINAL CORD	LYMPHOMA [M]	S	0.8223	2	1	1	1
SPLEEN	HEMANGIOSARCOMA [M]	S	0.7408	1	0	1	0
SPLEEN	HISTIOCYTIC SARCOMA [M]	M	0.0442	0	0	1	2
SPLEEN	LYMPHOMA [M]	M	0.6884	7	5	5	5
STOMACH	LYMPHOMA	S	0.4903	3	1	4	2
SUBMANDIBULAR LYMPH NODE(S)	LYMPHOMA [M]	S	0.5162	3	2	3	3
THORACIC CAVITY	LYMPHOMA [M]	S	0.7716	2	1	0	1
THYMUS	LYMPHOMA [M]	M	0.4286	5	3	5	4
THYROID GLAND	LYMPHOMA [M]	S	0.5996	2	0	2	1
TONGUE	LYMPHOMA [M]	S	0.5688	1	0	3	0
URINARY BLADDER	LYMPHOMA [M]	S	0.8850	3	4	3	1
UTERUS	HISTIOCYTIC SARCOMA [M]	M	0.4456	3	3	2	3
UTERUS	LEIOMYOMA LEIOMYOSARCOMA	S	0.5409	0	1	2	0
UTERUS	LYMPHOMA [M]	S	0.2283	2	1	2	3
VAGINA	LYMPHOMA	S	0.6948	1	3	2	1
ZYMALAR'S GLAND(S)	LYMPHOMA	S	0.7703	2	1	2	1

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**Table 4**  
**Intercurrent Mortality Rates in the Rat Study**

Time(wks)	Dose				
	Control	Low	Med1	Med2	High
<b>Male</b>					
0-52	3 / 60 (5.0 %)		2/60 (3.3 %)	3 / 60 (5.0 %)	
53-78	7 / 57 (16.7 %)		10 / 58 (20.0 %)	16 / 57 (31.7 %)	
79-92	26 / 50 (60.0%)		21 / 48 (55.0 %)	20 / 41 (65.0%)	
93-104	12 / 24 (80.0 %)		12 / 27 (75.0%)	5 / 21 (73.3 %)	
TERM. SAC.	12 / 60 (20.0 %)		15 / 60 (25.0 %)	16 / 60 (26.7%)	
<b>Female</b>					
0-52	5 / 60 ( 8.3%)		2/60 ( 3.3 %)	3 / 60 (5.0 %)	
53-78	10 / 55 (25.0 %)		8 / 58 (16.7%)	13 / 57 (26.7%)	
79-92	15 / 45 ( 50.0 %)		19 / 50 (48.3 %)	14 / 44 (50.0 %)	
93-104	11/30 (68.3 %)		12 / 31 (68.3%)	14 / 30 (73.3%)	
TERM. SAC.	19/60(31.7%)		19 / 60 (31.7%)	16 / 60 (26.7 %)	

APPEARS THIS WAY  
ON ORIGINAL

Table 5A

P-values of tests for linear trend in mortality in the mouse studyTest of homogeneity

Sex	Test	P-value
Male	Cox	.9021
	Wilcoxon	.5106
Female	Cox	.2485
	Wilcoxon	.1918

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Test of linear trend

Sex	Test	P-value
Male	Cox	.8905
	Wilcoxon	.6861
Female	Cox	.4849
	Wilcoxon	.4536

APPEARS THIS WAY  
ON ORIGINAL

Table 5B

P-values of pairwise test for the differences in mortality  
between treated groups in rat study

## Male Rat

GROUP	EXACT ONE TAIL TEST S CONSERVATIVE	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE
0 VS. 1	CHISQ PROB .5491	.0096 .9220	NEG	.2310 .6308	.2298 .6317	1.6781 .1952	1.6724 .1959
0 VS. 2	CHISQ PROB .4147	.0466 .8291	NEG	.1129 .7369	.1126 .7372	.0930 .7604	.0929 .7605
0 VS. 3	CHISQ PROB .3351	.1819 .6698	NEG	.0197 .8585	.0196 .8886	.9458 .3308	.9441 .3312
0 VS. 4	CHISQ PROB .5875	.0000 1.0000	POS	.0019 .9650	.0019 .9650	.1372 .7111	.1371 .7112
1 VS. 2	CHISQ PROB .4551	.0129 .9095	NEG	.7508 .3926	.7291 .3932	2.1969 .1383	2.1922 .1387
1 VS. 3	CHISQ PROB .3739	.1041 .7470	NEG	.0945 .7558	.0941 .7590	.1122 .7377	.1120 .7378
1 VS. 4	CHISQ PROB .5491	.0096 .9220	POS	.0538 .8166	.0536 .8169	.5215 .4702	.5205 .4706
2 VS. 3	CHISQ PROB .5000	.0000 1.0000	NEG	.2799 .5968	.2795 .5970	1.5975 .2063	1.5953 .2066
2 VS. 4	CHISQ PROB .4147	.0466 .8291	POS	.2590 .6108	.2587 .6110	.5331 .4653	.5328 .4654
3 VS. 4	CHISQ PROB .3351	.1819 .6698	POS	.0075 .9309	.0075 .9309	.3302 .5655	.3299 .5657

## Female Rat

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ PROB .4211	.0397 .8421	POS	.0019 .9652	.0019 .9652	.0008 .9777	.0008 .9777
0 VS. 2	CHISQ PROB .5777	.0000 1.0000	POS	.0172 .8957	.0172 .8957	.2391 .6248	.2390 .6249
0 VS. 3	CHISQ PROB .4211	.0397 .8421	POS	.0057 .9400	.0057 .9400	.0053 .9417	.0053 .9418
0 VS. 4	CHISQ PROB .3503	.1482 .7003	NEG	.4885 .4682	.4800 .4884	.9268 .3357	.9261 .3359
1 VS. 2	CHISQ PROB .4211	.0397 .8421	NEG	.0983 .7539	.0981 .7541	.2786 .5976	.2783 .5978
1 VS. 3	CHISQ PROB .5802	.0000 1.0000	POS	.0075 .9309	.0076 .9308	.0032 .9545	.0032 .9546
1 VS. 4	CHISQ PROB .2179	.6078 .4356	NEG	.7469 .3875	.7461 .3877	.8854 .3467	.8846 .3469
2 VS. 3	CHISQ PROB .4211	.0397 .8421	POS	.0891 .7653	.0891 .7654	.2955 .5867	.2954 .5868
2 VS. 4	CHISQ PROB .3503	.1482 .7003	NEG	.2086 .6471	.2094 .6473	.2206 .6386	.2204 .6388
3 VS. 4	CHISQ PROB .2179	.6078 .4356	NEG	.7175 .3969	.7172 .3971	.9676 .3253	.9671 .3254

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**Table 6**  
**Tumor rates of the tested tumor types for positive linear trend**

Male Rat Organ Name / Tumor Name	MSFLG	Exact P-Value	C	L	M1	M2	H
ADRENAL GLAND(S) CORTICAL CELL CARCINOMA OR ADENOM	S	0.4701	0	0	1	1	0
ADRENAL GLAND(S) LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.8128	1	1	0	1	0
ADRENAL GLAND(S) PHEOCHROMOCYTOMA, BENIGN OR MALIGNANT	S	0.7956	9	8	16	5	9
AORTA LARGE GRANULAR-CELL LYMPHOMA [M]	S	1.0000	1	0	0	0	0
BONE MARROW GRANULOCYTIC LEUKEMIA [M]	S	0.4036	0	0	0	1	0
BONE MARROW LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	M	0.8981	4	1	0	1	1
BRAIN ASTROCYTOMA/OLIGODENDROGLIOMA [M]	M	0.5177	2	0	0	1	1
BRAIN LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	M	0.9942	2	1	0	0	0
CECUM LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	1.0000	2	0	0	0	0
EYE(S) LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9993	3	1	0	0	0
HARDERIAN GLAND(S) LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9993	3	1	0	0	0
HEART LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9718	1	1	0	0	0
JEJUNUM INTESTINAL ADENOCARCINOMA [M]	S	0.4061	0	0	0	1	0
JEJUNUM LARGE GRANULAR-CELL LYMPHOMA [M]	S	1.0000	1	0	0	0	0
JOINT(S) LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	1.0000	3	0	0	0	0
KIDNEY(S) LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9376	4	1	0	2	0
KIDNEY(S) TUBULAR CARCINOMA/ADENOCARCINOMA OR ADENOM	S	0.2355	0	0	1	0	1
LACRIMAL GLAND(S) LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9929	2	1	0	0	0
LIVER HEPATOCELLULAR CARCINOMA OR ADENOMA	M	0.4856	2	4	0	1	3
LIVER HISTIOCYTIC SARCOMA/FIBROUS HISTIOCYTOMA [M]	S	0.0331	0	0	0	1	2
LIVER LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	M	0.8421	4	2	0	2	1
LUNG LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.8922	4	1	0	1	1
MAMMARY GLAND(S) FIBROADENOMA [B]	M	0.0597	1	1	2	4	3
MAMMARY GLAND(S) LARGE GRANULAR-CELL LYMPHOMA [M]	S	1.0000	1	0	0	0	0
MAMMARY GLAND(S) MAMMARY ADENOCARCINOMA OR ADENOMA	M	0.1022	1	0	0	3	1
MESENTERIC LYMPH NODE(S) LYMPHOMA/LARGE GRAN-CELL LYM [M]	S	0.9478	3	1	0	1	0
NASAL CAVITY/TURBINATE(S) LYMPHOMA/LARGE GRAN-CELL LYM [M]	S	0.9993	3	1	0	0	0
NASAL CAVITY/TURBINATE(S) SQUAMOUS CELL CARCINOMA [M]	M	0.6245	0	3	0	2	0
PANCREAS HISTIOCYTIC SARCOMA/FIBROUS HISTIOCYTOMA [M]	S	0.5882	0	0	1	0	0
PANCREAS SLET CELL CARCINOMA OR ADENOMA	S	0.9624	4	2	3	2	0
PANCREAS LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9973	2	1	0	0	0
PANCREAS PANCREATIC ADENOMA [B]	S	0.7824	2	1	1	0	1
PARATHYROID GLAND(S) PARATHYROID ADENOMA [B]	S	0.0750	0	1	0	1	2
PITUITARY LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	1.0000	3	0	0	0	0
PITUITARY PITUITARY CARCINOMA OR ADENOMA	M	0.3091	33	32	31	39	32
PROSTATE LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9993	3	1	0	0	0
SALIVARY GLAND(S) LYMPHOMA [M]	S	0.9718	1	1	0	0	0
SEMINAL VESICLE(S) LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9992	2	1	0	0	0
SKELETAL MUSCLE LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9896	1	1	0	0	0
SKIN:SUBCUTIS BASOSQUAMOUS CARCINOMA OR BASAL CELL TUMOR	M	0.9184	0	2	3	0	0
SKIN:SUBCUTIS FIBROSARCOMA OR FIBROMA	M	0.5324	8	1	4	4	5
SKIN:SUBCUTIS HISTIOCYTIC SARCOMA/FIBROUS HISTIOCYTOMA [M]	S	0.1132	0	0	0	1	1
SKIN:SUBCUTIS LYMPHOMA [B]	S	0.3685	0	1	0	2	0
SKIN:SUBCUTIS SQUAMOUS CELL CARCIN OR PAPILLO OR KERATOACANTHIO LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	M	0.5772	7	3	6	3	6
STOMACH LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.8342	4	2	0	2	1
SUBMANDIBULYMNOD(S) LYMPHOMA/LARGE GRANUL-CELL LYMPHOMA [M]	S	0.6715	1	1	0	0	1
TESTIS(ES) INTERSTITIAL CELL ADENOMA [B]	S	0.7903	3	1	0	1	1
THYMUS LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.6292	1	1	2	1	1
THYMUS THYMOMA [M]	M	0.9468	3	1	0	1	0
THYROID GLAND C-CELL CARCINOMA OR ADENOMA	M	0.3835	0	2	0	1	1
THYROID GLAND FOLLICULAR-CELL CARCINOMA OR ADENOMA	M	0.7776	7	6	3	3	5
THYROID GLAND LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.1201	0	1	0	0	2
URINARY BLADDER LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.9896	1	1	0	0	0
ZYMBAL'S GLAND(S) ZYMBAL'S GLAND CARCINOMA OR ADENOM	M	0.9896	1	1	0	0	0
	M	0.4691	0	1	1	2	0

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**Table 6**  
**Tumor rates of the tested tumor types for positive linear trend**

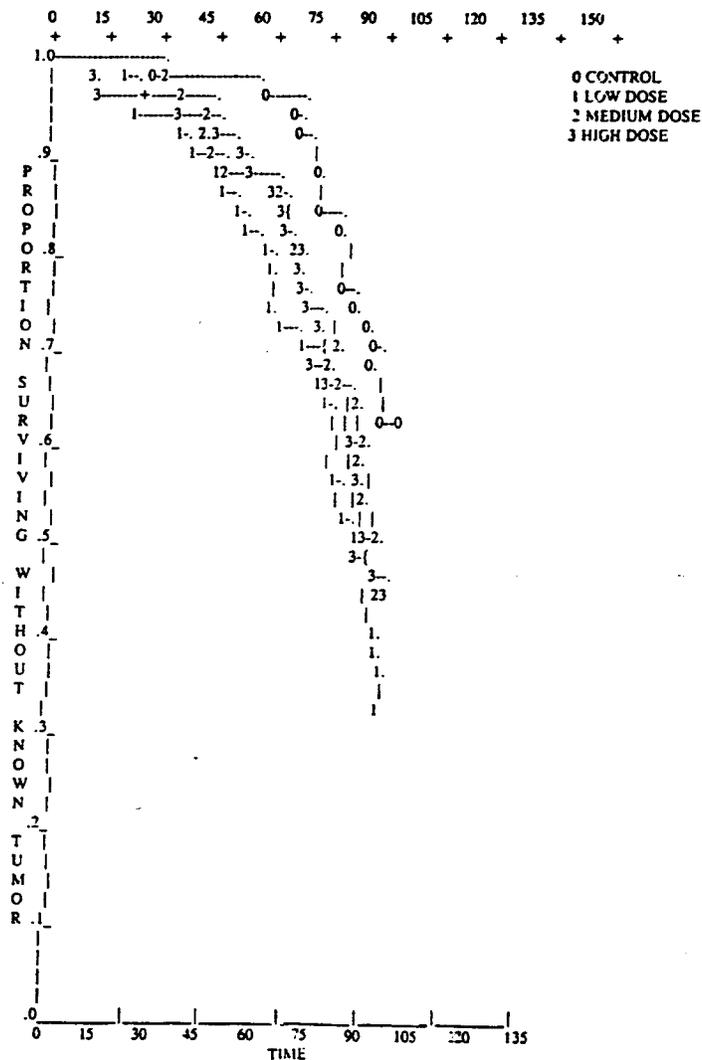
Female Rat Organ Name /Tumor Name		Exact MSFLG P-Value	C	L	MI	M2	H
ADRENAL GLAND(S) CORTICAL CELL CARCINOMA OR ADENOMA	M	0.6976	5	0	7	3	3
ADRENAL GLAND(S) PHEOCHROMOCYTOMA, BENIGN OR MALIGNANT	S	0.4316	0	3	5	3	2
AORTA UNDIFFERENTIATED SARCOMA [M]	S	0.2213	0	0	0	0	1
BRAIN ASTROCYTOMA/OLIGO [M]	M	0.6467	1	0	0	1	0
CECUM HEMANGIOSARCOMA [M]	S	1.0000	1	0	0	0	0
JEJUNUM LEIOMYOMA [B]	S	0.7912	0	1	0	0	0
KIDNEY(S) SQUAMOUS CELL CARCINOMA [M]	S	0.7912	0	1	0	0	0
KIDNEY(S) TRANSITIONAL CELL CARCINOMA [M]	S	0.7912	0	1	0	0	0
KIDNEY(S) TUBULAR CARCINOMA/ADENOCARCINOMA OR ADENOMA	S	0.3412	0	1	0	2	0
LIVER HEPATOCELLULAR CARCINOMA OR ADENOMA	S	0.5478	0	0	2	1	0
LIVER LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	1.0000	1	0	0	0	0
MAMMARY GLAND(S) FIBROADENOMA [B]	M	0.9259	36	36	35	35	30
MAMMARY GLAND(S) MAMMARY ADENOCARCINOMA OR ADENOMA	M	0.3652	17	11	10	8	19
NASAL CAVITY/TURBINATE(S) SQUAMOUS CELL CARCINOMA [M]	S	1.0000	1	0	0	0	0
OVARY(IES) GRANULOSA-CELL/GRANULOSA-THECA CELL TUMOR, BENIGN OR MALIGNANT	M	0.1768	1	0	0	2	1
OVARY(IES) SERTOLI CELL TUMOR, BENIGN OR MALIGNANT	S	0.4603	0	0	1	1	0
PANCREAS ISLET CELL CARCINOMA OR ADENOMA	S	0.3928	3	0	1	4	1
PANCREAS PANCREATIC ADENOMA [B]	S	0.2308	0	0	0	0	1
PARATHYROID GLAND(S) PARATHYROID ADENOMA [B]	S	0.7353	1	0	0	1	0
PITUITARY PITUITARY CARCINOMA OR ADENOM	M	0.3398	47	46	46	51	49
SALIVARY GLAND(S) SALIVARY ADENOCARCINOMA [M]	S	0.7912	0	1	0	0	0
SKIN/SUBCUTIS BASOSQUAMOUS CARCINOMA OR BASAL CELL TUMOR	S	0.2440	0	0	1	0	1
SKIN/SUBCUTIS FIBROSARCOMA OR FIBROMA	M	0.3892	3	0	6	2	4
SKIN/SUBCUTIS HEMANGIOSARCOMA [M]	M	0.5581	0	1	0	1	0
SKIN/SUBCUTIS HISTIOCYTIC SARCOMA FIBROUS HISTIOCYTOMA [M]	S	0.6800	0	1	2	1	0
SKIN/SUBCUTIS LIPOMA [B]	M	0.0883	0	0	0	3	0
SKIN/SUBCUTIS NEURILEMMIOMA [B]	S	0.8425	0	1	0	0	0
SKIN/SUBCUTIS SQUAMOUS CELL CARCINOMA OR PAPILLOMA	M	0.2341	1	1	0	1	2
STOMAC OR KERATOACANTHOMA SQUAMOUS PAPILLOMA [B]	S	0.6154	0	0	1	0	0
THYMUS HISTIOCYTIC SARCOMA/FIBROUS HISTIOCYTOMA [M]	S	0.6129	0	0	1	0	0
THYMUS LYMPHOMA/LARGE GRANULAR-CELL LYMPHOMA [M]	S	0.8425	0	1	0	0	0
THYROID GLAND C-CELL CARCINOMA OR ADENOMA	M	0.7536	3	7	5	3	4
THYR GL FOLLICUL-CELL CARCINO OR ADENO	S	1.0000	3	0	0	0	0
UTERUS ENDOMETRIAL ADENOCARCINOMA [M]	S	0.6154	0	0	1	0	0
UTERUS ENDOMETRIAL STROMAL SARCOMA OR POLYP	M	0.9178	2	2	3	0	1
VAGINA HEMANGIOMA [B]	S	0.6096	0	0	1	0	0
VAGINA LEIOMYOMA [B]	S	0.3993	0	0	0	1	0

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**Figure 1a**

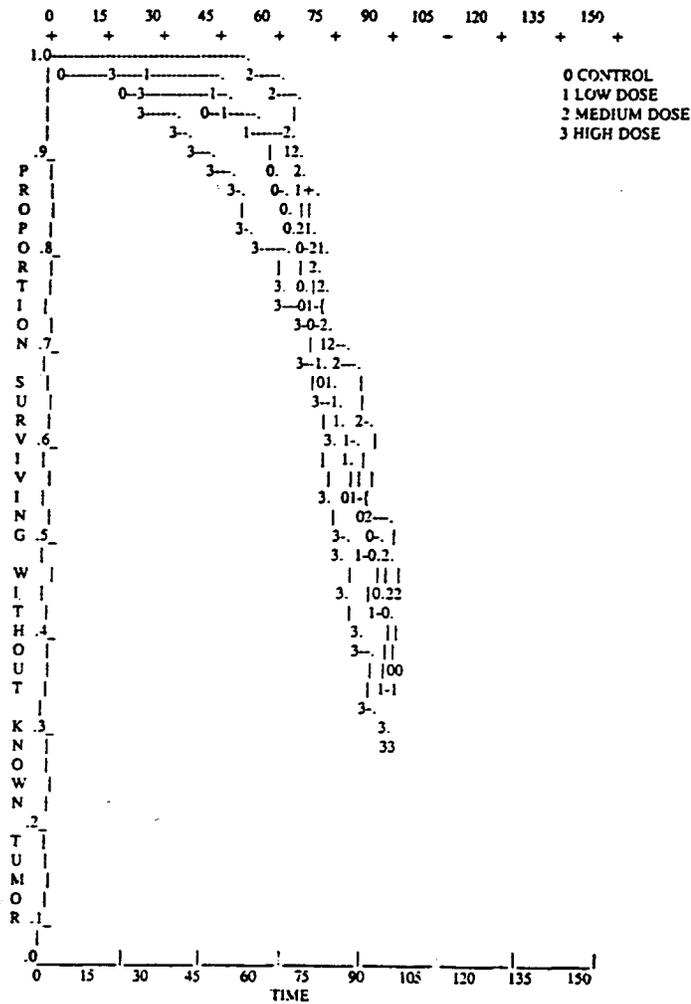
**Kaplan-Meier estimates of the survival distributions(Male mice)**



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**Figure 1b**  
**Kaplan-Meier estimates of the survival distributions(Female mice)**



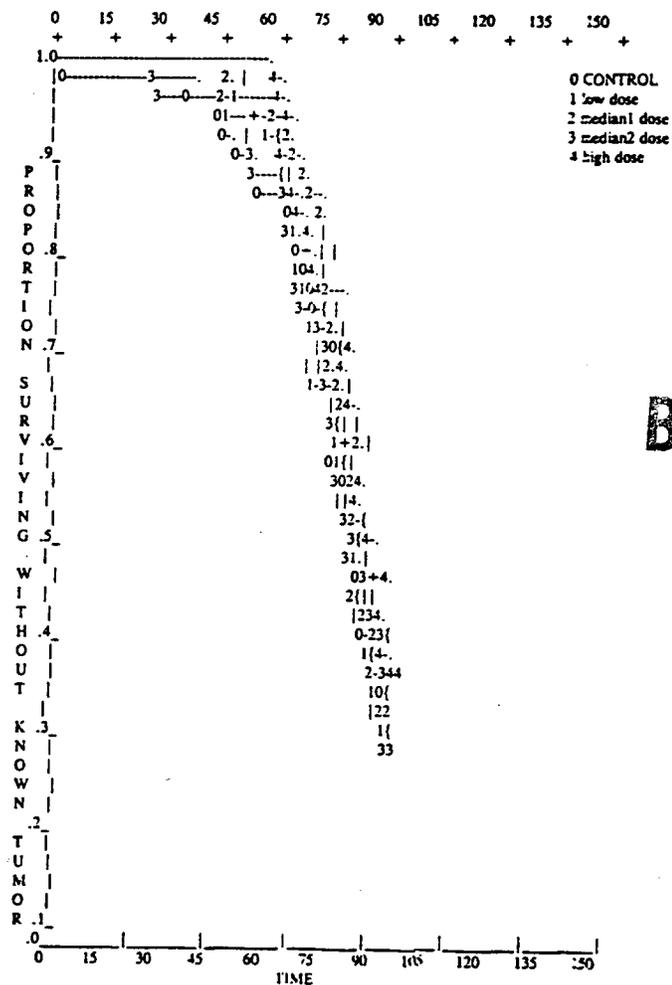
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Figure 2b

Kaplan-Meier estimates of the survival distributions (Female rats)



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**STATISTICAL REVIEW AND EVALUATION**

APR 15 1997

**NDA:** 19-651/S-005

Date: ~~APR 17 1997~~

**APPLICATION:** Procter & Gamble Company

**NAME OF DRUG:** Asacol (Mesalamine) Tablets.

**INDICATION:** Maintenance of Remission of Ulcerative Colitis.

**DOCUMENT REVIEWED:** NDA Volumes 1 & 133 through 151; Dated 4 June 1996.

**MEDICAL REVIEWER:** This review has been discussed with medical officer, Robert Prizont, MD., (HFD-180).



**I. INTRODUCTION**

Asacol (mesalamine) is an oral preparation which, unlike sulfasalazine, does not contain sulfapyridine. Asacol contains a core of 400 mg 5-ASA. the same amount contained in one gram of sulfasalazine. This           enveloped by a PH-sensitive,           until the tablet reaches an environment of pH 7 or above.

The           designed to deliver effective concentrations of 5-ASA in the colon with low systemic absorption.

This statistical review addresses the pivotal Study # 87086 and pooled efficacy analysis for four positive-controlled studies (Studies C.1, C.2, C.6, and C.15), submitted to support the use of Asacol in the maintenance of remission of ulcerative colitis. The purpose of the pooled efficacy analysis on the four positive-controlled studies (Studies C.1, C.2, C.6, and C.15), as indicated by the sponsor, "is to provide evidence that Asacol dose not different significantly from sulfasalazine with regard to efficacy in the maintenance of remission of patients with ulcerative colitis."

As indicated by the sponsor, the NDA for the use of Asacol in the maintenance of remission of ulcerative colitis was not approved. Following the recommendation from the Agency, the sponsor conducted a pivotal study, Study# 87086, and provided further analyses on the four previously submitted positive-control studies (Studies C.1, C.2, C.6, and C.15) to support the single pivotal study (Study # 87086).

## II. STUDY# 87086/U.S. STUDY

### 2.1 Design

This study was a multi-center, double-blind, placebo-controlled, parallel group, randomized clinical trial. A total of 264 patients with quiescent ulcerative colitis, between \_\_\_\_\_ were randomized. Out of these, a total of 189 patients completed the study and were eligible for the primary efficacy analysis. Patients were required to be in remission for 1 to 12 months prior to study entry. Entry criteria included remission of symptoms maintained by the use of \_\_\_\_\_ of sulfasalazine or any oral product with a dose of \_\_\_\_\_ of 5-ASA for at least 1 month prior to study entry. Patients were excluded if they had received rectal steroids or 5-ASA enemas during the month prior to study entry.

After the prestudy screening, patients who satisfied the entry criteria were randomized to one of the three treatment groups: Placebo, Asacol 0.8 g/day, or Asacol 1.6 g/day. After randomization, patients were to take medication for 6 months and were to return to the clinic for follow-up visits at Months 1, 3, and 6. At each follow-up visit, patients were to undergo physical examination, proctosigmoidoscopy, laboratory analyses, and pregnancy testing.

### 2.2 Sponsor's statistical analysis and results

Sponsor's Table 7 through 10 (see Appendix A) provide summary of demographic and baseline data. Demographic variables include Age, Sex, and Race, and the baseline characteristics include length of history of ulcerative colitis, prestudy medication for ulcerative colitis, and prestudy stool frequency. This summary is for both the completed patient data base and for the intent-to-treat (ITT) data base; the completed data base was used for the primary efficacy analysis.

There was a significantly smaller percentage of females in the Placebo group as compared to the Asacol 1.6 g/day group for the completed patient data base: Placebo 32%, Asacol 1.6 g/day 57%; 2-Sided  $p=0.006$  (by the Fisher's Exact test). There were no other significant baseline or demographic differences among the treatment groups for the variables analyzed and reported.

Sponsor's Table 11 through 12 (see Appendix B) summarize the most commonly prescribed concomitant medications. The results in these tables indicate that the proportions of patients in Asacol 1.6g/day taking Systemic antibiotics/anti-infective were 13% and 17% more than those in placebo for the ITT and completed patient data bases.

To assess the effectiveness of the two Asacol dosages, the sponsor performed two efficacy analyses: the primary efficacy analysis and the secondary efficacy analysis. The primary efficacy analysis was prospectively defined to be the "evaluable" patient analysis in the protocol. It was also referred to as the "completed" patient analysis in the Study report. Completed patients were those who were compliant with the protocol until they discontinued the study because of endoscopic relapse or adverse event or until they had concluded 6 months of study therapy. In regard to this analysis, the protocol stated: " The primary analysis will be based only upon those subjects considered evaluable. Subjects

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will not be considered evaluable if they are discontinued for reasons unrelated to efficacy or adverse effects. These subjects will be categorized as being withdrawn from the study. If a subject discontinues the study for any reason related to the efficacy of the drug in maintaining remission, that subject will be categorized as relapsed and included in the analysis."

The secondary efficacy analysis was to be an "intent-to-treat" analysis including all randomized patients.

In the primary efficacy analysis, treatment success was defined in the Study report by the sponsor as "remission (proctosigmoidoscopy or colonoscopy scores of 0) at the six month study visit. Treatment failure was defined as relapse (proctosigmoidoscopy or colonoscopy scores of 1 or greater) at any time during the study, withdrawal due to an adverse event, or intolerance to study medication."

In the ITT analysis, treatment success was defined by the sponsor as "remission (confirmed by proctosigmoidoscopy or colonoscopy scores of 0) at each scheduled visit, regardless of whether or not the patient concluded the 6-month treatment period. If the endoscopic examination was not performed at the final visit, treatment success was defined as remission (confirmed by proctosigmoidoscopy or colonoscopy scores of 0) at the last visit where an endoscopic exam was performed. Treatment failure was defined as relapse (confirmed by procto-sigmoidoscopy or colonoscopy scores of 1 or greater) at any visit, after the baseline visit, withdrawal due to an adverse event, or intolerance to study medication."

The patient disposition for the trial was as in Table 2.2.1 (below).

Table 2.2.1 (Reviewer) Distributions of all patients and completed patients by treatment groups

	Placebo	Asacol 0.8g/day	Asacol 1.6g/day	Total
All Patients	33% (87/264)	34% (90/264)	33% (87/264)	264
Completed Patients	33% (63/189)	36% (68/189)	31% (58/189)	189
Withdrawal Rates	28% (24/87)	24% (22/90)	33% (29/87)	75

Note: Please see sponsor's Table 5 (attached) for more detail regarding patient disposition.

Statistical results of the sponsor's efficacy analyses were as summarized below.

a. The primary efficacy analysis

Table 2.2.2 (below) summarizes efficacy results for the primary efficacy analysis. In this analysis, the proportion of treatment success of the Asacol 0.8g/day group (59%) was significantly greater than that of the Placebo group (40%); the difference of 19% had 2-Sided  $p=0.036$  (by the Fisher exact test). In addition, the proportion of treatment success of the Asacol 1.6g/day group (66%) was significantly greater than that of the Placebo group (40%); the difference of 26% had 2-Sided  $p=0.006$  (by the Fisher exact test).

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Table 2.2.2 (Sponsor)  
Primary Efficacy Analysis Results  
(Completed Patients Data Set)

Patient Outcomes	Placebo n (%)	Asacol 0.8g/day n (%)	Asacol 1.6g/day n (%)
Treatment Success	25 (40%)	40 (59%)	38 (66%)
Treatment Failure	38 (60%)	28 (41%)	20 (34%)
N	63	68	58

Asacol 0.8 g/day vs. Placebo: two-sided  $p = 0.036^*$

Asacol 1.6 g/day vs. Placebo: two-sided  $p = 0.006^*$

\*: Significant after adjustment for multiple comparisons (Hochberg Procedure).

The sponsor also performed the following loglinear model based analyses to assess the drug effects:

- 1) Main effect model on the patient outcome by treatment group and patient age;
- 2) Main effect model on the patient outcome by treatment group and patient sex;
- 3) Main effect model on the patient outcome by treatment group, age, and sex.

The results from the above three analyses indicated that both Asacol 0.8g/day and Asacol 1.6g/day were significantly better than Placebo after adjusting for age and sex; the effects of age and sex on the patient outcomes were not significant. Table 2.2.3 (below) presents sponsor's p-values for treatment comparisons after age and sex adjustments.

Table 2.2.3 (Sponsor) Treatment comparison after adjustments by age and sex

Asacol 0.8 g/day vs. Placebo	P-value = 0.022
Asacol 1.6 g/day vs. Placebo	P-value = 0.007

b. The secondary efficacy analysis (Intent-to-treat (ITT) analysis)

For the ITT analysis, which was the secondary efficacy analysis by the protocol, the results were as in the following Table 2.2.4:

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Table 2.2.4 (Sponsor)  
 Patient Outcome - All Patients  
 ITT Analysis (Secondary Analysis by Protocol)

Patient Outcomes	Placebo n (%)	Asacol 0.8g/day n (%)	Asacol 1.6g/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

Asacol 0.8 g/day vs. Placebo: two-sided p-value=0.05\*

Asacol 1.6 g/day vs. Placebo: two-sided p-value=0.006\*.

\*: Significant after adjustment for multiple comparisons (Hochberg Procedure).

For the ITT analysis, the sponsor also performed the following loglinear model based analyses to assess the drug effects:

- 1) Main effect model on the patient outcome by treatment group and patient age;
- 2) Main effect model on the patient outcome by treatment group and patient sex;
- 3) Main effect model on the patient outcome by treatment group, age, and sex.

The results from the above three analyses indicated that the two treatment groups Asacol 0.8g/day and Asacol 1.6g/day were effective in comparison to Placebo after adjusting for age and sex; the effects of age and sex on the patient outcomes were not significant. Table 2.2.5 (below) presents p-values of treatment comparisons after age and sex adjustment.

Table 2.2.5 (Sponsor) Treatment comparison after adjustments by age and sex

Asacol 0.8 g/day vs. Placebo	P-value = 0.038
Asacol 1.6 g/day vs. Placebo	P-value = 0.004

Based on the above results, the sponsor claimed that Asacol at doses of 0.8 and 1.6 g/day is more effective than Placebo when used for the maintenance of remission in patients with ulcerative colitis in remission.

### **2.3 Reviewer's Analyses and Comments**

This pivotal study involved eighteen (18) investigators. Among these eighteen investigators, six investigators recruited five or less patients.

The observed dropout rate of 28% (see Table 2.2.1 in section 2.2) in the trial was higher than the 10% postulated in the protocol. However, there is no significant difference among three treatment groups with respect to dropout rate: the  $p=0.4$  by the Mantel-Haenszel test.

In order to validate the robustness of the drug efficacy claimed by the sponsor, this reviewer performed the following several analyses for the completed patient and the ITT data bases. The patient outcomes (Success/Failure) provided by the sponsor on a data diskette were used in these analyses. For the completed patient data base, the following three analyses were carried out:

- I. Mantel-Haenszel test for the treatment effects,
- ii. Logistic regression analysis including the clinical baseline variables, and
- iii. Center consistency analysis.

For the ITT data base, the following two analyses were performed:

- I. Logistic regression analysis including the clinical baseline variables, and
- ii. Center consistency analysis.

Although the ITT based analysis was planned as a secondary analysis, in this reviewer's assessment, it is an important analysis for this trial given the fact that the trial has a high dropout rate of 28%; the ITT analysis is likely to be more protective of bias caused by the high dropout rate.

#### **2.3.1. Completed patient data set analysis**

- I. Mantel-Haenszel test for the treatment effects

Since the definition of treatment Success/Failure based on the data of completed patients was the primary endpoint to measure the drug efficacy, this reviewer evaluated the drug efficacy using the data of completed patients by two methods (see Table 2.3.1.1).

**APPEARS THIS WAY  
ON ORIGINAL**

Table 2.3.1.1 (Reviewer's) Proportions of Success/Failure for three treatment groups  
(Completed Patient Data)

	Success	Failure	P-value vs. Placebo
Placebo	40% (25/63)	60% (38/63)	---
Asacol 0.8 g/day	59% (40/68)	41% (28/68)	0.036 (Fisher Exact test)* 0.029 (Mantel Haenszel test)*
Asacol 1.6 g/day	66% (38/58)	34% (20/58)	0.006 (Fisher Exact test)* 0.005 (Mantel Haenszel test)*

\*: Significant result at the significant level of 0.05.

The Mantel-Haenszel tests show that the proportion of success (59%) in the Asacol 0.8 g/day was significantly greater than that of the Placebo group (40%);  $p=0.029$ . Similarly, the proportion of success (66%) in the Asacol 1.6 g/day was significantly greater than that of the Placebo group;  $p=0.005$ .

ii. Logistic regression analyses on the including baseline variables:

This reviewer applied the logistic regression analysis to the completed patients data set to assess if the following five covariates affect the patients' outcomes (Success/Failure):

1. Pre-study Medication (PREM),
2. Length of years of having ulcerative colitis (UCLYEAR),
3. Stool Frequencies (STOLFREQ),
4. Extent of disease (EX), and
5. Steroid use (STERD).

[For the definitions of the categories for the five covariates see Appendix C.]

The results of the goodness of fit tests from the logistic regression analyses indicated that the patient outcomes were fitted by the logistic regression model with main effects of two factors: treatment effect and one covariate variable from each of the five covariates: PREM, UCLYESR, STOLFREQ, EX, and STERD.

Therefore, this reviewer first separately applied the logistic regression analysis with main effect model on each of the five covariates to test if the treatment effect was still significant. Then Wald statistics was performed to test if the covariate variable used in the logistic regression model significantly affect the patient outcomes. The results of these five analyses are summarized below in Table 2.3.1.2.

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Table 2.3.1.2 (Reviewer) P-values for comparing Asacol groups versus placebo  
(Completed Patients Analysis)

	Asacol 0.8 g/day vs. Placebo	Asacol 1.6g/day Vs. Placebo
Reviewer's Logistic Regression Analysis after adjusting for covariates:		
1. PREM	0.029*	0.005*
2. UCLYEAR	0.029*	0.005*
3. STOLFREQ	0.017*	0.003*
4. EX	0.036*	0.007*
5. STERD	0.023*	0.004*

\*: Significant result at the significant level of 0.05.

Thus, the above analyses derived from the completed patient data indicate that both dosages of Asacol are more effective than Placebo. However, these results may be biased because of high dropout rate in the trial..

### iii. Center consistency analysis

In this analysis, this reviewer used five centers, Hanauer, Mayle, Power, Robinson, and Combined, to evaluate the center by center consistency. The Combined center consisted of patients from the study sites other than Hanauer, Mayle, Power, and Robinson. The patient outcomes for each treatment group and study site were as presented in Table 2.3.1.3 (below). Since the number of completed patients in center ELSON is only 16, unlike the ITT center consistency analysis (in section 2.3.2), patients from this center were pooled together with other centers which had the number of completed patients less than 16.

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ON ORIGINAL

Table 2.3.1.3 (Review) Patient Outcomes by treatment groups and study sites  
(Completed Patients Analysis)

	Placebo		Asacol 0.8g/day		Asacol 1.6 g/day		Total Patients
	Success	Failure	Success	Failure	Success	Failure	N
Power	27% (3/11)	73% (8/11)	60% (6/10)	40% (4/10)	56% (5/9)	44% (4/9)	30
Robinson	36% (4/11)	64% (7/11)	70% (7/10)	30% (3/10)	73% (8/11)	27% (3/11)	32
Hanauer	38% (3/8)	62% (5/8)	57% (4/7)	43% (3/7)	75% (3/4)	25% (1/4)	19
Mayle	29% (2/7)	71% (5/7)	44% (4/9)	56% (5/9)	40% (2/5)	60% (3/5)	21
Combined#	50% (13/26)	50% (13/26)	59% (19/32)	41% (13/32)	69% (20/29)	31% (9/29)	87
Overall Percentage	40% (25/63)	60% (38/63)	59% (40/68)	41% (28/68)	66% (38/58)	34% (20/58)	189

#: Elson included in "Combined" because of small number of completed patients.

As seen in this table, the success rates for the two treated groups, Asacol 0.8g/day and Asacol 1.6g/day were consistently greater than those of Placebo across the five study sites.

### 2.3.2. Intent-to treat data set analysis

I) Logistic regression analysis on including the baseline variables:

Table 2.3.2.1 presents the results similar to that for Table 2.3.1.2 on the five baseline covariates, but for the ITT data set.

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Table 2.3.2.1 (Reviewer) P-values for comparing Asacol group with placebo group  
(Intent-to-Treat Data Set)

	Asacol 0.8 g/day vs. Placebo	Asacol 1.6g/day Vs. Placebo
Reviewer's Logistic Regression Analysis after adjusting for covariates:		
1. PREM	0.043*	0.003*
2. UCLYEAR	0.052	0.003*
3. STOLFREQ	0.047*	0.003*
4. EX	0.062	0.005*
5. STERD	0.039*	0.0034*

\*: Significant result at the significance level of 0.05.

As seen in this table, after adjusting the covariate ULCLYEAR or EX, the treatment effect Asacol 0.8 g/day vs. Placebo is not significant at the significance level of 0.05.

ii) Center consistency analysis.

Table 2.3.2.2 presents results similar to that for the Table 2.3.1.8 but for the ITT data base.

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Table 2.3.2.2 (Review) Patient Outcomes by treatment groups and study sites  
(Intent-to-Treat Data Set)

	Placebo		Asacol 0.8g/day		Asacol 1.6 g/day		Total Patients N
	Success	Failure	Success	Failure	Success	Failure	
Power	36% (5/14)	64% (9/14)	71% (12/17)	29% (5/17)	69% (11/16)	31% (5/16)	47
Robinson	44% (7/16)	56% (9/16)	64% (9/14)	35% (5/14)	79% (11/14)	21% (3/14)	44
Hanauer	40% (4/10)	60% (6/10)	60% (6/10)	40% (4/10)	90% (9/10)	10% (1/10)	30
Mayle	38% (3/8)	62% (5/8)	50% (5/10)	50% (5/10)	40% (4/10)	60% (6/10)	28
Elson	71% (5/7)	29% (2/7)	86% (6/7)	14% (1/7)	57% (4/7)	43% (3/7)	21
Combined	56% (18/32)	44% (14/32)	59% (19/32)	41% (13/32)	73% (22/30)	27% (8/30)	94
Overall Percentage	48% (42/87)	52% (45/87)	63% (57/90)	37% (33/90)	70% (61/87)	30% (26/87)	264

As seen in this table, the success rates for the two treated groups, Asacol 0.8g/day and Asacol 1.6g/day were consistently greater than those of Placebo group across the six study sites. Breslow-Day tests showed that there were no treatment by center interactions for both of Asacol 0.8g/day versus Placebo and Asacol 1.6g/day versus Placebo ( $p=0.80$  for Asacol 0.8g/day vs. Placebo;  $p=0.33$  for Asacol 1.6g/day vs. Placebo).

The results for the treatment comparisons for the two dosages of Asacol versus Placebo were as in Table 2.3.2.3 (below).

Table 2.3.2.3 (Reviewer) Results of treatment comparisons  
(Intent-to-Treat Data Set)

Asacol 0.8 g/day vs. Placebo	P-value = 0.041*
Asacol 1.6 g/day vs. Placebo	P-value = 0.003*

\*: Significant result at the significance level of 0.05 (by the Mantel-Haenszel test after adjustment for center).

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### **III. ADDITIONAL COMMENTS/STUDY# 87086**

The medical officer, Dr. Robert Prizont, M.D. raised a number of concerns about the inconsistencies in the reported data set. This reviewer addresses some of these in this section.

#### **3.1. Issue on the effect of protocol amendment**

The data indicate (also, the medical officer pointed out) that the sponsor amended the protocol with respect to the baseline endoscopic score two years after commencing the trial to allow patients to enter the trial with mild signs of rectal inflammation, i.e., mild edema, mild erythema, mild hyperemia, etc. According to the sponsor, eight patients were affected by this amendment: the sponsor apparently changed the final outcomes after the end of the trial. The changes occurred as follows:

Table 3.1.1. (Reviewer) Effect of protocol amendment on the patient outcome

Patient #	Treatment group	Original scoring system		Amended scoring system	
		Primary analysis	Intent-to-treat analysis	Primary analysis	Intent-to-treat Analysis
15050201	Asacol 1.6g/day	Failure	Failure	Ineligible	Success
16330209	Asacol 1.6g/day	Ineligible	Failure	Ineligible	Success
28100212	Placebo	Failure	Failure	Ineligible	Success
15580214	Placebo	Failure	Failure	Failure	Failure
15580215	Asacol 1.6g/day	Failure	Failure	Success	Success
35120210	Asacol 1.6g/day	Failure	Failure	Success	Success
28100213	Asacol 1.6g/day	Failure	Failure	Success	Success
35120209	Asacol 1.6g/day	Failure	Failure	Success	Success

Among these eight patients, two patients were in Placebo group and six patients were treated with Asacol 1.6 g/day. However, the outcomes of the patient# 15580214 were the same for both systems. Dr. Prizont suggested that this reviewer conduct a sensitivity analysis using the original outcomes for these eight patients to compare the treatment effects for Asacol 1.6 g/day vs. Placebo based on the data sets of the completed patients and the intent-to-treat patients. Since there was a change in the Placebo group, p-values in the sensitivity analyses would be affected for both treatment groups. The results of this sensitivity analysis using Mantel-Haenszel tests were as presented in Table 3.1.2 (below).

Table 3.1.2. (Reviewer) Results of the sensitivity analysis using original outcomes

Analysis	Asacol 0.8g/day (Success rate)	Asacol 1.6g/day (Success rate)	Placebo (Success rate)	Asacol Vs. Placebo	
				0.8 g/day	1.6 g/day
Amended outcome					
Primary analysis	59% (40/68)	66% (38/58)	40% (25/63)	0.029*	0.005*
ITT Analysis	63% (57/90)	70% (61/87)	48% (42/87)	0.044*	0.003*
Original outcome					
Primary analysis	59% (40/68)	58% (34/59)	39% (25/64)	0.024*	0.04*
ITT analysis	63% (57/90)	63% (55/87)	47% (41/87)	0.031*	0.033*

\*: Significant result at the significance level of 0.05 (by the Mantel-Haenszel test).

### **3.2. Issue on the exclusion of six patients from the ITT Analysis**

The medical officer discovered that the following six patients were not included in the ITT analysis:

#34090209  
 #34090216  
 #19780203  
 #19780206  
 #18800219  
 #15580211.

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It is not clear whether these patients were randomized after the screening visit for eligibility into the trial. The sponsor has been asked to clarify this and perform an "all randomized patients" analysis on the data set including these six patients if they were randomized (see attached Reference #1).

### **3.3. Issue on the inclusion of three ineligible patients in the ITT analysis**

Dr. Prizont indicated that the three patients (#15050205, #19780208, and #34090232) with baseline endoscopies greater than zero were not eligible for entering trial, according to the "patient inclusion criteria" stated in the protocol. Therefore, Dr. Prizont suggests that these three patients should be excluded from the ITT analysis. The results of the sensitivity analysis using Mantel-Haenszel tests for the inclusion and exclusion of the three patients is presented in Table 3.3.1 (below).

Table 3.3.1. (Reviewer) Sensitivity analysis on the three ineligible patients

Placebo vs. Asacol 0.8 g/day (ITT Analysis)	Sponsor (Fisher Exact test)	Reviewer (Mantel-Haenszel test)
On including three patients	(42/87 vs. 57/90) p=0.05*	(42/87 vs. 57/90) P = 0.044*
On excluding three patients	----	(42/84 vs. 57/90) P = 0.077
On excluding two patients	----	(42/85 vs. 57/90) P = 0.064
On excluding one patient	----	(42/86 vs. 57/90) P = 0.053

\*: Significant result at the significance level of 0.05.

Before concluding that the efficacy of Asacol 0.8 g/day is not significantly better than that of Placebo at the 0.05 level based on the analysis of excluding the three patients ( $p = 0.072$ ), one may need to consider the following two points: 1) these patients qualified under protocol amendment which allowed patients in the trial with non-zero baseline endoscopic score; 2) the trial is a blinded and randomized trial and the ITT analysis by plan is to include all randomized patients.

#### **3.4. Issue on the four extra treatment-failure patients**

The medical reviewer, Dr. Prizont, indicated that all relapses in Placebo group counted from Table 22, page 65, Volume 43, was 37. In the Placebo group, four patients were withdrawn due to adversary event (AE). Therefore, the total number of treatment-failure (TF) patients for Placebo group should add up to 41. However, the number of TF patients from Table 17, page 60, Volume 43 (or from the data diskette provided by the sponsor), was 45. This reviewer could not identify these extra four patients who were classified as TF in the Placebo group. This needs to be clarified by the sponsor (please see attached Reference #1).

#### **3.5 Issue on the numerous unscheduled endoscopies**

The medical officer, Dr. Prizont, indicated : "review of sigmoidoscopy evaluations revealed numerous unscheduled endoscopies performed during the course of the trial. Also, it appears that many visits occurred long after the final 6-month visit (24 weeks). For instance, in Center 3409 (Dr. Powers), I counted 22 instances of Final visits after 26 weeks of therapy." In order to resolve this issue, this reviewer has requested the sponsor to perform additional analyses in the attached Reference #1.

#### **IV. POOLED ANALYSIS OF POSITIVE-CONTROL TRIALS (C.1, C.2, C.6, C.15)**

In order to support the single pivotal study #87086, the sponsor conducted a pooled analysis on the four previously submitted positive-control studies (C.1, C.2, C.6 C.15). As indicated earlier, the purpose of this pooled analysis as claimed was to provide evidence that Asacol does not differ

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significantly from Sulfasalazine with regard to efficacy in the maintenance of remission of patients with ulcerative colitis .

#### **4.1 Design**

Studies C.1, C.2, C.6, and C.15 were designed as parallel group comparisons of Asacol versus Sulfasalazine (SAS) in patients with ulcerative colitis in remission verified by histopathologic findings on sigmoidoscopy. Studies C.1, C.6, and C.15 were randomized double blind trials. However, Study C.2 was not completely randomized. The primary efficacy endpoint was the sigmoidoscopy score at study conclusion. Study duration ranged from 16 weeks to 12 months and there were no significant differences in patient age and disease duration between the two treatment groups across the four studies.

Patients randomized to the Asacol treatment groups in these studies (not applicable to C.15) were assigned to an Asacol dose according to his/her pre-study Sulfasalazine dose for maintaining remission. Similarly, in each of the four studies, the dosage for a patient who was assigned to the Sulfasalazine group was based on his/her pre-study maintenance Sulfasalazine dose. The sponsor indicated that fifty-one (51) of the patients who participated in C.2 had previously participated in C.1. Among the fifty-one patients, twenty-seven (27) of the patients who received Sulfasalazine in C.1 were enrolled in study C.2 and cross over to the Asacol treatment group. Twenty-two (22) of the patients who received Asacol in C.1 crossed over to receive Sulfasalazine in C.2. One patient received Asacol in both C.1 and C.2 and one patient received Sulfasalazine in both C.1 and C.2. Design characteristics of the four positive-control studies are summarized in Table 4.1 (below).

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Table 4.1 (Reviewer's) Design characteristics of the four positive-control trials

	C.1	C.2	C.6	C.15
Study Design	Randomized; Double Blind; Parallel Group Comparison	Randomized; Double Blind; Parallel Group Comparison	Randomized; Double Blind; Parallel Group Comparison	Randomized; Double Blind; Parallel Group Comparison
Study Duration	16 Weeks	24 Weeks	12 Months	12 Months
# of Asacol/SAS Patients Entered	36/36	35/32	49/50	18/27
# of Patient Not Completed Study (Asacol/SAS)*	5/7	7/7	2/5	3/5
Mean Asacol Dose g/d/(range)	1.4	2.7	0.9	0.8
Mean SAS Dose g/d/(range)	2.4	2.25	2.3	2.0
primary Endpoint	Maintenance of remission as evidenced by grade 1 or 2 Sigmoidoscopy Score at the end of the study.	Maintenance of remission as evidenced by grade 1 or 2 Sigmoidoscopy Score at the end of the study.	Number and severity of relapses as evidenced by increases in bowel frequency, numbers of stools with blood/mucus and abdominal pain.	Number and severity of relapses as evidenced by increases in bowel frequency, numbers of stools with blood/mucus and abdominal pain.

\*: These eight numbers are calculated based on the data diskette submitted by the sponsor.

NA: not applicable.

Treatment outcome (success/failure) was determined by sigmoidoscopy scores. The proctosigmoidoscopy scores across all four studies used a 5-point scale. A patient was defined as a treatment failure if 1) the patient had a post-treatment sigmoidoscopy score of > 1 (in studies C.6 and C.15) or a score of > 2 (in studies C.1 and C.2); 2) the post-treatment score was equal to or greater than a one point increase from baseline. A patient with a post-baseline sigmoidoscopy score(s) other than described above was defined as a treatment success.

## **4.2 Sponsor's statistical analysis and results**

The sponsor applied the statistical method of DerSimonian and Laird (Controlled Clinical Trials, 1986;7:177-188) to analyze the pooled data for the four positive-controlled trials. In order to pool the differences in success rates between the Asacol and Sulfasalazine groups, the homogeneities of the four positive-control studies were tested. If the hypothesis of the study homogeneity can not be rejected then a test based on the pooled four differences in success rates were used to test if the remission rate difference between Asacol and Sulfasalazine equal to zero across four studies. The pooled remission rates for both Asacol and Sulfasalazine across the four studies were also estimated. The sponsor also estimated the 95% confidence intervals for the pooled remission rates and the differences in the success rates. The analysis conducted for completed patients included those patients whose treatment outcome was known; patients with missing observations were excluded. The intent-to-treat analysis included all patients. Those patients in the intent-to-treat analysis whose treatment outcome was unknown were classified as treatment failures.

Since fifty one (51) patients were 'crossed over' from Study C.1 to Study C.2, three scenarios were used for treating the data from the 51 'crossover' patients to evaluate the sensitivity caused by the 'crossover' patients when estimating the pooled remission rates.

Scenario 1: The first analysis assumed that the 51 patients were 'independent' in each study and were included in both C.1 and C.2. As a result, there were 283 patients counted in this analysis.

Scenario 2: The second analysis counted the 51 patients only once. The results from C.1 for these 51 patients were included and the results from C.2 were excluded. Thus, two-hundred thirty-two (232) patients were included in this analysis.

Scenario 3: The third analysis excluded all the data from the 51 patients. Therefore, one-hundred eighty-one (181) patients were included in this analysis.

The results from the homogeneity test both for the completed patients and ITT data indicated that the null hypothesis of study homogeneity across the four positive-control studies was not rejected. Similarly, the result using all completed patients for testing the difference in success rates between Asacol and Sulfasalazine across four positive-control studies indicated that the remission rates were not significantly different between Asacol and Sulfasalazine.

Table 4.2.1 and Table 4.2.2 summarize the pooled remission rates along with their 95% confidence intervals based on the completed patients and intent-to-treat patients for the three scenarios.

Table 4.2.1 (Sponsor's) Pooled Remission Rates (adjusted for study): Completed patients

Scenario	Overall Remission Rate (95% confidence interval)		Difference in Remission Rate (95% confidence interval)
	Asacol	Sulfasalazine	Asacol - Sulfasalazine
1	0.62 (0.54, 0.71)	0.70 (0.62, 0.78)	-0.08 (-0.20, 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)

Table 4.2.2 (Sponsor's) Pooled Remission Rates (adjusted for study): Intent-to-Treat patients

Scenario	Overall Remission Rate (95% confidence interval)		Difference in Remission Rate (95% confidence interval)
	Asacol	Sulfasalazine	Asacol - Sulfasalazine
1	0.54 (0.46, 0.62)	0.58 (0.50, 0.66)	-0.04 (-0.16, 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)	-0.06 (-0.2, 0.08)

Based on Table 4.2.1, the sponsor claimed that among completed patients, Sulfasalazine had higher remission rates than Asacol, but these differences were not statistically significant.

#### **4.3 Reviewer's Analysis and Comments**

Since the 51 patients who participated in Study C.2 had previously participated in Study C.1, the two studies, C.1 and C.2 are not independent. In addition, the information in page 388 of the volume 141, for Study C.2, indicated that the treatment assignments for those 51 patients, in Study C.2, were not random and double-blind. In order to avoid bias caused by the 51 patients, this reviewer calculated 90% confidence intervals for the differences in success rates for the following two scenarios to assess the clinical equivalence between Asacol and Sulfasalazine.

Scenario 1. The 51 'crossover' patients were included in Study C.1 but excluded from. Study C.2.  
Scenario 2. The patients in Study C.2 were excluded.

The differences in remission rates along with their 90% confidence intervals using data based on two scenarios were as follows (Table 4.2.3).

Table 4.2.3 (Reviewer's)

90% Confidence intervals for differences in success rates using completed patients\*

Scenario 1

	Success rate 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

Scenario 2

	Success rate Differences (Asacol - Sulfasalazine)	Lower Bound	Upper Bound
Study C.1	-0.146 (19/31 - 22/29)	-0.34	0.049
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	-0.11	-0.22	0.01

\* Completed patient analysis is appropriate, because these trials are clinical equivalence trials. ITT analysis would bias the results towards zero.

The results in Table 4.2.3 indicate the following:

1. Since Success rate differences between treatments Asacol and Sulfasalazine were all negative for the four studies, the efficacy of treatment Asacol was tended to be numerically inferior to that of Sulfasalazine.

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2. Since the upper bound of the 90% confidence interval for the success rate difference of Study C.15 was less than zero, the efficacy of Asacol presented in this study was significantly worse than that of Sulfasalazine using the significance level of 10% by the 2-sided test and significance level of 5% by the 1-sided test.

3. Since the lower bounds of the 90% confidence intervals for the pooled p-value differences for the two scenarios were less than -20%, the 90% confidence intervals for the pooled success rate differences were not contained in the clinical equivalence interval (-20%, 20%).

Therefore, the pooled analysis did not provide sufficient evidence to reject the null hypothesis that treatment Asacol was in fact inferior to Sulfasalazine by 20% or more.

## V. SUMMARY AND CONCLUSION

### Study# 87086

The protocol planned primary efficacy analysis was based on the data of completed patients. In addition to the primary analysis, the sponsor also performed a secondary analysis using the data of intent-to-treat (ITT) patients. Based on the results of the treatment efficacy analyses using two-sided Fisher exact tests, loglinear model analyses, and subgroup analyses, the sponsor claimed that Asacol at doses of 0.8 and 1.6 g/day are more effective than Placebo when used for the maintenance of remission in patients with quiescent ulcerative colitis.

Although the completed patient data analysis, which was defined as the primary analysis, suggests that both doses of Asacol, i.e., 0.8 g/day and 1.6 g/day, are effective in comparison to Placebo, the trial had a dropout rate of 28%. In order to minimize bias due to such a high dropout rate, the ITT analysis seems to be important. The ITT results for the low dose Asacol 0.8g/day was marginal by the sponsor's analysis (2-Sided  $p=0.05$  by the Fisher exact test). This reviewer did a number of sensitivity analyses addressing the robustness of this result. The results of these analyses show some p-values greater than 0.05. For example, in a sensitivity analysis, when three patients whose baseline endoscopies were not zero were excluded from the ITT analysis, the p-value of Asacol 0.8g/day versus Placebo changed from  $p=0.044$  to  $p=0.077$  by the Mantel-Haenszel test. Thus, the effectiveness result for the Asacol 0.8g/day was borderline in this trial.

Moreover, the efficacy data as pointed out by the medical officer, exhibit some inconsistencies. This reviewer has addressed some of these in section III "Additional Comments", page 13-15. This reviewer, in this regard, has also requested additional information and re-analyses (see Reference #1, attached). The results of these new analyses and/or information may change the above effectiveness conclusion, particularly, for the Asacol 0.8 g/day dose.

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**Pooled analysis of positive-control trials (C.1, C.2 C.6, and C.15)**

Since fifty one (51) patients were 'crossed over' from Study C.1 to Study C.2, the sponsor applied the statistical method of DerSimonian and Laird on the three scenarios (see section 3.2.a for details) to test if the remission rates were significantly different between Asacol and Sulfasalazine. Based on the results using the completed patient data set, the sponsor claimed that the remission rates were not significantly different between Asacol and Sulfasalazine.

In order to validate the sponsor's claim on the four positive-controlled trials, this reviewer performed the 90% confidence intervals for the differences in success rates using data based on the following two scenarios to assess the clinical equivalence between treatments: Asacol and Sulfasalazine.

Scenario 1. The 51 'crossover' patients were included in Study C.1 but excluded from. Study C.2.

Scenario 2. The patients in Study C.2 were excluded.

The results from the pooled analysis did not provide sufficient evidence to reject the null hypothesis that Asacol was inferior to Sulfasalazine by 20% or more.

**VI. OVERALL CONCLUSION****Study # 87086**

The efficacy result of the Asacol 1.6g/day dose was convincing. However, another confirmatory trial is needed to validate the efficacy of the Asacol 0.8g/day dose which was marginal in this trial ( $p=0.05$ , by the sponsor's ITT analysis).

However, the efficacy data of this trial exhibit some inconsistencies, this reviewer has requested additional analyses and information. The results of these new analyses or information may change the above conclusions.

**Pooled analysis of positive-control trials (C.1, C.2 C.6, and C.15)**

The results from the pooled analysis did not provide sufficient evidence to reject the null hypothesis that treatments Asacol was inferior to Sulfasalazine by 20% or more.

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Wen-Jen Chen Ph.D.,  
Mathematical Statistician

Concur: Dr. Huque

/S/ 4/15/97

Dr. Smith

/S/ 4/15/97

(This review contains 22 pages of text and 11 pages of attachments)

cc: Original NDA 19-651/S-005

- HFD-180/Dr. Fredd
- HFD-180/Dr. Prizont
- HFD-180/Ms. McNeil
- HFD-720/Dr. Smith
- HFD-720/Dr. Huque
- HFD-720/Dr. Chen
- HFD-720/File Copy

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Table 5 (Sponsor) 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>	<b>63</b>	<b>68</b>	<b>58</b>	<b>189</b>
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>	<b>24</b>	<b>22</b>	<b>29</b>	<b>75</b>
Entry Criteria Violations	12	10	12	34
Post-Study Entry Protocol Violations	12	12	17	41
<b>Entry Criteria Violations:</b>	<b>12</b>	<b>10</b>	<b>12</b>	<b>34</b>
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>	<b>12</b>	<b>12</b>	<b>17</b>	<b>41</b>
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.

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**Table 7**  
**Demographics - All Patients**

	Placebo N = 87	Asacol 0.8 g/day N = 90	Asacol 1.6 g/day N = 87
<b>Age (yrs):</b>			
Mean (SEM)	42.2 (1.44)	41.9 (1.37)	42.1 (1.45)
<b>Sex:</b>			
Male n (%)	54 (62.1%)	55 (61.1%)	37 (42.5%)*
Female n (%)	33 (37.9%)	35 (38.9%)	50 (57.5%)
<b>Race:</b>			
Caucasian n (%)	86 (98.9%)	86 (95.6%)	84 (96.6%)
Non-Caucasian n (%)	1 (1.1%)	4 (4.4%)	3 (3.4%)

N = number of patients in treatment group. n = number of patients in demographic category. % = n/N.

\* p = 0.015, compared with Placebo (Fisher's exact test, 2-tail).

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**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.

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**Table 9**  
**Demographics - Completed Patients**

	Placebo N = 63	Asacol 0.8 g/day N = 68	Asacol 1.6 g/day N = 58
<b>Age (yrs):</b>			
Mean (SEM)	42.8 (1.77)	41.4 (1.56)	41.6 (1.72)
<b>Sex:</b>			
Male n (%)	43 (68.3%)	42 (61.8%)	25 (43.1%)*
Female n (%)	20 (31.7%)	26 (38.2%)	33 (56.9%)
<b>Race:</b>			
Caucasian n (%)	62 (98.4%)	65 (95.6%)	57 (98.3%)
Non-Caucasian n (%)	1 (1.6%)	3 (4.4%)	1 (1.7%)

N = number of patients in treatment group. n = number of patients in demographic category. % = n/N.  
\* p = 0.006, compared with Placebo (Fisher's exact test, 2-tail).

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**Table 10**  
**Baseline Characteristics - Completed Patients**

	<b>Placebo</b> N = 63 n (%)	<b>Asacol 0.8 g/day</b> N = 68 n (%)	<b>Asacol 1.6 g/day</b> N = 58 n (%)
<b>Length of History of Ulcerative Colitis (years):</b>			
< 1	7 (11.1%)	10 (14.7%)	6 (10.3%)
1 - 5	16 (25.4%)	15 (22.1%)	14 (24.1%)
> 5 - 10	16 (25.4%)	17 (25.0%)	15 (25.9%)
> 10	24 (38.1%)	26 (38.2%)	23 (39.7%)
<b>Extent of Disease:</b>			
proctitis	11 (17.5%)	10 (14.7%)	10 (17.2%)
proctosigmoiditis	14 (22.2%)	20 (29.4%)	11 (19.0%)
left-sided	9 (14.3%)	12 (17.6%)	11 (19.0%)
pancolitis	18 (28.6%)	19 (27.9%)	17 (29.3%)
unknown	11 (17.5%)	7 (10.3%)	9 (15.5%)
<b>Prestudy Medication for Ulcerative Colitis:</b>			
sulfasalazine	38 (60.3%)	45 (66.2%)	37 (63.8%)
any oral 5-ASA product	25 (39.7%)	23 (33.8%)	21 (36.2%)
<b>Stool Frequency:</b>			
one per day	18 (28.6%)	31 (45.6%)	24 (41.4%)
two per day	27 (42.9%)	23 (33.8%)	26 (44.8%)
three per day	11 (17.5%)	8 (11.8%)	4 (6.9%)
four or more per day	7 (11.1%)	6 (8.8%)	4 (6.9%)
mean number per day (SEM)	2.14 (0.132)	1.87 (0.126)	1.81 (0.119)

N = number of patients in treatment group. n = number of patient in baseline characteristic category. % = n/N.

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Appendix B

Table 11  
Most Commonly Prescribed Concomitant Medications - All Patients

	Placebo N = 87 n (%)	Asacol 0.8 g/day N = 90 n (%)	Asacol 1.6 g/day N = 87 n (%)
Non-aspirin, non-narcotic analgesics	40 (46.0%)	43 (47.8%)	50 (57.5%)
Cough/cold agents	31 (35.6%)	25 (27.8%)	31 (35.6%)
Systemic antibiotics/anti-infectives	19 (21.8%)	26 (28.9%)	30 (34.5%)
Nutritional supplements	24 (27.6%)	20 (22.2%)	24 (27.6%)
Antihistamines	19 (21.8%)	22 (24.4%)	26 (29.9%)
Anti-diarrheals/antispasmodics <sup>a</sup>	20 (23.0%)	13 (14.4%)	22 (25.3%)
Non-steroidal anti-inflammatory agents	13 (14.9%)	15 (16.7%)	13 (14.9%)
Narcotic analgesics	15 (17.2%)	15 (16.7%)	10 (11.5%)
Aspirin-containing agents	9 (10.3%)	14 (15.6%)	11 (12.6%)
Contraceptives	7 (8.0%)	8 (8.9%)	15 (17.2%)
Anti-anxiety agents	12 (13.8%)	11 (12.2%)	6 (6.9%)
Bulking agents/stool softeners	10 (11.5%)	7 (7.8%)	11 (12.6%)
Anti-hypertensive/anti-anginal agents	8 (9.2%)	10 (11.1%)	8 (9.2%)
Dermatologies	7 (8.0%)	8 (8.9%)	9 (10.3%)
H <sub>2</sub> Blockers	10 (11.5%)	4 (4.4%)	7 (8.0%)
Hormones	6 (6.9%)	9 (10.0%)	6 (6.9%)
Antacids	5 (5.7%)	6 (6.7%)	7 (8.0%)
Diuretics	5 (5.7%)	4 (4.4%)	8 (9.2%)
Folate Supplements	6 (6.9%)	6 (6.7%)	2 (2.3%)
Thyroid Replacements	6 (6.9%)	3 (3.3%)	5 (5.7%)
Laxatives	5 (5.7%)	1 (1.1%)	7 (8.0%)
Anti-Depressants	4 (4.6%)	5 (5.6%)	3 (3.4%)
Bronchodilators	3 (3.4%)	3 (3.3%)	5 (5.7%)
Iron Supplements	3 (3.4%)	3 (3.3%)	3 (3.4%)
Hypotensive Agents	1 (1.1%)	3 (3.3%)	3 (3.4%)
Potassium Supplements	2 (2.3%)	2 (2.2%)	3 (3.4%)
Skeletal Muscle Relaxants	4 (4.6%)	3 (3.3%)	9 (10.3%)
Systemic Corticosteroids	2 (2.3%)	3 (3.3%)	1 (1.1%)
Topical Ophthalmics	4 (4.6%)	1 (1.1%)	1 (1.1%)
Anticholinergics	0 (0.0%)	3 (3.3%)	2 (2.3%)
Other & Miscellaneous drugs	17 (19.5%)	25 (27.8%)	23 (26.4%)
No concomitant medications	12 (13.8%)	7 (7.8%)	5 (5.7%)

Patients could be taking multiple medications.  
N = total number of patients exposed to treatment. n = number of patients exposed who took specific medication. % = n/N.

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**Table 12**  
**Most Commonly Prescribed Concomitant Medications - Completed Patients**

	Flarebo N = 43 n (%)	Asacol 0.3 g/day N = 48 n (%)	Asacol 1.6 g/day N = 58 n (%)
Non-aspirin, non-narcotic analgesics	27 (62.8%)	33 (68.8%)	35 (60.3%)
Cough/cold agents	21 (48.8%)	22 (45.8%)	23 (39.7%)
Antihistamines	12 (27.9%)	19 (39.6%)	17 (29.3%)
Nutritional supplements	18 (41.9%)	13 (27.1%)	16 (27.6%)
Systemic antibiotics/anti-infectives	10 (23.3%)	16 (33.3%)	19 (32.8%)
Antidiarrheals/antispasmodics/ anticholinergics	13 (30.2%)	10 (20.8%)	16 (27.6%)
Non-steroidal anti-inflammatory agents	7 (16.0%)	12 (25.0%)	9 (15.5%)
Aspirin-containing agents	7 (16.0%)	12 (25.0%)	7 (12.1%)
Narcotic analgesics	7 (16.0%)	11 (22.9%)	6 (10.3%)
Bulking agents/stool softeners	7 (16.0%)	6 (12.5%)	8 (13.8%)
Contraceptives	4 (9.3%)	6 (12.5%)	11 (19.0%)
Dermatologics	5 (11.6%)	8 (16.7%)	7 (12.1%)
Anti-anxiety agents	6 (13.9%)	8 (16.7%)	5 (8.6%)
Antihypertensives/Anti-Anginal Agents	6 (13.9%)	5 (10.4%)	4 (6.9%)
Antacids	3 (6.9%)	6 (12.5%)	5 (8.6%)
Hormones	5 (11.6%)	4 (8.3%)	5 (8.6%)
Folate Supplements	6 (13.9%)	4 (8.3%)	2 (3.4%)
H <sub>2</sub> Blockers	5 (11.6%)	4 (8.3%)	3 (5.2%)
Diuretics	4 (9.3%)	2 (4.2%)	5 (8.6%)
Thyroid Replacements	5 (11.6%)	3 (6.2%)	3 (5.2%)
Laxatives	3 (6.9%)	1 (2.1%)	6 (10.3%)
Anti-depressants	2 (4.7%)	4 (8.3%)	3 (5.2%)
Iron Supplements	3 (6.9%)	2 (4.2%)	2 (3.4%)
Bronchodilators	2 (4.7%)	2 (4.2%)	2 (3.4%)
Hypoglycemic Agents	1 (2.3%)	3 (6.2%)	2 (3.4%)
Systemic Corticosteroids	1 (2.3%)	3 (6.2%)	1 (1.7%)
Topical Ophthalmics	3 (6.9%)	1 (2.1%)	1 (1.7%)
Other & Miscellaneous drugs	13 (29.9%)	21 (43.8%)	18 (31.0%)
No concomitant medications	9 (20.9%)	6 (12.5%)	3 (5.2%)

Patients could be taking multiple medications.  
 N = total number of patients exposed to treatment, n = number of patients exposed who took specific medication, % = n/N.

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Appendix C  
Definition Of the category for the five covariates

1. Pre-study Medication (PREM)

The pre-study drug was classified into three categories:  
the first category - patients took Sulfasalazine or Azulfidine for pre-study medication,  
the second category - patients took Asacol, Dipentum, and Pentasa for pre-study medication, and  
the third category - patients took pre-study drugs not described in above two categories.

2. Length of years of having ulcerative colitis (UCLYEAR)

The length of ulcerative colitis measured by year was divided into four categories:  
the first category - patients with UCLYEAR less than one year ,  
the second category - patients with UCLYEAR greater than or equal to one and less than or equal to five years,  
the third category - patients with UCLYEAR greater than five and less than or equal to ten years, and  
the fourth category - patients with UCLYEAR greater than ten years.

3. Stool Frequencies (STOLFREQ)

The stool frequencies were divided into four categories:  
the first category - patients with STOLFREQ equal to one,  
the second category - patients with STOLFREQ equal to two,  
the third category - patients with STOLFREQ equal to three, and  
the fourth category - patients with STOLFREQ greater than or equal to four.

4. Extent of disease (EX).

The extent of disease were divided into five categories:  
the first category - patients with EX Pancolitis,  
the second category - patients with EX Proctosigs,  
the third category - patients with EX Proctitis,  
the fourth category - patients with EX left-sided, and  
the fifth category - patients with EX Unknown.

5. Steroid Use (STEROID).

The steroid use were classified into two categories:  
the first category - patients marked steroid\_use, and  
the second category - patients marked not steroid\_use.

APPROVED THIS MAY  
ON GENERAL

Reference # 1

h. Chen

NDA 19-651/S-005

31

MAR 31 1997

Procter & Gamble Pharmaceuticals  
Attention: Melanie Bruno, Ph.D., M.B.A.  
11450 Grooms Road  
Cincinnati, OH 45242

Dear Dr. Bruno:

Please refer to your pending June 4, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol (mesalamine) Tablets.

To complete our review of the clinical and statistical sections of your application, we have the following comments and requests regarding pivotal Study# 87086 entitled, "An Oral Preparation Of Mesalamine As Long-Term Maintenance Therapy For Ulcerative Colitis: A Randomized, Placebo-Controlled Trial," in which patients were administered Asacol 0.8 gm/day, Asacol 1.6 gm/day, or placebo (PBO):

1. According to the application, the following patients were declared ineligible for the trial but were given patient number assignments and study medication. We could not locate them in the Intent-To-Treat (ITT) analysis:

#34090209  
#34090216  
#19780203  
#19780206  
#18800219  
#15580211

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Please provide the following information:

- a. The reason each patient was ineligible for the trial.
- b. If these patients were randomized, please indicate the treatment group to which they were assigned and perform an ITT efficacy analysis which includes them. If ineligibility was due to non-endoscopic reasons, please perform the ITT analysis by using these patients' baseline endoscopy endpoint readings and carrying them forward to the subsequent three visits, i.e. Last Observation Carried Forward (LOCF).
- c. Please provide original case report forms for these patients which include their baseline endoscopy (Visit 1).

2. According to Table 22, (Volume 43, Page 65), the number of relapses which occurred in the PBO, Asacol 0.8 gm, and Asacol 1.6 gm 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 of ITT patients for the PBO, Asacol 0.8 gm, and Asacol 1.6 gm groups should be 41, 33, and 26, respectively. In Table 17 (Volume 43, Page 60), however, the number of treatment failures from the ITT analysis is shown as 45, 33, and 26, respectively.
  - a. Please explain the reason for the four additional treatment failures in the PBO group.
  - b. If the four additional treatment failures in the PBO group were incorrectly included in the ITT analyses, please redo the analyses, excluding these four PBO patients.
3. We note that numerous unscheduled endoscopies were conducted throughout the study. In addition, it appears that many visits occurred after the final 6-month visit (24 weeks).
  - a. For both the ITT and the primary analysis efficacy data set, please tabulate the frequency distribution for each treatment group, by the prospectively established scheduled visits. In addition, please perform an analysis of group comparability, based on the frequency of scheduled endoscopies. Define the scheduled visit windows as follows: Visit 2=from week 3 to week 5; Visit 3=from week 11 to week 13; Visit 4=from week 23 to week 25. Please provide treatment comparison analyses of relapses by visit by counting relapses only if the endoscopies were done within the visit window.
  - b. For all patients who relapsed within each visit window, please provide a list of patient numbers, drug assignments, and endoscopy grade at relapse.
4. Please provide the prospective randomization plan, the date created, and seed number.

We would appreciate your prompt written response so we can continue our ongoing evaluation of your supplemental application. Your response should be submitted in triplicate (Archival [blue], Clinical [tan], and Statistical [green] copies). In addition, please provide the data from any analyses on SAS diskettes, as 6.10 files (extension .sd2).

If you have any questions, please contact Melodi McNeil, Consumer Safety Officer, at (301) 443-0483.

Sincerely yours,

/S/ 3/28/97

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Stephen B. Fredd, M.D.  
Director  
Division of Gastrointestinal and Coagulation  
Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Original NDA 19-651/S-005  
HFD-180/Div. Files  
HFD-180/CSO/M.McNeil  
HFD-180/Prizont  
HFD-720/Huque  
HFD-720/Chen

/S/ 3/28/97

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Drafted by: mm/March 26, 1997/c:\wpfiles\cso\n\19651703.ir

Initialed by: KJohnson 3/26/97

RPrizont 3/27/97, 3/28/97

SFredd 3/28/97

final: March 28, 1997

INFORMATION REQUEST (IR)

MAY - 1 1997

*Michael*

1

Statistical Review and Evaluation - Carcinogenicity Study  
(Addendum)

**NDA:** 19 - 651/SE1 - 005

**Date:** 5/1/97

**Applicant:** Proctor and Gamble Pharmaceuticals

**Name of Drug:** ASACOL (Mesalamine) Delayed-Release Tablets



**Documents Reviewed:**

1. Original NDA volumes 18 to 39 with date referred June 24, 1996.
2. Original data submitted through CANDAs by the sponsor.
3. Corrected data on a floppy diskette supplied by the sponsor on November 14, 1996.

A statistical review and evaluation report on the animal carcinogenicity study data of this NDA was issued on March 31, 1997, by the division of Biometrics III.

Dr. K. Zhang, the reviewing pharmacologist at HFD 180, requested the division of Biometrics III to perform additional statistical analyses for both mouse and rat studies. For the mouse study, he requested to perform the statistical analyses on the combined data sets over the organs in the hematopoietic system separately for each of the two tumor types Lymphoma and Histiocytic Sarcoma. For the rat study, he requested to perform the statistical analyses on the combined data sets over the organs in the hematopoietic system for the pooled two tumor types Histiocytic Sarcoma and Fibrous Histiocytoma.

This reviewer applied permutation tests with one stratum to perform the trend tests for the requested tumor types for each sex of both species. The p-values of the trend tests for these tumors types in male and female mice as well as male and female rats are presented in Table 1.1 (below).

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[Signature]

Table 1.1: (Reviewer's): Tumor Rates Pooled Over Organs

<u>Male Mouse</u>		<u>Tumor Rate</u>				<u>P-value</u>
<u>Tumor type</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>		
	50		50			
Lymphoma	4		3			0.4100
Histiocytic Sarcoma	1		0			0.6240

<u>Female Mouse</u>		<u>Tumor Rate</u>				<u>P-value</u>
<u>Tumor type</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>		
	50		50			
Lymphoma	9		8			0.6220
Histiocytic Sarcoma	9		5			0.7540

<u>Male Rats</u>		<u>Tumor Rate</u>				<u>P-value</u>
<u>Tumor type</u>	<u>C</u>	<u>L</u>	<u>M1</u>	<u>M2</u>	<u>H</u>	
	60		60	60		
Histiocytic Sarcoma/ Fibrous histiocytoma	0		3	2		0.0634

<u>Female Rats</u>		<u>Tumor Rate</u>				<u>P-value</u>
<u>Tumor type</u>	<u>C</u>	<u>L</u>	<u>M1</u>	<u>M2</u>	<u>H</u>	
	60		60		60	
Histiocytic Sarcoma/ Fibrous histiocytoma	0		3		0	0.6800

Table 1.1 indicated that there were no significant trends found for the above requested tumor types after the multiplicity p-value adjustments using the division of Biometrics rule.

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**/S/**

**M. Mushfiqur Rashid, Ph.D.  
Mathematical Statistician**

APPEARS TRUE WAY

Concur:

**/S/**

Dr. Huque

✓ 5/1/97

Dr. Smith

**/S/** 5/1/97

cc:

- Archival : NDA: 19 - 651/SE1 - 005 ASACOL (Mesalamine) Delayed-Release Tablets
- HFD-180/Dr. Talarico
- HFD-180/Dr. Choudary
- HFD-180/Dr. Zhang
- HFD-720/Dr. Smith
- HFD-720/Dr. Huque
- HFD-720/Dr. Rashid
- HFD-720/Dr. Chen
- HFD-720/Chron Co
- HFD-720/File Co

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**STATISTICAL REVIEW AND EVALUATION**  
**(ADDENDUM)**

**NDA:** 19-651/S-005

Date: **May 28, 1997**

**APPLICATION:** Procter & Gamble Company

**NAME OF DRUG:** Asacol (Mesalamine) Tablets.

**INDICATION:** Maintenance of Remission of Ulcerative Colitis.

**DOCUMENT REVIEWED:** NDA Volumes Dated 14 April 1997, 6 May 1997, and 16 May 1997.

**MEDICAL REVIEWER:** This review has been discussed with medical officer,  
Robert Prizont, MD., (HFD-180).

**I. INTRODUCTION**

Original statistical review and evaluation report was issued on April 17, 1997. The sponsor has responded to the issues raised in this statistical review. This review evaluates the appropriateness of the sponsor's responses of 4/14/97, 5/6/97, and 5/16/97. The statistical analyses performed by this reviewer for this review are based on the sponsor's data sets of 6/4/96 and 4/14/97.

**II. SPONSOR'S RESPONSE**

The sponsor's responses to the three questions made in the previous report are summarized below.

**Question 1.**

According to the application, the following patients were declared ineligible for the trial but were given patient number assignments and study medication. We could not locate them in the Intent-To-Treat (ITT) analysis:

- #34090209
- #34090216
- #19780203
- #19780206

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#18800219  
#15580211

please provide the following information:

- a. The reason each patient was ineligible for the trial.
- b. If these patients were randomized, please indicate the treatment group to which they were assigned and perform an ITT efficacy analysis which includes them. If ineligibility was due to non-endoscopic reasons, please perform the ITT analysis by using these patients' baseline endoscopy endpoint readings and carrying them forward to the subsequent three visits, ie., Last Observation Carried Forward (LOCF).
- c. Please provide the original case report forms for these patients which include their baseline endoscopy (Visit 1).

Response 1

The sponsor indicated that only one (#15580211) of the six patients listed above had a single endoscopy baseline score and none of them took medication. Among the six patients, five subjects (#15580211, #18800219, #19780206, #34090209, and #34090216) were assigned to Placebo and one subject (#19780203) was assigned to Asacol 0.8 g/day.

The sponsor performed an ITT sensitivity analysis using the Fisher's Exact test to compare the treatment outcomes assuming the six subjects participated in the study. There are 270 subjects included in this sensitivity analyses: 92 in Placebo, 91 in Asacol 0.8 g/day, and 87 in Asacol 1.6 g/day. There are 12 scenarios for the possible combinations on the outcomes of these six subjects if they were in the study. Table 1.1 (below) presented the results of the sensitivity analyses for the 12 scenarios.

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Table 1.1 (Sponsor's) Treatment comparisons assuming the 6 subjects participated in the study  
(P- values for the 12 scenarios)

Number of subjects on Placebo were treatment failure	Number of subject on Asacol 0.8g/day was treatment failure	P-value Asacol 0.8g/day vs. Placebo	P-value Asacol 1.6g/day vs. Placebo
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

Question 2.

According to Table 22 (Volume 43, page 65), the number of relapses which occurred in PBO, Asacol 0.8gm, and Asacol 1.6gm 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 of ITT patients for the PBO, Asacol 0.8gm, and Asacol 1.6gm groups should be 41, 33, and 26, respectively. In Table 17, (Volume 43, page 60), however, the number of treatment failures from the ITT analysis is shown as 45, 33, and 26, respectively.

- a. Please explain the reason for the four additional treatment failures in the PBO group.
- b. If the four additional treatment failures in the PBO group were incorrectly included in the ITT analyses, please redo the analyses, excluding these four PBO patients.

### Response 2.

The sponsor indicated that in the Placebo group, the four subjects (#15050205, #18800211, #19780208, and #34090232) discontinued from the study due to protocol violations. Each of these four subjects had "a non-normal baseline proctosigmoidoscopy score and/or had a non-observable time to endoscopic relapse." Since these 4 patients received at least one dose of the study drug, they were included in the ITT analysis. In Table 22 (Time to Relapse Results-All patients, original NDA), these four subjects were taken into account in the time-to-relapse analysis as "censored" subjects.

The sponsor re-analyzed the treatment outcomes using the Fisher's Exact test and the time to relapse using the survival analysis method. These analyses compared the treatment effects based on the ITT data set excluding the above four subjects from Placebo. Table 2.1 (below) and Table 2.2 (below) give the results of the re-analysis on the treatment outcomes and on the time to relapse, respectively.

Table 2.1 (Sponsor's) Re-analysis for treatment outcome - excluding 4 subjects

	Proportion of Success	P-value vs. Placebo (Fisher Exact test)
Placebo	50.6% (42/83)	---
Asacol 0.8 g/day	63.3% (57/90)	0.124
Asacol 1.6 g/day	70.1% (61/87)	0.012*

\*: Significant result at the significant level of 0.05.

Table 2.2 (Sponsor's) Re-analysis for survival analysis - excluding 4 subjects

Asacol 0.8 g/day vs. Placebo	P-value =0.0735
Asacol 1.6 g/day vs. Placebo	P-value = 0.0074*

\*: Significant result at the significance level of 0.05

The sponsor claimed that the results of the survival analyses from Table 2.2 for both Asacol 0.8g/day versus Placebo and Asacol 1.6g/day versus Placebo were similar to the results reported in Table 22, Volume 43, Page 65.

### Question 3.

We note that numerous unscheduled endoscopies were conducted through the study. In addition, it appears that many visits occurred after the final 6-month visit (24 weeks).

a. For both the ITT and the primary analysis efficacy data set, please tabulate the frequency

distribution for each treatment group by the prospectively established scheduled visits. In addition, please perform an analysis of group comparability, based on the frequency of scheduled endoscopies. Define the scheduled visit windows as follows: Visit 2=from week 3 to week 5; Visit 3=from week 11 to week 13; visit 4=from week 23 to 25. Please provide treatment comparison analysis of relapses only if the endoscopies were done within the visit window.

- b. For all patients who relapsed within each visit window, please provide a list patient numbers, drug treatments, and endoscopy grade at relapse.

### Response 3.

For each of the three defined visit windows, the sponsor performed the group comparability analysis based on the frequency of the scheduled endoscopies within the visit window. In addition, the sponsor performed the treatment comparison analyses of relapses only for those endoscopies examined within the visit window. Table 3.1 (below) and Table 3.2 (below) present the results of the group comparability analysis and the treatment comparison analysis, respectively.

Table 3.1 (Sponsor's) The results of group comparability analysis  
(Number of patients who follow visit window)

#### ✓ Asacol 0.8g/day vs. Placebo

ITT		Placebo n (%=n/N)	Asacol 0.8g/day n (%=n/N)	Total N	p-value <sup>#</sup>
	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					
	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 (49.7)	72	0.099

#: Chi-square test was used for this analysis.

Table 3.1 (Sponsor's) The results of group comparability analysis (Continued)  
(Number of patients who follow visit window)

✓ Asacol 1.6g/day vs. Placebo

ITT		Placebo n (%=n/N)	Asacol 1.6g/day n (%=n/N)	Total N	p-value <sup>#</sup>
	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 (43.6)	57 (56.4)	101	0.196
Primary					
	Visit 2	54 (50.5)	53 (49.5)	107	0.923
	Visit 3	38 (46.3)	44 (53.7)	82	0.508
	Visit 4	29 (42.6)	39 (57.4)	68	0.225

#: Chi-square test was used for this analysis.

Based on the analysis results, the sponsor concluded that there were no significant differences in the frequency distributions between Asacol 0.8g/day versus Placebo and between Asacol 1.6g/day versus Placebo for both ITT and Primary data sets, with respective to each of the three visit windows.

Table 3.2 (Sponsor's) The results of treatment outcome comparisons for relapse rates

✓ Asacol 0.8g/day vs. Placebo

ITT		Placebo			Asacol 0.8g/day			p-value <sup>#</sup>
		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								
	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

Table 3.2 (Sponsor's) The results of treatment outcome comparisons for relapse rates (Continued)

## ✓ Asacol 1.6g/day vs. Placebo

ITT		Placebo			Asacol 1.6g/day			p-value <sup>#</sup>
		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								
	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: no. of relapses

N: no. of subjects that had a scheduled endoscopy within the visit window

#: Fisher Exact test was used for this analysis

\*: significant result at the significance level of 0.05.

Based on the analysis results, the sponsor concluded that the significant result was found only for the treatment comparison between Asacol 1.6g/day versus Placebo at visit 3: the number of relapses in Asacol 1.6g/day was significantly lower than those of Placebo (p=0.003 for ITT analysis; p=0.008 for Primary analysis) by Fisher Exact test.

**III. REVIEWER'S COMMENTS ON THE SPONSOR'S RESPONSES****1. Comment on response 1**

Table 1.1 shows that the treatment effect of Asacol 1.6g/day is consistently significantly superior to Placebo at the significance level of 0.05. However, for the Asacol 0.8g/day, the p value for the treatment effect (Asacol 0.8 g/day versus Placebo) ranges from 0.018 to 0.136 for the 12 scenarios. Therefore, the treatment effect of the Asacol 1.6g/day is robust, but this is not the case for the Asacol 0.8g/day.

**2. Comment on response 2**

Table 2.1 and Table 2.2 show that after excluding the four subjects from Placebo, the treatment effect of Asacol 1.6g/day is still significantly superior to that of Placebo (p-value=0.012 by the Fisher Exact test; p-value=0.0074 by the survival analysis method) at significance level of 0.05.

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However, the result for the low dose Asacol 0.8g/day is not significant at the 0.05 level. The new survival analysis excluding those four subjects has a p-value of 0.0735. This result is about the same on including these four subjects with censored observations in the old sponsor's survival analysis, p-value=0.074. Therefore, in this reviewer's assessment, the treatment effect of Asacol 0.8g/day is at best only marginal.

### 3. Comment on Response 3

In the response 3, the sponsor claimed that there were no significant differences in the frequency distributions between Asacol 0.8g/day versus Placebo and between Asacol 1.6g/day versus Placebo. Therefore, according to the sponsor, the scheduled endoscopies within each of the three visit windows were not related to treatment groups.

However, in this reviewer's assessment, the non-significant results on the comparisons of the frequency distributions for Asacol 0.8g/day versus Placebo and Asacol 1.6g/day versus Placebo with respect to each of the three visit windows could be due to small sample sizes. There are consistently (at least numerically) more off-scheduled patients for the Placebo group than those for the treated groups. This imbalance may still impact the results of the treatment efficacy analyses. Therefore, in order to address this imbalance, this reviewer performed the efficacy analysis (based on ITT data sets of 6/4/96 and 4/14/97) stated below to compare the treatment effects for Asacol 0.8g/day versus Placebo and Asacol 1.6g/day versus Placebo.

#### 3.1 Reviewer's efficacy analysis and results based on ITT data sets of 6/4/96 and 4/14/97.

In this analysis, the patients are divided into two groups: the scheduled group and the non-scheduled group. The scheduled group (SCHED = 'YES') consists of the patients who were endoscoped within the three visit windows defined in Question 3. The non-scheduled group (SCHED = 'NO') consists of the patients who are not in the scheduled group. The Mantel-Haenszel test using covariate SCHED as a stratum variable is applied on ITT data set to compare the treatment effects for Asacol 0.8g/day versus Placebo and Asacol 1.6g/day versus Placebo. Table 3.1, below, present the efficacy results of the Mantel-Haenszel tests for ITT patient data.

Table 3.1(Reviewer's) The success rates of the treatment groups for the ITT data set  
✓Asacol 0.8g/day vs. Placebo

SCHED	Asacol 0.8g/day	Placebo	Difference (Asacol - Placebo)
YES	89% (49/55)	84% (36/43)	5%
NO	23% (8/35)	14% (6/44)	9%

Note: The Mantel-Haenszel test is not significant at the significance level of 0.05 (p-value=0.194).

Table 3.1(Reviewer's) The success rates of the treatment groups for the ITT data set  
(Continued)

✓Asacol 1.6g/day vs. Placebo

SCHED	Asacol 1.6g/day	Placebo	Difference (Asacol - Placebo)
YES	89% (50/56)	84% (36/43)	5%
NO	35% (11/31)	14% (6/44)	21%

Note: The Mantel-Haenszel test is not significant at the significance level of 0.05 (p-value=0.03).

For Asacol 0.8g/day versus Placebo, Table 3.1 shows that the two differences of success rates (calculated based on the ITT data set) for the two groups, scheduled and non-scheduled, are positive (5% for the scheduled group; 9% for the non-scheduled group). In addition, the result of the Breslow-Day test for testing the interaction between treatment effect (Asacol 0.8g/day versus Placebo) and covariate SCHED is not significant at the level of 0.05 (p-value=0.843). Thus, the result from the Mantel-Haenszel test using covariate SCHED as a stratum variable is reliable, and it indicates that the treatment effect of Asacol 0.8g/day is not significantly superior to that of Placebo at the significance level of 0.05 (p=0.194).

However, for Asacol 1.6g/day versus Placebo, Table 3.1 shows that the two differences of success rates (calculated based on ITT data set) for both of the two groups, scheduled and non-scheduled, are positive (5% for the scheduled group; 21% for the non-scheduled group). In addition, the result of the Breslow-Day test for testing the interaction between treatment effect (Asacol 1.6g/day versus Placebo) and covariate SCHED is not significant at the level of 0.05 (p-value=0.356). Thus, the result from the Mantel-Haenszel test using covariate SCHED as a stratum variable is reliable, and it indicates that the treatment effect of Asacol 1.6g/day is significantly superior to that of Placebo at the significance level of 0.05 (p=0.03).

#### **IV. OVERALL CONCLUSION**

From the sponsor's three responses and the efficacy analysis performed by this reviewer, the efficacy result of the Asacol 1.6g/day dose is still convincing. However, overall, the efficacy of the Asacol 0.8g/day dose is at best marginal.

APPEARS THIS WAY  
ON ORIGINAL

APPROVE THIS WAY

/S/

Wen-Jen Chen Ph.D.,  
Mathematical Statistician

Concur:

/S/

5/28/97

*Jen*

/S/

5/28/97

cc: Original NDA 19-651/S-005

- HFD-180/Dr. Talarico
- HFD-180/Dr. Prizont
- HFD-180/Ms. McNeil
- HFD-720/Dr. Smith
- HFD-720/Dr. Huque
- HFD-720/Dr. Chen
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