DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER REVIEW

MAY 20 1998

NDA: 20,610

Sponsor: Salix Pharmaceuticals Inc.

Drug: Balsalazide Disodium (Colazide®) 750 mg Oral Capsules

Indication: Treatment of Mildly to Moderately Active Ulcerative Colitis

Date Hard-Copies Received by the DGICDP (HFD-180): June 24, 1997

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Date Completed: May 15, 1998

Medical Officer: Robert Prizont, MD

This application includes results from five randomized double-blind controlled clinical trials on efficacy and safety of balsalazide (Colazide®) in the treatment of mildly to moderate active ulcerative colitis. Balsalazide is a non-absorbable 5-ASA derivative and its action is topical in the colonic mucosa. Two of the submitted controlled multi center studies, the USA CP099301 and the British-Irish 57-3001 were reported by Salix as pivotal Phase III clinical trials. Two small British clinical trials, 0028/011 and 0028/017, were submitted as supportive clinical studies. All of these four trials compared the 8-12 week efficacy Colazide 6.75 g/d to a lower Colazide dose and/or to therapeutic doses of an approved formulation of mesalamine (Asacol®) or sulfasalazine. Additionally, the sponsor submitted a placebo-controlled multi center trial conducted in the USA. Efficacy endpoints were symptomatic and sigmoidoscopic improvement. Included in this NDA is the safety on 1034 patients, exposed one or more times to this Salix' balsalazide formulation.

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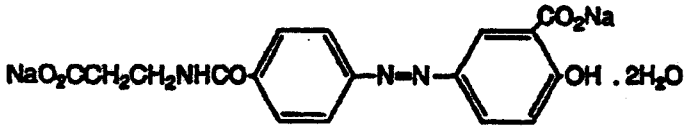
A. BACKGROUND.

i. BRIEF SUMMARY OF CHEMISTRY AND PHARMACOLOGY OF COLAZIDE®.

1. Chemistry. Colazide®, chemically defined as balsalazide disodium, is a prodrug formulation designed to deliver mesalamine (5-ASA) to the colon. Balsalazide (BSZ) was initially developed by Biorex Labs. (London, England), simultaneously with another similar chemical and pharmacological compound named ipsilazide. Designed to reduce the toxic properties of sulfasalazine, it links the active compound 5-aminosalicylic acid to an inactive β-alanine carrier (4-amino benzoyl-β-alanine) via an azo-bond. The following is the balsalazide disodium structural formula (as taken from the submitted *Chemistry Section, Page 3, Vol. 1003*).

Fig 3.A.1.b-1



Colazide® gelatin capsules contain 750 mg of balsalazide disodium, — magnesium stearate and — colloidal silicon dioxide.

2. Pharmacology. Balsalazide (BSZ) is formulated to reach unaltered the lower levels of the intestinal tract, such as the colon, normally inhabited by a complex ecological system of microorganisms. In the colon, BSZ is cleaved by bacteria azoreduction to release equimolar quantities of the active compound (5-ASA) and the inactive carrier, 4-amino benzoyl-β-alanine (4-ABA). Similar to mesalamine, (ASA), the anti-inflammatory action of BSZ is topical. This topical anti-inflammatory action on a damaged GI tract was shown in a number of animal models, as noted by the sponsor in its following summarized statement: The mechanism of action of ASA appears to be topical. The anti-inflammatory properties of BSZ or ASA were demonstrated in a variety of efficacy models: carrageenin-induced paw edema in the rat, ethanol and TNBS induced recto colonic lesions, ethanol-induced necrosis in the rat, and acid-induced writhing in the mouse. The active portion of BSZ, ASA, showed anti-inflammatory and analgesic activities similar to BSZ. Although sulfasalazine (SASP) has shown anti-inflammatory and analgesic activities similar to BSZ, SASP potentiated chemically-induced recto colonic damage (*taken from the NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SUMMARY*).

After the release by bacterial action in the colon, the active ASA and the carrier 4-ABA are further metabolized into NASA (N-acetyl-5-aminosalicylic acid) and NABA (N-acetyl-4-amino benzoyl-β-alanine), respectively.

The sponsor performed a number of pharmacokinetic studies to determine the degree of BSZ absorption (if any), and of its metabolites. The list of studies are shown in the following Salix table, *(taken from the INTEGRATED PHARMACOLOGY AND PHARMACOKINETICS SUMMARY).*

Study No.	Study Site	Study Design	Oral Dose of Colazide®	Dosage Form	# of Subjects
0500242	Japan	a) parallel, ascending single dose b) single dose crossover	a) 1.1, 2.2, 3.3 g b) 4.4 g (fed/fasting)	Granule	24 males
20060	U.K.	two single dose crossovers vs. Salazazopyrin® and Asacol®	2.25 g fed	750 mg capsule	24 males
20061	U.K.	single and multiple dose	1.5 g and 2.25 g b.i.d. fed	750 mg capsule	12 males
0500301	Japan	multiple dose	3.3 g t.i.d. x 1 day fed	Granule	6 males
0600235	Japan	a) single dose crossover bioequivalence b) ascending sinige and multiple dose c) single and multiple dose	a) 2.2 g fed b) 2.2, 2.48 2.85 g t.i.d. x 1 day fed c) 2.85 g. t.i.d. x 7 d fed	Granule	a) 6 males b) 16 males c) 6 males
GLY 01/93	U.K.	nonrandomized, multiple dose	1.5, 2.25 and 3.0 g b.i.d. fed	750 mg capsule	None (29 males and 25 females)

The pharmacokinetic studies revealed minimal intestinal absorption of BSZ (<0.3%). The major fraction of oral BSZ (90%) is delivered intact to the colon and subjected to bacterial cleavage with release of 5-ASA and 4-ABA.

Salix concluded the following:

"The pharmacokinetics studies in both normal healthy volunteers and patients on long term maintenance therapy demonstrate that balsalazide disodium efficiently delivers 5-ASA, the active moiety, to the lower bowel together with low systemic exposures to the parent drug and carrier metabolites. A small amount of balsalazide is absorbed systemically to give dose proportional peak plasma concentrations within 1-2 hours. Upon repeated administration, there was little or no accumulation. While urinary and fecal excretions of the parent drug were low, there was a high fecal recovery of total ASA and total ABA following single and multiple doses of balsalazide disodium suggesting a high availability of the active metabolite to the site of action. Food tended to decrease the absorption of balsalazide with a corresponding decrease in the percentage of balsalazide excreted in the urine. However, except for a decrease in Cmax for NABA, there was no significant alterations in the computed pharmacokinetics parameters of the other metabolites in plasma, urine or feces".

B. PROPOSED LABEL.

- The following are the proposed indication and usage, dosage and administration, and pediatric information, of the submitted label (as taken directly from the *PROPOSED TEXT OR LABELING FOR THE DRUG-ANNOTATED).*

C. SCIENTIFIC RATIONALE FOR THE PROPOSED INDICATION.

i. Ulcerative Colitis (UC), the first nonspecific inflammatory bowel disease described in the English medical literature, *(the initial descriptions date back to the latter part of the 19th century)*, is a bowel inflammation of unknown etiology. An estimated 250,000 Americans have ulcerative colitis. It occurs most often in young people, ages 15 to 40, although children and older people sometimes develop the disease. This colonic inflammation affects equal proportion of males and females. UC is.localized exclusively on the rectum and colon, and in over 50% of the patients, UC is manifested as proctitis, recto sigmoiditis and left sided colitis. Pathologically, UC is characterized by congestion, edema, friability and diffuse shallow mucosal ulcerations. Recto colonic mucosal biopsies from patients with acute UC, reveal microscopic hemorrhages mixed with thrombotic foci, diffuse mucosal infiltration by lymphocytes and plasma cells, and crypt abscesses displaying a plethora of polymorphonuclear white cells invading the cells and lumen of colonic crypts. Clinically, UC has a chronic course characterized by acute flare ups and remissions. During a flare up, symptoms include frequent and urgent defecation of small volume bloody-mucus stools with or without accompanying diarrhea, and rectal tenesmus. Diagnosis of an acute UC episode is usually made by a rectosigmodoscopic endoscopy showing congestion, friability. and in the more severe cases, the pathognomic presence of uniform shallow mucosal ulcerations. The most serious complications of an acute episode are massive lower rectal bleeding, fever associated with weakness (fulminant form), and toxic megacolon.

ii. From the mid 1950's to the early 1980's, the traditional therapy for mild or moderate UC recurrences included oral administration of sulfasalazine (SAS), alone or, more frequently, in combination with steroid enemas. Sulfasalazine is a chemical blend of

sulfapyridine and amino salicylate linked by an azo bond. Synthesized over 50 years ago, it intended to treat rheumatoid arthritis and ulcerative colitis, inflammatory conditions thought at that time to be caused by an infectious microorganism. A limiting factor for the universal use of SAS was a dose-related intolerance experienced by some patients, and/or allergic or toxic reactions to the sulpha component. The experimental and clinical studies by Peppercorn and Goldman in the USA and Truelove in England, carried out in the 1970's, demonstrated that contrary to the original belief, the active therapeutic moiety in SAS was the amino salicylate (5-ASA). Subsequent to these experimental findings, controlled clinical trials with 5-ASA and SAS demonstrated their therapeutic similarity in improving or reverting UC acute flare ups, and in prolonging remissions between recurrences. A number of oral and rectal 5-ASA formulations have been approved for the treatment of mild or moderately active UC, i.e., mesalamine, olsalazine. Most of the pharmaceutical ASA formulations incorporate delivery systems to prevent gastric acid degradation or proximal absorption of 5-ASA and, thus, preserve the active agent for delivery to the colonic mucosa.

iii. Regarding the transition of BSZ from the experimental phase to the clinical phase, Salix notes that *"Following the demonstration that balsalazide delivers the prodrug balsalazide disodium to the colon where bacterial azoreductases liberate the active moiety 5-ASA, clinical trials were initiated to test the efficacy and safety of this product, primarily in mild to moderate ulcerative colitis"*.

Key References

1. Hale-White W. On simple ulcerative colitis and other rare intestinal ulcers. Guy's Hosp Rep, 45:131, 1888.

2. Morson BC. Pathology of ulcerative colitis. Proc R Soc Med, 64:976-977, 1971.

3. McInerney GT et al. Fulminating ulcerative colitis with marked colonic dilatation. A clinico-pathologic study. Gastroent. 42:244-257, 1962.

4. Powel-Truck J et al. Correlations between defined sigmoidoscopy appearances and other measures of disease activity in ulcerative colitis. Dig Dis & Sci. 17:533-537, 1982.

5. Svartz N. Sulfasalazine: II; some notes on the discovery and development of salazopyrin. Am J Gastroent. 83:497-503, 1988.

6. Dick AD et al. Controlled trial of sulphasalazine in in the treatment of ulcerative colitis. Gut, 5:437-442,1964.

7. Peppercorn MA and Goldman P. The role of intestinal bacteria in the metabolism of salicylazosulfapyridine. J Pharmacol Exp Ther. 181:555-562, 1972.

8. Azad Khan AK et al. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet, 2:892-895, 1977.

9. Chan RP et al. Studies of two novel sulfasalazine analogs, ipsalazide and balsalazide. Dig Dis & Sci. 28:609-615, 1983.

10. Hanauer SB. Medical therapy of ulcerative colitis. 342:412-416, 1993.

D. PIVOTAL CLINICAL TRIALS.

Salix designated controlled clinical studies CP099301 and 57-3001 as pivotal trials to support the claim of balsalazide effectiveness for the treatment of mildly to moderately active ulcerative colitis. In this section, I will briefly summarize the study protocols, the sponsor's descriptive of these trials and then will include my comments on the findings and results presented by the sponsor.

1. PIVOTAL CLINICAL TRIAL CP099301.

i. Study Protocol CP099301. The prospective protocol, created for this controlled clinical trial was finalized on May 3, 1994. It designated Dr. Marvin H. Sleisenger M.D. as Study Medical Monitor, the Biometric Research Institute as Study Clinical Monitor and it was titled as follows: *"A PHASE III RANDOMIZED, DOUBLE-BLIND, DOSE-RESPONSE COMPARISON OF COLAZIDE® (BALSALAZIDE DISODIUM) 6.75 G DAILY VS. COLAZIDE® 2.25 G DAILY AND ASACOL® (MESALAMINE) 2.4 G DAILY IN PATIENTS WITH ACTIVE MILD OR MODERATE ULCERATIVE COLITIS" (taken from Salix's CANDA, Page 294, Vol. 1.069).*

(a) Design. According to the prospective protocol, this study was designed as a *"Randomized, double-blind, double-dummy controlled, dose response comparison of Colazide® 6.75 g/day vs. Colazide® 2.25 g/day and Asacol® 2.4 g/day".*

(b) Patient Population. This protocol planned for an enrollment of 165 patients 18 to 80 years of age, at 10 to 15 centers. The number of patients planned to complete the study was approximately 150. In addition to the determination of clinical efficacy, the protocol included an assessment of the pharmacokinetic profile of the experimental drug, to be conducted in up to three centers, with inclusion of up to 15 patients per site. In a few centers, the protocol planned for analyzes of plasma 5-ASA and its acetylated metabolite.

(c) Inclusion Criteria. The following were relevant criteria for patient enrollment *(Copy taken from Salix's CANDA).*

- Newly diagnosed or recently-relapsed (within twelve weeks) patients with active mild to moderate ulcerative colitis.
- Diagnosis must be confirmed by the finding of friable (moderate) or spontaneously-bleeding (severe) mucosa by flexible sigmoidoscopy (greater than 10 cm) performed at screening visit, and negative stool culture.

(d) Exclusion Criteria. The following were relevant criteria for patient exclusion *(Copy taken from Salix's CANDA),*

- Severe colitis manifested by any of the following: More than eight bloody stools/day with any of the following: a hemoglobin 10 g/dl or serum albumin <3.5 g/dl, temperature of >101 N F and resting pulse >100 beats/min.,
- Toxic megacolon,
- Unequivocal rebound tenderness associated with temperature of >98.6 N F,
- Anemia with hematocrit less than 30% or hemoglobin less than 10 g/dl.
- Patients known to be intolerant of or allergic to salicylate.
- Patients with a stool culture positive for: enteric pathogens (including salmonella , shigella, campylobacter, yersinia, aeromonas, and plesiomonas), C. difficile, ova, or parasites.
- Patients taking antibiotics within 14 days prior to screening.
- Patients taking steroids (including enemas) within 14 days prior to screening.
- Patients with Crohn's Disease.
- Patients with hepatic disease manifested by twice upper limit of normal on any of the following liver function tests: ALT, AST, GGT, alkaline phosphatase or total bilirubin (except in isolated elevation of unconjugated bilirubin) or renal disease manifested by 1.5 times upper limit of normal serum creatinine or BUN levels.
- Patients taking immunosuppressant drugs within 90 days prior to screening.

(k) Flexible Sigmoidoscopy. The following will be the degree of mucosal severity:

Normal: Normal mucosa
Mild: Edema, loss of vascular pattern, fine granularity without ulceration
Moderate: Friability, petechiae, coarse granularity with pinpoint ulceration
Severe: Visible ulcers, spontaneous bleeding

(l) Flow Chart. The following chart lists time-schedules for visits, chemistries and sigmoidoscopy *(taken from the Study Protocol, Appendix A, Salix's CANDA).*

Blinded Phase Study Assessment

Assessments	Screen Day -7	Baseline* Day 0	Week 2 Day 14	Week 4 Day 28	Week 8 Day 56
History & Physical Exam	✓				
Physician's Global Assessment	✓	✓	✓	✓	✓
Weight, Vital Signs, Symptom Assessment	✓	✓	✓	✓	✓
Volunteered Complaints/Adverse Events	✓	✓	✓	✓	✓
Laboratory Evaluations	✓		✓	✓	✓
Serum Pregnancy Test for Women of Child Bearing Potential	✓		✓	✓	✓
Stool Culture	✓				
Flexible Sigmoidoscopy	✓		✓	✓	✓
Rectal Biopsy	✓	✓ At Termination Only			
Quality of Life Assessment		✓	✓	✓	✓
Administrative					
Dispense Treatment		✓	✓	✓	
Dispense/Check Diary	✓	✓	✓	✓	✓
Collect Treatment Supplies			✓	✓	✓

* Baseline may be consolidated with Screening. Refer to Section 5.1.5 for provision.

ii. Study Descriptive. The following is a brief summary descriptive of relevant issues related to the study results. Relevant issues are patient enrollment, demographics, patient disposition and actual efficacy results reported by the sponsor. When feasible and appropriate, text or tables will be taken directly from the electronic data (CANDA) submitted by the sponsor.

1. Patient Enrollment and Disposition. Salix states that **the first patient was enrolled in the study on June 17, 1994, and the last patient terminated treatment on March 15, 1996.** Salix notes that **"Of the 163 individuals who were initially screened, 154 were enrolled and treated by 13 Investigators.** Nine persons who failed screening were

not assigned to a treatment group. Screening failures were due to sigmoidoscopic scores or clinical laboratory findings which excluded eligibility. One-hundred fifty patients were available for analysis at Week 2, 125 were available for analysis at Week 4, and 109 were available for analysis at study termination. The rules used to evaluate patients terminating at unscheduled visits between these time points are listed in the footnote to Table 1". The following is Salix Table 1, Page 255, Vol. 1.069.

Table 1. Number of Patients Evaluated at Each Study Week [1]

Overall Study Period	Colazide 2.25 g/day	Colazide 6.75 g/day	Asacol	Total
Screened:	50	53	51	163[2]
Randomized/Enrolled:	50	53	51	154
Not treated	0	0	0	0
Treated	50	53	51	154
Week 2:	49	52	49	150
Week 4:	39	45	41	125
Week 8:	34	37	38	109

[1]Unscheduled visits were categorized using the following rule: if the visit day was more than or equal to 1 day and less than 22 days, then it was a Week 2 visit. If the visit was more than or equal to 22 days and less than 36 days, then it was a Week 4 visit. If the visit was more than 37 days, then it was a Week 8 visit. If a patient had a Week 4 visit, any subsequent unscheduled visit was counted as a Week 8 visit.
[2]Contains 9 patients not categorized into a treatment group.

According to the reported by Salix, **of the 109 who were available for analysis on the week 8 visit, 106 patients completed the full 8 weeks of treatment (33 low- dose balsalazide patients, 37 high-dose balsalazide patients, and 36 Asacol patients).** Salix explains that "the difference is due to 3 patients (Nos. 5005, 5101, and 5359) who terminated the study at unscheduled visits between their scheduled Week 4 and Week 8 visits and therefore had data available for analysis after their 4 -week time point. Three additional patients (Nos. 5560, 5611, and 5708), who completed 4 weeks of treatment but did not complete their 8 -week visit, did not have termination data (lost to follow -up) and could therefore not be analyzed at Week 8".

Salix notes that the reason for premature withdrawal and the exact timing of **withdrawal of the 48 patients not completing 8 weeks** are summarized in the following Salix Table 4, taken from Page 258, Vol. 1.069 (CANDA).

Table 4. Post-Randomization Study Discontinuations

Discontinuation Reasons	Colazide 2.25 g/day N=50 No. (%)	Colazide 6.75 g/day N=53 No. (%)	Asacol N=51 No. (%)	Total N=154 No. (%)
Adverse Event:	2 (04.0)	1 (01.9)	2 (03.9)	5 (03.2)
Inadequate Therapeutic Effect				
Treatment Failure:	8 (16.0)	2 (03.8)	4 (07.8)	14 (09.1)
Adverse Event Worsening of Ulcerative Colitis Symptoms:	3 (06.0)	0 (00.0)	3 (05.9)	6 (03.9)
Patient Request/Worsening of Ulcerative Colitis Symptoms:	0 (00.0)	3 (05.7)	1 (02.0)	4 (02.6)
Sponsor/Investigator Request:	1 (02.0)	1 (01.9)	0 (00.0)	2 (01.3)
Intercurrent Medical Event:	1 (02.0)	3 (05.7)	2 (03.9)	6 (03.9)
Patient Request:	0 (00.0)	3 (05.7)	1 (02.0)	4 (02.6)
Noncompliance:	2 (04.0)	3 (05.7)	2 (03.9)	7 (04.5)
Completed Study:	33 (66.0)	37 (69.8)	36 (70.6)	106 (68.8)
Total Enrolled:	50 (100.)	53 (100.)	51 (100.)	154 (100.)
Time of Discontinuation:				
0–7 days	1 (02.0)	2 (03.8)	3 (05.9)	6 (03.9)
8–14 days	6 (12.0)	2 (03.8)	3 (05.9)	11 (07.1)
15–21 days	4 (08.0)	2 (03.8)	2 (03.9)	8 (05.2)
22–28 days	2 (04.0)	1 (01.9)	4 (07.8)	7 (04.5)
29–35 days	3 (06.0)	3 (05.7)	1 (02.0)	7 (04.5)
36–42 days	0 (00.0)	3 (05.7)	1 (02.0)	4 (02.6)
43–49 days	1 (02.0)	1 (01.9)	1 (02.0)	3 (01.9)
50–56 days	0 (00.0)	0 (00.0)	0 (00.0)	0 (00.0)
>56 days	0 (00.0)	2 (03.8)	0 (00.0)	2 (01.3)
Total Discontinued:	17 (34.0)	16 (30.2)	15 (29.4)	48 (31.1)

2. Demographics. The sponsor notes that there were no treatment group differences in baseline variables in the *"efficacy-eligible population"*. Salix states that the mean age for the 147 patients eligible for efficacy analyses was 42 years and that there was equal proportion of males and females (app. 50%). The sponsor notes that although there were more smokers in the Colazaide 2.25 g/d group (20%) than in either of the other 2 groups (Colazide 6.75 g/d 10%, Asacol 2.4 g/day 12), this difference was not statistically significant. The sponsor also notes that *"although there was no statistically significant difference between the groups in disease duration, the Asacol group showed the longest duration (81 months) and the Colazide 6.75 g/d group the shortest (64 months)"*. The following Table 6, taken from Page 262, Vol. 1.069 illustrates this point (transferred directly from CANDA).

Table 6. Demographics and Baseline Characteristics (Efficacy-Eligible Patients)

Variable	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Total	Between-Groups P-value 6.75 g/d versus	
					2.25 g/d	Asacol
Number of Patients:	N=49	N=49	N=49	N=147		
Sex:						
Male (%)	26 (53.1)	25 (51.0)	23 (46.9)	74 (50.3)	0.855 CMH	0.903 CMH
Female (%)	23 (46.9)	24 (49.0)	26 (53.1)	73 (49.7)		
Age:						
Mean (SE)	40.7 (2.2)	42.3 (1.8)	42.8 (2.2)	42.0 (2.1)	0.249 T	0.981 T
Median	38.0	41.0	39.0	39.0	0.338 S	0.154 S
Min, max	19.0, 77.0	19.0, 73.0	20.0, 76.0	19.0, 77.0	0.322 T*S	0.789 T*S
Smoking History:						
Never (%)	23 (46.9)	30 (61.2)	24 (49.0)	77 (52.4)	0.295 CMH	0.953 CMH
In past (%)	16 (32.7)	14 (28.6)	19 (38.8)	49 (33.3)		
Current (%)	10 (20.4)	5 (10.2)	6 (12.2)	21 (14.3)		
Disease Duration (mo):						
Mean (SE)	67.6 (10.4)	64.0 (9.9)	80.7 (12.6)	70.8 (6.3)	0.533 T	0.194 T
Median	43.5	50.9	59.9	50.9	0.091 S	0.703 S
Min, max	6, 288.3	6, 274.9	0, 415.5	0, 415.5	0.923 T*S	0.707 T*S
Newly diagnosed (%)	9 (18.4)	7 (14.3)	8 (16.3)	24 (16.3)	0.495 CMH	0.754 CMH
Recently relapsed (%)	40 (81.6)	42 (85.7)	41 (83.7)	123 (83.7)		
Extent of Disease:						
>60 cm (%)	12 (24.5)	11 (22.4)	15 (30.6)	38 (25.9)	0.737 CMH	0.878 CMH
<60 cm (%)	37 (75.5)	38 (77.6)	34 (69.4)	109 (74.1)		
Range Categories of Relapses in Last 2 Years:						
0 (%)	0 (00.0)	4 (09.3)	3 (07.5)	7 (05.7)	0.381 T	0.746 T
1-3 (%)	31 (77.5)	26 (61.9)	26 (65.0)	83 (68.0)	<0.001 S	0.123 S
4-6 (%)	6 (15.0)	10 (23.8)	8 (20.0)	24 (19.7)	0.034 T*S	0.659 T*S
>6 (%)	3 (07.5)	2 (04.8)	3 (07.5)	8 (06.6)		
Missing	9	7	9	25		
Mean (SE)	2.8 (0.3)	2.6 (0.3)	2.8 (0.3)	2.7 (0.5)		
Duration of Current Relapse (weeks):						
Mean (SE)	4.7 (0.6)	5.4 (0.8)	5.1 (0.7)	5.1 (0.7)	0.657 T	0.951 T
Median	3.0	5.0	4.0	4.0	0.104 S	0.240 S
Min, max	0.0, 20.0	0.0, 33.0	0.0, 26.0	0.0, 33.0	0.711 T*S	0.107 T*S

Statistical parameters and abbreviations follow: two-way ANOVA; T=treatment effect, S=site effect, T*S=treatment-by-site interaction; CMH= Cochran-Mantel-Haenszel Test.

Relevant to the course and outcome of the experimental medication, is the *"disease activity"*, as measured by the sigmoidoscopic score, extent of disease, biopsy grade, and Physician's Global Assessment (PGA) at entry. As presented in the next table, the sponsor states that *"All treatment groups were equally matched for grade of severity and for extent of disease. Although there was no statistically significant difference in PGA scores at entry, the **Colazide 6.75 g/d treated group had almost twice (7 versus 4) the numbers of patients whose disease activity was assessed as mild at entry** and consequently fewer patients as moderate or severe"*.

Next Salix Table VII, taken from Page 217, Vol. 1.069, exemplifies this point.

Table VII. Disease Activity Scores at Entry for Efficacy-Eligible Patients

Entry Characteristic	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs 2.25	Between-Group P-value 6.75 vs Asacol
Sigmoidoscopic Grade	N=49	N=49	N=49	bWMW	bWMW
Mild	0 (0)	2 (04.1)	0 (0)	0.621	0.960
Moderate	42 (85.7)	36 (73.5)	41 (83.7)		
Severe	7 (14.3)	11 (22.4)	8 (16.3)		
Extent of Disease	N=49	N=49	N=49		
>60 cm	12 (24.5)	11 (22.4)	15 (30.6)	0.737	0.878
<60 cm	37 (75.5)	38 (77.6)	34 (69.4)		
Biopsy Grade	N=45	N=48	N=45		
Inactive	4 (08.9)	7 (14.6)	3 (06.7)	0.701	0.653
Mild	6 (13.3)	4 (08.3)	7 (15.6)		
Moderate	9 (20.0)	15 (31.1)	12 (26.7)		
Severe	16 (35.6)	11 (22.9)	16 (35.6)		
Severe/Erosion	10 (22.2)	11 (22.9)	7 (15.6)		
Physician's Global Assessment	N=49	N=49	N=49		
Mild	4 (08.2)	7 (14.3)	4 (08.2)	0.245	0.226
Moderate	42 (85.7)	40 (81.6)	41 (83.7)		
Severe	3 (06.1)	2 (04.1)	4 (08.2)		

bWMW– Wilcoxon-Mann-Whitney Test, blocked by site

3. Primary Endpoints Efficacy Results. Data Sets Analyzed. I will present the inter-treatment efficacy results as shown in Salix's Intention-To-Treat (ITT) population, and, as shown in the sponsor's per-protocol eligible (evaluable) patient population. The following explanation, Pages 215-216, Vol. 1.069, details reasons for exclusion in the sponsor's patient-eligible data set.

"The primary data set analyzed for efficacy was those patients meeting the per-protocol eligibility criteria. Eleven of the 154 patients who were randomized, 3 Asacol-treated patients and 4 patients from each of the high-or low-dose Colazide-treated groups, did not strictly meet eligibility requirements (Table 2). However, prior to unblinding, each of these patients was reviewed by the Sponsor, the Medical Monitor, and the Study Monitor, and only 2 of these 11 patients were excluded from the efficacy-eligible analyses, both for having relapsed greater than 12 weeks prior to Screening. Among the remaining 9 patients, 5 patients were admitted to the study with out-of-range laboratory values, 2 had entry sigmoidoscopy scores that were categorized as mild, 1 patient did not have a Screening stool culture result, 1 patient had been given a single dose of antibiotics during sigmoidoscopy at Screening as a prophylactic measure due to preexisting mitral valve prolapse. In addition to the 2 patients discussed previously who were excluded from the efficacy-eligible patient population, 5 other patients (2 for interfering concomitant medications and 3 patients for treatment noncompliance) were excluded from all efficacy-eligible analyses because their protocol violations occurred prior to the

Week 2 visit. This yielded 154 patients eligible for safety and intent-to-treat analyses, and 147 patients eligible for efficacy analyses. In addition to the 7 patients excluded from the efficacy-eligible group from entry and discussed previously, review of patient protocol compliance prior to unblinding also identified 12 other patients who were ineligible for analysis after 2 or 4 weeks due to protocol violations. These included 4 patients ineligible after 2 weeks (3 due to interfering concomitant medication and 1 medication compliance) and 8 patients ineligible after 4 weeks (4 due to interfering concomitant medication and 4 due to medication compliance). Comparison of the patient disposition shows that the final efficacy-eligible group differs from the intent-to-treat group by only 8 patients".

Table 2, Page 256, Vol. 1.069, lists patients who met eligibility, according to Salix

Table 2. Protocol Eligibility of Enrolled Patients

Study Patient Status	Colazide 2.25 g/day N=50 No. (%)	Colazide 6.75 g/day N=53 No. (%)	Asacol N=51 No. (%)	Total N=154 No. (%)
Met Eligibility Criteria:	46 (92.0)	49 (92.5)	48 (94.1)	143 (92.9)
Did Not Meet Eligibility Criteria:	4 (08.0)	4 (07.5)	3 (05.9)	11 (07.1)
Sponsor approved	0 (00.0)	1 (01.9)	1 (02.0)	2 (01.3)
Sponsor unapproved	4 (08.0)	3 (05.7)	2 (03.9)	9 (05.8)
Total Enrolled:	50 (100.)	53 (100.)	51 (100.)	154 (100.)

(a) Stool Blood. The sponsor reminds the reader the primary efficacy established in the study protocol: "The primary measurement of treatment efficacy stated in the protocol was statistically significant improvement in rectal bleeding and statistically significant improvement in at least 1 other symptom or sign at the final assessment. Improvement in rectal bleeding is therefore considered first among all symptoms and signs measured followed by the remaining symptoms and signs".

Salix reports that there were differences in stool blood improvement for each of the three experimental treatments; according to Salix, "The proportion of Colazide 6.75 g/d patients, who improved, reached 50% as early as the interim 1 assessment and further increased to 60% at the interim 2 assessment, leveling off at 65% at the final assessment. The percent of Asacol-treated patients that improved varied from 43% at the interim 1 assessment to 62% at the interim 2 assessment but declined to 53% at the final assessment. The group treated with low-dose Colazide remained at 39% at 2 and 4 weeks and dropped to 32% at the final assessment. **The between-group differences were not statistically significantly different at the early assessment periods, and the only statistically significant between-group comparison was high-versus low-dose Colazide (65% versus 32%, p=0.006) at the final assessment. The improvement among Asacol-treated patients did not statistically differ from the high-dose Colazide group.** These results are also reflected in the number of patients in each treatment

group that reported no stool blood at the final assessment. Only 35% of patients in the Colazide 2.25 g/d treatment group reported no rectal bleeding at the 8-week visit, while 65% of patients in the Colazide 6.75 g/d treatment group and 47% of patients in the Asacol treatment group reported no rectal bleeding".

In Table VIII, Page 219, Salix shows stool blood improvement in the evaluable subset. At each scheduled week visit (2, 4 or 8), patients stool blood encompass a 4 day window period (96 hours).

Table VIII. Improved Stool Blood at Interim and Final Assessments (96-Hour Data)

Stool Blood Change	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Improved at Interim 1	17 (38.6%)	22 (50.0%)	18 (42.9%)	0.299 CMH	0.467 CMH
Total	44	44	42		
Improved at Interim 2	16 (39.0%)	24 (60.0%)	24 (61.5%)	0.065 CMH	0.855 CMH
Total	41	40	39		
Improved at Final	11 (32.4%)	22 (64.7%)	19 (52.8%)	0.006 CMH	0.275 CMH
Total	34	34	36		
Final Score Change:	N=34	N=34	N=36		
Mean (SE)	-0.42 (0.12)	-0.69 (0.12)	-0.59 (0.15)	0.036 T	0.516 T
Median	-0.24	-0.51	-0.57		
Min, max	-2.25, 0.67	-2.39, 0.46	-2.65, 2.02		

Statistical abbreviations: CMH= Cochran-Mantel-Haenszel Test, controlling for initial PGA value; T= 2-way ANOVA controlling for site.

The following Table E2.2, shows inter-treatments stool blood improvement in an ITT comparison, as reported by Salix on Page 138, Vol. 1.070 (CANDA).

Table E2.2. Improved Stool Blood (96-Hour Data) (ITT Patients)

Stool Blood Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment:	N=45	N=46	N=43		
Improved	17 (38.6%)	22 (48.9%)	18 (41.9%)	0.348 CMH	0.471 CMH
Not Improved	27 (61.4%)	23 (51.1%)	25 (58.1%)		
Missing	1	1	0		
Total	44	45	43		
Interim 2 Assessment:	N=44	N=43	N=42		
Improved	16 (38.1%)	25 (58.1%)	26 (63.4%)	0.055 CMH	0.752 CMH
Not Improved	26 (61.9%)	18 (41.9%)	15 (36.6%)		
Missing	2	0	1		
Total	42	43	41		
Final Assessment:	N=40	N=37	N=40		
Improved	13 (33.3%)	22 (61.1%)	20 (50.0%)	0.020 CMH	0.356 CMH
Not Improved	26 (66.7%)	14 (38.9%)	20 (50.0%)		
Missing	1	1	0		
Total	39	36	40		

Statistical abbreviations:
CMH= Cochran-Mantel-Haenszel Test, controlling for entry PGA

(b) Stool Frequency. Salix states the following: "Stool frequency was assessed as a score relative to the patient's normal bowel frequency (normal, mild =1-2 above normal, moderate =3-4 above normal, severe = > 5 above normal). There were no treatment group differences in daily stool frequency greater than normal at the initial assessment for diary data. During the course of the study, the groups progressed differently with respect to changes in the proportions of patients who improved relative to their normal stool frequency (Table E2.6). By the end of the study, the only statistically significant between-group comparison was high-versus low-dose Colazide (59% versus 29%, p=0.008)".

Table E2.6, Page 142, Vol. 1.070, shown below, displays treatment comparisons in stool frequency improvements, according to the sponsor's ITT analysis.

TableE2.6. Improved Stool Frequency (96-Hour Data) (ITT Patients)

Stool Frequency Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment:	N=45	N=46	N=43		
Improved	12 (27.3%)	17 (37.0%)	18 (41.9%)	0.315 CMH	0.611 CMH
Not Improved	32 (72.7%)	29 (63.0%)	25 (58.1%)		
Missing	1	0	0		
Total	44	46	43		
Interim 2 Assessment:	N=44	N=43	N=42		
Improved	14 (33.3%)	22 (51.2%)	24 (57.1%)	0.100 CMH	0.465 CMH
Not Improved	28 (66.7%)	21 (48.8%)	18 (42.9%)		
Missing	2	0	0		
Total	42	43	42		
Final Assessment:	N=40	N=37	N=40		
Improved	11 (28.2%)	21 (58.3%)	21 (52.5%)	0.008 CMH	0.684 CMH
Not Improved	28 (71.8%)	15 (41.7%)	19 (47.5%)		
Missing	1	1	0		
Total	39	36	40		

Statistical abbreviations:
CMH= Cochran-Mantel-Haenszel Test, controlling for entry PGA

(c). Patient Functional Assessment (PFA). Salix states that "There were no treatment group differences in Patient Functional Assessment at the initial assessment. For diary data averaged over 96 hours; the group means ranged from 2.2 for the group treated with high-dose Colazide to 2.6 for the Asacol -treated group. For purposes of perspective, the scale for these scores was 1=normal, 2=mild, 3=moderate, and 4=severe. There were no statistically significant between-group comparisons ($p>0.101$) at any of the assessment periods". Salix shows the *Patient Functional Assessment* results in the following Table X (Page 223, Vol. 1.069). (Next Salix Table X shows results in the per-protocol evaluable patient population)

Table X. Improved Patient Functional Assessment (96-Hour Data)

Patient Functional Assessment Change	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Improved at Interim 1	21 (46.7%)	14 (31.8%)	18 (42.9%)	0.183 CMH	0.291 CMH
Total	45	44	42		
Improved at Interim 2	20 (48.8%)	20 (50.0%)	22 (55.0%)	0.661 CMH	0.746 CMH
Total	41	40	40		
Improved at Final	19 (54.3%)	24 (70.6%)	22 (61.1%)	0.101 CMH	0.344 CMH
Total	35	34	36		
Final Score Change:					
Mean (SE)	-0.33 (0.15)	-0.71 (0.12)	-0.60 (0.13)	0.065 T	0.981 T
Median	-0.25	-0.75	-0.63		
Min, max	-2, 2	-2.5, 1	-2.25, 0.75		

Statistical abbreviations: CMH= Cochran-Mantel-Haenszel Test, controlling for initial PGA value; T= 2-way ANOVA controlling for site.

d) Abdominal Pain. No statistically significant efficacy differences between treatments were observed in improvement of abdominal pain, as seen in the next Salix Table XI. Salix states that "Of all symptoms measured, abdominal pain appeared to be the least sensitive measure of patient improvement over time or by treatment". (Table XI shows results in the per-protocol patient population).

Table XI. Improved Abdominal Pain (96-Hour Data)

Abdominal Pain Change	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Improved at Interim 1	11 (24.4%)	12 (27.3%)	13 (31.0%)	0.788 CMH	0.673 CMH
Total	45	44	42		
Improved at Interim 2	11 (26.8%)	15 (37.5%)	18 (45.0%)	0.184 CMH	0.570 CMH
Total	41	40	40		
Improved at Final	11 (31.4%)	14 (41.2%)	16 (44.4%)	0.346 CMH	0.722 CMH
Total	35	34	36		
Final Score Change:					
Mean (SE)	-0.08 (0.13)	-0.38 (0.09)	-0.42 (0.10)	0.067 T	0.780 T
Median	0	-0.38	-0.25		
Min, max	-2, 2	-1.75, 0.75	-1.75, 0.75		

Statistical abbreviations: CMH= Cochran-Mantel-Haenszel Test, controlling for initial PGA value; T= 2-way ANOVA controlling for site.

e) Sigmoidoscopy. In the following E2.16 Table, Salix displays the sigmoidoscopic scores at sequential visits and end of the end of the study period. This Salix table shows an ITT comparison as defined previously by Salix (see *Data Sets Analyzed* section). Salix notes that "high-dose Colazide was superior to low-dose Colazide only at the 8 week time point (p=0.055)".

Table E2.16. Improved Sigmoidoscopy (ITT Patients)

Sigmoidoscopy Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Week 2:	N=49	N=52	N=49		
Improved	20 (41.7%)	29 (55.8%)	15 (32.6%)	0.111 CMH	0.015 CMH
Not Improved	28 (58.3%)	23 (44.2%)	31 (67.4%)		
Missing	1	0	3		
Total	48	52	46		
Week 4:	N=46	N=46	N=46		
Improved	23 (51.1%)	31 (67.4%)	23 (53.5%)	0.103 CMH	0.170 CMH
Not Improved	22 (48.9%)	15 (32.6%)	20 (46.5%)		
Missing	1	0	3		
Total	45	46	43		
Week 8:	N=45	N=41	N=45		
Improved	24 (54.5%)	31 (75.6%)	27 (62.8%)	0.055 CMH	0.229 CMH
Not Improved	20 (45.5%)	10 (24.4%)	16 (37.2%)		
Missing	1	0	2		
Total	44	41	43		
Symptom Category					
Baseline:	N=50	N=53	N=51		
Normal	0	0	0	0.583 bWMW	0.968 bWMW
Mild	0	3 (05.7%)	0		
Moderate	43 (86.0%)	38 (71.7%)	43 (84.3%)		
Severe	7 (13.7%)	12 (22.6%)	8 (15.7%)		
Total	50	53	51		
Week 8					
Normal	11 (25.0%)	11 (26.8%)	11 (25.6%)	0.051 bWMW	0.242 bWMW
Mild	10 (22.7%)	17 (41.5%)	15 (34.9%)		
Moderate	15 (34.1%)	10 (24.4%)	11 (25.6%)		
Severe	8 (18.2%)	3 (07.3%)	6 (14.0%)		
Total	44	41	43		

Statistical abbreviations:
CMH= Cochran-Mantel-Haenszel Test, controlling for entry PGA; bWMW= Wilcoxon Mann Whitney Test, blocked by site.

(f) Physician Global Assessment (PGA). The next two Silex tables illustrate different comparisons of PGA as rated by enlisted physicians. Table XIII shows the PSA in Salix's per-protocol patient eligible population (evaluable). In this small subset of

eligible patient population, i.e., 106/154 (68%), the difference between high and low Colazide doses reaches significance at the final 8 week visit. In contrast, in Salix's Table E2.17, the sponsor Intention-To-Treat comparison, with inclusion of a larger patient population, i.e., 129/154 (84%), results in a numerical, but not statistically significant difference between the high and low Colazide doses.

Table XIII. Improved Physician Global Assessment (96-Hour Data)

Physician Global Assessment Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Improved at Week 2	18 (37.5%)	21 (43.8%)	15 (33.3%)	0.422 CMH	0.257 CMH
Total	48	48	45		
Improved at Week 4	24 (54.5%)	28 (65.1%)	24 (55.8%)	0.237 CMH	0.396 CMH
Total	44	43	43		
Improved at Week 8	20 (51.3%)	28 (73.7%)	24 (61.5%)	0.030 CMH	0.246 CMH
Total	39	38	39		
Week 8 Items:					
Quiescent	10 (25.6%)	17 (44.7%)	10 (25.6%)	0.001 bWMW	0.032 bWMW
Mild	11 (28.2%)	12 (31.6%)	15 (38.5%)		
Moderate	9 (23.1%)	8 (21.1%)	10 (25.6%)		
Severe	9 (23.1%)	1 (02.6%)	4 (10.3%)		
Total	39	38	39		

Statistical abbreviations: CMH= Cochran-Mantel-Haenszel Test, controlling for initial PGA value; bWMW= Wilcoxon-Mann-Whitney Test, blocked by site.

Table E2.17. Improved Physician Global Assessment (ITT Patients)

Physician Global Assessment Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Week 2:	N=49	N=52	N=49		
Improved	18 (37.5%)	22 (42.3%)	16 (34.0%)	0.472 CMH	0.313 CMH
Not Improved	30 (62.5%)	30 (57.7%)	31 (66.0%)		
Missing	1	0	2		
Total	48	52	47		
Week 4:	N=46	N=46	N=46		
Improved	25 (55.6%)	29 (63.0%)	25 (56.8%)	0.379 CMH	0.460 CMH
Not Improved	20 (44.4%)	17 (37.0%)	19 (43.2%)		
Missing	1	0	2		
Total	45	46	44		
Week 8:	N=45	N=41	N=45		
Improved	23 (52.3%)	28 (68.3%)	28 (63.6%)	0.123 CMH	0.632 CMH
Not Improved	21 (47.7%)	13 (31.7%)	16 (36.4%)		
Missing	1	0	1		
Total	44	41	44		
Symptom Category					
Baseline:	N=50	N=53	N=51		
Quiescent	0	0	0	0.298 bWMW	0.252 bWMW
Mild	4 (08.2%)	8 (15.1%)	4 (07.8%)		
Moderate	42 (85.7%)	43 (81.1%)	43 (84.3%)		
Severe	3 (06.1%)	2 (03.8%)	4 (07.8%)		
Missing	1				
	49	53	51		
Week 8:					
Quiescent	12 (27.0%)	17 (41.5%)	12 (27.3%)	0.014 bWMW	0.196 bWMW
Mild	13 (29.5%)	12 (29.3%)	17 (38.6%)		
Moderate	10 (22.7%)	10 (24.4%)	11 (25.0%)		
Severe	9 (20.5%)	2 (04.9%)	4 (09.1%)		
	44	41	44		

Statistical abbreviations:
CMH= Cochran-Mantel-Haenszel Test, controlling for entry PGA; bWMW= Wilcoxon Mann Whitney Test, blocked by site.

(g) Overall Symptom Assessment. The sponsor defines the Overall Symptom Assessment (OSA), the final primary efficacy endpoint, in this next descriptive sentence: **"Overall Symptom Assessment is a composite measure and was calculated from the percentage of patients improved in Physician's Global Assessment plus 1 other symptom or sign without worsening in any symptom or sign".** The following Salix Table E2.18, taken from Page 154, Vol. 1.070, illustrates the sequence of overall symptomatic improvement in the sponsor ITT's comparison. As noticed, though the high Colazide dose is numerically superior to the low Colazide dose, the difference does not reach statitical significance. No difference could be observed between the high Colazide dose and Asacol in OSA comparisons.

Table E2.18. Improved Overall Symptom Assessment (96-Hour Data) (ITT Patients)

Overall Symptom Assessment Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment:	N=49	N=52	N=49		
Improved	9 (19.1%)	16 (34.8%)	12 (26.7%)	0.048 CMH	0.310 CMH
Not Improved	38 (80.9%)	30 (65.2%)	33 (73.3%)		
Missing	2	6	4		
Total	47	46	25		
Interim 2 Assessment:	N=46	N=48	N=47		
Improved	20 (46.5%)	24 (58.5%)	22 (50.0%)	0.181 CMH	0.351 CMH
Not Improved	23 (53.5%)	17 (41.5%)	22 (50.0%)		
Missing	3	7	3		
Total	43	41	44		
Final Assessment:	N=45	N=41	N=45		
Improved	20 (47.6%)	22 (61.1%)	25 (59.5%)	0.222 CMH	0.883 CMH
Not Improved	22 (52.4%)	14 (38.9%)	17 (40.5%)		
Missing	3	5	3		
Total	42	36	42		

Statistical abbreviations:
CMH= Cochran-Mantel-Haenszel Test, controlling for entry PGA

4. Secondary Endpoint Efficacy Results. The most relevant of the secondary endpoints was achievement of a remission status from the acute UC episode. Protocol CP099301 defines remission in the following manner:

"Remission is defined as the resolution of clinical symptoms attributed to ulcerative colitis and endoscopically documented mucosal healing at both levels (sigmoidoscopy finding of normal or mild). Resolution of symptoms requires all of the following:

- No blood in stool for 48 hours prior to visit.
- Normal (for patient) stool frequency for 48 hours prior to visit.
- Physician's Global Assessment score of Quiescent".

By the end of the 8 week study period, no treatment differences were observed in the proportion of patients on remission, as seen in the next Salix Table E2.20, Page 156, Vol. 1.070, Noticeable, is that only 23/117 (20%) of all patients included in the sponsor's table were declared in remission from active UC, after an 8 week treatment by either low or high Colazide doses, or by the use of 2.4 g/day Asacol.

Table E2.20. Remission Status (96-Hour Data) (ITT Patients)

Remission Status Change	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment:	N=45	N=46	N=43		
In remission	0 (00.0%)	0 (00.0%)	1 (02.3%)		0.226
Not in remission	45 (100.%)	46 (100.%)	42 (97.7%)		
Total	45 (100.%)	46 (100.%)	43 (100.%)		
Interim 2 Assessment:	N=44	N=43	N=42		
In remission	2 (04.5%)	3 (07.0%)	2 (04.8%)	0.625	0.663
Not in remission	42 (95.5%)	40 (93.0%)	40 (95.2%)		
Total	44 (100.%)	43 (100.%)	42 (100.%)		
Final Assessment:	N=40	N=37	N=40		
In remission	8 (20.0%)	8 (21.6%)	7 (17.5%)	0.861	0.648
Not in remission	32 (80.0%)	29 (78.4%)	33 (82.5%)		
Total	40 (100.%)	37 (100.%)	40 (100.%)		

5. **Salix Summary of Primary and Secondary Endpoints Analyses**. In the following Tables XVIII and XIX, the sponsor summarizes the efficacy results in the per-protocol eligible patient population, and in the Salix ITT analysis, respectively. The results in the per-protocol eligible patient subset reveal better efficacy than in the ITT comparisons. In its conclusion, the sponsor refers to the statistical adjustment required for multiple endpoints comparisons. In reference to the low efficacy results in the ITT analysis, Salix notes that "The primary analysis of the intent-to-treat patient population also showed a statistically significant difference in rectal bleeding at 8 weeks between the high and low-dose Colazide groups. In addition, among the other symptoms and signs assessed in the primary analysis, stool frequency also showed a statistically significant difference between patient groups treated with the 2 Colazide doses. Again correcting for the multiple comparison issue, the associated p-value for stool frequency of p=0.008 is lower than the corrected sixth α=0.05/6=0.0083 and the null hypothesis is rejected".

Table XVIII. Summary of Primary and Secondary Analyses of Symptom/Sign Improvement in Efficacy-Eligible Patients

Primary Endpoints	Between-Group P-Values Colazide 6.75 g/d vs Colazide 2.25 g/d	
Symptom/Sign	Primary Analysis (% Improved)	Secondary Analysis (Mean Score Change)
Rectal Bleeding	0.008 CMH	0.036 T
Stool Frequency	0.008 CMH	0.009 T
Sigmoidoscopy	0.015 CMH	N/A
PGA	0.020 CMH	N/A
Overall Symptom Assessment	0.073 CMH	N/A
PFA	0.101 CMH	0.065 T
Abdominal Pain	0.346 CMH	0.067 T

Statistical abbreviations: CMH= Cochran-Mantel-Haenszel Test, controlling for initial PGA value; T=2-way ANOVA= Analysis of Variance controlling for site.

Table XIX. Summary of Primary and Secondary Analyses of Symptom/Sign Improvement in Intent-to-Treat Patients

Primary Endpoints	Between-Group P-Values Colazide 6.75 g/d vs Colazide 2.25 g/d	
Symptom/Sign	Primary Analysis (% Improved)	Secondary Analysis (Mean Score Change)
Rectal Bleeding	0.020 CMH	0.086 T
Stool Frequency	0.008 CMH	0.002 T
Sigmoidoscopy	0.055 CMH	N/A
PGA	0.123 CMH	N/A
Overall Symptom Assessment	0.222 CMH	N/A
PFA	0.545 CMH	0.062 T
Abdominal Pain	0.346 CMH	0.053 T

Statistical abbreviations: CMH= Cochran-Mantel-Haenszel Test, controlling for initial PGA value; T=2-way ANOVA= Analysis of Variance controlling for site.

iii. Reviewer Comments.

1. In this pivotal double-blind, multi center trial, conducted in 12 USA centers and one Puerto Rico center, Salix compared the efficacy of two balsalazide doses, a high dose (6.75 g/day) and a low dose (2.25 g/dose), on the treatment of mild to moderately active ulcerative colitis. Patients were also treated with an approved mesalamine preparation (Asacol®), included as active third treatment comparison. The study design did not include placebo as treatment control. In the absence of a placebo control, efficacy hinged in demonstrating a significant superiority of the high Colazide dose over the low Colazide dose, and in showing a comparable, though not necessarily equivalent efficacy, between the high Colazide dose and the approved mesalamine preparation.

To demonstrate primary efficacy of the experimental drug, the protocol required to show significant improvement in blood stool plus improvement in at least 1 other primary symptom, chosen out of five symptoms, in evaluations made by either physicians or treated patients.

The **primary efficacy results**, as presented by the sponsor in its intention-to-treat populations (ITT) and as defined in the study protocol, **showed significant but minimal superiority of the high balsalazide** dose over the low dose.

The most relevant therapeutic benefit observed in patients on the high Colazide (BSZ) dose, **was in the number of patients exhibiting a reduction in stool blood;** stool blood being the cardinal symptom in actively inflamed ulcerative colitis. Reduction or resolution of blood in stools, has been traditionally the hallmark to assign success to any experimental therapy designed to benefit ulcerative colitis patients. In this particular case, **though a larger proportion of patients on high BSZ dose did show improvement** in stool blood, the **degree of improvement, or the actual reduction of blood in stools, was not different across treatments.** According to the sponsor's results, improvement in stool blood was evaluated by the proportion of patients improved, and, by a *"symptom score"*. In order to assign scores to blood stool improvement, the sponsor, apparently, derived numbers from the daily recording in patient diaries, e.g, no blood=0, streaks of blood=1, obvious blood=2 or 3, and, blood alone=>3 *(it should be noted that the prospective protocol did not include any quantitation of blood assessments)*. My review of the sponsor's ITT revealed that overall, **patients on the high BSZ dose improved from obvious stool blood at baseline to just streaks of blood in stools, after the 8 weeks of treatment,** *[app. from a median score of 2 (1.9) to a median score of 1]*. Noteworthy, patients improved on the low BSZ dose or on Asacol, achieved a similar degree of reduction in stool blood (p=0.086 between high and low BSZ), **This observation suggest that the majority of patients, regardless of treatment, did not achieve a complete resolution of blood in stools.**

Stool frequency, or daily number of bathroom trips needed to attend bowel urgency, was the only other symptom that revealed significant superiority of the high BSZ over the low BSZ dose, in the sponsor's intention-to-treat analysis.

Recognizable in Salix' ITT, is the borderline superiority of the high BSZ dose in the sigmoidoscopic improvement of the inflamed mucosa. Any sigmoidoscopic difference between the high and low BSZ dose was due to a change from a *moderately* inflamed rectosigmoid mucosa *(friability, coarse granularity)* to a *mildly* inflamed mucosa *(edema, loss of vascular pattern, fine granularity)*, as illustrated in the sponsor's Table E.2.16 (see my *Descriptive* section). This degree of improvement in UC sigmoidoscopic inflammation matches the partial resolution in symptoms associated with rectal inflammation, i.e., from overt blood in stools to streaks of blood in stools. Combined,

these two partial therapeutic gains observed in patients on the high BSZ dose, reflect a modest, albeit concrete, clinical improvement. By the end of the study period, only one fourth (25%) of patients from any of the three treatments, had returned to a normal sigmoidoscopic mucosa,

2. In its primary ITT efficacy analyses, Salix presented a subset of the 154 randomized patients. Hence, the sponsor ITT included 40 pts on 2.25 g BSZ, 37 pts on 6.75 BSZ, and 40 pts on Asacol. These three treated patient groups represent only three fourths of the total randomized patients, i.e., 117/154 (76%). My review of this ITT revealed an imbalance among treatments in the proportion of excluded patients, and, inconsistencies in the populations included to assess the results of primary symptoms. The following MO Table 1 illustrates this point.

Medical Officer Table 1

Patient Populations Excluded and Included in Salix' Intention-To-Treat

Salix ITT Populations	Colazide 2.25 g	Colazide 6.75 g	Asacol 2.40 g
RANDOMIZED	*50*	*53*	51
EXCLUDED: Patient Population	*10/50 (20%)*	*16/53 (30%)*	11/51 (22%)
INCLUDED FOR:			
Stool Blood	40	37	40
Stool Frequency	40	37	40
Rectosigmoidoscopy	44	41	43
Physician Global	44	41	44
Patient Global	40	36	40
Overall Symptom	45	41	45

In order to fully assess the impact of exclusions upon the robustness of the primary efficacy results, this reviewer requested from the sponsor two additional Intention-To-Treat efficacy analyses. In ITT-1, the sponsor was required to include All-Randomized-Patients, a rigorous test for robustness in efficacy. In the ITT-2, the sponsor was required to include All-Randomized-And-Treated-Patients, which is perhaps clinically, a more relevant assessment of efficacy, as long as the excluded patients represent <10% of the overall randomized population.

In the following Tables 20, 21, and 22, Salix displays the efficacy in stool blood, stool frequency and sigmoidoscopic scores in an ITT-2 patient population comparison. As seen, the significant superiority of the high BSZ dose over the low BSZ dose is still evident. The comparisons of the BSZ dose and Asacol rendered no overall significant differences, though of interest, is to note the superiority of the high BSZ dose vs. Asacol in sigmoidoscopic scores, by the final assessment visit.

Table 20: Intent to Treat 2 Patient Population, Improved Stool Blood (96 Hours)

Stool Blood Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment	N=49	N=49	N=49		
Improved	17 (34.7%)	22 (44.9%)	18 (36.7%)	0.323 CMH	0.376 CMH
Not Improved	32 (65.3%)	27 (55.1%)	31 (63.3%)		
Missing	1	4	2		
Total	50	53	51		
Interim 2 Assessment	N=49	N=49	N=49		
Improved	18 (36.7%)	26 (53.1%)	28 (57.1%)	0.096 CMH	0.737 CMH
Not Improved	31 (63.3%)	23 (46.9%)	21 (42.9%)		
Missing	1	4	2		
Total	50	53	51		
Final Assessment	N=49	N=49	N=49		
Improved	17 (34.7%)	27 (55.1%)	22 (44.9%)	0.045 CMH	0.309 CMH
Not Improved	32 (65.3%)	22 (44.9%)	27 (55.1%)		
Missing	1	4	2		
Total	50	53	51		

Statistical abbreviations:
CMH = Cochran-Mantel-Haenszel Test, controlling for entry PGA

Table 21: Intent to Treat 2 Patient Population, Improved Stool Frequency (96 Hours)

Stool Frequency Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment	N=49	N=49	N=49		
Improved	12 (24.5%)	17 (34.7%)	18 (36.7%)	0.268 CMH	0.79 CMH
Not Improved	37 (75.5%)	32 (65.3%)	31 (63.3%)		
Missing	1	4	2		
Total	50	53	51		
Interim 2 Assessment	N=49	N=49	N=49		
Improved	14 (28.6%)	22 (44.9%)	24 (49 %)	0.11 CMH	0.614 CMH
Not Improved	35 (71.4%)	27 (55.1%)	25 (51 %)		
Missing	1	4	2		
Total	50	53	51		
Final Assessment	N=49	N=49	N=49		
Improved	12 (24.5%)	24 (49 %)	21 (42.9%)	0.013 CMH	0.614 CMH
Not Improved	37 (75.5%)	25 (51 %)	28 (57.1%)		
Missing	1	4	2		
Total	50	53	51		

Statistical abbreviations:
CMH = Cochran-Mantel-Haenszel Test, controlling for entry PGA

Table 22: Intent to Treat 2 Patient Population, Improved Sigmoidoscopy (96 Hours)

Sigmoidoscopy Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment	N=50	N=53	N=51		
Improved	20 (40 %)	29 (54.7%)	15 (29.4%)	0.095 CMH	0.006 CMH
Not Improved	30 (60 %)	24 (45.3%)	36 (70.6%)		
Missing	0	0	0		
Total	50	53	51		
Interim 2 Assessment	N=50	N=53	N=51		
Improved	24 (48 %)	33 (62.3%)	23 (45.1%)	0.143 CMH	0.074 CMH
Not Improved	26 (52 %)	20 (37.7%)	28 (54.9%)		
Missing	0	0	0		
Total	50	53	51		
Final Assessment	N=50	N=53	N=51		
Improved	26 (52 %)	39 (73.6%)	27 (52.9%)	0.031 CMH	0.032 CMH
Not Improved	24 (48 %)	14 (26.4%)	24 (47.1%)		
Missing	0	0	0		
Total	50	53	51		

Statistical abbreviations:
CMH = Cochran-Mantel-Haenszel Test, controlling for entry PGA

The remaining symptom-endpoints analyzed by an ITT-2, i.e., PGA, PFA, Abdominal Pain and Overall Assessment did not reveal differences between the high Colazide and the low Colazide doses. ***Salix Tables 23, 24, 25 and 26 are included as Appendix 1.***

Noteworthy, in the ITT-1 efficacy comparisons of all-randomized patients, significant superiority of the high dose over the low Colazide dose were observed in stool frequency and sigmoidoscopic scores, but not in stool blood improvement, though there was a numerical advantage in favor of the high Colazide dose (p=0.088).

3. The prospective study protocol was completed on May 3, 1994. The last patient enrolled completed the trial on March 15, 1996. Approximately three months after completion of the trial, on June 26, 1996, Salix amended the protocol in the section related to the length of period prospectively established to assess the group of symptoms used in the primary efficacy. The period for symptom assessment was changed from the original 24 hour, to an extended 96 hour period. The issue of possible infringement in the blinding, to be considered in a post-trial amendment of the protocol, was explain by Salix in the following paragraph (as taken from CANDA):

> **Patient enrollment into this study terminated January 15, 1996 and treatment of the last enrolled patient ended on March 15, 1996. The database to date has not been unblinded and no analysis of these data has been undertaken. However, an initial analysis has been performed on a prior study, CP069101 which was conducted under a similar protocol and analysis plan. Use of a 96hr rather than 24hr data collection period for patient symptom data was found to provide much more stable data with less intra-patient variability.**
>
> **This amendment formalizes the following changes to the protocol:**
>
> **Primary symptom analyses will be based on the percentage of patients showing improvement of symptoms and will compare an initial assessment period (Days 1-4 following randomization) with a two week and a four week assessment (2 days prior to and 2 days following the two and four week visits), and an eight week assessment (four days preceding the eight week visit). All data will be derived directly from the patient diaries and will be scored as an average symptom score per 24 hr period. Criteria for symptom score improvement and statistical tests for significance between treatment groups have not been changed.**

The following Salix Tables E2.5 reports the Week 8 improvement data in stool blood, made during an assessment period of 24 hours. Even if blinded, it might be easy to deduct, from the presented data, that there are no significant differences among treatments. From a general viewpoint, and perhaps more in accordance with this reviewer's view, the 96 hour assessment might be preferable, in a disease like ulcerative colitis, sometimes characterized by short remission or relapses, even on treatment. Under the menace of this clinical variability, it would not be uncommon to miss actual improvements in short assessment periods.

Table E2.5. Improved Stool Blood (24-Hour Data) (ITT Patients)

Stool Blood Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Week 2:	N=49	N=52	N=49		
Improved	24 (49.0%)	31 (60.8%)	28 (59.6%)	0.208 CMH	0.869 CMH
Not Improved	25 (51.0%)	20 (39.2%)	19 (40.4%)		
Missing	0	1	2		
Total	49	51	47		
Week 4:	N=46	N=46	N=46		
Improved	24 (55.8%)	29 (67.4%)	30 (66.7%)	0.247 CMH	0.918 CMH
Not Improved	19 (44.2%)	14 (32.6%)	15 (33.3%)		
Missing	3	3	1		
Total	43	43	45		
Week 8:	N=45	N=41	N=45		
Improved	22 (50.0%)	23 (60.5%)	31 (73.8%)	0.379 CMH	0.155 CMH
Not Improved	22 (50.0%)	15 (39.5%)	11 (26.2%)		
Missing	1	3	3		
Total	44	38	42		

Statistical abbreviations:
CMH= Cochran-Mantel-Haenszel Test, controlling for entry PGA

4. Secondary efficacy endpoints of relevance included induction of remission and histological assessments made from rectosigmoid tissue obtained by endoscopic biopsies. As mentioned in my *Descriptive* of this study, and shown in Salix Table E2.20, only a handful of patients achieved remission and there were no differences among treatments. In the opinion of this reviewer, very little weight can be placed on the reported histological examinations, in spite of the sponsor's claim of benefit in favor of the high balsalazide dose. My rationale is based on two fundamental observations, taken from the submitted Appendix F, Vol. 1.070, namely: (a) **about 40% of patients (±57 patients) did not either have baseline or final biopsies**, (b) or did not have histological reports, (c) or the reports excluded baseline or final readings, and, (d) in spite of patients being symptomatic when entering the study, many **histological examinations were reported with *"inactive"* ulcerative colitis at baseline**. This mismatch between symptoms and histology may either represent a lack of a representative tissue, **rather uncommon in ulcerative colitis, or, that the inflamed mucosa had "skip" areas with no inflammation. In the latter event, a rather strong argument could be made that some enrolled patients were entered in the study with the wrong diagnosis of ulcerative colitis**, when indeed they were Crohn's colitis or undetermined colitis cases. Misreading Crohn's disease for ulcerative colitis by rectal histology, occurs in app. 10-20% of cases.

Appendix F, Pages 306-315, Vol. 1.070, is included as Appendix 2 of this review.

2. PIVOTAL CLINICAL TRIAL 57-3001.

I. Study Protocol. Th prospective study protocol 57-3001 included designs for assessment of balsalazide vs. Asacol in the acute ulcerative colitis phase and in the chronic (maintenance) phase. The following sections only pertain to the design for assessment of tolerance and efficacy of balsalazide therapy in acute ulcerative colitis. This protocol was completed and signed on 8/3/1993.

(a) Title. "A Balsalazide/5-ASA Comparison in Ulcerative Colitis".

> Patients with sigmoidoscopically verified (grade 2-4) symptomatic (moderate or severe on patient's assessment) ulcerative colitis will be randomised to receive double-blind either balsalazide (Colazide™, Astra) 2.25g t.d.s. or mesalazine (Asacol®, SK&F) 0.8g t.d.s. for 4 weeks, or if necessary, 8 or 12 weeks. All patients in symptomatic remission (see Section 3.4.1.6.1) at 4 or 8 weeks will undergo a sigmoidoscopy/colonoscopy (sigmoidoscopy); all patients in both sigmoidoscopic remission (grade 0-1) and symptomatic remission will proceed to be re-randomised into the chronic phase. All remaining patients will undergo a sigmoidoscopy at 12 weeks;

(b) Design. Randomized, double-blind-double-dummy, active-parallel control, multi center, with patients treated for up to 4-8 or 12-weeks (as taken from the CANDA)..

> Patients entering the study will be mainly hospital out-patients although in-patients are permitted providing the inclusion/exclusion criteria are met. It is intended that 37 hospitals each with an initial target recruitment of 8 patients over a maximum of 1 year will participate in the study

(c) Patients and Centers. The design planned for the following number of centers and patients per center:

(d) Inclusion Criteria. The protocol considers eligible the following patients.

The following section were scanned, unaltered, from Salix' CANDA, Vol. 1.72, Appendix A.

Appendix F, Pages 306-315, Vol. 1.070, is included as Appendix 2 of this review.

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(c) Patients and Centers. The design planned for the following number of centers and patients per center:

(d) Inclusion Criteria. The protocol considers eligible the following patients.

The following section were scanned, unaltered, from Salix' CANDA, Vol. 1.72, Appendix A.

1. Aged 18-80 years.

2. Ulcerative colitis (grade 2-4; extent >12cms measured from the anal margin) verified by sigmoidoscopy or colonoscopy no more than 3 days before initiation of therapy. If required, barium enema or other assessment may be used to verify the disease extent, in conjunction with sigmoidoscopy.

3. Symptomatic ulcerative colitis (moderate or severe on the patients' assessment, see section 3.4.1.3)

(e) Exclusion Criteria. The following are the relevant criteria for exclusion

1. Any use of oral steroids or i.v. steroids, within 30 days before trial entry (see section 3.3.10).

2. A daily requirement for rectal steroids to maintain remission, prior to current relapse, or use of rectal steroids outside the product licence within 14 days before trial entry.

3. Use of immunosuppressive agents e.g. azathioprine, cyclosporin and methotrexate within 3 months before trial entry.

4. Introduction or increase in dose of 5-ASA releasing compounds e.g. sulphasalazine, olsalazine, mesalazine and balsalazide, or their regular use within 14 days before the trial at doses from which greater than 1.2g/day

5. Use of antibiotics for reasons related to the primary diagnosis or for other GI related conditions within 14 days before trial entry.

6. Use of any investigational drug within 30 days before trial entry.

7. Co-existing Crohn's disease or idiopathic proctitis.

8. Current complications of ulcerative colitis requiring i.v. steroids and/or oral steroids e.g. passage of more than 6 bloody stools daily associated with any one of the following signs of systemic disturbance : temperature >37.5°C, pulse >100/min, haemoglobin <10g/dl or serum albumin <35g/dl [15,16].

12. History of G.I. tract resection.

13. Malignancy.

14. Significant disease (past or present) as judged by the Investigator, e.g. significant cardiovascular, renal or liver disease
Note: Asacol® is contraindicated in patients with severe renal impairment (GFR <20ml/min).

18. The presence of parasites, toxins or pathogens in stool culture.

(f) "Objectives" (Endpoints). This protocol did not include specific primary and secondary endpoints. In lieu of the inclusion of specific primary endpoints, this reviewer will include the *"Objectives"* and *"aims"* as sections dealing with possible endpoint statements. Next *objective (section 2, OBJECTIVES)*, was taken from *Appendix A.*

- To assess the cumulative proportion of patients discontinuing treatment due to intolerance to balsalazide 2.25g t.d.s. (to be taken three times a day) or mesalazine 0.8g t.d.s. by 12 weeks.

The following *"aim"* paragraph was taken from the Protocol's *INTRODUCTION section.*

The aim of the present study is to compare balsalazide and mesalazine in terms of tolerance and remission rates in the acute and maintenance treatment of ulcerative colitis.

(g) Assessment of Clinical Improvement. The protocol includes sigmoidoscopic examination of the rectosigmoid mucosa as one of the assessments in the clinical follow up examinations. The 4 grade score used in this European study is similar to the 4 grade score used for the previously described USA study (i.e., 0=normal, 1=erythema, 2=friability, 3=spontaneous bleeding, 4=frank ulcerations). In order to be eligible for this study, patients needed to have a 2-4 sigmoidoscopic score.

Patients were given diaries to describe Day (AM) and Night (PM) symptoms. Patients were supposed complete daily cards and a weekly checklist of symptoms. The next AM assessment form for stool blood illustrates this point:

AM assessment

1. Approximate time (hours and minutes) and consistency (normal, slightly loose, loose) of any stools passed during the previous night; total number of visits to the lavatory to pass stool (i.e. not just urine) (n).

2. Blood: on stools (Y/N)

(h). Rescue Medication and Overall Visit Schedule. The protocol included the use of rescue medicine, in the event of increase in severity of UC symptoms. **The administration rescue medication, i.e., hydrocortisone acetate 10% in enema formulation, was supposed to be used when necessary, and the number of enemas used recorded in the patient's diary card.**

(i) Data Analysis. The protocol states that the Intention-To-Treat (ITT) will include *"all patients who entered the study except patients withdrawn due to abnormal pre-entry laboratory values necessitating immediate withdrawal or to the presence of parasites, toxins or pathogens in the pre-entry stool culture. In the subsidiary Per-Protocol (PP) approach all patients with major protocol violations will be excluded".*

ii. Study Descriptive. The following is a summary of the relevant text, demographics, and results reported by the sponsor.

1. Patient Enrollment and Demographics. The first patient was enrolled in July 1993, and the last patient was completed on March 1995. Salix reports that **this study enrolled and randomized 101 patients, of which 100 took study medication.** Patients were enrolled throughout 19 centers located in England and Ireland (21 investigators).

As stated, **this study randomized 101 patients, 52 on Colazide and 49 on Asacol, of which 51 randomized to Colazide and 49 randomized to Asacol took medication.** The following Salix Table 4, illustrates the relevant ulcerative colitis patient history. Number in parenthesis indicate number of patients included in the two treatment groups.

Table 4. Ulcerative colitis history.

	Balsalazide	Mesalazine
Duration of current episode of symptoms (weeks)		
Mean ± SD (n)	15.3 ± 16.7 (80)	13.8± 18.7 (45)
Range	6 days - 2 yrs	5 days - 2 yrs
Duration of ulcerative colitis symptoms (months)		
Mean ± SD (n)	45.7 ± 64.1 (89)	34.9 ± 47.6 (45)
Range	1 mth - 20 yrs	0 - 15 yrs
Sigmoidoscopically proven ulcerative colitis diagnosed at visit 1 (Yes : No)		
n	30 : 30	29 : 20
(%)	60 : 40	59 : 41
Duration of proven ulcerative colitis (months) *(Only patients diagnosed prior to visit 1)*		
Mean ± SD (n)	74.9 ± 65.9 (20)	56.5 ± 59.9 (20)
Range	0.5 mth - 19 yrs.	0.5 mth - 15 yrs
Number of acute attacks in last year		
Mean ± SD (n)	1.2 ± 1.2 (25)	1.8 ± 2.0 (25)
Range	0 - 5	0 - 8
Time since last relapse (months)		
Mean ± SD (n)	14.0 ± 16.2 (12)	24.2 ± 32.8 (19)
Range	25 days - 54.6 mth	2.8 mth-9.8 yrs
Previous complications (Yes : No)		
n	4 : 22	4 : 20
(%)	15 : 85	17 : 83
Previous stool culture* (Yes : No)		
n	20 : 30	19* : 29
(%)	40 : 60	40 : 60
History of GI surgery (Yes : No)		
n	2 : 48	2 : 46
(%)	4 : 96	4 : 96
Usual bowel habit:		
Bowel motions/day		
Mean ± SD (n)	2.3 ± 2.1 (49)	2.1 ± 2.0 (47)
Range	0 - 12	0 - 10
Bowel motions/night		
Mean ± SD (n)	0.02 ± 0.16 (45)	0.26 ± 0.94 (39)
Range	0 - 1	0 - 5

* - These data relate to whether a stool culture had been performed for a patient during a disease exacerbation, since their original diagnosis of ulcerative colitis.
* - One patient (3161) presented with a positive previous stool culture result. This was due to an apparent infection contracted in Australia and was reported approximately 3 years prior to entry into the study.

Between 67% to 70% of randomized patients were entered in the study with UC symptoms classified as *"moderate"* and 30% as *"severe"* (information taken from Salix Table 5, Page 48, Vol. 1.72).

2. Patient Disposition. The following Tables 10a and Tables 10b lists the number of patients discontinued in the Colazide and Asacol group, the reasons for patient discontinuation and the withdrawals due to treatment failure.

Table 10a. Reasons for withdrawal from the study.

Reason	*Balsalazide*	*Mesalazine*
Treatment failure (*see definition)	6[a]	16[b]
Non-compliance with study protocol	6	3
Unacceptable adverse event	1	1
Treatment with excluded medication	1	1
Erroneous inclusion	1	2
TOTAL	15	23

[a] - One patient also took excluded medication and one also recorded the reason as at wish of the patient/investigator.
[b] - Two patients also took excluded medication and five also recorded the reason as at wish of the patient/investigator.

Table 10b. Withdrawals due to a treatment failure reported as a deterioration/complication of ulcerative colitis.

Length of treatment	*Balsalazide (n)*	*Balsalazide (patients)*	*Mesalazine (n)*	*Mesalazine (patients)*
Up to 4 weeks	2	1202; 1302	7	1048; 1144; 1145*; 1207; 1461*; 1482*; 1543*
Up to 8 weeks	2	1522; 1549	5	1141; 1201; 1242; 1301; 1401
Up to 12 weeks	0	-	1	1064
TOTAL	4		13	

* Deterioration/complication constituted an adverse event.

In the following text, Salix includes the reason for treatment failure withdrawals: "The treatment failure category (*) included those patients who withdrew from the study as a result of a complication of their ulcerative colitis requiring active intervention, and those patients whose acute condition failed to improve during study medication and were therefore withdrawn prior to the maximum 12 week treatment period. Since deteriorations and complications of existing disease (ulcerative colitis) were not defined in the protocol as constituting an adverse event, those patients withdrawn from the study for this reason were not classified as 'withdrawals due to an unacceptable adverse event'. In order to ensure consistency in this report the four reported serious adverse events were therefore also not classified as 'withdrawals due to an unacceptable adverse event'. In all patients treatment failure resulted in permanent interruption of the study drug".

3. Efficacy Results. In this section, Salix showed remission rates at week 12, and remission rates at 4 and 8 weeks. According to Salix, there was significant superiority in remission rates of Colazide over Asacol, in all scheduled visits. Salix explains:

"The primary efficacy variable was to assess the cumulative number of patients achieving complete remission after a maximum of 12 weeks of treatment. Patients were defined as being in complete remission if they were in symptomatic remission (none or mild symptoms), had not used relief medication in the 4 days prior to the visit assessment and had grade 0 or 1

ulcerative colitis on sigmoidoscopy. Complete remission was also assessed after 4 and 8 weeks. At the 4 and 8 week scheduled visits, patients who were in symptomatic remission and had not used relief medication during the previous 4 days were given a sigmoidoscopy. The percentage of patients in complete remission after 4 weeks and the cumulative percentages after 8 and 12 weeks are presented in Table 16.

Table 16. Proportion of patients in complete remission.

	Balsalazide (n=50) n (%)	Mesalazine (n=49) n (%)	P-value
4 weeks	19* (38%)	6 (12%)	p=0.0050
8 weeks	27 (54%)	11 (22%)	p=0.0018
12 weeks	31 (62%)	18 (37%)	p=0.0159

At each clinic visit, patients were asked to grade their overall evaluation of symptoms during the previous 3 days as either none, mild, moderate or severe. Symptomatic remission was defined as either none or mild symptoms. The percentage of patients in symptomatic remission at 2 weeks and the cumulative percentages after 4, 8 and 12 weeks are presented in Table 17."

Table 17. Proportion of patients in symptomatic remission.

	Balsalazide (n=50) n (%)	Mesalazine (n=49) n (%)	P-value
2 weeks	32 (64%)	21 (43%)	p=0.0146
4 weeks	35 (70%)	25 (51%)	p=0.0656
8 weeks	39 (78%)	22 (45%)	p=0.0009
12 weeks	44 (88%)	28 (57%)	p=0.0007

As regards to symptomatic assessment at week 12 for withdrawn patients, Salix notes: "The last value extended principle has been used to generate this data. Consequently, patients leaving the acute phase of the study in complete remission after 4 or 8 weeks with mild symptoms were recorded as having mild symptoms at all future time points. As a result, the proportion of patients reported as experiencing mild symptoms at the 8 and 12 week assessments may be higher than would be first anticipated".

Salix Appendix 6, Page 110, Vol. 1.72, which include individual symptomatology assessment from patient daily cards, is here included as Appendix 3.

In the following Table 18, the sponsor shows the sigmoidoscopic grade in patients with symptomatic remission.

Table 18. Sigmoidoscopic grade in patients achieving symptomatic remission.

Ulcerative colitis grade	*Balsalazide n (%)*	*Mesalazine n (%)*	*P-value*
4 weeks:			
0 or 1	19 (83%)	7 (44%)	
2, 3 or 4	4 (17%)	9 (56%)	p=0.0172
No sigmoidoscopy	12	9	
8 weeks:			
0 or 1	28 (90%)	11 (65%)	
2, 3 or 4	3 (10%)	6 (35%)	p=0.0510
No sigmoidoscopy	8	5	
12 weeks:			
0 or 1	34 (87%)	19 (73%)	
2, 3 or 4	5 (13%)	7 (27%)	p=0.1972
No sigmoidoscopy	5	2	

iii. Reviewer Comments.

1. *This reviewer will accept the claim that, **in this study**, there was comparable, and perhaps some symptomatic superiority of BSZ over mesalamine.* The use of *"symptomatic"* relates to a *"general"* improvement in symptomatology, i.e., *"from severe or moderate symptoms which interfere with normal functioning, to mild symptomatology or none".* But when considered individual *relevant* ulcerative colitis symptoms, the superiority is more confounded or is turned into comparability between the two treatments. As noted in the submitted Salix Appendix 6, which includes the patient evaluation of relevant individual ulcerative colitis symptoms, i.e., stool blood, stool frequency, *(Appendix 3 of this review)*, the assessment of individual symptoms encompassed only a subset of all randomized patients. For instance, in stool blood assessment, a cardinal symptom in acute ulcerative colitis, data from 25% of BSZ patients and 27% of mesalamine patients was excluded from the analysis. Hence, *information on stool blood from 25 patients, out of the total 100 ulcerative colitis patients treated in this experimental study*, was absent from this very relevant symptomatic tabulation. Noteworthy, assessment of stool frequency in BSZ and mesalamine patients, which also excluded app. 25% of all treated patients, revealed *no* differences between the two treatment groups (2.8 times/day for Colazide vs. 2.5 times/day Asacol).

2. *This reviewer will <u>not</u> accept the claim of BSZ superiority over mesalamine in remission from the acute episode.* My reasons for the unacceptance are the following:

(a) The definition of remission from an acute ulcerative colitis episode should include symptomatic, endoscopic and histologic resolution. This definition or remission, stated by Dr. S. Hanauer in the guidelines to assess clinical endpoints in ulcerative colitis trials, is mentioned by Salix in its DISCUSSION section:

> Riley *et al.* defined symptomatic remission as the resolution of rectal bleeding and less than three stools per day whereas Hanauer complete relief of symptoms, a biopsy result indicating clinically normal mucosa or inactive UC and a sigmoidoscopic index score of 0-4 points.

As stated, some patients were declared in remission with mild symptoms of ulcerative colitis and without sigmoidoscopic or histologic confirmation. Of the 31 balsalazide and 18 mesalamine patients declared as *in remission, only 18 (58%) and 10 (56%) had histologic readings* at entry and after completion of treatments. More relevant, *only 10/18 (56%) balsalazide histologies and 4/10 (40%) mesalamine histologies of patients declared in remission, were considered inactive or normal by the end of therapy*, as seen in the following Table 25.

Table 25. Biopsy classification at entry and completion for patients in remission after 4, 8 or 12 weeks.

Parameter	*Balsalazide (n=18)* n (%)		*Mesalazine (n=10)* n (%)	
	Entry	Completion	Entry	Completion
Classification*:				
normal	0	4 (22)	1 (10)	0
inactive	1 (6)	6 (33)	0	4 (40)
mild	4 (22)	5 (28)	1 (10)	2 (20)
moderate	9 (50)	2 (11)	4 (40)	3 (30)
severe	4 (22)	1 (6)	4 (40)	1 (10)

* for the full definition of each disease activity classification see section 4.4.2.4.
Missing patient data: balsalazide = 13; mesalazine = 8

Based on these histologic readings, only 20% (10/50) of the balsalazide patients and 8% (4/49) of the mesalamine patients could be considered in remission. Though still numerically favoring balsalazide, this remission rate is too low for any type of unequivocal indication or claim.

(b) As shown in *Salix Table 4, Ulcerative colitis history*, (see first section in my *Descriptive* of this study), **20 balsalazide patients (40%)** and **20 mesalamine patients (41%)**, had *No sigmoidoscopically proven ulcerative colitis diagnosed at visit 1*. There is concern about a lack of definite baseline ulcerative colitis rectosigmoidoscopic diagnosis in 40% of enrolled patients. This reviewer's concern is that patients with Crohn's colitis or undetermined colitis were erroneously enrolled in this ulcerative colitis trial. This endoscopic misdiagnosis dose not occur in 40% of IBD patients, but rather in 10% of examined patients. Another possibility, though also uncommon, is that 40% of patients were entered into the trial with positive symptomatology but with an endoscopically inactive or quiescent ulcerative colitis mucosa. A third possibility, is that 40% of all enrolled patients did not have rectosigmoidoscopies done at baseline, also a concerning omission. Regardless of the reason, the lack of baseline endoscopic

confirmation of ulcerative colitis inflammation in 40% of all enrolled patients, is a confounding variable which further makes it difficult, and inappropriate, any claim of *a "remission"* status after administration of the experimental therapy.

(c) This trial was prospectively designed with an acute, *and chronic maintenance phase.* The acute phase would treat ulcerative colitis patients with Colazide or Asacol until symptomatic or more complete resolution for *either* 4, 8 or 12 weeks. If after *either 4, 8* or 12 weeks of treatment with Colazide or Asacol, patients were considered improved from the acute episode, there were ~~*withdrawn*~~ from the acute phase and re-randomized to the chronic maintenance phase. Thus, there was no prospectively established duration of treatment (like the eight weeks was in the previous USA multi center trial), or, rather, comparable duration of treatments to assess this claim of efficacy. In this regard, the lack of a placebo control or an inactive dose control, further confounds the picture, for the active-active drug design makes it difficult to assess spontaneous remissions, not unusual in IBD diseases.

(d) Use of rescue topical hydrocortisone enemas is an additional confounding variable. Steroid enemas are approved and effective medications for treatment of acute ulcerative colitis, even if administered intermittently and at low doses.

2. This study had as objective to compare the tolerance to Colazide and Asacol in ulcerative colitis patients. There were no differences in intolerance to the experimental drugs, i.e., 1 in the Colazide group and 1 in the Asacol group.

E. SUPPORTIVE CLINICAL TRIALS, and, A PLACEBO-CONTROLLED STUDY.

In this section, I will briefly describe the two small controlled studies, included by the sponsor as clinical data supportive of the proposed balsalazide indication. Both of these supportive clinical trials included active-active comparisons between balsalazide (BSZ) and sulfasalazine (SAS), both were conducted in the United Kingdom, and enlisted 3-4 centers in each trial. Subsequent to my sequential presentation of protocols and descriptive for each supportive study, I will comment on the reported efficacy results.

The sponsor also submitted a four-week placebo-controlled study, which appears not to support the data reported in the preceding active-active drug controlled trials. The brief **presentation of this placebo-controlled clinical study will follow the descriptive of these supportive trials and my comments on the presented efficacy of these two trials.**

1. Trial 0028/011.

i. Protocol - Brief Summary. This protocol was titled *DOUBLE BLIND COMPARISON OF CAPSULES OF SULPHASALAZINE 3g DAILY WITH BALSALAZIDE 6.75g DAILY IN THE INITIAL MANAGEMENT OF PATIENTS WITH ULCERATIVE COLITIS.*

- The protocol planned for a trial with completed treatment on 50 ulcerative colitis patients, 25 in each treatment group.

- The criteria for **patient inclusion** was *"newly-diagnosed or recently-relapsed "* ulcerative colitis *"who are not on any treatment other than symptomatic management. The diagnosis will have been confirmed by the finding of friable or spontaneously-bleeding mucosa at sigmoidoscopy and negative stool culture".*

- The following was the **exclusion** criteria for (scanned from the CANDA):

  Patients known to be intolerant of sulphasalazine.

  Patients with a positive stool culture.

  Patients with Crohn's Disease.

  Patients who are, or may become, pregnant while taking the drug.

  Patients with hepatic or renal disease.

  Patients taking corticosteroids or azathioprine, or having had any 5-ASA preparations over the preceeding 2 months.

- The protocol established a clinical trial *of "2 month duration with the option to withdraw at any time should patient or clinician choose. A clinical assessment will be undertaken after 2 weeks when withdrawal for alternative treatment (e.g. steroids) will be undertaken if progress is unsatisfactory. The first 48 h of treatment will be matching placebo (lactose) to establish the normal stool pattern and consistency".*

- There was no primary efficacy endpoint established in this short protocol. In the INTRODUCTION section, the protocol states that *"The present trial is designed to compare the acceptability and therapeutic effects of orally-administered sulphasalazine (3g/kg) and balsalazide, at a dose equivalent to twice that of sulphasalazine on a molar basis (6.75g/day)".*

ii. Descriptive.

This study started in January 1989 and ended in January 1992. It randomized and treated 50 patients, **26 allocated to balsalazide and 24 to sulfasalazine.** Treatment groups were well balanced for age, gender, body weight and sex, about two thirds of the patients were male. Most of patients were entered with the **first acute** episode of ulcerative colitis (23/26 BSZ and 17/24 SAS); most of the patients had proctosigmoiditis or left-sided colitis, over 85% had biopsies taken at entry, and over 85-90% of patients never had any previous treatment with sulfasalazine or mesalamine.

The following Salix table, Page 6, Vol. 1.75, illustrates the overall study outcome

Table 6 : Study Outcome

Outcome	Balsalazide 6.75g/day		Sulphasalazine 3g/day		Summary of analysis
	N	%	N	%	
Completed study, in remission	13	50	9	38	P > 0.2
Completed study, not in remission	8	31	2	8	P = 0.077
Withdrew, protocol deviation	2	8	1	4	P > 0.2
Withdrew, adverse event	1	4	9	38	P = 0.004
Withdrew treatment ineffective	2	8	3	13	P > 0.2
TOTAL	26	100	24	100	

Percentages may not add up to 100% due to rounding errors.

The sponsor states the following: The only differences between treatments is that more patients were withdrawn for adverse events when taking sulphasalazine than when taking balsalazide (Table 6, P=0.004). There were **more patients on balsalazide completing the study not in remission** compared with those on sulphasalazine (P=0.077).

The ITT comparison, with inclusion of all randomized and treated patients, had 58% (15/26) BSZ and 59% (13/22) SAS patients with remission rates by the end of the 8-week study period.

The following is the sponsor's description on stool blood improvement:

"Improvements in stool blood were observed from entry to 2 weeks for both treatment groups with 14/25 (56%) patients improving in the balsalazide group and 13/22 (59%) patients improving in the sulphasalazine group. By 4 weeks, the majority of patients had improved, although one patient in the sulphasalazine group became worse. Overall 19/22 (86%) of the patients completing the study showed an improvement in stool blood in the balsalazide group compared to 10/12 (83%) patients in the sulphasalazine group. The differences between treatments were insufficient to be considered true treatment effects (P>0.2), whilst the within treatment comparisons were all highly significant (usually P<0.001, but P=0.004 from entry to week 4 and P=0.003 from entry to the end of the study for the sulphasalazine group)".

This next paragraph states the between-treatment comparison on stool frequency:

"Overall 14/22 (64%) of the patients completing the study showed an improvement in bowel frequency in the balsalazide group compared to 6/12 (50%) patients in the sulphasalazine group. The differences between treatments were insufficient to be considered true treatment effects (P>0.2). However, the within balsalazide comparisons were significant from entry to week 2 (P=0.011), from entry to week 4 (P=0.011) and from entry to the end of the study (P<0.001), whilst the only within sulphasalazine comparison that was significant was from entry to week 4 (P=0.030) indicating a greater improvement for balsalazide".

The following Salix Table 19, describes the sigmoidoscopic appearance at entry, 4 weeks and final 8 weeks in the balsalazide and SAS treatment groups.

Table 19 : Summary of sigmoidoscopic appearance scores reported at each visit

Week or Period	Sigmoidoscopic appearance category (score)	Balsalazide 6.75g/day		Sulphasalazine 3g/day		Summary of analysis
		N	%	N	%	
Entry	Normal (0)	0	0	0	0	P = 0.13
	Mild mixed/no bleeding (1)	1	4	5	22	
	Contact bleeding (2)	17	65	14	61	
	Spontaneous bleeding (3)	8	31	4	17	
	Median score	2		2		
4 weeks	Normal (0)	3	14	1	7	P > 0.2
	Mild mixed/no bleeding (1)	12	57	11	79	
	Contact bleeding (2)	4	19	2	14	
	Spontaneous bleeding (3)	2	10	0	0	
	Median score	1		1		
8 weeks (or final)	Normal (0)	7	33	6	50	P > 0.2
	Mild mixed/no bleeding (1)	7	33	4	33	
	Contact bleeding (2)	6	29	0	0	
	Spontaneous bleeding (3)	1	5	2	17	
	Median score	1		0		

Treatments compared using Wilcoxon Rank Sum test which takes account of increasing severity of the scores. Percentages may not add up to 100% due to rounding errors.

The following is a conclusion from the sponsor, taken from Page 42, Vol. 1.75:

"The difference in proportion of patients able to complete the trial is inclined to confound estimates of efficacy. No difference emerged in the proportion of patients obtaining remission of the acute attack (about 60% in each group). The grading and measurements of symptoms and signs were consistent with clinical improvement in both drug groups. There were, however, some interesting, if minor differences between the groups. Weight gain was somewhat better for the balsalazide group. Changes in sigmoidoscopy and, particularly, bowel frequency scores, while showing no statistically significant differences between the groups, showed trends supporting a relatively improved result with balsalazide".

Note from the Reviewer. My comments on the aforementioned efficacy described in supportive trial 0028/011 will follow my descriptive of next trial 0028/017.

2. Trial 0028/017.

i. Protocol. It planned for enrollment of 60 patients; 30 in each treatment group, It was titled *DOUBLE-BLIND COMPARISON OF SULPHASALAZINE 3g DAILY WITH BALSALZIDE 6.75g DAILY IN PATIENTS RELAPSING WITH ULCERATIVE COLITIS.*

- Criteria for **inclusion** was *"newly-diagnosed or recently-relapsed patients with ulcerative colitis who may or may not be prescribed any other treatment for the relapse, Diagnosis will be confirmed by the finding of friable or spontaneously-bleeding mucosa at sigmoidoscopy and negative stool culture".*
- **Excluded** were patients intolerant to SAS, with a positive stool culture, with Crohn's disease, with hepatic or renal disease, or expected to be pregnant.
- The trial was planned with 3 month duration, *"with the option to withdraw at any time should patient or clinician choose".*
- The aim of this study was the same as the one included in the previous supportive study.
- The protocol states that patients *"may also receive steroids, and the time to withdrawal of these, or the dose still required at 12 weeks, and the time to achieve remission compared between groups".*
- The protocol defined remission as follows:

Remission is defined as a return to stool frequency (with or without pain) to that present before relapse, without presence of blood, and confirmed by biopsy.

ii. Descriptive. This study enrolled 67 patients; 28 to BSZ and 29 to SAS. The following is a summary of demographics: Most of the enrolled patients had proctosigmoiditis or left sided disease on entry proctosigmoidoscopic examination.

> *Population at entry:* Reasonably evenly balanced between the treatment groups for age, body weight, height, and activity of disease (judged on frequency of relapse). Larger proportion of females in sulphasalazine group, which also has a larger proportion of patients with first acute attacks (11 vs. 6). Disease extent was somewhat greater in the balsalazide group. At stratification, 15 patients were classified as 'mild' (8 allocated to the balsalazide group, 7 to sulphasalazine), 26 as 'moderate' (12 to balsalazide, 14 to sulphasalazine), 16 as 'severe' (8 to balsalazide, 8 to sulphasalazine).

Next table shows an ITT comparison of "remission", as rated by investigators, As observed, there were no differences between the BSZ and SAS treated groups.

Table 9 : Remission Rates for all Treated Patients					
Remission	Balsalazide 6.75g/day		Sulphasalazine 3g/day		Summary of analysis
	N	%	N	%	
Yes	21	75	19	68	$\chi^2_1 = 0.35$
No	7	25	9	32	
TOTAL	28	100	28	100	P > 0.2

On stool blood improvement, the sponsor states as follows:

"Improvements in stool blood were observed from entry to 2 weeks for both treatment groups with 19/27 (70%) patients improving in the balsalazide group and 12/26 (46%) patients improving in the sulphasalazine group (P=0.098). By 4 weeks, the majority of patients had improved. Similarly at 8 weeks, the majority of patients had improved although one patient in each treatment group became worse. Overall 21/26 (81%) of the patients completing the study showed an improvement in stool blood in the balsalazide group compared to 13/18 (72%) patients in the sulphasalazine group. The differences between treatments were insufficient to be considered true treatment effects (P>0.2)",

Stool frequency improvement were summarized as follows:

"No patients became worse when compared to entry at week 4 or week 8. At 12 weeks, 20/26 (77%) patients in the balsalazide group showed an improvement in bowel frequency compared to 15/18 (83%) patients in the sulphasalazine group. There was no evidence of a treatment difference in changes in bowel frequency (P>0.2) since both treatments showed significant improvements over time (P<0.001)".

Next Tables 21 and 23 summarize changes in sigmoidoscopic appearance and histology.

Table 21 : Summary of sigmoidoscopic appearance scores reported at each visit

Week	Stool blood category (score)	Balsalazide 6.75g/day		Sulphasalazine 3g/day		Summary of analysis
		N	%	N	%	
Entry	Normal (0)	0	0	0	0	P > 0.2
	Mild minimal/no bleeding (1)	9	32	7	25	
	Contact bleeding (2)	18	64	18	64	
	Spontaneous bleeding (3)	1	4	3	11	
	Median score	2		2		
4 weeks	Normal (0)	5	19	5	29	P > 0.2
	Mild minimal/no bleeding (1)	13	50	10	59	
	Contact bleeding (2)	7	27	1	6	
	Spontaneous bleeding (3)	1	4	1	6	
	Median score	1		1		
8 weeks	Normal (0)	13	57	12	67	P > 0.2
	Mild minimal/no bleeding (1)	8	35	3	17	
	Contact bleeding (2)	2	9	1	6	
	Spontaneous bleeding (3)	0	0	2	11	
	Median score	0		0		
12 weeks (or final)	Normal (0)	16	62	12	67	P > 0.2
	Mild minimal/no bleeding (1)	8	31	5	28	
	Contact bleeding (2)	2	8	1	6	
	Spontaneous bleeding (3)	0	0	0	0	
	Median score	0		0		

Treatments compared using Wilcoxon Rank Sum test which takes account of increasing severity of the scores. Percentages may not add up to 100% due to rounding errors.

Table 23 : Summary of histological grade reported at each visit						
Week	Histological grade (score)	Balsalazide 6.75g/day		Sulphasalazine 3g/day		Summary of analysis
		N	%	N	%	
Entry	Normal (0)	0	0	1	5	
	Mild ulcerative colitis (1)	11	48	5	23	
	Moderate ulcerative colitis (2)	12	52	14	64	P = 0.18
	Active ulcerative colitis (3)	0	0	2	9	
	Median score	2		2		-
12 weeks (or final)	Normal (0)	10	50	9	60	
	Mild ulcerative colitis (1)	8	40	3	20	
	Moderate ulcerative colitis (2)	1	5	0	0	P > 0.2
	Active ulcerative colitis (3)	0	0	1	7	
	No grading assigned	1	5	2	13	
	Median score	0.5		0		
Treatments compared using Wilcoxon Rank Sum test which takes account of increasing severity of the scores. Percentages may not add up to 100% due to rounding errors. "Minimal inflammation" refers to "minimal inflammation, but not active disease".						

The study protocol allowed the use of steroids if investigators consider its use clinically justified, In the following section, Salix describes the use of steroids during the study.

"At entry, patients with mild relapse were not prescribed any corticosteroid. Patients with moderate relapse were prescribed corticosteroid enemas and used an average dose of 28mg/day. Patients with severe relapse were prescribed oral corticosteroid and took an average dose of 35mg/day; four of these patients (1 allocated to balsalazide and 3 allocated to sulphasalazine) were also prescribed corticosteroid enemas and used an average dose of 28mg/day.

Corticosteroid use tended to decrease during the study period. A decrease in dose was observed for those patients who continued to use corticosteroid and a number of patients stopped using corticosteroid altogether"