DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER REVIEW

MAR - 2 2000

NDA: 20-610/A2/Safety Update

Sponsor: SALIX Pharmaceuticals, Inc.

Drug: Balsalazide Disodium Capsules

Indication: Treatment of Mildly to Moderately Active Ulcerative Colitis

Dates Documents Received By the DGICDP (HFD-180): August 9, September 24, 1999

Dates Documents Received by the Medical Officer: October 11, 1999, February 7, 2000

Document Received by Medical Officer: Biopharmacology of Control Drug (October 11, 1999), Safety Update (February 7, 2000).

Date of Draft: February 25, 2000

Medical Officer: Dr. Robert Prizont, M.D.

Abstract. This review includes two Salix supplements. In one of the supplements, Salix submitted the worldwide Safety Update (SU) of Balsalazide, oral capsules, up to April 30, 1999. This SU includes revised safety information from the two pivotal clinical trials submitted in 1997 to support safety and efficacy of Balsalazide, 6.75 g/d for treatment of mildly to moderately active ulcerative colitis. It also includes safety from maintenance studies of Balsalazide administered up to 1 year to ulcerative colitis patients in remission. These studies were conducted in Germany and the United Kingdom. In addition, the SU contains safety information obtained from foreign postmarketing experience. Balsalazide was approved for marketing in the United Kingdom in July 14, 1997, and in 1998 was approved in Austria, Denmark, Sweden, Luxembourg, Italy and Belgium. My review of this SU revealed no untoward risks of concern. A small proportion of patients experienced ADEs described with treatment of 5-aminosalicylate preparations, i.e., interstitial nephritis, but the majority of AEs were exacerbation's of ulcerative colitis due to treatment failure. Salix also submitted requested information on the active control comparator, i.e., the Asacol manufactured and marketed in the United Kingdom. The information included chemistry formulations, biopharmacological dissolution experiments and clinical data with the UK Asacol and the US Asacol. This reviewer commented on the submitted data and added comments on the balsalazide dose-comparison included in the randomized, double-blind, US pivotal trial CP099301.

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1 BACKGROUND

1.1 Original Submission and Brief Summary of Balsalazide Properties.

i. Salix initially submitted this NDA on paper form on June 24, 1997, and on Electronic Submission (CANDA) on September 22, 1997. This Medical Officer (MO) review was completed on May 15, 1998. This MO recommended approval of Salix's balsalazide disodium (Colazide®) capsules for the treatment of mildly to moderately active ulcerative colitis. The recommended dose was 6.75 grams/day, administered as three simultaneous 750 mg (2.5 g) capsules three times a day.

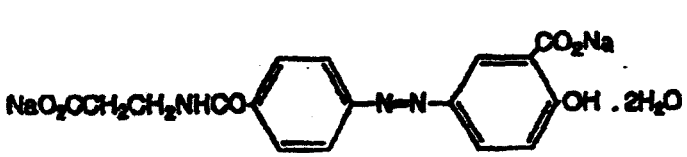
Subsequently, the trade name for balsalazide (Colazide®) was deemed unacceptable by this Agency. The revised Salix Indication, submitted on September 1999 is the following *[scanned]*:

> **INDICATIONS AND USAGE:** TRADE NAME capsules are indicated for the treatment of mildly to moderately active ulcerative colitis.

The revised dosage and duration of treatment submitted on September 24 reads as follows *[scanned]*:

> **DOSAGE AND ADMINISTRATION:**
>
> For Treatment of Active Ulcerative Colitis: The usual dose in adults is three 750 mg capsules to be taken three times a day for a total daily dose of 6.75 grams for a duration of 8 weeks. Some patients in the clinical trials required treatment for up to 12 weeks.

ii. The following chemical and pharmacological properties were copied *[scanned]* from Page 4 of my 1998 review. Balsalazide (BSZ) was initially developed by Biorex (London, England) simultaneously with another 5-amino-salicylate named ipsilazide, and was designed to reduce the toxic properties of sulfasalazine. It links the active compound 5-aminosalicylic acid to an inactive β-alanine carrier via an azo-bond, as illustrated by the following structural formula:



The protective action of a carrier link by azo bond, BSZ will 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.

1.2 SCIENTIFIC RATIONALE FOR THE PROPOSED INDICATION.

The following was taken from Pages 6-7 of my May 1998 review [scanned].

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. Some oral mesalamine preparations have resin-coating with pH-dependent materials or encapsulation of mesalamine into ethyl cellulose micro spheres. Other preparations have the active mesalamine linked via an azo-bond to either another mesalamine molecule, i.e., olsalazine (Dipentum®) or as in the Colazide case, or to an inactive carrier,i.e., ABA.

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".*

2 SAFETY UPDATE

2.1.1 Safety Overview

i. Salix states that the submitted Safety Update (SU) summarizes additional safety information as of April 30, 1999.

- Salix explains that, as compared to the originally submitted Integrated Safety Summary (ISS), some changes have been made in this SU, i.e., in the way adverse events were ascribed to a study. In this SU, adverse events (AE) with an onset prior to the first date of medication were excluded. Similarly, AEs that occurred 30 days after the last dose of study medication were excluded. AEs are attributed by date to the study in which they occurred, rather than by CRF when they were recorded. AEs with a missing onset date were assumed to have occurred during the study date recorded in the CRF. As a consequence of the changes, Salix notes the following differences *[scanned]*:

  The main impact of the rule changes to the acute studies is the exclusion of events that occurred prior to study drug treatment, resulting in lower incidence rates in this Safety Update compared with the ISS. For the maintenance studies, the adverse event incidence rates are slightly higher in this Safety Update than in the ISS because a smaller denominator resulted from the patient-stratified method. The patient-stratified method is adopted in this Safety Update to achieve independence among treatment units.

The SU includes AEs from two new maintenance studies conducted in the UK and Germany, and an acute study conducted in Japan with a sachet formulation. The 3 new studies are the following *[scanned]*:

- *57-3001b, controlled maintenance study in the UK (N = 99),*
- *57-3002, controlled maintenance study in Germany (N = 133),*
- *0600376, uncontrolled acute study in Japan (n = 35).*

2.1.2 Demographics

ii. The following table illustrates the demographics of patients treated with balsalazide in controlled and uncontrolled acute or maintenance studies. A total of 1186 patients were treated with balsalazide; 522 participated in more than one study, resulting in a 1708 patient-trials on balsalazide. In addition, in acute controlled studies 100 patients were treated with mesalamine, 53 with sulfasalazine and 35 with placebo. For the acute studies, 92 % were adults ages 18-64 years old; 8% were elderly patients (≥65 years). Except for one patient 17 years of age, no pediatric patients were enrolled in controlled clinical trials; 12 pediatric patients were treated under a compassionate use program. In controlled studies, 56%.were males; >75% were white.

Table 7: Demographics of All Patients by Study Type

Demographic	Controlled Acute N = 542	Controlled Maintenance N = 649	PK & Pharmacology N = 177	Non-UC & Compassionate Use N = 271	Uncontrolled Acute N = 77	Uncontrolled Maintenance N = 342
Age (years)						
<18	0	1	0	12	0	0
18-64	498	590	170	223	62	313
≥65	44	58	7	34	15	29
missing	0	0	0	2	0	0
Sex						
Male	305	364	147	136	49	177
Female	237	285	30	135	28	165
Race						
White	283	132	93	0	0	179
Black	17	0	0	0	0	10
Hispanic	22	0	0	0	0	16
Asian	5	1	60	0	35	4
Other, .	7	0	0	0	0	5
Missing[b]	208	516	24	271	42	128
Drug						
Balsalazide[a]	352	502	165	270	77	342
Mesalamine	100	94	6	0	0	0
sulfasalazine	53	38	6	0	0	0
placebo	35	15	0	1	0	0
missing	2	0	0	0	0	0

a: A total of 1186 unique patients were treated with Balsalazide; 522 participated in more than one study.
b: Race was missing in some European studies; these subjects were likely to be Caucasian.

2.1.3 Comparison of ISS and Updated Safety

iii. In the following table, Salix compares the incidence of common AEs in the ISS and the submitted SU in acute controlled studies. Noticeable, are the decrease in the SU in the proportion of patients included as AEs due to fatigue, flatulence and diarrhea

Table 1: Incidence of Common (≥3%) Adverse Events in Acute and Maintenance Clinical Studies of Balsalazide

Adverse Event	Acute Studies		Maintenance Studies	
	ISS N = 397	Safety Update N = 429	ISS N = 1265[a]	Safety Update N = 864[b]
Headache	95 (24%)	80 (19%)	148 (12%)	120 (14%)
Abdominal Pain	83 (21%)	71 (17%)	137 (11%)	104 (12%)
Fatigue	72 (18%)	40 (9%)	79 (6%)	70 (8%)
Flatulence	54 (14%)	23 (5%)	92 (7%)	76 (9%)
Diarrhea	51 (13%)	32 (8%)	98 (8%)	71 (8%)
Nausea	49 (12%)	40 (9%)	114 (9%)	86 (10%)
Dyspepsia	43 (11%)	36 (8%)	52 (4%)	46 (6%)
Dizziness	23 (6%)	21 (5%)	44 (3%)	37 (4%)
Respiratory Infection	18 (5%)	16 (4%)	57 (5%)	67 (8%)
Pain	17 (4%)	17 (4%)	65 (5%)	56 (7%)
Vomiting	16 (4%)	16 (4%)	18 (1%)	14 (2%)
Back Pain	14 (4%)	14 (3%)	56 (4%)	45 (5%)
Rash	12 (3%)	9 (2%)	41 (3%)	36 (4%)
Cramps	11 (3%)	11 (3%)	7 (0.6%)	5 (0.6%)
Flu-like Disorder	11 (3%)	11 (3%)	14 (1%)	15 (2%)
Constipation	6 (2%)	6 (1%)	29 (2%)	24 (3%)
Infection Viral	2 (0.5%)	5 (1%)	35 (3%)	32 (4%)
Arthralgia[c]	<3%	9 (2%)	<3%	29 (3%)
Malaise[c]	<3%	5 (1%)	<3%	30 (4%)
Pharyngitis[c]	<3%	4 (1%)	<3%	25 (3%)

a: Patient-dose-stratified method was used.
b: Patient-stratified method was used.
c: Incidence rate was lower than 3% in the ISS.
A complete list of adverse events is presented in Table U6c-2 for acute studies and in Table U6e-5 for maintenance studies.

2.1.4 Adverse Events in Well-Controlled Studies

iv. The following table displays the update of common AEs incidence in the three adequate and well-controlled acute clinical trials. Placebo patients were enrolled in a 4-week randomized, double-blind, dose-ranging study conducted in the USA.

Table 2: Incidence of Common (≥ 1%) Adverse Events in Three Adequate and Well-Controlled Studies of Balsalazide (Volunteered Complaints Excluded)

Adverse Event	Balsalazide 6.75 g/d N = 175	Mesalamine 2.4 g/d N = 180	Placebo N = 36
Headache	13 (7%)	28 (20%)	3 (9%)
Abdominal pain	11 (6%)	4 (4%)	1 (3%)
Diarrhea	8 (5%)	3 (3%)	1 (3%)
Nausea	6 (3%)	7 (7%)	2 (6%)
Respiratory infection	6 (3%)	5 (5%)	5 (14%)
Arthralgia	5 (3%)	3 (3%)	
Vomiting	5 (3%)	4 (4%)	2 (6%)
Cramps	3 (2%)	1 (1%)	
Dyspepsia	3 (2%)	5 (5%)	
Fatigue	3 (2%)	2 (2%)	
Flu-like disorder	3 (2%)	5 (5%)	
Hemorrhage rectum	3 (2%)	3 (3%)	1 (3%)
Stools frequent	3 (2%)		1 (3%)
Accident and/or injury	2 (1%)	1 (1%)	1 (3%)
Anorexia	2 (1%)		
Back pain	2 (1%)	5 (5%)	1 (3%)
Bowel irregularity	2 (1%)		
Colitis ulcerative aggravated	2 (1%)	5 (5%)	
Constipation	2 (1%)	1 (1%)	
Dizziness	2 (1%)	2 (2%)	2 (6%)
Dyspnea	2 (1%)	1 (1%)	
Ear infection	2 (1%)		
Fever	2 (1%)	3 (3%)	
Insomnia	2 (1%)	1 (1%)	
Melena	2 (1%)	1 (1%)	
Dry mouth	2 (1%)		
Myalgia	2 (1%)	2 (2%)	
Pain	2 (1%)	5 (5%)	1 (3%)
Pruritus	2 (1%)		1 (3%)
Rhinitis	2 (1%)	3 (3%)	

Note: This table includes events with incidence rates ≥ 1% in patients treated with Balsalazide 6.75 g/d.
A complete list of adverse events is presented in Table U6e-4.

The complete list of infrequent AEs reported by patients taking balsalazide during acute clinical trials (N=429 Pts) or collected from foreign post-marketing surveillance, Pages 15-16, Vol. 3 of this submission, is included as Appendix 1 of this review.

2.1.5 Adverse Events in Maintenance Studies

v. Salix listed the AEs in maintenance studies in Table 11, Pages 32-33, Vol. 3. For maintenance studies, the most common AEs were headache, abdominal pain, nausea, diarrhea, flatulence, pain, fatigue, and respiratory infections. Incidence in these maintenance trials were lower than in the acute trials. Salix noted that back pain, dyspepsia, dizziness, rash, malaise, and viral infections had incidence rates of 4% to 6%.

Table 11, Pages 32-33, Vol. 3, is included as Appendix 2 of this review.

2.1.6 Adverse Events in Ongoing Studies

vi. This submission includes a list of AEs reported from an ongoing clinical trial. This study (CP079071) comprised a double-blind, acute-phase comparing balsalazide 6.75 g/d vs. mesalamine 2.4 g/d, and an open-label maintenance phase with administration of balsalazide 3 g/d. The sponsor notes that as of April 30, 1999, the study was blinded. Salix states that the AEs

seen in this study were similar to those seen in the adequate and well-controlled clinical trials. The next Table 10, lists the number and proportion of AEs.

Table 10: Incidence of Adverse Events in Study CP079701

Adverse Event	*Blinded Acute Phase Balsalazide 6.75 g/d or Mesalamine 2.4 g/d N = 175*	*Open-Label Maintenance Phase Balsalazide 3 g/d N = 141*
Headache	*23(13.1%)*	*8 (5.7%)*
Nausea	*21(12.0%)*	*7 (5.0%)*
Abdominal pain	*17 (9.7%)*	*17(12.1%)*
Diarrhea	*14 (8.0%)*	*9 (6.4%)*
Fever	*12 (6.9%)*	*3 (2.1%)*
Arthralgia	*10 (5.7%)*	*3 (2.1%)*
Fatigue	*9 (5.1%)*	*3 (2.1%)*
Flatulence	*9 (5.1%)*	*4 (2.8%)*
Pharyngitis	*9 (5.1%)*	*4 (2.8%)*
Insomnia	*7 (4.0%)*	*4 (2.8%)*
Rhinitis	*7 (4.0%)*	*2 (1.4%)*
Vomiting	*7 (4.0%)*	
Sinusitis	*6 (3.4%)*	*7 (5.0%)*
Coughing	*5 (2.9%)*	*4 (2.8%)*
Dizziness	*5 (2.9%)*	*1 (0.7%)*
Pain	*5 (2.9%)*	*4 (2.8%)*
Dyspepsia	*4 (2.3%)*	*2 (1.4%)*
Haematuria	*4 (2.3%)*	
Rectal disorder	*4 (2.3%)*	*6 (4.3%)*
Rigors (chills)	*4 (2.3%)*	*1 (0.7%)*

Note: This table includes events with incidence rates ≥2% in the blinded phase.

2.1.7 Patients with Biochemical Abnormalities

vii. In Pages 56-59, Vol. 3, this submission includes narratives of patients who were treated with balsalazide and developed serum biochemical abnormalities of LFTs, or from abnormal renal function. Most of them were unrelated to balsalazide administration.

Pages 56-59, Vol. 3, with narratives of patients who were treated with balsalazide and developed abnormal LFTs or biochemical abnormalities due to renal insufficiency, are included as Appendix 3 of this review.

2.1.8 Deaths and Serious AEs

viii. The sponsor reports one patient died (#2388) during a clinical study (53-3001b) after a 30 day dosing. This patient was on mesalamine and not on balsalazide.

My review of the submitted CRFs (3 Volumes) detected two other deaths, which occurred after discontinuation of balsalazide. Patient # 1020 was a 57 year old female with a 20 year history of ulcerative colitis + thromboembolism. Balsalazide was discontinued on September 1994. This patient died suddenly of a massive pulmonary embolism on December 1994. ——— 3114, SRS, Page 33,Vol. 9, was a 67 year old male with ulcerative colitis started on balsalazide, 3 g/day on September 1994 for a flare-up. On September 1995 the patient had a colectomy. On December 1995, he died of pulmonary and cardiac complications, apparently unrelated to BSZ *[Note: One of the submitted volumes contained CRFs written in German].*

Table 16, Pages 43-45, Vol. 3, which lists all discontinuations due to serious AEs occurred in balsalazide studies is included as Appendix 4 of this review.

2.2 REVIEWER COMMENTS.

My comments are similar to those stated in my initial review of May 15, 1998. Balsalazide is, essentially, a relatively safe drug. Most of the AEs reported were recurrences of the acute ulcerative colitis due to treatment failure. This statement is supported by the following brief report from the two year post-marketing experience in the UK *[scanned]*. As with other mesalamine preparations[1], (Asacol®) balsalazide may cause some kidney damage. Some other complications recently shown to occur after mesalamine administration are not as well known, i.e., pericarditis (pediatric)[2], thrombocytopenia[4], granulomatous hepatitis[5], lupus[6], pancreatitis[3], drug interaction with warfarin[7].

Colazide (Balsalazide) has been marketed in the UK since July 14, 1997. In addition, it has not been launched in these countries. From launch through December 31, 1998, a total of — capsules were sold in the UK. This amounts to — eatment days at — apsules per day or about — patients assuming an eight-week course of treatment.

Adverse events seen in post-marketing surveillance have been submitted to the IND. Most of the events involved hospitalization due to relapse or exacerbation of ulcerative colitis. These adverse events include: abdominal pain, anaemia haemolytic, angioedema, urthralgia, diarrhea, flatulence, fatigue, granulocytopenia, headache, interstitial nephritis, malaise, pancreatitis, pharyngitis, rash purpuric, renal failure acute, tremor, and weight increase.

References Cited by the Reviewer

1. Agharazii M et al. Chronic interstitial nephritis due to 5-aminosalicylic acid. Am J Nephrol, 19:373-376, 1999.

2. Sentongo TA et al. Recurrent pericarditis due to mesalamine hypersensitivity: a pediatric case report and review of the literature: J Pediatr Gastroenterol Nutr, 27:344-347, 1999.

3. Fernandez J et al. Acute pancreatitis after long-term 5-aminosalicylic acid therapy. Am J Gastroenterol, 92:2302-2303, 1997.

4. Farrell RJ et al. Mesalamine-induced thrombocytopenia. Am j Gastroenterol, 94:2304-2306, 1999.

5. Braun M et al. Mesalamine-induced granulomatous hepatitis. Am J Gastroenterol, 94:1973-1974, 1999.

6. Gunnarsson J et al. Mesalazine-induced lupus [letter]. Lupus, 8:486-488, 1999.

7. Marinella MA. Mesalamine and warfarin therapy resulting in decreased warfarin effect [letter]. Ann Pharmacother, 32:841-842, 1998.

3 Salix Response to Active Control Used in Pivotal Clinical Trials.

3.1 The Question

In a letter to Salix, dated March 16, 1999, the ODE III Acting Director requested information on comparability of the active control drug, i.e. Asacol, used in the Salix pivotal trials CP099301 and 57-3001. The letter states that this Agency has learned that the Asacol used as active comparator in Salix clinical trials is not approved for use in the US. Salix was requested to provide chemical and clinical data, which will support comparability between the Asacol used in Salix pivotal clinical trials and the Asacol marketed in the US. The relevant segments of the March 16, 1999 letter are shown below in italics *[scanned]*:

> *According to 21 CFR 314.126(b)(2)(iv), active treatment concurrent control occurs when the test drug is compared with effective therapy. We have recently learned that the formulation of "Asacol" employed in both pivotal studies as the active comparator may not be currently approved for marketing in the United States. This development calls into question the validity of the clinical database upon which the June 15, 1998 approvable action was based, since the safety and/or effectiveness for the "Asacol" formulation used in the pivotal studies may never have been evaluated by the Agency.*
>
> *For each pivotal study, please specify whether the formulation of the active comparator was the formulation of Asacol currently approved for marketing in the United States. If, for either study, an unapproved formulation of "Asacol" was used as the active comparator, it will be necessary for you to address the following deficiency (in addition to the deficiencies identified in the June 15, 1998 approvable letter) before this application can be approved.*
>
> *Information regarding the specific comparability between the "Asacol" formulation used in each pivotal clinical trial and the one approved for marketing in the United States could not be located in the original NDA or subsequent submissions. Please submit this information, or provide a reference (by submission date and page number) where these data can be found. Your response should include, at a minimum, a side-by-side comparison of the formulations for each product, a discussion of the clinical comparability between the unapproved and approved formulations, comparative dissolution data, and other clinical and physical chemical characteristics, as well as the manufacturing source, of the unapproved "Asacol" formulation. The data showing comparability between the unapproved and approved formulations must be sufficient to demonstrate that the results of Studies CP099301 and 57-3001 remain valid.*

3.2 *Salix Response*

Salix replied that ***it believes that the Asacol formulation obtained in the United Kingdom (UK) and used in the pivotal clinical trials CP099301 and 57-3001, is chemically and clinically equivalent to the Asacol formulation approved in the United States (US). Thus, Salix believes that the proposed labeling identifying Asacol as the active comparator is appropriate.***

- In the following paragraphs, I will briefly summarize the relevant chemical, biopharmacological and clinical statements included in the Salix response.

3.2.1 Formulations

In Table 2, Salix displays the qualitative comparison of the US Asacol formulation and the 1993 UK Asacol formulation used by Salix in the pivotal clinical trials. Salix notes that the UK Asacol formulation is based upon a personal communication between Salix Pharmaceuticals and the medical information of SmithKline and French Laboratories, UK. This table also displays the 1997 UK Asacol formulation and the 1999 US Asacol formulation. Salix notes that the only difference *[minor]* is the presence of colloidal silicon dioxide (CSD) in the US formulation *(CSD is contained in talc)*.

Table 2 : Qualitative Asacol Formulation Comparison

Ingredient	1993 Asacol Formulations		1997 UK Asacol Formulation[4]
	UK[1]	US[2,3]	
Mesalamine	400 mg	400 mg	400 mg
Colloidal silicon dioxide	–	√	–
Dibutyl phthalate	√	√	√
Edible black ink[5]	–	√	–
Iron oxide red	√	√	√
Iron oxide yellow	√	√	√
Lactose	√	√	√
Magnesium stearate	√	√	√
Methacrylic copolymer B (Eudragit S), dissolves at pH 7	√	√	√
Polyethylene glycol	√	√	√
Povidone (polyvinylpyrrolidone)	√	√	√
Sodium starch glycollate	√	√	√
Talc	√	√	√

1 Based on 1993 personal communication with SmithKline French, UK medical information department.
2 Data from 1993 US Asacol package insert.
3 Data from 1997 US Asacol package insert.
4 Data from 1997 UK Asacol Patient Information Leaflet.
5 The UK Asacol tablets do not contain an imprinted name or code identifier.

3.2.2 Manufacturing Sites

Salix notes the possible similarities between the manufacturer of the UK Asacol and US Asacol, according to the EC Directives. The next paragraph *[scanned]* and table, illustrate this point.

The Patient Information Leaflet provided with the 1993 UK Asacol material identifies SmithKline Beecham Pharma GmbH, Germany as the manufacturer. However, based on EC Directives 92/27 EC and 75/319 EC, the definition in Europe of the manufacturer is interpreted as the site responsible for the release of product, i.e., location of the Qualified Person. Thus, contrary to the US requirement, the site listed on the labeling as the manufacturer may not necessarily be the actual site where the product is produced. Additionally, it is Salix Pharmaceuticals, Inc.'s understanding that Proctor and Gamble Pharmaceuticals purchased the Röhm Pharma, GmbH facility sometime in 1994.

Table 4 : Site of Manufacture Information

Manufacturer Identified in Product Labeling	UK Asacol Formulations		US Asacol Formulations	
	1993 Asacol[1]	1997 Asacol[2]	1993 Asacol[3]	1999 Asacol[4]
SmithKline Beecham Pharma GmbH, Germany	√			
Wülfing Pharma GmbH, Bethelner Landstr. 18, D31028 Gronau, Germany		√		
Röhm-Pharma, GmbH D-6108 Weiterstadt 1 Germany			√	
D-64331 Weiterstadt 1 Germany				√

1 Data from 1993 UK Patient Information Leaflet (refer to Attachment 3).
2 Data from current UK Patient Information Leaflet (refer to Attachment 3)..
3 Data from 1993 US package insert (refer to Attachment 4).
4 Data from current US package insert (refer to Attachment 4).

3.2.3 Comparative Dissolution Data

The following Salix Table 8 summarizes the dissolution rates of the UK Asacol and US Asacol.

Table 8 : Mean Dissolution Results (Percent Dissolved)

Time	1993 UK Asacol Lot BN307070	1993 US Asacol	1997 UK Asacol	1999 US Asacol
	Mean Percent Dissolved (n = 12) ± Standard Deviation			
Acid stage				
120 minutes				
Buffer stage				
30 minutes				
60 minutes				
90 minutes				
120 minutes				

Salix concludes the following *[scanned, relevant points]*:

For each Asacol lot, no dissolution was detected during the acid dissolution stage. The absence of dissolution during the acid stage indicates that the enteric coatings of UK and US Asacol formulations are functionally equivalent. The demonstration of equivalency in the acid dissolution stage is considered critical as the tablet must pass through the acidic environment of the stomach intact in order to reach the colon the intended site of therapeutic action.

Regardless of formulation, the buffer stage dissolution was most variable at the earlier time points, e.g., 30 and 60 minute time points. The variation at these earlier time points is expected as this is the time period during which the enteric coating is dissolving. At the subsequent 90 and 120 minute dissolution time points the intra-lot variability decreased. At the 90 and 120 minute time points the variability of the 1993 UK and 1993 US Asacol formulation were comparable, i.e., relative standard deviations (% RSD) about 4% - 10%. The % RSDs for the 1997 UK and 1999 US Asacol formulations at 90 and 120 minutes ranged from about

3.2.4 Clinical Comparability Between the UK Asacol and US Asacol.

Salix included a number of tables to demonstrate comparability between the efficacy results by the UK Asacol in the Salix pivotal US trial CP09931 and the efficacy results shown Norwich Eaton in Trial C14, which was the only study that served for approval of the Norwich Eaton Asacol in the US, at the dose of 2.4 g/day.

This reviewer will not go into the details of the comparabilty, but rather include the UC, symptomatology comparison at entry, demographics, and the odds ratio comparison for symptom improvement submitted by the sponsor *[In the Salix study, the interim visit-points were at 2, 4, and 8 weeks. In the Norwich Eaton C15 study the interim visit-points were at 3 and 6 weeks].*

Table 12 : Symptom Severity at Entry

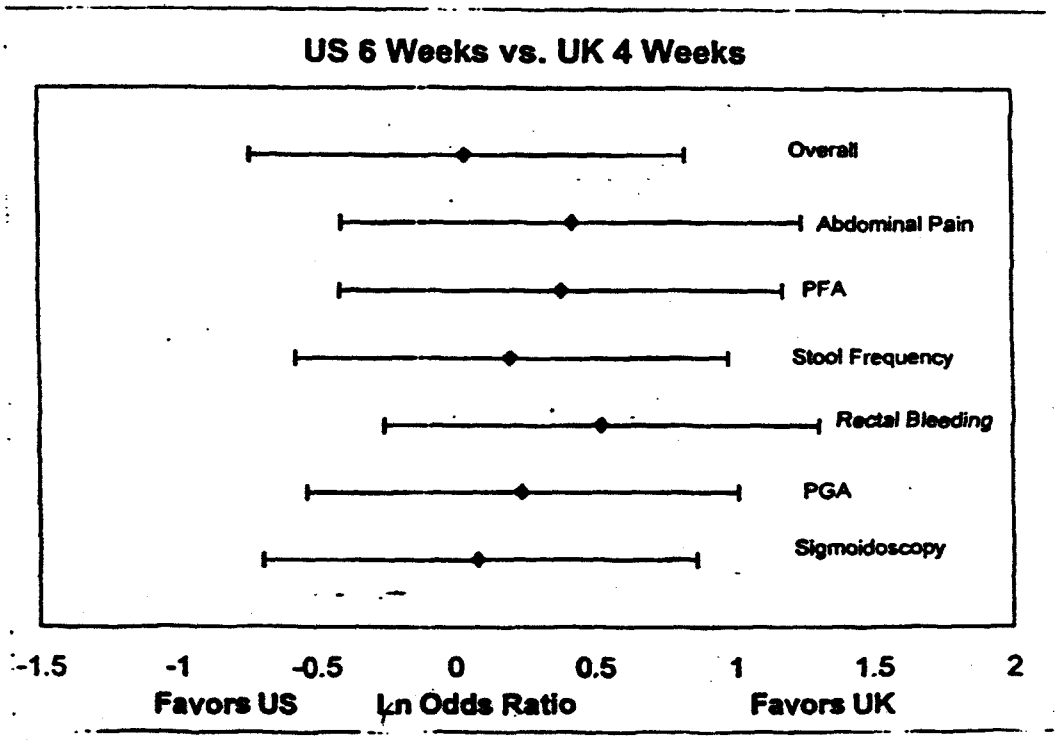
	Study	
	Salix CP099301	Norwich Eaton C.14
	N=51	N=53
Sigmoidoscopy		
Normal	0%	0%
Mild	0%	43%
Moderate	84%	47%
Severe	16%	9%
Not done	0%	0%
Physician Global Assessment		
Normal	0%	0%
Mild	8%	51%
Moderate	84%	45%
Severe	8%	4%
Not done	0%	0%
Rectal Bleeding		
Normal	12%	21%
Mild	27%	45%
Moderate	41%	30%
Severe	16%	4%
Missing	4%	0%
Stool Frequency		
Normal	6%	19%
Mild	25%	32%
Moderate	24%	26%
Severe	41%	23%
Missing	4%	0%
Patient Functional Assessment		
Normal	6%	28%
Mild	24%	60%
Moderate	37%	9%
Severe	29%	2%
Missing	4%	0%
Abdominal Pain		
Normal	20%	30%
Mild	37%	58%
Moderate	37%	8%
Severe	2%	4%
Missing	4%	0%

Table 11 : Demographics and Disease History at Entry

	Study			
	Salix Study CP099301		Norwich Eaton Study C.14	
Patients , n	51		53	
Sex, n (%)				
Male	24	(47)	24	(45)
Female	27	(53)	29	(55)
Race				
Caucasian	41	(80)	49	(92)
Black	4	(8)	3	(6)
Hispanic	5	(10)	0	(0)
Asian	0	(0)	1	(2)
Other	1	(2)	0	(0)
Age, years				
Mean	42		43	
Range	20-76		20-73	
SEM	2.19		1.97	
Newly Diagnosed, n (%)	8	(16)	5	(9)
Duration of disease, years				
Mean	6.7		7.2	
Range	0-36		0-26	
SEM	1.70		1.04	
Extent of disease, n (%)[a]				
>40 or 60	16	(31)	24	(45)
20 to 40 or 60	19	(38)	20	(38)
<20	16	(31)	9	(17)

[a] Salix study used the criteria of >60 cm as evidence of pan-colonic involvement while the Norwich Eaton study used >40 cm.

Figure 7 : Odds ratio comparison for symptom improvement for Salix CP099301 study patients (UK formulation) at 4 weeks versus Norwich Eaton C.14 study patients (US formulation) at 6 weeks. Bars represent 95% confidence intervals.



Salix concludes the following *[scanned]*:

The similar clinical study design of Salix Study CP099301 and Norwich Eaton Study C.14 allows for a direct efficacy comparison of the UK and US Asacol formulation. Although patients participating in Norwich Eaton Study C.14 appeared to be slightly less active in terms of symptom severity, the extent of patient improvement over the study duration was similar for both the UK and US Asacol groups. In addition, the safety profile between the UK and US Asacol formulations are comparable in nature and extent of the events that occurred. Based on the clinical analysis, the data indicates that the UK and US Asacol formulations are clinically equivalent. Thus, the UK formulation is considered to be a clinically acceptable active control comparator for the pivotal Phase III study submitted in the NDA.

3.3 Reviewer Comments.

i. Regulatory Interpretation. This medical reviewer's understanding of CFR 314.26(b)(2)(iv) is that it requires that the active control be a *"known effective therapy"*, without intended mention of the country where this control drug was shown to be *effective*.

CFR 314.26(b)(iv) and also (i) and (ii) also enable the use a *dose-comparison concurrent control as a placebo comparable control* in addition to the active-control, as possible placebo-comparator *(lower-dose)*.

ii. The Dose-Comparator. Salix randomized, double-blind, multi-center pivotal US trial included two balsalazide doses: a high *therapeutic* 6.75 g/day does, and a low presumably *ineffective* 2.25 g day dose. To disregard the low balsalazide ineffective dose used in the Salix pivotal US trial is, **implicitly**, to consider the low balsalazide dose therapeutically inferior to placebo. This issue requires some comments:

(a) Balsalazide has as active moiety 5-amino-salicilyc acid, linked by an azo bond to a therapeutically ineffective chemical element, i.e., alanine. This is basically the same therapeutic principle as found in the approved sulfasalazine, in which the active 5-amino-salicylate is linked via an azo bond to the traditionally considered inactive (or low active) sulfapyridine. In other preparations like olsalazine (Dipentum®), the 5-amino-salicylate is linked via an azo bond to another molecule of mesalamine. The therapeutic activity of 5-amino-salicylate as a colonic anti-inflammatory compound, effective in the treatment of active ulcerative colitis, was shown 23 years[8] ago.

(b) Effectiveness of 5-amino-salycilate in ulcerative colitis has been shown in oral preparations regardless of the presence, ***or absence***, of delayed coating systems. In the case of balsalazide, Salix has performed PK studies showing that most of the administered oral drug is recovered in feces, as I understand, at any dose. The activity of the balsalazide dose was illustrated in the improvement of the presence of blood in stool of the UC patients enrolled in the US trial. Hence, Table 20, Page 29, 1998 MO review, shows that

between 36% to 35% of treated patients improved after either, 4 or 8 weeks of treatment. The high 6.75 g/day balsalazide dose was numerically superior to the low 2.25 g/day balsalazide dose at the 4-week visit, and significantly superior at the final 8-week visit.

iii. Efficacy Comparison Between the UK and US Asacol. It could be argued that a comparison of drug efficacy in separate trials might not be synonymous to assessment of drug efficacy in a head-to-head single trial comparison. However, we are comparing two identically active compounds *(5-aminosalicylate)*, administered, for each compound, to ulcerative colitis patients diagnosed and treated in the US, who had, in each case, similar demographic characteristics.

iv. Dissolution Comparison. The only difference was at the 30-60 minutes of the alkaline-buffer experiment. This experiment is used to sham the conditions in the small intestine. As such, it is inadequate, for the small intestinal milieu contains potent pancreatic and brush border enzymes, which might alter the enteric coating. In view of the proven clinical activity of 5-aminosalicylate, the relevance of this *in vitro* experiment is dubious, at best.

v. PK Kinetics of the UK Asacol. The PK assessment of the UK Asacol is the crux of the matter in this comparison, at least in the view of this reviewer. There are numerous studies demonstrating that administration of the US Asacol leads to absorption of 20-25% of the dose whereas the remaining 80% is eliminated in feces[9,10]. A similar PK of the UK Asacol would allow demonstration of relevant comparability.

References (continues)

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

9. Dew MJ et al. Comparison of the absorption and metabolism of sulphasalazine and acrylic-coated 5-amino salicylic acid in normal subjects and patients with colitis. Br J Clin Pharmacol, 17:474-476, 1984.

10. Corey AE et al. Bioavailability of single and multiple doses of enteric-coated mesalamine and sulphasalazine. J Int Med Res, 18:441, 453, 1990.

4 RECOMMENDATION OF REGULATORY ACTIONS.

The Salix pivotal US study CP099301 includes two doses of balsalazide, a high 6.75 g/day dose, and a low 2.24 g/day dose. The high balsalazide dose was significantly superior to the low dose in improving relevant symptomatology, i.e., blood in stool and sigmoidoscopic assessment of inflammation, in patients with moderately active ulcerative colitis. According to regulation, this dose-comparison should suffice to accept efficacy of balsalazide, since the active compound of balsalazide, 5-aminosalicylic acid, has been proven to be an effective drug in ulcerative colitis.

I would further recommend the following:

1. Remove the trade name Asacol and replace it with the generic name European Mesalamine Formulation.

There are no recommendations, at this moment, of safety issues.

/S/

Robert Prizont, M.D.

cc:
NDA 20-610
HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/RPrizont
HFD-181/MMcNeil
HFD-180/JChoudary
HFD-180/LZhou
f/t 2/29/00 jgw
N/20610002.0RP

Concur. March 2, 2000

/S/

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5 APPENDIX 1

5.1 Infrequent AEs in Acute Clinical Trials

Table 2: Incidence of Common (≥ 1%) Adverse Events in Three Adequate and Well-Controlled Studies of Balsalazide (Volunteered Complaints Excluded)

Adverse Event	Balsalazide 6.75 g/d N = 175	Mesalamine 2.4 g/d N = 100	Placebo N = 35
Headache	13 (7%)	20 (20%)	3 (9%)
Abdominal pain	11 (6%)	4 (4%)	1 (3%)
Diarrhea	8 (5%)	3 (3%)	1 (3%)
Nausea	6 (3%)	7 (7%)	2 (6%)
Respiratory infection	6 (3%)	5 (5%)	5 (14%)
Arthralgia	5 (3%)	3 (3%)	
Vomiting	5 (3%)	4 (4%)	2 (6%)
Cramps	3 (2%)	1 (1%)	
Dyspepsia	3 (2%)	5 (5%)	
Fatigue	3 (2%)	2 (2%)	
Flu-like disorder	3 (2%)	5 (5%)	
Haemmorrhage rectum	3 (2%)	3 (3%)	1 (3%)
Stools frequent	3 (2%)		1 (3%)
Accident and/or injury	2 (1%)	1 (1%)	1 (3%)
Anorexia	2 (1%)		
Back pain	2 (1%)	5 (5%)	1 (3%)
Bowel irregularity	2 (1%)		
Colitis ulcerative aggravated	2 (1%)	5 (5%)	
Constipation	2 (1%)	1 (1%)	
Dizziness	2 (1%)	2 (2%)	2 (6%)
Dyspnea	2 (1%)	1 (1%)	
Ear infection	2 (1%)		
Fever	2 (1%)	3 (3%)	
Insomnia	2 (1%)	1 (1%)	
Melena	2 (1%)	1 (1%)	
Dry mouth	2 (1%)		
Myalgia	2 (1%)	2 (2%)	
Pain	2 (1%)	5 (5%)	1 (3%)
Pruritus	2 (1%)		1 (3%)
Rhinitis	2 (1%)	3 (3%)	

Note: This table includes events with incidence rates ≥ 1% in patients treated with Balsalazide 6.75 g/d.
A complete list of adverse events is presented in Table U6e-4.

1.3 INFREQUENT ADVERSE EVENTS BY BODY SYSTEM

In addition to the common adverse events in Table 2, the following adverse events have also been reported by patients taking Balsalazide during acute clinical trials (n = 429, see Table U6e-2 in Section 20) or collected from foreign post-marketing surveillance (see Section 9.1). In most cases no relationship to Balsalazide has been established.

Body as a Whole: *abdomen enlarged, asthenia, chest pain, chills, edema, malaise*

Cardiovascular and vascular: *bradycardia, deep venous thrombosis, hypertension, leg ulcer, palpitations, pericarditis*

Gastrointestinal: *eructation, fecal incontinence, flatulence, gastroenteritis, glossitis, hemorrhoids, neoplasm benign, pancreatitis, ulcerative stomatitis, tenesmus*

Hematologic: *anemia, epistaxis, fibrinogen plasma increase, hemorrhage*

Liver and biliary: *hepatic function abnormal*

Lymphatic: *eosinophilia, granulocytopenia, leukocytosis, leukopenia, lymphadenopathy, lymphoma-like disorder, lymphopenia*

Metabolic and nutritional: *hypocalcemia, hypokalemia, hypoproteinemia, LDH increase*

Musculoskeletal: *stiffness in legs*

Nervous: *aphasia, dysphonia, gait abnormal, hypertonia, hypoaesthesia, migraine, paresis, spasm generalized, tremor*

Psychiatric: *anxiety, depression, nervousness, somnolence*

Reproductive: *cervicitis, female fertility decrease, menstrual disorder*

Resistance Mechanism: *abscess, bacterial infection, immunoglobulines decrease, viral infection*

Respiratory: *bronchospasm, coughing, hemoptysis, phayngitis, sinusitis*

Skin: *alopecia, angioedema, dermatitis, dry skin, erythema nodosum, erythematous rash, pruritis ani, psoriasis, skin ulceration*

Special Senses: *conjunctivitis, earache, iritis, parosmia, taste perversion, vision abnormal*

Urinary: *hematuria, interstial nephritis, micturition frequency, polyuria, pyuria, renal calculus, urinary tract infection.*

2. STUDY DESIGNS AND EXPOSURE TO STUDY MEDICATION

2.1 GENERAL INFORMATION OF ALL STUDIES

The general information for the studies included in this Safety Update is presented in Table 3a for controlled acute and maintenance studies, Table 3b for uncontrolled acute and maintenance studies, Table 3c for clinical pharmacology and pharmacokinetics studies, and Table 3d for studies on other indications and compassionate use programs. Only eight patients were enrolled in studies for other indications. *The final study reports for the new studies 57-3001b, 57-3002, and 0600376 were submitted under*

6 APPENDIX 2

6.1 AEs in Maintenance Studies

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Table 11: Incidence of Common (≥1%) Adverse Events in Maintenance Studies of Balsalazide

Adverse Event	Balsalazide N = 844	Mesalamine N = 94	Sulfasalazine N = 38	Placebo N = 15
BODY AS A WHOLE	195 (23%)	21 (22%)	4 (11%)	2 (13%)
Accident or Injury	18 (2%)	1 (1%)		
Asthenia	11 (1%)			
Back Pain	45 (5%)	4 (4%)		
Fatigue	70 (8%)	4 (4%)	3 (8%)	1 (7%)
Flu-like Disorder	15 (2%)	2 (2%)		
Malaise	30 (4%)			1 (7%)
Pain	56 (7%)	5 (5%)		
GASTROINTESTINAL	297 (35%)	20 (21%)	11 (29%)	5 (33%)
Abdominal Pain	104 (12%)	4 (4%)	2 (5%)	
Colitis Ulcerative aggravated	*16 (2%)*			
Constipation	24 (3%)			
Diarrhea	71 (8%)	5 (5%)	2 (5%)	
Dyspepsia	46 (6%)	2 (2%)	2 (5%)	3 (20%)
Flatulence	76 (9%)	3 (3%)	2 (5%)	1 (7%)
Hemorrhage rectum	9 (1%)			
Hemorrhoids	11 (1%)			1 (7%)
Melena	13 (2%)		1 (3%)	
Nausea	86 (10%)	3 (3%)	1 (3%)	1 (7%)
Stomatitis Ulcerative	*9 (1%)*		*1 (3%)*	
Stools Frequent	*10 (1%)*			
Tenesmus	*11 (1%)*	*1 (1%)*		
Tooth Disorder	*10 (1%)*		*1 (3%)*	
Vomiting	14 (2%)			
MUSCULOSKELETAL	66 (8%)	4 (4%)	5 (13%)	1 (7%)
Arthralgia	29 (3%)	2 (2%)	4 (11%)	
Arthritis	11 (1%)			
Arthropathy	*12 (1%)*		*1 (3%)*	*1 (7%)*
Myalgia	17 (2%)			
NERVOUS SYSTEM	142 (17%)	8 (9%)	1 (3%)	3 (20%)
Dizziness	37 (4%)			2 (13%)
Headache	122 (15%)	8 (9%)	1 (3%)	2 (13%)
Migraine	*9 (1%)*			
PSYCHIATRIC	46 (6%)	2 (2%)	3 (8%)	1 (7%)
Anorexia	*11 (1%)*	*1 (1%)*		
Depression	15 (2%)			
Somnolence	*11 (1%)*		*2 (5%)*	
RESISTANCE MECHANISM	58 (7%)	4 (4%)		
Infection	14 (2%)	1 (1%)		
Infection Viral	32 (4%)	3 (3%)		
RESPIRATORY	99 (12%)	16 (17%)	2 (5%)	
Bronchitis	*10 (1%)*	*2 (2%)*		
Coughing	14 (2%)	1 (1%)		

Table 11: Incidence of Common (≥1%) Adverse Events in Maintenance Studies of Balsalazide

Adverse Event	Balsalazide N = 844	Mesalamine N = 94	Sulfasalazine N = 38	Placebo N = 15
Pharyngitis	25 (3%)	5 (5%)		
Respiratory Infection	67 (8%)	11 (12%)	2 (5%)	
Sinusitis	10 (1%)	1 (1%)		
SKIN AND APPENDAGES	95 (11%)	5 (5%)	6 (16%)	4 (27%)
Pruritus	19 (2%)	1 (1%)		1 (7%)
Rash	36 (4%)		1 (3%)	1 (7%)
Skin disorder	*9 (1%)*			
OTHER				
Hypertension	*9 (1%)*			
Anemia	*10 (1%)*	*3 (3%)*		
Weight Increase	*9 (1%)*			

Note: This table includes events with incidence rates ≥1% in patients treated with Balsalazide.
A complete list of adverse events is presented in Table U6e-5.

For Balsalazide patients in the maintenance trials, the most common adverse events (incidence rates ranging from 7% to 15%) were headache, abdominal pain, nausea, diarrhea, flatulence, pain, *fatigue*, and *respiratory infections*. Compared to the acute trials, the maintenance trials had lower incidence rates of these events. Back pain, dyspepsia, dizziness, rash, *malaise*, and *viral infections* had incidence rates of 4% to 6%.

Adverse events exceeding the 1% threshold in the maintenance studies but not in the acute studies include accident or injury, hemorrhoids, stomatitis ulcerative, tooth disorder, arthritis, arthropathy, myalgia, migraine, depression, somnolence, infection, bronchitis, coughing, pharyngitis, sinusitis, pruritus, skin disorder, hypertension, anemia, and weight increase. Except for pharyngitis (3%), the incidence rates for all these events were 2% or under; no systematic pattern of unexpected events was observed with longer exposure of Balsalazide.

4.5 Incidence of Volunteered Complaints

A checklist containing typical symptoms seen in UC patients was used to capture additional safety data in both phases of two U.S. studies (acute phase: CP069101 and CP099301; maintenance phase: CP069102 and CP099302). The events were noted as volunteered complaints and were tabulated together with adverse event listings. Incidence rates of the volunteered complaints for acute studies are presented in Table U6c. The most common of these complaints, similar to adverse events, were fatigue, headache, abdominal pain, diarrhea, and nausea.

7 APPENDIX 3

7.1 AEs Due To Biochemical Abnormalities

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8.2.1.7 Patient Summaries

Because of the nature of the disease and concomitant diseases, abnormal baseline levels were seen in a number of patients. Those patients who showed one or more clinically significant abnormalities or a significant change in classification during treatment are discussed below.

Trial - Patient No.	Age/ Sex/ Trt	Summary
0028-001-60	78/M/ BSZ	Patient showed pre-treatment and 16-week post-treatment elevation of Alk. Phos (610-876 U/L), creatinine (2.486 – 2.373 mg/dL), Urea (36.7 – 39 mg/dL), all probably attributable to Paget's disease. It is unlikely that Balsalazide treatment contributed to these effects.
0028-011-1152	46/M/	Patient was withdrawn because of headaches after 20 day's treatment in a planned 8-week study. There were increases in SGOT (17 – 189 U/L) and GGT (18 – 180 U/L). No other symptoms, such as chest pain, were recorded; and no investigation was carried out to exclude MI.
0028-012-1210	78/M/ BSZ	Patient had an unexplained rise in alkaline phosphatase (155-389 U/L) during treatment with Balsalazide. Serum creatinine rose from a pre-treatment level of 1.062 mg/dL to 1.435 mg/dL during treatment. There were no concomitant conditions to account for these changes.
0028-017-1709	45/M/	Patient had an elevation of plasma bilirubin (0.9 -1.8 mg/dL); GGT was high at baseline and at the end (68-73 U/L) but other tests of liver function were normal. There were no other changes or concomitant illnesses to account for the change in plasma bilirubin.
0028-017-1764	35/M/ BSZ	Patient had a baseline plasma bilirubin of 0.7 which rose to 1.7 mg/dL at the final visit. Apart from an increase in SGOT from 9 to 23 units, there were no other changes in tests of liver function. He had an episode of abdominal pain with hematuria, thought to be renal colic, during the study. The elevation in bilirubin remains unexplained.
0028-019-1909	42/M/ BSZ	Patient had iron-deficiency anemia and psoriatic arthritis at baseline. Alkaline phosphatase was elevated at baseline and remained elevated throughout the 4-year maintenance study (946 – 356 U/L). It appears likely that this was related to the underlying arthritis and is unlikely to be related to Balsalazide.
57-3001-1087	76/M/ BSZ	Patient had elevated alkaline phosphatase at baseline and at the end of a 55-day treatment with Balsalazide (830 - 965 U/L). This was due to pre-existing Paget's disease and osteoarthritis.
57-3001-1481	24/M/ BSZ	Alk. .Phos: 437-626 Attributed to pre-existing liver function abnormality. But SGPT: 25-79; SGOT 22-58 suggests worsening during therapy. Probably related to disease progression rather than to drug treatment.
57-3001-1482	63/M/ MES	Alk. Phos: 476-242. There is no mention of underlying pathology to account for the baseline elevation of Alk. Phosphatase. K^+ decreased from 4.5 to 2.7 mEq/L. Probably due to exacerbation of U.C. Patient was withdrawn for lack of efficacy – required hospitalization and steroid treatment.
57-3001B-2081	36/M/ MES	Isolated increase in SGPT: 14-77.No significant change in other LFT or symptoms suggestive of liver or heart disease. Unlikely to be due to drug and is of no clinical significance.

57-3001B-2085	76/M/ MES	A. Phos: 965-1106 High level prior to trial treatment was probably due to severe ulcerative colitis.
57-3002-108	35/M/ BSZ	Bilirubin 2-3.4; progressive hyperbilirubinemia developed during treatment with study drug. This was not explained but was possibly due to drug or to disease progression.
57-3002-158	28/M/ BSZ	Bilirubin 0.7-3.25. There was a progressive rise in bilirubin over the 6 months of treatment. The level receded spontaneously after treatment was completed. Meulengracht disease (Functional Hyperbilirubinemia – Gilbert's Syndrome) was suspected but not confirmed.
CP069101-1202	23/F/ BSZ	Patient received Balsalazide treatment for only 5 days and was unwilling to continue the study. There were unexplained increases in alkaline phosphatase (253 to 339 U/L), GGT (210 to 335 U/L) and SGOT (52 to 178 U/L), with a minor elevation of SGPT (57 to 71 U/L). Baseline levels for all these parameters were already elevated, so it is difficult to assess the potential contribution of study drug.
CP069101/1310	26/M/ BSZ	Patient had clinically significant elevation of bilirubin at baseline (3.2mg/dL). He had prior treatment with Azulfidine for UC. After 14 days on Balsalazide, this had risen to 4.3 mg/dL and fell to 2.5 mg/dL on day 30 of treatment. It appears likely that these changes mirror the clinical course of the underlying disease and are unlikely to be directly related to Balsalazide.
CP069101-1404	63/F/ BSZ	Patient was withdrawn after 6 days of treatment of a planned 4-week course because of complaints of severe weakness and moderate difficulty in walking. Alkaline phosphatase had been elevated at baseline (187 U/L) and rose to 251 U/L on day 6. It is uncertain whether Balsalazide contributed to these changes. She also had baseline elevation of cholesterol (327 mg/dL at baseline and 276 mg/dL on day 6) and triglycerides (401 mg/dL at baseline).
CP069101-2612	56/M/ BSZ	Patient completed a planned 4-week course of Balsalazide. Plasma bilirubin was elevated at baseline (1.5 mg/dL) and increased to 2.3 mg/dL at 4 weeks. No concomitant disease or medication was recorded which might account for the abnormality. The relationship between study drug and the further elevation of plasma bilirubin is uncertain.
CP069102-1214	37/M/ BSZ	SGOT was 27-171; SGPT 60, and GGT 62 post-treatment. This is consistent with liver disease as a feature of Ulcerative Colitis.
CP069102-1515	51/M/ BSZ	A.Phos: 170-404 / GGT: 55-456 / SGOT: 21-107 / SGPT: 16-134. Abnormal values were recorded 2 weeks after starting a course of metronidazole, ciprofloxacin, iboprofen and cytotec for back pain, infection and inflammation (no further details given). Deterioration in liver function could be the result of balsalzide therapy or one or more of these concomitant medications.
CP069102-1808	54/M/ BSZ	Very slight elevation in SGOT (56-70 u/L) accompanied by minimal elevation of SGPT (to 57 u/L) and GGT (to 86 u/L). More likely related to disease process than to drug treatment.
CP069102-1901	58/M/ BSZ	Patient had severe vomiting and was treated with metoclopramide, acetominophen, acyclovir, and ranitidine. GGT rose to171 from a baseline of 29 u/L. Relationship of this indication of hepatotoxicity treatment to Balsalazide or to one of the concomitant medications is unclear.
CP069102-2504	44/F/ BSZ	Increases in GGT (65-262 u/L) and SGPT (20-90 u/L). This is possibly related to study medication or to disease progression.

CP099301-5252	31/M/ BSZ	Patient, who was on treatment with Synthroid for hypothyroidism, had anemia at baseline which remained essentially unchanged during treatment. He was withdrawn after 5 days of a planned 8-week course because of "abnormal liver tests". There were increases on plasma bilirubin (0.9-1.2 mg/dL), alkaline phosphatase (242-295 U/L), and GGT (277-313 U/L). No clinical symptoms or adverse events were recorded. The relationship of these changes to Balsalazide treatment is uncertain.
CP099302-5302	35/F/ BSZ	This patient had only 11 days of treatment in the open phase. It was discovered he was taking mesalamine and he was discontinued. The rise in LDH (177-474 u/L) could possibly be due to treatment with either drug.
CP099302-5403	38/M/ BSZ	Elevated liver function test results were recorded as an adverse event, SGPT 50-91. This elevation resolved spontaneously after the treatment had been completed. Relationship to Balsalazide treatment is possible.

8.2.2 Renal Function (Serum Creatinine, Urea, and Potassium)

Balsalazide and the comparative drugs had no consistent effect on serum creatinine or urea levels (page A13, B18-19). The majority of patients (92% and 91%, respectively) showed levels within the normal range both before and after treatment with Balsalazide.

In the Balsalazide treatment group there were 1104 patients with serum K^+ measurements available (page A17, B25); 994 of these (90%) had normal levels before and after treatment. There were 17 patients (2%) whose levels increased from normal to high and 14 patients (1%) whose serum K^+ fell from the high range to within normal limits. Twenty-nine patients (3%) had normal levels pre-treatment falling to low post treatment, while 38 (3%) increased from low pre-treatment levels to normal post-treatment levels. In contrast, both mesalamine and sulfasalazine treatment groups had slightly higher proportions with K^+ decreasing from normal pre-treatment levels to low post-treatment levels, though the numbers were too small to draw definite conclusions.

8.2.2.1 Patient Summary

Clinical significant increases in creatinine, urea, or potassium were seen in the following patients.

Trial - Patient No.	Age/ Sex/ Trt	Summary
0028-001-60	78/M/ BSZ	Patient with Paget's disease had persistently elevated creatinine (2.486 – 2.373 mg/dL) and urea (36.7 – 39.0 mg/dL) before and after treatment. This most likely reflects renal involvement of the Paget's disease; there was no evidence of any deterioration related to treatment with Balsalazide.
0028-002-106	45/F/ PLC	Patient had a serum potassium level of 3.6 mEq/L pre-treatment which was recorded as rising to 7.4 mEq/L at the end. There were no abnormalities of serum creatinine, urea, Na^+ or other electrolytes and no clinical symptoms. This seems likely to be an erroneous reading.

0028-010-1086	62/M/ BSZ	Patient was under treatment with NSAIDs for arthritis and beta blockers for hypertension, both of which could have contributed to the pre-existing elevation in creatinine (1.70-2.68 mg/dL) and urea (27.7 – 31.4 mg/dL). It is possible that the further elevation represented progression of underlying disease.
0028-011-1126	68/M/ BSZ	Patient had concomitant diabetes, treated with human insulin. Ulcerative colitis was described as "total" and he had elevated baseline and post-treatment serum creatinine (1.82-3.25 mg/dL) and urea (35.3-62.2 mg/dL). He required concomitant corticosteroid treatment after 2 weeks of Balsalazide to achieve remission of his disease; this may have contributed to the further elevation of creatinine and urea observed at eight weeks when the study concluded.
0028-011-1141	59/M/ BSZ	Patient had a prior laryngectomy for carcinoma of the larynx. No other concomitant diseases or treatments were recorded to account for the isolated elevation of serum creatinine. There was a further elevation during the eight-week treatment period with Balsalazide which was not accompanied by clinical symptoms. Blood urea remained normal throughout.
57-3002-44	54/M/ MES	This patient had a history of coronary heart disease, hypercholesterolemia and chronic renal insufficiency. Changes in blood urea: from 34-62 mg/dL would not be unexpected and are more likely to be related to pre-existing pathology than to drug treatment.
57-3002-76	55/M/ BSZ	Creatinine 1.6 – 1.3, Urea 115-127. This patient had terminal renal insufficiency and was on constant dialysis, accounting for the high and fluctuating levels of urea and creatinine.
57-3002-85	39/M/ MES	This patient had a mild increase in plasma urea from 35 u/L to a maximum of 55 u/L. This was accompanied by an increase in Alk Phos. to a maximum of 211 u/L; the increase persisted for 3 months, then resolved spontaneously while the increase in plasma urea did not. The changes were possibly related to treatment.
CP069101-1906	35/M/ BSZ	Patient showed elevation of creatinine from 1.1 to 2.1 mg/dL; in the maintenance phase, this patient's level fell from 2.1 to 0.9 mg/dL; there was no evidence of progressive deterioration of renal function.

All of these patients (with the exception of 0028-002-106 who had an isolated elevation in serum K^+ which was probably erroneous) had pre-existing impairment of renal function as evidenced by elevation of serum urea and/or creatinine to "clinically significant abnormal" levels before treatment. It is possible that Balsalazide may have contributed to the additional deterioration noted during the study although other factors could have contributed in the majority of cases.

8.2.3 Other Serum Chemistry

8.2.3.1 Total Protein

Of 892 patients on Balsalazide whose results were available (page A14, B20), 795 (89%) had normal total protein levels pre-and post treatment. In 16 patients (2%) there was a shift from normal to high and in the same number of patients a shift from high to normal. In the placebo group and the other treatment groups, the majority of patients had normal.

8 APPENDIX 4

8.1 Serious AEs

APPEARS THIS WAY
ON ORIGINAL

Vascular (Extracardiac) Disorders: *Cerebrovascular disorder, flushing, oedema peripheral, vasodilatory, peripheral ischaemia, phlebitis, vasodilation, vasospasm, vein pain*

Vision Disorders: *Blepharitis, corneal ulceration, diplopia, eye abnormality, eye infection nos, eye pain*

White Cell and Res Disorders: *basophilia, monocytosis*

6. INCIDENCE OF SERIOUS ADVERSE EVENTS

The incidence of serious adverse events are listed in Table 16. Many of these events were related to either worsening of the symptoms or relapse of the ulcerative colitis. *Events not reported in the ISS are shown in italics. New studies are added at the bottom of the listing.*

Table 16: Serious Adverse Events

Study	Treatment	Patient	Adverse Event
Controlled Acute Studies			
CP069101	Balsalazide 6.75	1209[a]	Pericarditis
	Balsalazide 6.75	1314[a]	Worsening of UC
	Balsalazide 6.75	1811[a]	Worsening of UC
CP099301	Balsalazide 6.75	5251[a]	Nausea and worsening of UC
	Balsalazide 2.25	5207[a]	Worsening of UC
	Balsalazide 2.25	5557[a]	Worsening of UC
	Balsalazide 2.25	5102[a]	Colonic polyps with dysplasia
	Mesalamine	5456[a]	Worsening of UC
	Mesalamine	5558[a]	Worsening of UC
57-3001	Mesalamine	1145	Severe abdominal pain, possible Crohn's disease
	Mesalamine	1482	Worsening of UC
	Mesalamine	1543	Joint pain, muscle ache, lethargy
	Mesalamine	1461	Very severe worsening of UC, increase ESR, CRP
0028-011	Balsalazide 6.75	1153	Allergic reaction (face edema)
	Sulfasalazine	1114	Acute pancreatitis
	Sulfasalazine	1110	Carcinoma of bronchus in smoker
0028-017	Balsalazide 6.75	1766	Deep vein thrombosis
	Balsalazide 6.75	1764	Hematuria, abdominal pain, vomiting (renal colic)
Controlled Maintenance Studies			
0028-005	Balsalazide 4	5061	toothache, erythematous rash, drug-induced vasculitis (to penicillin V)
	Balsalazide 4	5006	Relapse of UC
	Balsalazide 2	5017	Relapse of UC
0028-010	Balsalazide 6	1028	Anemia requiring transfusion
	Balsalazide 6	1096	R upper abdominal pain, vomiting, jaundice, pruritus (cholelithiasis)
	Balsalazide 6	1022	Worsening of UC
	Balsalazide 6	1030	Worsening of UC, lethargy, weakness

Table 16: Serious Adverse Events

Study	Treatment	Patient	Adverse Event
	Balsalazide 6	1081	Worsening of UC
	Balsalazide 3	1046	Cerebrovascular incident, pulmonary embolism
	Balsalazide 3	1041	Worsening of UC
0028-002	Balsalazide 2	113	Hernia operation
0028-016	Balsalazide 6	1091	Cholecystitis
	Balsalazide 3	1004	Breast cancer
	Balsalazide 3	1045	Diabetes mellitus (steroid-induced)
	Balsalazide 3	1102	Bladder cancer
	Balsalazide 3	1039	Relapse of UC
Uncontrolled Acute Studies			
28-open	Balsalazide	2808	Worsening of UC
0028-021	*Balsalazide*	*1198*	*Severe pain and dizziness*
Uncontrolled Maintenance Studies			
CP099302	Balsalazide 2.25, 6.75, 3.0	5506[a]	Lung cancer, death five months post study
0028-018	*Balsalazide*	*1002*	*Severe relapse, total colectomy and proctectomy*
	Balsalazide	*1004*	*Gallstones (cholecystectomy)*
	Balsalazide	*1020*	*Ischemic left leg, pulmonary embolism, death*
	Balsalazide	*1058*	*Discharge and bleeding from right nipple*
	Balsalazide	*1064*	*Myocardial infarct*
	Balsalazide	*1077*	*Ventricular fibrillation, myocardial infarct, asthma aggravated*
	Balsalazide	*1096*	*Obstructive jaundice*
	Balsalazide	*1107*	*Asthma*
0028-019	Balsalazide	1709	Carcinoma of transverse colon, abdominal pain, vomiting
	Balsalazide	1763	Pulmonary embolism
	Balsalazide	1764	Septic shock due to *Staphylococcus epidermidis*, kidney stones
	Balsalazide	1769	(Hospitalized for dilation of rectal stricture and for panproctocolectomy and ileostomy) loose stools, bowels open, pain, septic shock
	Balsalazide	1770	COAD (CHF, surgery on chronic anal fissure)
	Balsalazide	1774	Angina
	Balsalazide	1779	Itchy, scaly pustules
	Balsalazide	1907	UTI from *E. coli*
	Balsalazide	1912	Psychomotor retardation to hypomania, relapse of UC
	Balsalazide	1913	Thyrotoxicosis, relapse of UC
	Balsalazide	1931	Cellulitis on R leg
	Balsalazide	1917	Relapse of UC
Children	Balsalazide	4001	(Hospitalized for blood transfusion and IV steroids UC aggravated), anorexia, loose stools
	Balsalazide	*4002*	*Diarrhea*
	Balsalazide	4003	(Hospitalized for blood transfusion and IV steroids), relapse of UC, hypomania
	Balsalazide	4004	(Hospitalized for IV steroid for sclerosing cholangitis), relapse of UC
Named	Balsalazide 2-4	1006	Bloody diarrhea and L iliac fossa pain, relapse of UC

Table 16: Serious Adverse Events

Study	Treatment	Patient	Adverse Event
	Balsalazide 2-2.25	1015	Bilateral hearing loss, invasive adenocarcinoma, swollen left leg
	Balsalazide 2-3	1022	Repair of rectal prolapse, fell & hit head, posterior fossa hematoma, CVA
	Balsalazide 1-4	1049	Myocardial infarction
	Balsalazide 3	1074	Immune thrombocytopenic purpura, HIV positive
	Balsalazide 2-3	3001	Adenocarcinoma of sigmoid colon
	Balsalazide 1.5-2	3010	Relapse of UC
	Balsalazide 2-4	3072	(Persistent neutropenia and macrocytic anemia) acute myeloid leukemia, myelodysplasia, death
	Balsalazide 3-4.5	3060	Overdose of tricyclic antidepressants and alcohol
			Laparoscopy to investigate infertility, breathing arrested, death
	Balsalazide 6	3064	Severe diarrhea from Crohn's disease, weakness
	Balsalazide 2	3045	Emergency colectomy for uncontrolled bleeding
	Balsalazide 2	3074	Relapse of UC (diarrhea)
	Balsalazide 3-6	3032	(Exacerbation of UC) total colectomy, intramucosal adenocarcinoma
	Balsalazide 3	3113	(Ankle edema, septic arthritis, anemia) pyoderma gangrenosum
	Balsalazide	*1036*	*Hip replacement*
	Balsalazide	*1041*	*Flare-up of UC*
	Balsalazide	*1054*	*Colonoscopy*
	Balsalazide	*3070*	*Anal stretch*
	Balsalazide	*3100*	*UC exacerbated*
	Balsalazide	*3106*	*Vaginal repair*
	Balsalazide	*3136*	*Myocardial infarct*
	Balsalazide	*3144*	*Flare-up of UC*
New Studies [b]			
57-3001b	*Balsalazide*	*2102*	*Fractured wrist*
	Balsalazide	*2551*	*Possible spigelian hernia (abdominal pain)*
	Mesalamine	*2388*[a]	*Cardiac arrest and death*
	Mesalamine	*2149*	*(Relapse of UC) abdominal pain and bleeding; UTI; Lab tests abnormal*
57-3002	*Balsalazide 6*	*48*	*Pancreatitis*
0600376	*Balsulazide 6.75*	*III-02-1*[a]	*Systemic eruption (rash)*
CP079701	*Blinded phase*	*08231*	*Appendicitis*
	Blinded phase	*20108*	*Automobile accident*
	Open Label		
	Balsalazide 3	*05209*	*Severe odynophagia*
	Open Label		
	Balsalazide 3	*18414*	*Viral Meningitis*

a: Adverse event is not coded as serious in database, but was identified as such in the study report
b: Studies 57-3001b and 57-3002 previously reported blinded.
Source: Individual Study Reports