

A Randomized, Double Blind, Dose-Response Comparison of Balsalazide (6.75 g), Balsalazide (2.25 g), and Mesalamine (2.4 g) in the Treatment of Active, Mild-to-Moderate Ulcerative Colitis

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OBJECTIVE: Balsalazide is a new innovative, mesalamine-containing prodrug that is activated by bacteria in the colon. Balsalazide has been shown previously to be well tolerated and effective in the treatment of acute ulcerative colitis. The aim of this study was to determine the dose-response of balsalazide for efficacy and safety in active, mild-to-moderate ulcerative colitis and to compare this profile with that of mesalamine, pH-dependent, delayed-release tablets.

METHODS: A multicenter, randomized, active control, double-blind, double-dummy, dose-response, parallel-group study was performed comparing balsalazide (6.75 g daily), balsalazide (2.25 g daily), and mesalamine (2.4 g daily), administered for 8 wk to 154 patients with active, mild-to-moderate ulcerative colitis as verified by sigmoidoscopy.

RESULTS: Eight weeks of treatment with 6.75 g of balsalazide daily provided significantly greater improvement than did balsalazide (2.25 g daily) in rectal bleeding (64.7% [6.75-g balsalazide] vs 32.4% [2.25-g balsalazide], $p < 0.006$), stool frequency (58.8% vs 29.4%, $p < 0.006$), sigmoidoscopic score (78.9% vs 52.5%, $p < 0.015$), and Physician's Global Assessment (73.7% vs 51.3%, $p < 0.03$). The efficacy of balsalazide showed a significantly more rapid onset of action than that of mesalamine (2.4 g daily) (2-wk sigmoidoscopic score improvement, 54.7% [6.75-g balsalazide] vs 29.4% [2.4-g mesalamine], $p = 0.006$) with numerically greater improvement at 8 wk in five of seven measured signs and symptoms. Balsalazide (6.75 g daily) was well tolerated, and the safety profile did not differ

significantly from that of balsalazide (2.25 g daily) or mesalamine.

CONCLUSIONS: Eight weeks of treatment with balsalazide (6.75 g daily) is significantly more effective than balsalazide (2.25 g daily) and more rapid in onset than mesalamine (2.4 g daily) in improving signs and symptoms of acute ulcerative colitis. Balsalazide (6.75 g daily) is well tolerated, and the safety profile does not differ from that of balsalazide (2.25 g daily) and mesalamine (2.4 g daily). (Am J Gastroenterol 2002;97:1398–1407. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

Mesalamine (5-aminosalicylic acid [5-ASA]) therapy has become the primary treatment for mild-to-moderate forms of ulcerative colitis (1). Mesalamine acts locally at the inflammatory site in the colon (2, 3). Therefore, oral formulations have been developed that target 5-ASA delivery to the colon. These formulations generally fall into two categories: those using a delayed-release mechanism achieved by pH shift or sustained-release formulations, and those using azo-bonded prodrug forms.

Delayed-release formulations may be problematic because early release increases absorption of 5-ASA in the proximal small intestine, increasing systemic exposure to 5-ASA and leading to possible nephrotoxicity (4). Both early and late release of 5-ASA will also lower the concentration of colonic 5-ASA available for therapy at the inflammatory site.

In contrast to delayed-release mesalamine formulations, the azo-bonded prodrugs are patterned on the original mesalamine-containing drug, sulfasalazine. The azo-bonded prodrugs release 5-ASA only in the colon in response to the action of colonic azoreductase produced by colonic bacteria (5, 6). Azo-bonded drugs should, therefore, provide a more reproducible and reliable delivery of 5-ASA to the colon, resulting in more rapid improvement of symptoms and in-

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duction of remission. However, some safety and tolerability problems have been reported with both of the other azo-bonded drugs. The high intolerance rate to sulfasalazine (7) has been extensively reported, whereas the induction of secretory diarrhea by olsalazine (8) has limited its use in the treatment of active ulcerative colitis.

Balsalazide is an orally administered prodrug of 5-ASA in which an inert carrier molecule, 4-aminobenzoyl- β -alanine, has been substituted for the sulfapyridine moiety of sulfasalazine (5, 9). After administration, colonic bacteria split balsalazide into 5-ASA and 4-aminobenzoyl- β -alanine, releasing the active 5-ASA into the colon with minimal systemic absorption of balsalazide, 5-ASA, or 4-aminobenzoyl- β -alanine (5, 9). Balsalazide has been shown to deliver 5-ASA to the colon with a reduced side effect profile relative to that observed with sulfasalazine and olsalazine (10, 11). In addition, balsalazide has been shown to be as effective and well tolerated as delayed-release mesalamine in the chronic treatment of ulcerative colitis (12) with better relief of nocturnal symptoms in chronic treatment than mesalamine (12). In acute treatment of active, mild-to-moderate ulcerative colitis, balsalazide has been reported to provide more rapid relief of symptoms (13) and induce complete remission in a greater percentage of patients than pH-dependent, delayed-release mesalamine (13).

In the present study, 6.75 g of *p.o.* balsalazide daily is compared with a lower dose of balsalazide (2.25 g daily) and a pH-dependent, delayed-release formulation of mesalamine, dosed at 2.4 g daily in the treatment of patients with mild-to-moderate active ulcerative colitis. High-dose and low-dose balsalazide are compared to evaluate the dose-response characteristics of balsalazide. Mesalamine is included as an active comparator to balsalazide to evaluate the relative safety and efficacy of the different systems of 5-ASA delivery.

PATIENTS AND METHODS

Patients

The study was conducted at 15 clinical investigative sites in the United States and Puerto Rico. The study protocol was approved by the Institutional Review Board at each study center or for some centers by Western Institutional Review Board, Olympia, WA. Patients gave written informed consent. Patients were enrolled if they were between 18 and 80 yr of age and had newly diagnosed or recently relapsed (within 12 wk) mild-to-moderate ulcerative colitis confirmed by flexible sigmoidoscopy. Patients were excluded from the study if they had severe colitis, intolerance of or allergy to salicylates, Crohn's disease, hepatic disease, renal disease, evidence of enteric pathogens or parasites, or any malignancy. Patients were also excluded if they had used 5-ASA oral products, topical therapies, or enemas within the last 7 days, had received antibiotics within the last 2 wk, had taken immunosuppressive drugs within the prior 3 months, or had been treated with any investigational drug or device

within the prior month. Pregnant women, women of child-bearing potential not using adequate birth control, and patients breast-feeding infants were also excluded.

Methods

The study was a randomized, multicenter, double-blind, active control, double-dummy, parallel-group comparison of balsalazide (6.75 g daily), balsalazide (2.25 g daily), and 2.4 g of mesalamine (pH 7.0-dependent, delayed-release formulation) daily for 8 wk.

Balsalazide was supplied as hard gelatin capsules containing 750 mg of balsalazide disodium. Mesalamine was supplied as tablets containing 400 mg of mesalamine. Placebos were identical in appearance to the balsalazide capsules and mesalamine tablets. Balsalazide (active and placebo) capsules were manufactured by Anabolic, Irvine, CA. Mesalamine tablets were commercially purchased from SmithKline and French Laboratories, Welwyn Garden City, UK and are marketed in the UK as Asacol. The placebo mesalamine tablets were manufactured by Penn Pharmaceuticals, Wales, UK.

Patients were randomly assigned to one of three fixed-dose regimens that included high-dose balsalazide (6.75 g daily), low-dose balsalazide (2.25 g daily), and the approved dose of mesalamine (2.4 g daily). This design provided two controls: a dose-comparison control (2.25 g of balsalazide daily) to provide information on the dose-related efficacy profile of balsalazide in active disease, and an active treatment control to compare the relative efficacy of 6.75-g balsalazide with 2.4-g mesalamine. Patients received blister packs for each week of treatment with each well containing three capsules (balsalazide/placebo) and two tablets (mesalamine/placebo). Patients were instructed to take the contents of one blister well three times daily.

Clinical Assessments

At the time of screening, patients underwent a physical examination, provided a history, and were questioned about stool frequency, presence or absence of rectal bleeding, degree of abdominal pain, and their functional status over the past 24 h. Patients visited investigators for evaluation at weeks 2, 4, and 8 after study entry. At each visit, body weight, vital signs, concomitant medications, smoking habits, and adverse events were recorded. Flexible sigmoidoscopy was performed at screening to determine the area of most severe involvement, determine the upper margin of disease activity (categorized as ≤ 60 cm or > 60 cm) and to provide a pretreatment sigmoidoscopic score of disease activity.

Sigmoidoscopic score was graded as follows:

Normal: normal mucosa (excluded at entry).

Mild: edema, loss of vascular pattern, fine granularity without ulceration (excluded at entry).

Moderate: friability, petechiae, coarse granularity with pinpoint ulceration.

Severe: visible ulcers, spontaneous bleeding.

Flexible sigmoidoscopy was also performed after 2, 4, and 8 wk of treatment, and the score was recorded at the same location as that scored at screening. Rectal biopsies were taken at screening and after 8 wk of treatment (or at the patient's last visit). Laboratory evaluations were performed at each visit, including complete blood count, chemistry panel, and urinalysis with microscopic analysis.

Investigators provided a Physician's Global Assessment of the patient's condition based on symptoms and sigmoidoscopic score (4-point scale: quiescent, mild, moderate, or severe) at study entry and each subsequent visit. Patients were given diaries in which they were asked to record the number of stools passed per day (stool frequency), degree of rectal bleeding, degree of abdominal pain, and to complete a self-assessment of functional status (Patient Functional Assessment). Data from these patient diaries were also recorded at each visit.

Patients were removed from the study if adverse events were considered too severe to allow continuation or if treatment failed as indicated by worsening of sigmoidoscopy, rectal bleeding, or Physician's Global Assessment by one grade or more at week 2 or any subsequent visit. Other reasons for discontinuation from the study included intercurrent medical problems precluding study completion, pregnancy, patient request, and noncompliance.

Efficacy Endpoints

The primary measure of efficacy was a statistically significant difference between treatment groups in rectal bleeding and in at least one other symptom or sign. Symptom data recorded in the daily diaries were analyzed for improvement by determining an average score within the 96 h before follow-up visits compared with the 96 h after the baseline visit. Improvement was defined as improvement by at least one category in the four-category disease activity scale (*i.e.*, normal, mild, moderate, severe). Secondary measures of efficacy included remission status (normal stool frequency and no blood in stool for 48 h before visit, Physician's Global Assessment score of "quiescent," and a sigmoidoscopy score of mild or normal), rectal biopsy score, and Inflammatory Bowel Disease Questionnaire assessment score.

Populations Analyzed

Both intent-to-treat and eligible-for-efficacy analyses were performed. The intent-to-treat population included all patients randomized, and the last observation carry-forward procedure was used for all missing data. If baseline diary data were missing, the next visit at which data were available was used as the baseline visit. Patients whose diary data were missing for individual nonbaseline symptom assessments were excluded from the analysis for that specific symptom. The prospectively defined "eligible for efficacy population" included all patients receiving at least one dose of medication. The last observation carry-forward procedure

was used for completing patients with missing data and for missing data from patients terminating early because of adverse events, treatment failure or patient request because of worsening of symptoms. Patients with missing baseline diary data or whose data were missing because they were lost to follow-up were not included in the analysis.

Statistical Methods

At entry, comparisons between treatment groups for continuous data and baseline variables were made using χ^2 tests and two-way analysis of variance. Categorical data were analyzed using the Cochran-Mantel-Haenszel test or Wilcoxon-Mann-Whitney test. Different tests were used for efficacy assessments. For symptom changes within treatment groups, the mean change from initial value was analyzed using the Wilcoxon signed rank test and the paired *t* test. Between-group changes in symptoms were analyzed using a two-way analysis of variance model with factors of treatment, center, and treatment-by-center interaction and by the Cochran-Mantel-Haenszel test, controlling for site. Proportions of each treatment group improving were analyzed with the Cochran-Mantel-Haenszel test, controlling for the Physician's Global Assessment rating at entry. Proportions achieving remission at 2, 4, or 8 wk were compared by χ^2 tests. The last-value-extended principle was used for assessment of symptoms and signs. A correction for multiple comparisons was applied to the primary efficacy analysis according to Hochberg and Benjamini (14). The numbers of patients reporting adverse events were compared by the χ^2 test. The change in laboratory test results from baseline to discontinuation was analyzed by the paired *t* test and the Wilcoxon rank sum test.

Plasma 5-ASA and N-Acetyl-5-ASA Measurements

Plasma samples taken at the 2-wk visit before the first dose of study drug on that day were stored frozen at -70°C and processed batch-wise for analysis of steady-state levels of 5-ASA and N-acetyl-5-ASA. Samples stored at less than -70°C or where verification of sample storage conditions was lacking were not analyzed. Analysis was performed by liquid chromatography/mass spectrometry methodology. The assay had a lower quantitative limit of 20 ng/ml. Values below the quantitative limit were assigned a value of 20 ng/ml.

RESULTS

A total of 154 patients were enrolled into the study and randomized to one of the three treatment groups (50, balsalazide [2.25 g daily]; 53, balsalazide [6.75 g daily]; 51, mesalamine [2.4 g daily]). Seven patients were not eligible for the efficacy analysis because of protocol violations before screening or during treatment. Thus, 154 patients were eligible for safety and intent-to-treat analyses, and 147 patients were eligible for efficacy analyses. There were no significant differences between the intent-to-treat population

Table 1. Demographics and Baseline Characteristics of the Eligible-for-Efficacy Population

Variable	Balsalazide (2.25 g/day)	Balsalazide (6.75 g/day)	Mesalamine (2.4 g/day)	Total	Between-Group <i>p</i>	
					6.75 vs 2.25	Mesalamine
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	0.985 CMH
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
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
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)		
Relapses in last 2 yr						
Mean (SE)	2.8 (0.3)	2.6 (0.3)	2.8 (0.3)	2.7 (0.3)		
Duration of current relapse (wk)						
Mean (SE)	4.7 (0.6)	5.4 (0.8)	5.1 (0.7)	5.1 (0.7)	0.657 T	0.951 T

Statistical parameter: CMH = Cochran-Mantel-Haenszel test; T = two-way analysis of variance analyzed for treatment effect.

and the eligible-for-efficacy population in baseline demographic and disease history and activity characteristics. Because of this, only the baseline demographics and disease history and activity characteristics for the eligible-for-efficacy population are presented. Treatment groups were comparable for baseline demographic characteristics (Table 1). The mean duration of ulcerative colitis since first diagnosis was 71 months. The mesalamine treatment group showed the longest disease duration (81 months) and the high-dose balsalazide treatment group the shortest (64 months), but the difference was not statistically significant ($p = 0.194$). Among patients previously diagnosed, the average number of episodes of ulcerative colitis in the past 2 yr was 2.7 with 74% of the patients experiencing three or fewer episodes. The overall median duration of the current episode was 4.0 wk.

All three treatment groups were equally matched for grade of severity of disease activity as measured by the

sigmoidoscopic score, extent of disease, biopsy grade at entry, and Physician's Global Assessment (Table 2). Although there was no statistically significant difference in Physician's Global Assessment scores at entry, the high-dose balsalazide treatment group had almost twice (seven vs four) the number of patients whose disease activity was assessed as "mild" at entry and consequently fewer patients assessed as "moderate" or "severe." All primary efficacy analyses, therefore, controlled for this difference by using Physician's Global Assessment (PGA) as a covariate.

Clinical Efficacy

PRIMARY ENDPOINT IN THE INTENT-TO-TREAT POPULATION. The signs and symptoms measured in the primary efficacy endpoint were first subjected to an intent-to-treat analysis. This included all patients randomized to

Table 2. Disease Activity Scores at Entry for the Eligible-for-Efficacy Population

Entry Characteristic	Balsalazide (2.25 g/day)	Balsalazide (6.75 g/day)	Mesalamine (2.4 g/day)	Between-Group <i>p</i>	
				<i>p</i> (6.75 g/day vs 2.25 g/day)	<i>p</i> (6.75 g/day vs Mesalamine)
Sigmoidoscopic grade	N = 49	N = 49	N = 49	bWMW	bWMW
Mild	0 (0)	2 (4.1)	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)		
Biopsy grade	N = 45	N = 48	N = 45		
Inactive	4 (8.9)	7 (14.6)	3 (6.7)	0.701	0.653
Mild	6 (13.3)	4 (8.3)	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 (8.2)	7 (14.3)	4 (8.2)	0.245	0.226
Moderate	42 (85.7)	40 (81.6)	41 (83.7)		
Severe	3 (6.1)	2 (4.1)	4 (8.2)		

bWMW = Wilcoxon-Mann-Whitney test, blocked by site.

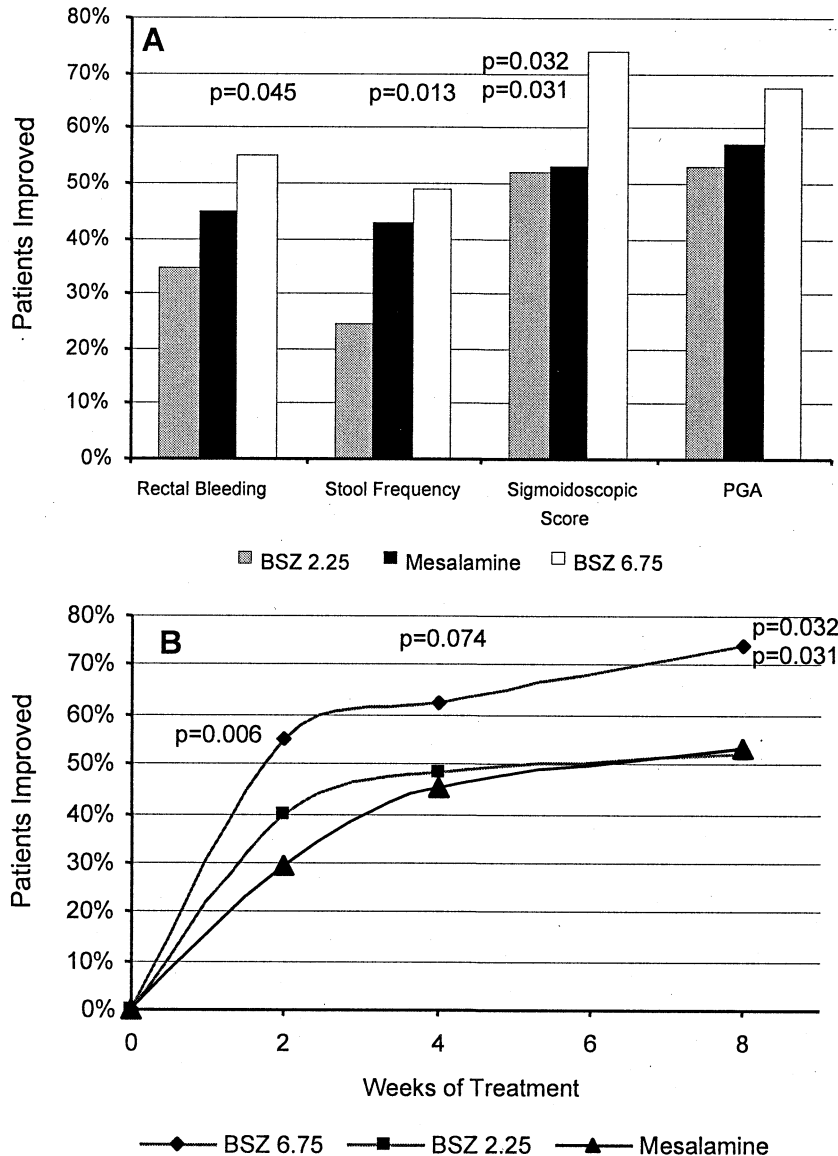


Figure 1. Improvement in signs and symptoms after 8 wk of treatment in the intent-to-treat population. (A) Percentage of patients improved for each sign or symptom is shown for each of the three treatment groups at the week 8 follow-up visit. *p* values are for the comparison of balsalazide (6.75 g daily) vs balsalazide (2.25 g daily) with the exception of sigmoidoscopic score improvement where both comparisons revealed a significant difference. (B) Percentage of patients improved in their sigmoidoscopic score at each of the follow-up visits. *p* values at 2 and 4 wk are for the comparison of balsalazide (6.75 g daily) vs mesalamine. The statistical comparison used the Cochran-Mantel-Haenszel test controlling for PGA at entry. BSZ = balsalazide.

treatment. The primary efficacy measure was a significant difference in improvement of rectal bleeding plus a significant difference in improvement in at least one other measured sign or symptom. As measured at 8 wk, three of the key signs and symptoms were found to show a significant difference in the intent-to-treat analysis between balsalazide (6.75 g/day) and balsalazide (2.25 g/day) (Fig. 1A). These were rectal bleeding improvement (55% vs 35%, $p = 0.045$), stool frequency improvement (49% vs 25%, $p = 0.013$), and sigmoidoscopic score improvement (74% vs 52%, $p = 0.031$). In addition, the intent-to-treat analysis revealed a significant difference in sigmoidoscopic im-

provement between the 6.75 g/day balsalazide group (74%) and the mesalamine group (45%, $p = 0.032$). For this parameter, assessment of the interim time points revealed that the greater sigmoidoscopic improvement rate for patients treated with balsalazide (6.75 g/day) was observed as early as the 2-wk visit (55%) compared with patients treated with mesalamine (29%, $p = 0.006$) (Fig. 1B).

PRIMARY ENDPOINT IN THE ELIGIBLE-FOR-EFFICACY ANALYSIS POPULATION. The primary population specified in the study protocol for analysis of efficacy was the eligible-for-efficacy population. Table 3

Table 3. Improvement in Signs and Symptoms After 8 Weeks of Treatment in the Eligible-for-Efficacy Population

Group	Patients Improved at 8 Weeks						
	Rectal Bleeding n (%)	Stool Frequency n (%)	Sigmoidoscopy Score n (%)	Physician's Global Assessment n (%)	Overall Symptom Assessment n (%)	Patient Functional Assessment n (%)	Abdominal Pain n (%)
Balsalazide (2.25 g/day)	11/34 (32.4)	10/34 (29.4)	21/40 (52.5)	20/39 (51.3)	17/37 (45.9)	19/35 (54.3)	11/35 (31.4)
Balsalazide (6.75 g/day)	22/34 (64.7)	20/34 (58.8)	30/38 (78.9)	28/38 (73.7)	22/34 (64.7)	24/34 (70.6)	14/34 (41.2)
Mesalamine (2.4 g/day)	19/36 (52.8)	21/36 (58.3)	23/38 (60.5)	24/39 (61.5)	22/38 (57.9)	22/36 (61.1)	16/36 (44.4)
<i>p</i> (6.75 g/day vs 2.25 g/day)*	0.006	0.006	0.015	0.030	0.073	0.101	0.346
<i>p</i> (6.75 g/day vs mesalamine)*	0.275	0.946	0.096	0.246	0.495	0.344	0.722

*Cochran-Mantel-Haenszel test controlling for Physician's Global Assessment at entry.

summarizes results for the primary efficacy endpoint at week 8 in this population.

A significantly greater proportion of patients receiving balsalazide (6.75 g daily) than patients receiving balsalazide (2.25 g daily) showed improvement in rectal bleeding (65% vs 32%, $p = 0.006$), stool frequency (59% vs 29%, $p = 0.006$), sigmoidoscopic score (79% vs 53%, $p = 0.015$) and Physician's Global Assessment (74% vs 51%, $p = 0.030$). No significant between-group differences were observed for overall symptom improvement, patient functional assessment, or abdominal pain improvement, although each of these measures did demonstrate significant within-group changes from baseline during the course of treatment. These results are similar to the intent-to-treat analysis with the exception that the Physician's Global Assessment was also significant in this population.

For the comparison of the patients receiving balsalazide (6.75 g daily) versus mesalamine (2.4 g daily), five of the seven signs and symptoms measured showed improvement percentages that were numerically greater, although none of these reached statistical significance. These were rectal bleeding (65% vs 53%), sigmoidoscopic score (79% vs 61%), PGA (74% vs 62%), overall symptom assessment (65% vs 58%), and patient functional assessment (71% vs 61%).

Correction for multiple endpoints. The outcome of the eligible-for-efficacy analysis was subjected to a correction for multiple comparisons using Hochberg's procedure for more powerful multiple significance testing (14). After applying this correction, the primary endpoint of the study was still met for the comparison between the two balsalazide groups. Per protocol, the stool blood null hypothesis stood alone to be rejected at $p \leq 0.05$, whereas one remaining sign or symptom was required to meet the Hochberg-corrected $\alpha \leq 0.0083$. Thus, the difference between the high- and low-dose balsalazide groups for the two symptoms of rectal bleeding improvement ($p = 0.006$) and stool frequency improvement ($p = 0.006$) met the criteria defined for the primary efficacy endpoint of the study.

SECONDARY ENDPOINTS. Disease activity score distribution. The four key signs and symptoms identified in the primary analysis of the eligible-for-efficacy group as show-

ing a significant difference between balsalazide (6.75 g/day) and balsalazide (2.25 g/day) were further analyzed for their distribution of disease activity scores at baseline and after 8 wk of treatment. In this analysis, a significant difference in disease symptom activity scores was observed between the high-dose balsalazide and both comparator groups. As shown in Figure 2, no differences were observed in the baseline distribution of disease activity scores. However, three of the four measured signs and symptoms, rectal bleeding score, sigmoidoscopic score, and Physician's Global Assessment score, but not stool frequency score, showed distributions at the study end that were significantly more favorable for the patients treated with balsalazide (6.75 g/day) than patients treated with mesalamine (2.4 g/day). This was primarily because of a greater percentage of patients achieving disease activity scores of normal or mild in the 6.75 g/day balsalazide group than in the mesalamine group and a greater percentage of patients remaining in the severe score category in the 2.4 g/day mesalamine group than in the 6.75 g/day balsalazide group (Fig. 2).

Complete remission and histological healing. The prospectively specified complete remission definition included no rectal bleeding, normal stool frequency, a sigmoidoscopic score of normal or mild and a Physician's Global Assessment score of quiescent disease activity. Using this strict remission definition, the rates of complete remission did not differ significantly among the three treatment groups. At week 8, the proportion of patients achieving complete remission were balsalazide (6.75 g): 23%, balsalazide (2.25 g): 20%, mesalamine: 19% (Table 4). Inspection of the distribution of disease activity scores at week 8 (Fig. 2) suggests that the modest rate of complete remission observed in this study was a result of the rather low percentage of patients achieving their normal stool frequency level by week 8.

After 8 wk, patients treated with balsalazide (6.75 g daily) did have a significantly greater decrease in mean biopsy score than patients treated with balsalazide (2.25 g daily) (-1.13 vs 0.66 , $p = 0.018$). Patients treated with mesalamine showed a decrease of -1.0 at 8 wk, which was not significantly different than patients treated with balsalazide (6.75 g daily).

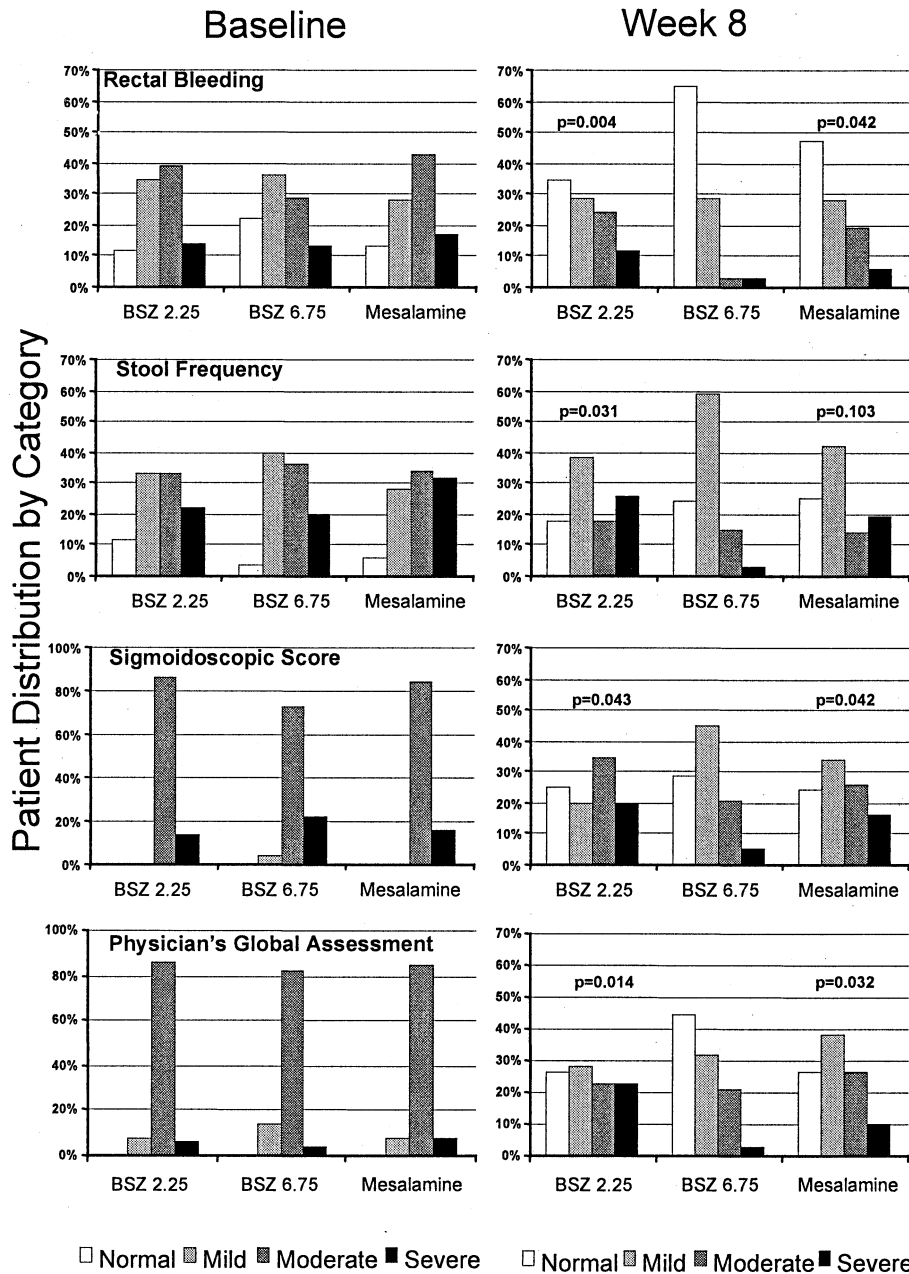


Figure 2. Distribution of disease activity scores at entry and week 8 in the eligible-for-efficacy population. The distributions show the percentage of patients in each severity category for rectal bleeding, stool frequency, sigmoidoscopic score, and Physician's Global Assessment. The statistical comparison used the Wilcoxon-Mann-Whitney test controlling for study investigative site. *p* values represent the comparison of the 6.75-g balsalazide group with each of the other two groups. BSZ = balsalazide.

Tolerability and Safety

Forty-eight patients (31%) (16, balsalazide [6.75 g]; 17, balsalazide [2.25 g]; and 15, mesalamine [2.4 g]) withdrew prematurely from the study before completing 8 wk of treatment. Patients who had worsening of sigmoidoscopy scores, rectal bleeding, or Physician's Global Assessment scores by grade 1 or more at week 2, or at any time thereafter, were considered treatment failures and were discontinued from the study. Almost one-half (eight of 17) of premature withdrawals in the 2.25-g balsalazide group were

attributed to treatment failure, whereas only one-eighth (two of 16) in the 6.75-g balsalazide group and almost one-fourth (four of 15) in the mesalamine group were attributed to treatment failure. However, differences in withdrawal rates between groups were not significant. When the three adverse event-related causes for patient withdrawals (worsening of symptoms, patient request because of worsening of symptoms, and treatment failure) were combined under one category, "withdrawal because of lack of therapeutic effect," the high-dose balsalazide group had the lowest pro-

Table 4. Complete Remission and Histological Scores in the Eligible-for-Efficacy Population

	Balsalazide (2.25 g/day)	Balsalazide (6.75 g/day)	Mesalamine (2.4 g/day)	Between-Group <i>p</i> (6.75 g/day vs 2.25 g/day)	Between-Group <i>p</i> (6.75 g/day vs Mesalamine)
Patients assessed for remission at 8 wk	N = 35	N = 35	N = 36		
In remission	7 (20.0%)	8 (22.9%)	7 (19.4%)	0.771 χ^2	0.725 χ^2
Histological scores of rectal biopsies					
Initial	N = 45	N = 47	N = 45		
Mean (SE)	2.49 (0.18)	2.28 (0.19)	2.38 (0.17)	0.464 bWMW	0.948 bWMW
Final	N = 35	N = 40	N = 30		
Mean (SE)	1.91 (0.29)	1.23 (0.24)	1.43 (0.25)		
Change	N = 32	N = 39	N = 28		
Mean (SE)	-0.66 (0.27)	-1.13 (0.22)	-1.0 (0.29)	0.018 bWMW	0.773 bWMW

bWMW = Wilcoxon-Mann-Whitney test, blocked by site.

portion of premature withdrawals among the three treatment groups. In the 6.75 g of balsalazide daily group, five (9%) patients withdrew because of lack of therapeutic effect, as compared with 11 (22%) patients in the 2.25 g of balsalazide daily group, and eight (16%) patients in the mesalamine group.

Six patients were withdrawn with serious adverse events, including three patients treated with balsalazide (2.25 g daily) (colonic polyp, two worsening symptoms), two patients treated with mesalamine (both worsening symptoms), and one patient treated with balsalazide (6.75 g daily) (worsening symptoms). The most commonly reported nonserious adverse events were headache, abdominal pain, aggravated disease symptoms, and nausea (Table 5). There were no significant differences between the groups in individual adverse events reported, and the adverse events reported in the two groups treated with balsalazide did not seem to be dose related. There were no clinically significant changes in routine laboratory assessments, vital signs, and physical findings in any of the treatment groups.

Steady-State Plasma 5-ASA Levels

Plasma samples taken at the 2-wk visit were subjected to analysis of 5-ASA and *N*-acetyl-5-ASA steady-state levels. As shown in Figure 3, both 5-ASA and *N*-acetyl-5-ASA

levels from patients treated with either dose of balsalazide were significantly lower than those observed for patients treated with mesalamine. Although the two balsalazide doses differed by 3-fold (2.25 g daily vs 6.75 g daily), the mean 5-ASA plasma levels were only 1.7-fold higher for patients treated at the higher balsalazide dose (0.097 $\mu\text{g/ml}$ vs 0.16 $\mu\text{g/ml}$, $p = 0.10$), whereas patients treated with mesalamine had plasma 5-ASA levels 4.5-fold higher than those observed for the high-dose balsalazide group (0.74 $\mu\text{g/ml}$ vs 0.16 $\mu\text{g/ml}$, $p = 0.018$). Similar between-group differences were observed for the analysis of *N*-acetyl-5-ASA (balsalazide [6.75 g daily], 1.25 $\mu\text{g/ml}$ vs mesalamine [2.4 g daily], 2.56 $\mu\text{g/ml}$, $p = 0.011$).

DISCUSSION

This study was conducted to evaluate the dose-related efficacy of balsalazide in active ulcerative colitis and to compare the safety and efficacy of high-dose balsalazide (6.75 g daily) and mesalamine (2.4 g daily). These dosages deliver approximately equimolar amounts of 5-ASA.

The findings of this study indicate that among patients treated with balsalazide, improvement in signs and symptoms of ulcerative colitis was dose responsive. A signifi-

Table 5. Withdrawals Caused by Adverse Events (AEs) and Common AEs Reported for the Intent-to-Treat Population

	Balsalazide (2.25 g/day)	Balsalazide (6.75 g/day)	Mesalamine (2.4 g/day)
	N = 50	N = 53	N = 51
Patients with AEs			
Serious AEs	3	1	2
Withdrawals caused by AEs	5	1	5
Number with AEs	27	23	26
Number with causally related AEs	10	11	11
Common AEs (% of patients)			
Headache	14%	11.3%	13.7%
Abdominal pain	2.0%	9.4%	2.0%
Colitis aggravated	8.0%	1.9%	5.9%
Nausea	2.0%	9.4%	7.8%
Vomiting	10.0%	3.8%	3.0%
Skin disorders	6.0%	1.9%	8.0%

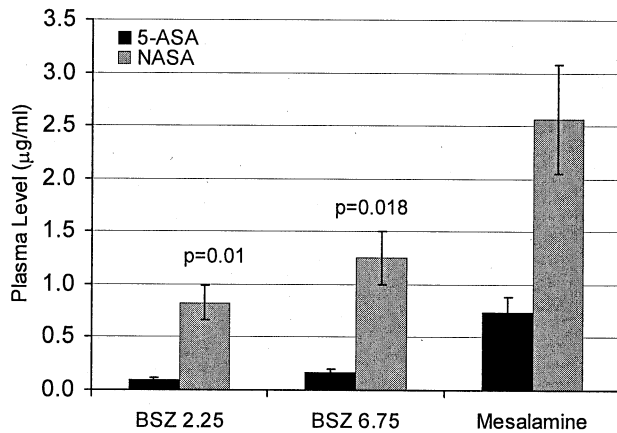


Figure 3. Plasma 5-ASA and *N*-acetyl-5-ASA levels measured at the week 2 visit. Values shown are the means \pm SEM for each group. The statistical analysis used a paired *t* test. BSZ = balsalazide.

cantly greater proportion of patients in the high-dose balsalazide group showed improvement in the primary endpoints of rectal bleeding and at least one other symptom, including stool frequency, sigmoidoscopy score, and Physician's Global Assessment, than did those patients treated with low-dose balsalazide ($p \leq 0.03$). The dose-response relationship was reflected in the degree of improvement observed in the hallmark symptoms of ulcerative colitis, rectal bleeding, and stool frequency, and in the definitive diagnostic sign, sigmoidoscopy score. Only 35% of patients in the 2.25 g of balsalazide daily group reported no rectal bleeding at the end of the 8-wk treatment period, as compared with 65% of patients in the 6.75 g of balsalazide daily group. A lower proportion (56%) of patients in the low-dose balsalazide group reported a normal-to-mild stool frequency score by 8 wk than in the high-dose balsalazide group (82%). Finally, in 74% of patients treated with balsalazide (6.75 g daily), mucosal inflammation based on sigmoidoscopic appearance had been reduced to normal or mild by 8 wk, whereas only 45% of patients treated with balsalazide (2.25 g daily) were found to have a normal or mildly inflamed mucosa at sigmoidoscopy. The improved mucosal appearance in the high-dose balsalazide group was also evident when using histological criteria; the mean biopsy score change from entry to termination was also significantly greater in the high-dose balsalazide group compared with that of the low-dose balsalazide group.

The comparison of high-dose balsalazide and mesalamine (pH-dependent, delayed-release formulation) was included to gain insight into the relative effectiveness of the two different 5-ASA delivery systems. In the intent-to-treat analysis, sigmoidoscopic score improvement was significantly greater in the balsalazide high-dose group than the mesalamine group as early as 2 wk (56% vs 32%, $p = 0.016$), and remained so at the 8-wk time point. The sigmoidoscopic measurements were performed at 10 cm or at the area of most severe involvement if different (a left colon measure-

ment in the majority of patients). The significant difference between the two groups in this measure may, therefore, reflect the superior efficacy of balsalazide in treating left-sided disease, an observation reported previously by Green *et al.* (13).

In the eligible-for-efficacy analysis, five of the seven parameters considered in the primary efficacy analysis at week 8 favored balsalazide (6.75 g daily) over mesalamine, whereas one (stool frequency) was equivocal, and one (abdominal pain) favored mesalamine. This difference was also supported by the observation that the disease activity score distributions for rectal bleeding, sigmoidoscopic score, and Physician's Global Assessment were significantly more favorable for the high-dose balsalazide group than the mesalamine-treated group. These results suggest that the primary difference between these two 5-ASA formulations may be in the rate of onset of disease symptom improvement, which appears to be more rapid with balsalazide (6.75 g daily) than with mesalamine (2.4 g daily), even though both formulations contain an equimolar quantity of 5-ASA. This more rapid onset of action could be attributed to a greater amount of the daily dose of 5-ASA actually reaching the colon from the azo-bonded delivery system of balsalazide compared with the pH-dependent delivery system of this mesalamine formulation. This possibility is supported by the observation that the mesalamine-treated patients in this study were found to have significantly higher 2-wk, steady-state plasma levels of 5-ASA and its *N*-acetylated metabolite (4.5-fold and 2.5-fold, respectively) than did the balsalazide-treated patients, suggesting the possibility of precolonic absorption of 5-ASA from the pH-dependent delayed-release mesalamine formulation.

A more rapid onset of action for balsalazide compared with mesalamine was also observed by Green *et al.* (13) in a previous study of both of these 5-ASA agents. In that study, the median time to the first day of complete relief of symptoms was 10 days for the 6.75 g of balsalazide daily group versus 25 days for the 2.4 g of mesalamine daily group. A significant difference between the balsalazide- and mesalamine-treated groups was also observed in all efficacy parameters measured and at all time points. However, in the study by Green *et al.* (13), 60% of the patients were newly diagnosed at the time of study entry, whereas only 16% of patients entered into the present study were newly diagnosed. The present study, therefore, enrolled a much higher percentage of patients with long-standing, relapsing disease, patients who may be more difficult to treat adequately with a single therapeutic agent.

Almost one-third ($n = 48$, 31%) of patients prematurely withdrew from the present study because of treatment failure or adverse events. Premature withdrawal because of lack of therapeutic effect was least likely in the high-dose balsalazide group ($n = 5$, 9%), followed by the mesalamine group ($n = 8$, 16%). The low-dose balsalazide group had the highest withdrawal rate ($n = 11$, 22%) among the three

treatment groups; however, differences between treatment groups in premature withdrawal rates were not significant.

At the 8-wk visit, the cumulative proportion of patients meeting all criteria for remission did not differ significantly among the three treatment groups. Remission was achieved in 23% of patients in the high-dose balsalazide group, 20% in the low-dose balsalazide group, and 19% in the mesalamine group. The remission rates observed in the present study, however, were not remarkably different from the 14% rate reported previously in another study of mesalamine (2.4 g daily) using the same remission criteria (15). The 23% complete remission rate observed for the high-dose balsalazide group is also not remarkably different than the 28% observed in another study of mesalamine 4.0 g daily (16).

Safety evaluations showed that reported adverse events were no more frequent during treatment with high-dose balsalazide than during treatment with the approved dosage of mesalamine. Balsalazide has, therefore, been shown both in long-term studies on the maintenance of remission (10, 12, 17, 18, 19) and now over the shorter term in active disease to exhibit no significant dose-related differences in safety evaluations over the dose range of 2–6.75 g daily.

This adequate and well-controlled study confirms that 8 wk of treatment with balsalazide (6.75 g daily) is safe, well tolerated, and effective in improving signs and symptoms of acute ulcerative colitis. In addition, the safety profile of balsalazide (6.75 g daily) did not differ significantly from that of balsalazide (2.25 g daily) and mesalamine (2.4 g daily).

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