U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - PEDIATRIC

NDA/Serial Number:	20-610/S-016
Drug Name:	Colazal (balsalazide disodium) capsules, 750 mg
Indication(s):	Treatment of active mildly to moderately ulcerative colitis
Applicant:	Salix Pharmaceuticals, Inc.
Date(s):	June 20, 2006
Review Priority:	Priority
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Milton C. Fan, Ph.D. , DB III
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Keywords: clinical study, ITT

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

There is an implicit assumption that the high dose (6.75 g/day) should work in children since it was found to be efficacious in adults (July 18, 2000). The design of this study allows only a description of different dose effects in children and no real conclusion can be drawn about efficacy.

For 5-to 17- year-old pediatric patients with mild to moderate active ulcerative, colitis, it was observed in this study that number of patients with clinical improvement for lower dose (2.25 g/day) was similar to that for high dose (6.75 g/day) (13 for 2.25 g/day vs. 15 for 6.75 g/day for ITT; 7 for 2.25 g/day vs. 8 for 6.75 g/day for PP). The similarity was also observed for number of patients achieving remission (3 for 2.75 g/day vs. 4 for 6.75 g/day for ITT; 3 for 2.25 g/day vs. 2 for 6.75 g/day for PP).

1.2 Brief Overview of Clinical Studies

1.2.1 Study BZUC3001

This was a multi-center (23 sites), double-blind study of balsalazide disodium in the treatment of 5- to 17-year-old pediatric patients with mild to moderate active ulcerative colitis.

The primary objective of this study was to evaluate the efficacy, safety and pharmacokinetics (PK) of 2 dosage regimens of balsalazide disodium (6.75 g/day or 2.25 g/day) in pediatric patients with mildly to moderately active ulcerative colitis (UC).

Patients were randomized to 8 weeks of treatment to receive either balsalazide disodium 6.75 g/day or balsalazide disodium 2.25 g/day. Daily doses were administered on a TID basis. Randomization was stratified based upon the 3 groups defined by patient age and agreement to participate in the PK portion of the study.

Blood samples were drawn from 12 patients (6 patients per dose group) to assess the multiple dose pharmacokinetics of the two doses of balsalazid disodium.

Male or female pediatric patients between 5 and 17 years of age with confirmed mild-to-moderate active UC with a baseline Modified Sutherland UC activity index (MUCAI) score between 4 and 10 were eligible to be enrolled into the study.

The MUCAI consists of 4 individual items: stool frequency, rectal bleeding, mucosal appearance, and physician’s rating of disease activity. Each individual item has 4 scores ranging from 0 to 3. The maximum of total MUCAI score is 12. The MUCAI was used to assess the overall disease activity of each patient during the Screening and Week 8/Final Visit.

The primary measure of efficacy was the proportion of patients with clinical improvement, defined as a reduction from baseline to Week 8 of the MUCAI total score by at least 3 points. Patients who terminated early from the study for any reason were classified as exiting the study without clinical improvement at Week 8, regardless of their clinical evaluation at the time of study withdrawal.

A total of 68 patients were randomized (33 in the 6.75 g/day group and 35 in the 2.25 g/day group). A total of 53 patients (28 in the 6.75 g/day group and 25 in the 2.25 g/day group) completed the study and had colonoscopies at Screening and Week 8 visits.

A total of 15 patients (5 in the 6.75 g/day group and 10 in the 2.25 g/day group) withdrew or were withdrawn early from the study.

A total of 29 patients (15 in the 6.75 g/day group and 14 in the 2.25 g/day group) were included in Per-Protocol Population (PP).

1.3 Statistical Issues and Findings

Sample size was based primarily on what was considered feasible rather than considerations of statistical power. A sample size of 35 evaluable patients per group would provide about 24% power to detect 15% difference observed in this study in the proportion of patients with clinical improvement, assuming 50% clinical improvement in 1 treatment and 35% clinical improvement in the other. It is insufficient power to detect treatment difference of 10% to 20%.

For primary efficacy endpoint, the proportion of patients with clinical improvement, defined as a reduction from baseline in the MUCAI total score by at least 3 points at Week 8, the sponsor's ITT analysis might be anti-conservative because of disproportionate withdrawals against the lower dose. For ITT patients who did not terminate the study early, there was no treatment difference.

There is am implicit assumption that the high dose (6.75 g/day) should work in children since it works in adults. The study design of this study allows only a description of different dose effects in children and no real conclusion can be drawn about efficacy.

2. INTRODUCTION

2.1 Overview

Colazal (balsalazide disodium) capsule was originally approved on July 18, 2000. The approved dose is 6.75 g/d. The original proposed pediatric development plan was submitted on November 9, 2000. FDA issued a Written Request – Amendment on December 15, 2005 which supersedes the Written Requests dated December 17, 2001 and December 18, 2002.

The Written Request stated that a single, pharmacokinetics (PK), safety, and efficacy study will be randomized, double-blind, and will include no less than 40 patients, 5 years to 17 years of age with mildly to moderately active ulcerative colitis. Eligible patients will be randomized to two dose levels of balsalazide disodium.

2.2 Data Sources

The sponsor has submitted one study for the claim. This study includes:

Study BZUC3001: A Multi-Center, Double-Blind Study of COLAZAL in the Treatment of 5- to 17-Year-Old Pediatric Patients with Mild to Moderate Active Ulcerative Colitis.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study BZUC3001

3.1.1.1 Study Design

This was a multi-center (23 sites), double-blind study of balsalazide disodium in the treatment of 5- to 17-year-old pediatric patients with mild to moderate active ulcerative colitis.

The primary objective of this study was to evaluate the efficacy, safety and pharmacokinetics (PK) of 2 dosage regimens of balsalazide disodium (6.75 g/day or 2.25 g/day) in pediatric patients with mildly to moderately active ulcerative colitis (UC).

Patients were randomized to 8 weeks of treatment to receive either balsalazide disodium 6.75 g/day or balsalazide disodium 2.25 g/day. Daily doses were administered on a TID basis. Randomization was stratified based upon the following 3 groups defined by patient age and agreement to participate in the PK portion of the study:

- Patient was 5 to 8 years of age;
- Patient was 9 to 17 years of age and agreed to participate in the PK portion of the study; or
- Patient was 9 to 17 years of age and did not agree to participate in the PK portion of the Study.

Blood samples were drawn from 12 patients (6 patients per dose group) to assess the multiple dose pharmacokinetics of the two doses of balsalazid disodium.

Male or female pediatric patients between 5 and 17 years of age with confirmed mild-to-moderate active UC with a baseline Modified Sutherland UC activity index (MUCAI) score between 4 and 10 were eligible to be enrolled into the study.

The MUCAI consists of 4 individual items: stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease activity. Each individual item has 4 scores ranging from 0 to 3. The maximum of total MUCAI score is 12. The MUCAI was used to assess the overall disease activity of each patient during the Screening and Week 8/Final Visit.

The pathology classification was used to assess the overall evaluation of histologic assessment of each patient during the Screening and Week 8/Final Visits. The grade of pathology classification ranges from 0 to 3.

A study patient was withdrawn from the study if, for 3 consecutive days, the patient experienced the following:

- an increase in stool frequency of 2 or more additional stools/day, or
- a clinically relevant increase in rectal bleeding based on the physician's assessment of patient diary responses.

The primary measure of efficacy was the proportion of patients with clinical improvement, defined as a reduction from baseline to Week 8 of the MUCAI total score by at least 3 points. Patients who terminated early from the study for any reason were classified as exiting the study without clinical improvement at Week 8, regardless of their clinical evaluation at the time of study withdrawal.

Secondary measures of efficacy included stool frequency, rectal bleeding, endoscopic mucosal appearance, physician's rating of disease activity, and histology index, and number of days of fever and abdominal cramps in the 7 days prior to the Week 4 and Week 8 visits.

In addition, the proportion of patients in each treatment group achieving remission as evidenced by a score of 0 or 1 (a score of 1 was only allowed on the stool frequency subscale) on the MUCAI at Week 8 was assessed. Patients who terminated early from the study were classified as exiting the study without achieving clinical remission at Week 8.

The sample size was based primarily on what was considered feasible rather than standard considerations of statistical power. However, a sample size of 40 evaluable patients (20 per group) would provide at least 80% power, using a Fisher's exact test with a 2-sided significance level of 5%, to detect a 50% difference in the proportion of patients with clinical improvement, assuming 70% clinical improvement in one treatment group and 20% clinical improvement in the other. If, however, the percentages of patients with clinical improvement were 70% and 30%, the study would have approximately 60% power.

3.1.1.2 Sponsor's Analysis

A total of 68 patients were randomized (33 in the 6.75 g/day group and 35 in the 2.25 g/day group). A total of 53 patients (28 in the 6.75 g/day group and 25 in the 2.25 g/day group) completed the study and had colonoscopies at Screening and Week 8 visits.

A total of 15 patients (5 in the 6.75 g/day group and 10 in the 2.25 g/day group) withdrew or were withdrawn early from the study.

A total of 29 patients (15 in the 6.75 g/day group and 14 in the 2.25 g/day group) were included in Per-Protocol Population (PP).

3.1.1.2.1 Planned Analysis

The primary efficacy analysis was based on an Intent-to-Treat (ITT) Population that includes all randomized patients. A Per-Protocol (PP) Population was identified, which consisted of ITT patients who did not violate the protocol and who were at least 70% compliant in taking study medication. The PP analysis utilized observed cases; no imputation was performed.

The primary efficacy endpoint was analyzed for the ITT and PP populations using a Fisher's exact test. Fisher's exact test was also used to compare the proportion of patients achieving remission between the treatment groups. Change from baseline to Week 8 in total MUCAI score was compared between treatment groups for the ITT population using analysis of covariance (ANCOVA) with dose group as a factor and baseline MUCAI value as a covariate. A rank transformation would be used if there was evidence that the data were not normally distributed. For patients that terminated early, the most recent postbaseline total MUCAI score at termination would be carried forward if available. If no postbaseline MUCAI score was available, that particular patient would be excluded from the analysis of change in total MUCAI from baseline to Week 8.

Changes from baseline at Week 8 in individual items of the MUCAI and the histological assessments were analyzed using the Wilcoxon rank-sum test. As with the analysis of total MUCAI scores at Week 8 for patients that terminated early, individual MUCAI item scores at early termination would be carried forward if available. If individual MUCAI item scores were not available postbaseline, that particular patient would be excluded from the analysis.

Similarly, Wilcoxon rank-sum tests were used to compare dose groups with respect to the number of days that abdominal cramps and fever were reported on individual patient diary card assessments in the 1-week periods preceding Week 4 and Week 8. For patients that terminated early from the study prior to Week 4 or Week 8, the most recent week of available diary data would be used to analyze number of days of abdominal craps and fever. If at least 1 week of postbaseline diary data was not available, patients would be excluded from analyses of diary data.

3.1.1.2.2 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for ITT population is given Appendix Table 1.

As seen from Appendix Table 1, no statistically significant differences between the two treatment groups were observed for demographic characteristics and baseline disease characteristics with the exception of duration of ulcerative colitis..

3.1.1.2.3 Sponsor's Analysis of Primary Efficacy Parameter

The primary measure of efficacy was the proportion of patients with clinical improvement, defined as a reduction from baseline in the MUCAI total score by at least 3 points at Week 8.

The result from sponsor's analysis of primary efficacy parameter is given below.

Proportion of Patients with Clinical Improvement

Analysis	Colazal 6.75 g/day	Colazal 2.25 g/day	Difference	95% C.I.	p-value
ITT	15/33 (45.5%)	13/35 (37.1%)	8.3%	(-15.0%, 31.7%)	0.6227
PP	8/15 (53.3%)	7/14 (50.0%)	3.3%	(-33.0%, 39.7%)	1.000

P-value was obtained using Fisher's exact test.
Copied from Tables14.2.1 and 14.2.2

As seen from table above, no statistically significant difference was observed for both ITT and PP populations.

3.1.1.2.4 Sponsor's Analysis of Secondary Efficacy Parameters

The secondary measures of efficacy were the proportion of patients achieving remission, as defined by a score of 0 or 1 (a score of 1 was only allowed on the stool frequency index) on the MUCAI at Week 8; change from baseline to Week 8 in the total score of the MUCAI; changes from baseline to Week 8 in the individual items of the MUCAI; change from baseline in pathology classification of histologic assessments of inflammation in colonic biopsies at Week 8; number of days abdominal cramps were reported on the individual patient diary card assessments in the 7 days prior to the Week 4 and Week 8 visits; and number of days fever was reported on the individual patient diary card assessment in the 7 days prior to the Week 4 and Week 8 visits.

3.1.1.2.4.1 Proportion of Patients Achieving Remission

The result from sponsor's analysis of proportion of patients achieving remission is given below.

Proportion of Patients Achieving Remission

Analysis	Colazal 6.75 g/day		Colazal 2.25 g/day		Difference 95% C.I. p-value
ITT	4/33 (12.1%)	3/35 (8.6%)	3.5%	(-10.9%, 18.0%)	0.7053

P-value was obtained using Fisher's exact test.
Copied from Table 14.2.3.

As seen from table above, no statistically significant difference was observed for ITT populations.

3.1.1.2.4.2 Change from Baseline to Week 8 in MUCAI Total Score

The results of the change from baseline to Week 8 in MUCAI total score for ITT population are summarized in Appendix Table 2.

As seen from Appendix Table 2, no statistical significant difference was observed between two treatment groups in mean change from baseline to Week 8 in MUCAI total score. Mean MUCAI total scores decreased 2.6 points in the Colazal 6.75 g/day group and 2.4 points in the Colazal 2.25 g/day group, indicating improvement in both treatment groups.

3.1.1.2.4.3 Categorical Change from Baseline to Week 8 in MUCAI Individual Items and Pathology Classification

The results of the categorical change from baseline to Week 8 in MUCAI individual items and pathology classification for ITT population are summarized in Appendix Table 3.

As seen from Appendix Table 3, higher proportions of patients in the Colazal 6.75 g/day than in the Colazal 2.25 g/day group showed improvement in the MUCAI individual items, although the differences between treatment groups were not statistically significant.

3.1.1.2.4.4 Change from Baseline to Week 8 in MUCAI Individual Items

The results of the change from baseline to Week 8 in MUCAI individual items and pathology classification for ITT population are summarized in Appendix Table 4.

As seen from Appendix Table 4, mean MUCAI individual item scores for stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease activity decreased in both treatment groups, indicating improvement. No statistically significant differences were observed between the 2 treatment groups in mean change from baseline to Week 8 in any of the MUCAI individual items.

3.1.1.2.4.5 Change from Baseline to Week 8 in Pathology Classification of Inflammation in Colonic Biopsies

Histologic assessments were available for a total 34 patients at baseline (21 in 6.75 g/day and 13 in 2.25 g/day) and 52 patients at Week 8 (26 in 6.75 g/day and 26 in 2.25 g/day). However, only 26 patients, 16 in the Colazal 6.75 g/day group and 10 in the Colazal 2.25 g/day group, had histologic assessments at both baseline and Week 8.

The results of the change from baseline to Week 8 in pathology classification of inflammation in colonic biopsies are summarized in Appendix Table 5.

As seen from Appendix Table 5, mean histologic classification decreased slightly in both treatment groups. No statistically significant difference was observed.

3.1.1.2.4.6 Number of Days with Abdominal Cramps and Fever Reported on Patient Diary Card

Patients recorded in their diary card the number of days they experienced abdominal cramps and the number of days they experienced fever.

The results of number of days with abdominal cramps, fever, and both fever and abdominal cramps reported on patient diary card by visit (LOCF) are summarized in Appendix Table 6.

As seen from Appendix Table 6, no statistically significant differences were observed between the 2 treatment groups in mean number of days with abdominal cramps, with fever, or with both fever and abdominal cramps during the 7 days prior to the Week 4 and Week 8.

3.1.1.3 Reviewer's Comments and Evaluation

3.1.1.3.1 Study Design

Sample size was based primarily on what was considered feasible rather than considerations of statistical power. A sample size 35 evaluable patients per group would provide about 24% power to detect 15% difference observed in this study in the proportion of patients with clinical improvement, assuming 50% clinical improvement in 1 treatment and 35% clinical improvement in the other. It is insufficient power to detect treatment difference of 10% to 20%.

3.1.1.3.2 Disproportionate Withdrawals

The Colazal 2.25 g/day group had higher withdrawal rate than the Colazal 6.75 g/day group (10/35 [28.6%] vs. 5/33 [15.2%], p=0.1822).

The number of patients withdrawn early from the study by reasons is given below.

Reasons for Withdrawal Early for the Study

Reaasons	Colazal 6.75g/day (n=33)	Colazal 2.25 g/day (n=35)
Adverse Event	1 (3.0%)	3 (8.6%)
Lack of efficacy	2 (6.1%)	2 (5.7%)
Protocol violation	0 (0.0%)	1 (2.9%)
Patient non-compliance	0 (0.0%)	1 (2.9%)
Patient request	1 (3.0%)	3 (8.6%)
Other	1 (3.0%)	0 (0.0%)
Total	5 (15.2%)	10 (28.6%)

3.1.1.3.3 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoints

The sponsor's ITT analysis might be anti-conservative because of disproportionate withdrawals against the lower dose.

The sponsor also performed an analysis of primary efficacy endpoint for patients who did not terminate from the study early. The results of this analysis are given below.

Proportion of Patients with Clinical Improvement
(ITT Patients who Did Not Terminate From the Study Early)

Colazal 6.75 g/day		Colazal 2.25 g/day	Difference	
			95% C.I.	p-value
15/28 (53.6%)	13/25 (52.0%)	1.6%	(-25.4%, 28.5%)	1.0000

P-value was obtained using Fisher's exact test.
Copied from Table 16.1.9.4.1.

As seen from table above, for ITT patients who did not terminate from the study early, there was not treatment difference.

3.1.1.3.4 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Endpoints

The sponsor also performed an analysis of secondary efficacy endpoint : proportion of patients achieving remission for patients who did not terminate from the study early. The results of this analysis are given below.

Proportion of Patients Achieving Remission
(ITT Patients who Did Not Terminate From the Study Early)

Colazal 6.75 g/day		Colazal 2.25 g/day		Difference	
				95% C.I.	p-value
4/28 (14.3%)	3/25 (12.0%)	2.3%	(-15.9%, 20.5%)		1.000

P-value was obtained using Fisher's exact test.
Copied from Table 16.1.9.4.2.

As seen from table above, for ITT patients who did not terminate from the study early, there was not treatment difference.

3.1.1.3.5 Reviewer's Comments on Sponsor's Analysis of Change from Baseline to Week 8 in Pathology Classification of Inflammation in Colonic Biopsies

There was a disproportionate pathology classification of inflammation in colonic biopsies at baseline (21/33 for 6.75 g/day vs. 13/35 for 2.25 g/day, p=0.0302).

3.2 Evaluation of Safety

3.2.1 Study BZUC3001

A total of 42 (62%) patients reported adverse events during the study (23 [70%] in the Colazal 6.75 g/day group and 19 [54%] in the Colazal 2.25 g/day group). Overall, the most common adverse events were headache (15%) and abdominal pain upper (13%). Most adverse events were mild or moderate in severity. No deaths were reported during the study.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

No conclusion on gender, race and age can be drawn due to limited sample size.

4.2 Other Special/Subgroup populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Sample size was based primarily on what was considered feasible rather than considerations of statistical power. A sample size of 35 evaluable patients per group would provide about 24% power to detect 15% difference observed in this study in the proportion of patients with clinical improvement, assuming 50% clinical improvement in 1 treatment and 35% clinical improvement in the other. It is insufficient power to detect treatment difference of 10% to 20%.

For primary efficacy endpoint, the proportion of patients with clinical improvement, defined as a reduction from baseline in the MUCAI total score by at least 3 points at Week 8, the sponsor's ITT analysis might be anti-conservative because of disproportionate withdrawals against the lower dose. For ITT patients who did not terminate the study early, there was no treatment difference.

5.2 Conclusions and Recommendations

There is an implicit assumption that the high dose (6.75 g/day) should work in children since it was found to be efficacious in adults (July 18, 2000). The design of this study allows only a description of different dose effects in children and no real conclusion can be drawn about efficacy.

For 5-to 17- year-old pediatric patients with mild to moderate active ulcerative, colitis, it was observed in this study that number of patients with clinical improvement for lower dose (2.25 g/day) was similar to that for high dose (6.75 g/day) (13 for 2.25 g/day vs. 15 for 6.75 g/day for ITT; 7 for 2.25 g/day vs. 8 for 6.75 g/day for PP). The similarity was also observed for number of patients achieving remission (3 for 2.75 g/day vs. 4 for 6.75 g/day for ITT; 3 for 2.25 g/day vs. 2 for 6.75 g/day for PP).

6. **APPENDIX**

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol BZUC3001

Characteristics	Colazal 6.75 g/Day (N=33)	Colazal 2.25 g/Day (N=35)	Between Treatment p-value
Sex			0.3458
Male	13 (39.4%)	10 (28.6%)	
Female	20 (60.6%)	25 (71/4%)	
Race			0.7628
White	29 (87.9%)	31 (88.6%)	
Black	2 (6.1%)	3 (8.6%)	
Asian	2 (6.1%)	1 (2.9%)	
Age (months)			0.6500
Mean (SD)	12.8 (3.6)	13.2 (3.4)	
Age			0.6507
5-8 years	5 (15.2%)	4 (11.4%)	
9-17 years	28 (84.8%)	31 (88.6%)	
Duration (Days) of UC			0.0647
Mean (SD)	253.5 (333.8)	463.7 (554.7)	
Previously Treated	23 (69.7%)	20 (57.1%)	
Diagnosis			0.1963
Proctitis	7 (21.9%)	4 (11.4%)	
Proctosigmoiditis	8 (25.0%)	4 (11.4%)	
Pancolitis	14 (43.8%)	20 (57.1)	
Intermediate colitis	3 (9.4%)	7 (20.0%)	
MUCAI Total Score	5.7 (1.6)	5.9 (1.5)	0.6174

Compiled by this reviewer. P-values were obtained by this reviewer.
Chi-square test was used for sex, age group and race. ANOVA was used for age, duration of UC, and MUCAI total score.

Table 2 Change from Baseline to Week 8 in MUCAI Total Score --- Protocol BZUC3001

Change from Baseline to Week 8 in MUCAI Total Score (ITT Population)

	Colazal 6.75 g/day	Colazal 2.25 g/day	Total	LSM Treatment Difference	p-value[a]	95% CIb
Baseline	n=33	n=35	n=68			
Mean (SD)	5.7 (1.61)	5.9 (1.49)	5.8 (1.54)			
Week 8/Final	n=29	n=27	n=56			
Mean (SD)	3.0 (2.48)	3.1 (2.11)	3.0 (2.29)			
Change from Baseline	n=29	n=27	n=56			
Mean (SD)	-2.6 (2.85)	-2.4 (1.97)	-2.5 (2.44)	-0.1	0.7185	-1.3%, 1.1%

CI = confidence interval; LSM = least squares mean.

[a] P-value from between-treatment comparison was calculated using an ANCOVA model with treatment group as a factor and baseline value as a covariate. A rank transformation was performed on the change from baseline to Week 8/Final variable for total MUCAI.

[b] The 2-sided 95% confidence interval was calculated using a normal approximation.

Table 3 Categorical Change from Baseline to Week 8 in MUCAI Individual Items and Pathology Classification --- Protocol BZUC3001

Categorical Change from Baseline to Week 8 in MUCAI Individual Items and Pathology Classification (ITT Population)

	Colazal 6.75 g/day N=33	Colazal 2.25 g/day N=35	Total N=68	p-value[a]
Change from Baseline to Week 8/Final				
Stool Frequency				0.8177
Improved[b]	11 (33%)	8 (23%)	19 (28%)	
Unchanged[c]	14 (42%)	17 (49%)	31 (46%)	
Worsened[d]	4 (12%)	2 (6%)	6 (9%)	
Rectal Bleeding				0.8038
Improved	21 (64%)	19 (54%)	40 (59%)	
Unchanged	6 (18%)	5 (14%)	11 (16%)	
Worsened	2 (6%)	3 (9%)	5 (7%)	
Mucosal Appearance				0.5389
Improved	20 (61%)	16 (46%)	36 (53%)	
Unchanged	7 (21%)	10 (29%)	17 (25%)	
Worsened	2 (6%)	1 (3%)	3 (4%)	
Physician's Rating of Disease Activity				0.7687
Improved	13 (39%)	11 (31%)	24 (35%)	
Unchanged	14 (42%)	14 (40%)	28 (41%)	
Worsened	2 (6%)	2 (6%)	4 (6%)	
Pathology Classification				0.4433
Improved	8 (24%)	3 (9%)	11 (16%)	
Unchanged	5 (15%)	5 (14%)	10 (15%)	
Worsened	3 (9%)	2 (6%)	5 (7%)	

[a] Based on the Cochran-Mantel-Haenszel Row Mean Scores test comparing the association between treatment and change-from-baseline status.

[b] Improved = reduction from baseline to Week 8/Final of the MUCAI subscore.

[c] Unchanged = MUCAI subscore was the same at baseline and at Week 8/Final.

[d] Worsened = increase from baseline to Week 8/Final of the MUCAI subscore.

Table 4 Change from Baseline to Week 8 in MUCAI Individual Items --- Protocol BZUC3001

Change from Baseline to Week 8 in MUCAI Individual Items (ITT Population)

	Colazal 6.75 g/day N=33	Colazal 2.25 g/day N=35	Total N=68	p-value[a]
Stool Frequency				
Baseline Mean (SD)	0.8 (0.74)	0.8 (0.86)	0.8 (0.80)	
Week 8/Final	n=29	n=27	n=56	
Mean (SD)	0.5 (0.87)	0.3 (0.47)	0.4 (0.71)	
Change from Baseline	n=29	n=27	n=56	
Mean (SD)	-0.2 (0.95)	-0.3 (0.66)	-0.3 (0.81)	0.8195
Rectal Bleeding				
Baseline Mean (SD)	1.6 (0.71)	1.6 (0.77)	1.6 (0.74)	
Week 8/Final	n=29	n=27	n=56	
Mean (SD)	0.6 (0.69)	0.6 (0.88)	0.6 (0.78)	
Change from Baseline	n=29	n=27	n=56	
Mean (SD)	-1.0 (0.98)	-0.9 (0.95)	-0.9 (0.96)	0.5280
Mucosal Appearance				
Baseline Mean (SD)	1.9 (0.70)	2.0 (0.86)	2.0 (0.78)	
Week 8/Final	n=29	n=27	n=56	
Mean (SD)	1.1 (0.94)	1.1 (0.72)	1.1 (0.83)	
Change from Baseline	n=29	n=27	n=56	
Mean (SD)	-0.9 (0.88)	-0.9 (0.91)	-0.9 (0.88)	0.9037
Physician's Rating of Disease Activity				
Baseline Mean (SD)	1.4 (0.56)	1.4 (0.61)	1.4 (0.58)	
Week 8/Final	n=29	n=27	n=56	
Mean (SD)	0.9 (0.74)	1.0 (0.73)	0.9 (0.74)	
Change from Baseline	n=29	n=27	n=56	
Mean (SD)	-0.5 (0.78)	-0.4 (0.80)	-0.5 (0.79)	0.8231

SD = standard deviation

[a] Based on a Wilcoxon rank-sum test comparing treatment groups.

Table 5 Change from Baseline to Week 8 in Pathology Classification of Inflammation in Colonic Biopsies --- Protocol BZUC3001

Change from Baseline to Week 8 in Pathology Classification of Inflammation in Colonic Biopsies

	Colazal 6.75 g/day N=33	Colazal 2.25 g/day N=35	Total N=68	p-value[a]
Pathology Classification				
Baseline	n=21	n=13	n=34	
Mean (SD)	1.8 (0.93)	1.5 (0.78)	1.7 (0.87)	
Week 8/Final	n=26	n=26	n=52	
Mean (SD)	1.5 (0.76)	1.5 (0.86)	1.5 (0.80)	
Change from Baseline	n=16	n=10	n=26	
Mean (SD)	-0.3 (0.79)	-0.2 (0.92)	-0.3 (0.83)	0.6132

[a] Based on a Wilcoxon rank-sum test comparing treatment groups.

Table 6 Number of Days with Abdominal Cramp, Fever, and both Fever and Abdominal Cramp Reported on Patient Diary Card by Visit (LOCF) --- Protocol BZUC3001

Number of Days with Abdominal Cramp, Fever, and both Fever and Abdominal Cramp Reported on Patient Diary Card by Visit (LOCF)

	Colazal 6.75 g/day	Colazal 2.25 g/day	Total	p-value[a]
Abdominal Cramps				
Week 4	n=31	n=30	n=61	
Mean (SD)	2.6 (2.78)	3.2 (2.94)	2.9 (2.85)	0.5381
Week 8/Final	n=31	n=30	n=61	
Mean (SD)	2.6 (2.94)	3.1 (2.65)	2.9 (2.79)	0.4190
Fever				
Week 4	n=31	n=30	n=61	
Mean (SD)	0.0 (0.00)	0.3 (1.28)	0.1 (0.90)	0.1538
Week 8/Final	n=31	n=30	n=61	
Mean (SD)	0.0 (0.00)	0.4 (1.45)	0.2 (1.02)	0.1538
Fever and Abdominal Cramps				
Week 4	n=31	n=30	n=61	
Mean (SD)	0.0 (0.00)	0.3 (1.28)	0.1 (0.90)	0.1538
Week 8/Final	n=31	n=30	n=61	
Mean (SD)	0.0 (0.0 0)	0.4 (1.45)	0.2 (1.02)	0.1538

[a] Based on a Wilcoxon rank-sum test comparing treatment groups.

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/s/

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11/20/2006 05:49:36 PM
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