

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022205Orig1s000**

**STATISTICAL REVIEW(S)**

## Memorandum of Statistical Review

Application: NDA 22205 (Review cycle 3)  
Drug: Giaso (balsalazide disodium)  
Submission date: 10/26/2009  
PDUFA date: 4/27/2010  
Medical Div: Gastroenterology Products

### *Background*

#### *Review Cycle 1*

The sponsor submitted a 505(b) (1) application for balsalazide disodium 1100 mg tablets for treatment of mildly to moderately active ulcerative colitis (UC) in adults. The balsalazide capsule formulation, Colazal, was approved in 2000. From a statistical perspective, the single clinical trial submitted in this application did not demonstrate clear evidence of efficacy that was consistent across gender subgroups.

The primary efficacy comparison showed a statistically significant difference between balsalazide (6.6 g/day bid) vs. placebo with regard to clinical improvement: 55% vs. 40% ( $p=0.02$ ). The male and female subgroups showed respectively: 57% vs. 20% and 54% vs. 58%. The first two components of the hierarchical secondary endpoint testing - clinical remission and mucosal healing - also showed statistically significant treatment effects. However, all these effects were mainly driven by the male subpopulation due to high placebo response in females, which was not adequately addressed by the sponsor. The Complete Response letter stated that because of the inconsistency in gender findings, the submitted study was not persuasive on its own and an additional study would be required.

#### *Review Cycle 2*

In the complete response, the sponsor provided results from an additional active-controlled study to support their claim (balsalazide disodium tables 6.6 g/day bid vs. Asacol (mesalamine) 2.4 g/day tid). The primary efficacy comparison showed the balsalazide treatment as no worse than (b) (4) of that of the control group. Both treatment groups showed a 56% rate for clinical improvement with 95% CI (b) (4). No gender differences were indicated although the female response rate for both groups was (b) (4) higher than that for males.

The sponsor conducted a meta-analysis of 16 placebo-controlled studies to justify their choice of non-inferiority margin; however, these studies were not consistent with regard to endpoints and patient populations, and only one of these studies was considered supportive for margin calculation. Based on this study, the lower confidence bound of the Asacol effect was estimated at 6%, and a 50% "preservation of effect" yielded a 3% margin.

The second complete response letter stated that based on the data supporting a much smaller margin than (b) (4) the submitted study did not show non-inferiority of balsalazide to Asacol, and moreover, without a placebo control, the new study could not provide reliable estimates of treatment effects within gender. Thus the deficiencies identified in the first review cycle were not resolved.

#### *Review Cycle 3*

The Sponsor's 10-26-2009 response to the second complete response letter was focused on the two remaining deficiencies: choice of non-inferiority margin, and gender differences in treatment effect. The sponsor argued that it was not reasonable to base the choice of a non-inferiority margin on a single study and that a 50% reduction of the lower confidence bound was not ideal. The sponsor re-analyzed the data from the pivotal study based on the endpoint in the supportive historical study to show that a (b) (4) margin was met. Additional analyses were also provided to further argue that a (b) (4) margin was supportable for the original endpoint. The sponsor re-

analyzed primary and secondary endpoints to support their contention that the high placebo response in females was a spurious finding for the primary endpoint and that treatment differences were consistent across secondary endpoints. However, the sponsor also argued that the high female placebo response may have resulted from the natural time-course of the disease in those subjects.

#### *Recommendations and Conclusions*

The sponsor's third cycle response did not provide a compelling justification for the choice of a (b) (4) non-inferiority margin. Although the statistical team agrees that it may not be appropriate to base a margin calculation on a single study. A margin choice that is satisfactory from both a sponsor and regulatory perspective remains to be determined.

The new analyses of potential gender effects are also not convincing since it seems clear that high female placebo response trends persisted in both primary and secondary endpoint comparisons. In the absence of an additional placebo controlled study, the resolution of this matter does not seem likely.

At the time of this review, the medical division is considering approval of this product for males only with a possible follow-up efficacy study in females under a post-marketing agreement. The statistical team agrees that the two clinical studies support efficacy of balsalazide for use in the male population and concurs with this regulatory action.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22205

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ORIG-1

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SALIX  
PHARMACEUTICA  
LS INC

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BALSALAZIDE DISODIUM  
TABLETS

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/s/  
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MICHAEL E WELCH

04/26/2010



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 22-205  
**Drug Name:** Balsalazide Disodium 6.6g/day BID Tablets (Giazo)  
**Indication(s):** Treatment of Mildly to Moderately Active Ulcerative Colitis  
**Applicant:** Salix Pharmaceuticals  
**Date(s):** Stamp: June 30, 2008; PDUFA December 31, 2008  
**Review Priority:** Standard  
**Biometrics Division:** Division of Biometrics III  
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**Keywords:** NDA review, clinical studies, non-inferiority

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

In our review of the original submission, we concluded that the single, placebo-controlled study of balsalazide disodium tablets did not demonstrate substantial evidence of efficacy for treatment of mildly to moderately active Ulcerative Colitis (UC). In this complete response, the sponsor provided results from an additional active-controlled study to support their claim; however, primarily due to an inappropriate non-inferiority margin, we find this additional study does not show clear evidence of efficacy.

### 1.2 Brief Overview of Clinical Study

This application is a complete response to the Agency's approvable letter dated June 30, 2008. In the original submission, the sponsor's single, placebo controlled study (BZUC3002) showed a statistically significant difference between balsalazide and placebo (55% vs.40%,  $p=0.02$ ), but this was not considered substantial evidence based on a single study. Additionally, the efficacy results were largely observed within the Male subgroup. In the Female subgroup of the placebo arm there was a numerically higher response rate compared to the balsalazide group. To address these issues, the sponsor submitted the results from Study BZUC3003, which was ongoing at the time of the original submission.

Study BZUC3003 was a phase 3, double-blind, randomized, parallel-group, active-controlled, multi-center trial to show non-inferiority (NI) of balsalazide disodium tablets, 6.6g/day BID, compared to Asacol (mesalamine) 2.4 g/day TID for the treatment of mildly to moderately active ulcerative colitis for the duration of 6 weeks in subjects 18 years or older. This study enrolled 410 subjects (212 balsalazide and 198 Asacol) in 69 U.S. centers. The primary objective of the study was to establish the efficacy and safety of a new tablet formulation and dosing regimen of balsalazide disodium dosed twice daily.

### 1.3 Statistical Issues and Findings

A primary concern for this study was the choice of the (b) (4) non-inferiority margin, defined for the primary analysis based on proportions of subjects with treatment response. To justify this margin, the applicant relied on judgment from clinicians with experience in the treatment of UC and studies in the published literature.

The sponsor conducted a meta-analysis of 16 placebo-controlled trials of which 11 were for induction of UC. These studies included subjects with mild to severe UC, and, except for one, the studies were not useful for calculation of effect size of the active control. The studies used different active treatments; used different primary endpoints; were of various durations; and were conducted in different patient populations.

The size of the NI margin should have been based on placebo controlled studies of the active control (Asacol 2.4 g/day) in the same patient population and with the same endpoints as currently being studied. Based on data from the original studies for Asacol, and on data from one study submitted by the sponsor, our findings indicate that the margin should not have exceeded 3%. Since the lower confidence bound of the 95% confidence interval for the treatment difference was less than (b) (4) we do not agree with the sponsor's conclusion that balsalazide was shown to be non-inferior to Asacol.

Additionally, the sponsor's complete response did not adequately address the issue of the high placebo response rate for the Female subgroup observed in the original study. The reasons for the differential gender response remain unresolved.

We also had concerns with regard to protocol and analytical plan changes made after the study was initiated. These changes included redefining the ITT population and modifying analysis methods for the primary and the secondary endpoints.

## **2. INTRODUCTION**

### **2.1 Background**

The sponsor submitted NDA 22205 for a new dosage form of balsalazide disodium tablets, 6.6g/day BID for the treatment of mildly to moderately active ulcerative colitis.

At the end-of-phase 2 and pre-NDA meetings (meeting minutes dated Aug. 8, 2005 and Aug. 27, 2007, respectively) the sponsor was advised to submit two adequate and well-controlled studies to support the labeling claim. If a single study was to be submitted, the sponsor was advised that such a study would have to be highly statistically significant, internally consistent across subgroups and endpoints and to have no significant review issues. The sponsor acknowledged that they had a second study underway (Study BZUC3003) but chose to submit only Study BZUC3002 in support of efficacy.

Study BZUC3002 showed a statistically significant difference between balsalazide and placebo (55% vs. 40%,  $p=0.02$ ) in regards to the primary endpoint variable. Additional analyses of the components of the primary endpoint and secondary endpoints also showed significant results, except for complete remission and improvement in bowel frequency. However, the efficacy results were largely observed within the Male subgroup. In the Female subgroup of the placebo arm there was a numerically higher response rate compared to the balsalazide group. Due to the lack of a highly statistically significant result and the inconsistent gender effect, the Agency concluded that the study did not show substantial evidence of efficacy, as required for a single study.

On June 30, 2008, the sponsor submitted a second study comprising their complete response. Study BZUC3003 is a Phase 3, double-blind, randomized, parallel-group, active-controlled, multi-center trial to investigate the non-inferiority of balsalazide disodium tablets to Asacol for the treatment of mildly to moderately active ulcerative colitis for the duration of 6 weeks in subjects 18 years or older.

### **2.2 Data Sources**

This NDA was submitted in paper format. Datasets were provided electronically and are located at: [\\FDSWA150\NONECTD\N22205\N\\_000\2008-06-30](\\FDSWA150\NONECTD\N22205\N_000\2008-06-30)

## **3. STATISTICAL EVALUATION**

### **3.1 Evaluation of Efficacy**

#### **Study Design**

This was a phase 3, multi-center, 6-week, double-blind, double-dummy, randomized, active-controlled, parallel-group study conducted in the U.S. to evaluate the effectiveness and safety of balsalazide disodium tables 3.3 g BID for a total of 6.6 g/day versus mesalamine tables 0.8 g TID for a daily total of 2.4 g in 410 subjects with mildly to moderately active UC. Eligible subjects were randomized in a 1:1 ratio to receive balsalazide disodium tables or mesalamine for 6 weeks. During the study period, subjects returned to the study site at 4 scheduled visits for assessment. A complete UC assessment utilizing the Modified Mayo Disease Activity Index (MMDAI) was done at Screening, Day 1/ Baseline (utilizing the endoscopy or sigmoidoscopy results from Screening), at Week 2 and at Week 6. If a subject was withdrawn from the study prior to Week 6, a complete UC assessment utilizing the MMDAI (including

sigmoidoscopy or colonoscopy) was performed at their early termination or at 6 week, the end-of-treatment visit (EOT).

**Primary Objective**

The primary objective of the study was to establish the efficacy and safety of a new tablet formulation and dosing regimen of balsalazide disodium dosed twice daily in achieving clinical improvement in subjects with mildly to moderately active UC after 6 weeks of therapy. The primary efficacy analysis was intended to demonstrate that efficacy of balsalazide disodium tablets was non-inferior to that of mesalamine tablets (Asacol) based on the treatment response rates. Non-inferiority was to be declared if the lower limit of the two-sided 95% (asymptotic) confidence interval of the difference in treatment group responder rates (balsalazide group minus mesalamine group) was greater than or equal to (b) (4)

**Primary Efficacy Endpoints**

The primary analysis efficacy endpoint is treatment response, based on achieving both clinical improvement and improvement in the rectal bleeding subscale of the Modified Mayo Disease Activity Index (MMDAI) at the end of 6 weeks. The MMDAI evaluated four indices each on a scale of 0 (normal) to 3 (severe) with a maximum total score of 12. For individual components of the MMDAI, refer to the table below. Clinical improvement was defined as a decrease from baseline of 3 points or more in the MMDAI total score (a MMDAI total score of 0 at EOT was considered as clinical improvement in the event subjects were enrolled with an MMDAI score of 2 or less). Improvement in the bleeding subscale of the MMDAI was defined as at least a 1 point decrease from baseline (a bleeding score of 0 at EOT was automatically considered improvement in the bleeding score).

**Modified Mayo Disease Activity Index (MMDAI) or Ulcerative Colitis Symptom Score (UCSS)**

<b>Bowel Frequency</b>	<b>Bleeding</b>	<b>Physician’s Global Assessment</b>	<b>Endoscopy/Sigmoidoscopy Findings</b>
0 = Normal number of stools per day for this subject	0 = No blood seen	0 = Normal	0 = Normal or inactive disease
1 = 1 to 2 more stools than normal	1 = Streaks of blood with stool less than half the time	1 = Mild disease	1 = Mild disease (erythema, decreased vascular pattern)
2 = 3 to 4 more stools than normal	2 = Obvious blood with stool most of the time	2 = Moderate disease	2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = 5 or more stools than normal	3 = Blood alone passed	3 = Severe disease	3 = Severe disease (spontaneous bleeding, ulceration)

For the bowel frequency calculation, a reference point of the normal number of daily bowel movements was obtained. A MMDAI bowel frequency grade from 0 to 3 was assigned on each day over the 3 days prior to the study visit. The average score over the previous 3 days was the overall MMDAI bowel frequency subscale score.

**Secondary Endpoints**

The key secondary analysis endpoints in hierarchical order are:

1. The proportion of subjects with clinical remission at Week 6/EOT, where clinical remission was defined as a score of 0 for rectal bleeding and a combined score of 2 or less for bowel frequency and physician’s assessment using the MMDAI subscales.

2. The proportion of subjects with mucosal healing at Week 6/EOT, where mucosal healing was defined as an endoscopy/sigmoidoscopy score of 0 or 1.
3. The proportion of subjects with improvement from baseline to Week 6/EOT in the MMDAI subscale of physician's assessment.
4. The proportion of subjects with improvement from baseline to Week 6/EOT in the MMDAI subscale of rectal bleeding.
5. The proportion of subjects with improvement from baseline to Week 6/EOT in the MMDAI subscale of bowel frequency.
6. The proportion of subjects achieving complete remission at Week 6/EOT, where complete remission was defined as a MMDAI score of at most 1.

### **Sample Size Calculation**

The sponsor assumed that 50% of the subjects receiving balsalazide tablets and 45% of the subjects receiving mesalamine would be treatment responders. The sponsor used a one-sided significance level of 2.5% and a non-inferiority margin of (b) (4). The sponsor determined that 200 subjects randomized to each treatment group would provide 85% power to reject the null hypotheses that balsalazide was inferior to mesalamine by more than (b) (4).

We remark that for NI sample size calculations, it is preferable to assume equal group response rates under the alternative hypothesis. If a response rate of 50% is assumed for both treatment groups, then 200 subjects per group gives only about 64% power to correctly reject the null hypothesis.

### **Multiple Comparison/Multiplicity**

The applicant planned statistical testing of the multiple secondary endpoints in a hierarchical step down manner to control the overall type I error at 0.05.

### **Analysis Population and Subject Allocation**

In the first protocol amendment the sponsor indicated that the analyses of efficacy were to be performed for the ITT population and that the per-protocol (PP) population was to be used as a sensitivity analyses. However, in the final submission, the primary statistical analysis was done using the PP population; and a sensitivity analysis was performed for the Intent-to-Treat (ITT) population. In this review, we analyzed and are reporting the data for ITT and PP populations, as well as all for all randomized subjects.

The sponsor's definition of ITT population was changed from all randomized subjects to all randomized subjects who took at least 1 dose of study drug and who met inclusion criterion # 6, which was described as "The subject had a baseline MMDAI score between 6 and 10, inclusive (i.e., mildly to moderately active UC). Additionally, subjects must have scored at least  $\geq 2$  on the MMDAI bleeding component and  $\geq 2$  on the MMDAI endoscopy/sigmoidoscopy component of the clinical study protocol".

The PP population included all subjects in the ITT population without a major protocol deviation and with at least one post-baseline primary efficacy assessment.

### **Changes to the Protocol**

The original protocol was dated February 15, 2006. The study initiated on May 10, 2006 and was completed on August 10, 2007. The protocol was amended 3 times during the study. Amendment 01 was

issued August 8, 2006, approximately 3 months after start of the study. Amendment # 02 was dated November 22, 2006, approximately 5.5 months after initiating the study. Amendment # 03 was dated August 3, 2007, near the study completion date of August 10, 2007.

Amendment #1:

- 1) The statistical analysis section was updated to clarify the statistical methods planned to be used.
- 2) The definition of Intent-to-Treat (ITT) population was changed from all randomized subjects to all randomized subjects who took at least 1 dose of study drug and who met inclusion criterion # 6, which was described as “The subject had a baseline MMDAI score between 6 and 10, inclusive (i.e., mildly to moderately active UC). Additionally, subjects must have scored  $\geq 2$  on the MMDAI bleeding component and  $\geq 2$  on the MMDAI endoscopy/sigmoidoscopy component of the clinical study protocol”.
- 3) The abbreviated MMDAI score calculation was added for efficacy assessments in this amendment
- 4) A Last Observation Carried Forward (LOCF) rule was specified for handling of missing data. Specifically, if components of the MMDAI were missing, the value of the component recorded at the closest prior visit was to be used.
- 5) Clarification was added that the analyses of baseline characteristics and efficacy were to be performed for the ITT population and that the primary efficacy analysis was to be performed on the PP population as a sensitivity analyses.
- 6) The planned efficacy analysis was updated to specify that treatment differences for mean change from baseline in each of the individual MMDAI subscales were to be analyzed at listed time points using a mixed effects model, adjusting for baseline value and analysis center. Further clarification was added to specify that treatment differences in the proportion for each MMDAI subscale were to be analyzed using the CMH test stratified by analysis center at each of the listed time points.
- 7) The definition of treatment failure was clarified to include subjects who terminated early due to lack of efficacy for GI reasons.

Amendment #2: No significant changes were made in this amendment.

Amendment #3: The sponsor updated their statistical analysis section to clarify the statistical methods planned for use. Also, the secondary efficacy endpoints were reorganized and divided between key secondary endpoints and other secondary endpoints to allow for hierarchical testing. The statistical analysis section of the protocol was also updated to reflect these changes in organization.

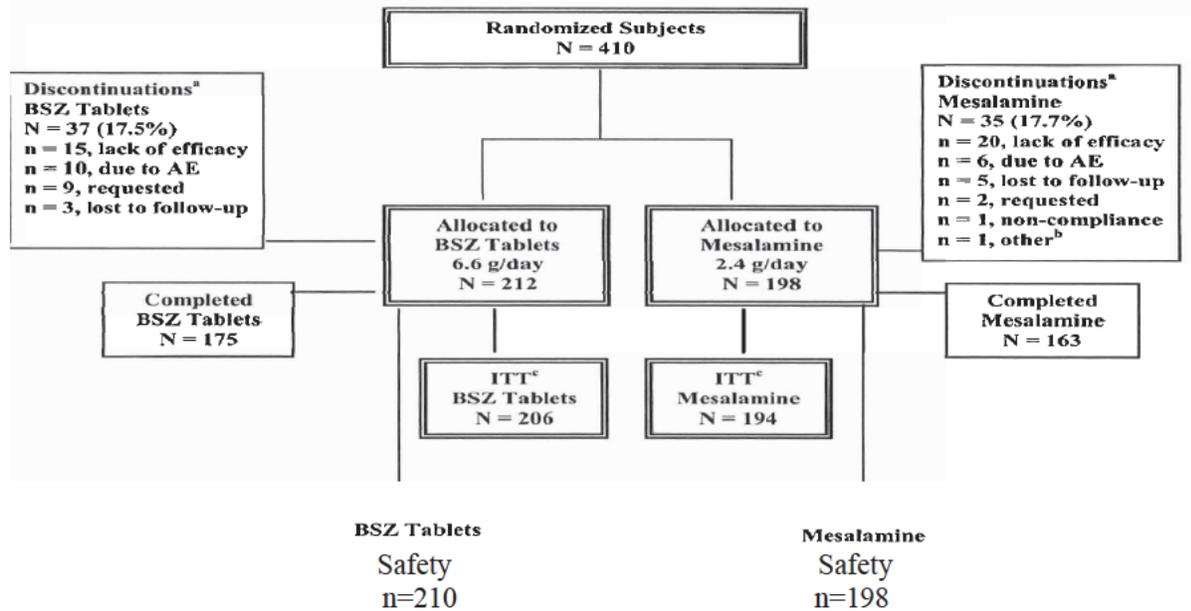
### **3.2 Efficacy Results**

#### **Subject Disposition, Demographics and Baseline Characteristics**

A total of 10 subjects (6 in balsalazide and 4 in Mesalamine treatment groups) were excluded from the ITT population because they did not meet the inclusion criterion # 6; meaning that the subject did not have a baseline MMDAI score between 6 and 10, inclusive (i.e., mildly to moderately active UC). Or, subject did not have a score of at least 2 on the MMDAI bleeding component and at least 2 on the MMDAI endoscopy/sigmoidoscopy component.

The population for this active-controlled study was primarily white (86%), had a mean age of 42 years (5% age 65 years or older) and 52% were female. The median baseline MMDAI total score was 8.2 (70% ≥ 8) with a median baseline subscale of 2.0 for all MMDAI subscales findings.

The figure below illustrates subject disposition. Additional tables on disposition and baseline characteristics are provided in the Appendix.



Source: Sponsor’s Submission – Figure 5 Subject Disposition, Page 65 of Vol. 1 of 59

**Analyses of the Primary Endpoint**

Table 1 shows the primary endpoint variable compared across both treatment groups for Study BZUC3003.

**Table 1: Proportion of Subjects Achieving Treatment Response – Primary Endpoint - Reviewer’s Results (Study BZUC3003 - PP Population)**

Balsalazide (6.6 g) (95% CI)	Mesalamine (2.4 g) (95% CI)	Difference (95% CI)
(b) (4) (61.7%) (b) (4)	(b) (4) (60.8%) (b) (4)	0.9% (b) (4)

\*95% CI was calculated using StatXact

As it is shown in Table 1, the lower bound of the 95% CI for the difference between balsalazide and mesalamine treatment response is (b) (4). These results are consistent with the sponsor’s.

**Sensitivity Analyses**

A sensitivity analysis was performed using the ITT population.

**Table 2: Proportion of Subjects Achieving Treatment Response – Primary Endpoint – Reviewer’s Results (Study BZUC3003 – ITT Population)**

Balsalazide (6.6 g) (95% CI)	Mesalamine (2.4 g) (95% CI)	Difference (95% CI)
(b) (4) = 56.3% (b) (4)	(b) (4) = 56.2% (b) (4)	0.1% (b) (4)

\* 95% CI was calculated using StatXact

As it can be seen in Table 2, the results of the analysis of ITT were comparable to that of the PP population. These results are consistent with the applicant’s results.

A total of 10 subjects had been excluded from the analyses of efficacy based on the sponsor’s revised definition of ITT. For this reason, we conducted an analysis which included all randomized subjects regardless of the amended inclusion criterion #6. For a conservative approach, we coded these subjects as failures. Furthermore, we conducted an analysis of ITT for all randomized subjects and coded subjects who withdrew from the study immaturely, as failures. Table 3 shows these results.

**Table 3: Proportion of Subjects Achieving Treatment Response – Primary Endpoint – Reviewer’s Results (Study BZUC3003 – All Randomized Population)**

	Balsalazide (6.6 g)	Mesalamine (2.4 g)	Difference (95% CI)
Sponsor’s Data**	(b) (4) = 54.7%	(b) (4) = 55.1%	-0.3% (b) (4)
Reviewer’s Data***	(b) (4) = 53.3%	(b) (4) = 54.6%	-1% (b) (4)

\*95% CI was calculated using StatXact

\*\*In this analysis Sponsor coded the drop outs as failures only for lack of efficacy or related AE reasons

\*\*\*In this analysis all drop outs are coded as failure; regardless of the reason

The results for all-randomized subjects were comparable to that of PP and ITT population analyses. However, when we considered all drop-outs as failures, regardless of the reason, the lower limit of the 95% CI for the difference in the induction rate exceeded the (b) (4) margin.

The analysis of the primary endpoint variable was repeated controlling for center effect, the results did not indicate a treatment-center interaction.

**Sponsor Justification for the Non-Inferiority Margin**

For the non-inferiority (NI) trial design, the NI margin that the sponsor chose was not appropriate. Their data and explanation for the (b) (4) NI margin is not convincing. To justify this margin, the applicant relied on "input from clinicians with experience in the treatment of active UC" or by referring to the published literature.

The sponsor conducted a meta-analysis of 16 placebo-controlled trials (between years 1967 to 1989); of which, 11 studies were for induction of UC. All these studies included subjects with mild to severe UC. However, these studies, except for one, cannot be used to support the choice of NI margin, for the following reasons:

- Different active treatments; only one study used Mesalamine as the comparator
- Various durations, ranging from 14 to 42 days

- Different inclusion/exclusion criteria
- Different primary endpoints

The one article the sponsor submitted that provides support for the Asacol effect size was based on Sninsky, et al. This study showed 10/44 (23%) patients in the Asacol 2.4 treatment arm and 21/43 (49%) patients in the placebo-treatment arm who achieved clinical improvement using a primary endpoint similar to the one in BZUC3003. A treatment effect for Asacol is estimated as 49% – 23% = 26% with a 95% Confidence Interval: (6%, 45%). According to the ICH E10 Guidance, the margin chosen for a non-inferiority trial “cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial”. Following Agency standard statistical practice, the *smallest* effect is estimated as 50% of the lower confidence bound, and would be 3% according to the Sninsky study. Based on data from the original studies for Asacol, a similar margin is obtained.

### **Analyses of the Secondary Endpoints**

For the key secondary efficacy endpoints, the proportion of subjects that achieved clinical remission (37.4% versus 34.0%), mucosal healing (51.5% versus 47.4%), improvement in physician’s assessment of disease (60.7% versus 55.7%), improvement in rectal bleeding (70.4% versus 71.6%), improvement in bowel frequency (53.4% versus 53.6%), and complete remission (13.1% versus 14.4%) was comparable between the balsalazide disodium tablet and mesalamine groups, respectively. The lower confidence bounds for the differences in proportions varied from -5% to -10%.

It should be noted that the sponsor was planning to perform a NI comparison for each of these endpoints; however, that would have required separate and sufficient margin justifications for each endpoint, which the sponsor did not provide; and since the primary endpoint results are in question, the interpretation of the secondary results should be considered exploratory.

**Table 4: Proportion of Subjects Achieving Response Secondary Endpoints – Reviewer’s Results (Study BZUC3003 – All Randomized Population)**

	<b>Balsalazide (6.6 g) (n=206)</b>	<b>Mesalamine (2.4 g) (n=194)</b>	<b>Difference (95% CI)</b>
clinical remission	77/206=37.4%	66/194=34.0%	3% (-6%, 13%)
mucosal healing	106/206=51.5%	92/194=47.4%	4% (-6%, 14%)
improvement in physician’s assessment	125/206=60.7%	108/194=55.7%	5% (-5%, 15%)
improvement in rectal bleeding	145/206=70.4%	139/194=71.7%	-1% (-10%, 8%)
improvement in bowel frequency	110/206=53.4%	104/194=53.6%	-0.2% (-10%, 10%)
Improvement in Sigmoidoscopy	119/206=57.8%	102/194=52.6%	5% (-5%, 15%)
complete remission	27/206=13.1%	28/194=14.4%	-1% (-8%, 6%)

\*95% CI was calculated using StatXact

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age and Other Special/Subgroup Populations

Table 5 shows the analysis of efficacy for the primary endpoint by gender, age category (<65 and =>65), race, disease severity and prior Colazal therapy.

In the exclusion criteria, the sponsor defined prior therapy as: “Had not taken greater than 4.8 g/day of Asacol, greater than or equal to 6.75 g/day of Colazal, or greater than 2.4 g/day of mesalamine or equivalent daily dose using any other 5-aminosalicylic acid (5-ASA) products at any time during the 14 days preceding the initiation of study medication.” The following subgroup efficacy analysis for prior 5-ASA use is based on whether or not a subject ever used Colazol.

**Table 5: Proportion of Subjects Achieving Treatment Response – Primary Endpoint by Subgroup Reviewer’s Results (Study BZUC3003 - ITT Population)**

	Balsalazide (6.6 g) (95% CI)	Mesalamine (2.4 g) (95% CI)	Difference (95% CI) *
Sex			
Male	(b) (4) =51%	(b) (4) =49%	2% (b) (4)
Female			(b) (4)
Age Category			
<65	107/194=55%	106/185=57%	-2% (-12%, 8%)
=>65	9/12=75%	3/9=33%	42% (-3%, 71%)
Race			
White	99/179=55%	89/165=54%	1% (-9%, 12%)
Non-White	17/27=63%	20/29=69%	-6% (-31%, 19%)
Disease Severity			
Mild	30/59=51%	34/59=58%	-7% (-25%, 11%)
Moderate	86/147=59%	75/135=56%	3% (-9%, 15%)
Prior 5ASA Use			
Yes	92/160=57.5%	86/159=54%	3% (-8%, 14%)
No	24/46=52%	23/35=66%	-14% (-34%, 8%)

\* 95% CI was calculated using StatXact

These results indicate that the balsalazide response rate for the Female subgroup is slightly higher than that for males; in the original study the the Male and Female responses were 57% and 54%, respectively. Due to the lack of a placebo control in this study, one cannot assess the differential gender response issue. Although the (b) (4) Female response is higher than the 58% Female placebo response observed in Study BZUC3002, this difference is not statistically significant.

The table below shows change from baseline in MMDAI component scores. Consistent with the above results, the Female subgroup appears to show better response to treatment compared to the Male subgroup.

**Table 6: Change from Baseline in Each Index of the MMDAI for Study BZUC3003 – By Gender - Reviewer’s Results**

	<b>Balsalazide (6.6 g)</b> Mean ± Std. (n)	<b>Mesalamine</b> Mean ± Std. (n)	Difference (95% CI) *
<b>Bleeding</b>			
Male	-1.05 ± 0.93 (98)	-1.02 ± 0.93 (94)	-0.03 (-0.29, 0.24)
Female			(b) (4)
<b>Bowl Frequency</b>			
Male	-0.61 ± 1.05 (98)	-0.73 ± 1.09 (94)	0.12 (-0.18, 0.43)
Female			(b) (4)
<b>Physician Assessment</b>			
Male	-0.66 ± 0.80 (98)	-0.64 ± 0.90 (94)	-0.02 (-0.27, 0.22)
Female			(b) (4)
<b>Endoscopy/Sigmoidoscopy</b>			
Male	-0.67 ± 0.79 (89)	-0.67 ± 0.85 (86)	<0.001 (-0.24, 0.25)
Female			(b) (4)

\* Using Proc GLM by gender in SAS

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

For the non-inferiority (NI) trial design, the NI margin that the sponsor chose was not appropriate. Their data and explanation for the (b) (4) NI margin is not convincing. To justify this margin, the applicant relied on "input from clinicians with experience in the treatment of active UC" or by referring to the published literature.

The choice of NI margin was not made on the basis of placebo controlled studies of the active control (Asacol 2.4 g/day) in the same patient population and with the same endpoints as currently being studied. Based on data cited by the sponsor as well as data from the original NDA studies for Asacol, and applying the Agency’s procedures for margin selection, our findings indicate that the margin should not exceed 3%. Based on that criterion, study BZUC3003 does not support the non-inferiority of balsalazide compared to Asacol.

### 5.2 Conclusions and Recommendations

In our review of the original submission, we concluded that the single, placebo-controlled study of balsalazide disodium tablets did not demonstrate substantial evidence of efficacy for treatment of mildly to moderately active Ulcerative Colitis (UC). In this complete response, the sponsor provided results from an additional active-controlled study to support their claim; however, due to the lack of a placebo control arm and an inappropriate non-inferiority margin, we find this additional study does not show clear evidence of efficacy.

**Appendix Table 1: Subject Disposition**

<b>Disposition</b>	<b>BSZ Tablets 6.6 g/day (N=212)</b>	<b>Mesalamine 2.4 g/day (N=198)</b>	<b>Total (N=410)</b>
<b>N (%) Subjects randomized</b>	212 (100.0)	198 (100.0)	410 (100.0)
<b>N (%) Subjects who completed the study</b>	175 (82.5)	163 (82.3)	338 (82.4)
<b>N (%) Subjects withdrawn early<sup>a</sup></b>	37 (17.5)	35 (17.7)	72 (17.6)
<b>Reasons for withdrawal</b>			
Adverse event	10 (4.7)	6 (3.0)	16 (3.9)
Lost to follow-up	3 (1.4)	5 (2.5)	8 (2.0)
Lack of efficacy	15 (7.1)	20 (10.1)	35 (8.5)
Subject request to withdraw	9 (4.2)	2 (1.0)	11 (2.7)
Noncompliance	0 (0.0)	1 (0.5)	1 (0.2)
Other	0 (0.0)	1 (0.5)	1 (0.2)
<b>Time to termination (days) (%)<sup>b</sup></b>			
1 day	0 (0.0)	0 (0.0)	0 (0.0)
>1 day to ≤ 7 days	0 (0.0)	0 (0.0)	0 (0.0)
>7 days to ≤ 14 days	5 (2.4)	2 (1.0)	7 (1.7)
>15 days to ≤ 42 days	47 (22.2)	58 (29.3)	105 (25.6)
>42 days	160 (75.5)	138 (69.7)	298 (72.7)
<b>Mean time to study termination (days)</b>			
N	212	198	410
Mean (SD)	45.2 (13.61)	44.7 (11.59)	44.9 (12.66)
Median	44.0	43.0	44.0
Min, Max	8, 127	8, 72	8, 127

Source: Sponsor's Submission – Table 5 Summary of Subject Disposition – All Randomized Subjects, Page 66 of Vol. 1 of 59

**Appendix Table 2: Subject Demographics and Baseline Characteristics**

<b>Parameter/Statistic</b>	<b>BSZ Tablets 6.6 g/day (N=206)</b>	<b>Mesalamine 2.4 g/day (N=194)</b>	<b>Total (N=400)</b>
<b>Age (years): n (%)<sup>a</sup></b>			
N	206	194	400
Mean (SD)	42.6 (12.97)	41.5 (13.49)	42.1 (13.22)
Median	42.0	40.0	41.0
Range (Min, Max)	18, 79	19, 72	18, 79
<b>Age group (years)</b>			
<65: n (%)	194 (94.2)	185 (95.4)	379 (94.8)
≥65: n (%)	12 (5.8)	9 (4.6)	21 (5.3)
<b>Sex: n (%)</b>			
Male	99 (48.1)	94 (48.5)	193 (48.3)
Female	107 (51.9)	100 (51.5)	207 (51.8)
<b>Race: n (%)</b>			
American Indian or Alaskan Native	2 (1.0)	2 (1.0)	4 (1.0)
Asian	4 (1.9)	3 (1.5)	7 (1.8)
Black or African American	20 (9.7)	23 (11.9)	43 (10.8)
White	179 (86.9)	165 (85.1)	344 (86.0)
Other	1 (0.5)	1 (0.5)	2 (0.5)
<b>Ethnicity: n (%)</b>			
Hispanic or Latino	27 (13.1)	21 (10.8)	48 (12.0)
Not Hispanic or Latino	179 (86.9)	173 (89.2)	352 (88.0)
<b>BMI (kg/m<sup>2</sup>)<sup>b</sup></b>			
N	206	193	399
Mean (SD)	27.52 (5.76)	27.56 (5.82)	27.54 (5.78)
Median	26.31	26.43	26.36
Range (Min, Max)	17.4, 47.4	17.5, 49.8	17.4, 49.8

Source: Sponsor's Submission – Table 9 Demographic Characteristics – ITT Population, Page 72 of Vol. 1 of 59

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this page is the manifestation of the electronic signature.**  
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Mike Welch

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BIOMETRICS

Submitting to DFS for Shahla Farr. Concur with review.



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 22-205 Ser 000  
**Drug Name:** Balsalazide Disodium Tablets  
**Indication(s):** Treatment of Mildly to Moderately Active Ulcerative Colitis  
**Applicant:** Salix Pharmaceuticals  
**Date(s):** Stamp: July 18, 2007; PDUFA May 18, 2008  
**Review Priority:** Standard  
**Biometrics Division:** Division of Biometrics III  
**Statistical Reviewer:** Shahla S. Farr, M.S.  
**Concurring Reviewer:** Mike Welch, Ph.D.  
**Medical Division:** Division of Gastroenterology Products  
**Clinical Team:** Fathia Gibril, M.D., Ruyi He, M.D. (TL)  
**Project Manager:** Heather Buck, M.S., M.B.A.

**Keywords:**

one study application, subgroup analysis

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## **1. EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

From a statistical perspective, the single clinical trial submitted in this application does not demonstrate substantial evidence of efficacy for Balsalazide Disodium tablets in treating subjects with mildly to moderately active Ulcerative Colitis. It is recommended that the sponsor provide results from one additional trial to replicate the results observed in this study.

### **1.2 Brief Overview of Clinical Study**

The principle efficacy study is BZUC3002, a multi-center, randomized, double blind, placebo controlled study of 250 subjects with mildly to moderately active Ulcerative Colitis (UC). Subjects were randomized 2:1 to receive the test product (Balsalazide) or placebo at three tablets two times daily for a total daily dose of 6.6 g for 8 weeks. The objective of this study was to demonstrate the safety as well as the <sup>(b) (4)</sup> of Balsalazide to placebo.

The primary analysis endpoint was the proportion of subjects who, at end of study, experienced both clinical improvement (defined as a 3 point or greater decrease from baseline in the Modified Mayo Disease Activity Index (MMDAI)) and improvement in rectal bleeding as defined by a decrease of at least 1 point in the rectal bleeding sub-score of the MMDAI.

### **1.3 Statistical Issues and Findings**

The primary efficacy comparison showed a statistically significant difference between Balsalazide and Placebo ( $p=0.02$ ). Additional analyses of the components of the primary endpoint and secondary endpoints also showed significant results, except for complete remission and improvement in bowl frequency. However, a p-value of .02 may not be considered as showing substantial evidence of efficacy for a single study. Achieving statistical significance at a level of .001 or less would have provided clearer evidence that the study results could have been replicated in a second study.

However, for a single study, it is expected that efficacy results are consistent across subgroups. In this study, the efficacy results are largely observed within the Male subgroup. In the Female subgroup of the placebo arm there is a numerically higher response rate compared to the Balsalazide group. This effect has not been adequately explained by the sponsor.

## **2. INTRODUCTION**

### **2.1 Overview**

The sponsor submitted a 505(b) (1) application for Balsalazide disodium 1100 mg tablets for treatment of mildly to moderately active ulcerative colitis (UC) in adults. The Balsalazide capsule formulation, Colazal Capsules, 750 mg, was approved under NDA 20610 in July, 2000.

At the end-of-phase 2 and pre-NDA meetings (meeting minutes dated Aug. 8, 2005 and Aug. 27, 2007, respectively) the sponsor was advised to submit two adequate and well-controlled studies to support the labeling claim. If a single study was to be submitted, the sponsor was advised that such a study would have to be highly statistically significant, internally consistent across subgroups and endpoints and not

have significant review issues. The sponsor acknowledged that they had a second study underway (Study BZUC3003) but chose to submit only Study BZUC3002 in support of efficacy.

Study BZUC3002 is a multi-center, randomized, double blind, placebo controlled study of 250 subjects with mildly to moderately active UC. Subjects, from 55 U.S. sites, were randomized 2:1 to receive the test product or placebo at three tablets two times daily for a total daily dose of 6.6 g for 8 weeks. (The corresponding daily dose for the capsule formulation is 6.75 g /day for eight weeks.)

The sponsor also submitted interim safety results from Study BZUC3005, an open-label, long-term safety study currently ongoing. Refer to the Medical Officer's review for the safety assessment.

## **2.2 Data Sources**

This NDA was submitted in paper format. Datasets were provided electronically and are located at: \\FDSWA150\NONECTD\N22205\N\_000\2007-07-16

In response to the reviewer's information request, the sponsor submitted another dataset which is located at: \\FDSWA150\NONECTD\N22205\N\_000\2007-11-21

## **3. STATISTICAL EVALUATION**

### **3.1 Evaluation of Efficacy**

#### **Study Design:**

This is a multi-center, randomized, double blind, placebo controlled study of 250 male and non-pregnant females ages 18 and older with mildly to moderately active UC. Subjects, from 55 US sites, were randomized 2:1 to receive the test product or placebo at three tablets two times daily for a total daily dose of 6.6 g for 8 weeks. (The corresponding daily dose for the capsule formulation is 6.75 g /day for eight weeks.) The study schedule allowed for five visits after a 3 to 7 day screening period. Efficacy evaluations based on the Modified Mayo Disease Activity Index (MMDAI) were conducted at each of five visits. The primary endpoint evaluation included a sigmoidoscopy examination, conducted at screening (Visit 0) and end of study (Visit 5). The study included a two-week follow-up period for additional safety data collection.

#### **Primary Objective:**

The objective of this study was to establish the efficacy and safety of a new tablet formulation and dosing regimen of Balsalazide disodium tablets dosed twice daily in achieving clinical improvement in subjects with mildly to moderately active UC after 8 weeks of therapy.

#### **Primary and Secondary Endpoint Efficacy:**

The primary analysis endpoint is the proportion of subjects who achieved both clinical improvement and improvement in the rectal bleeding as measured by the bleeding sub-scale of the MMDAI at the end of eight weeks of therapy. Clinical improvement is defined as a 3 point or greater improvement from baseline in the MMDAI, Improvement in rectal bleeding required an improvement from baseline by at least one unit on the MMDAI bleeding subscale.

The MMDAI consists of four indices, each on a scale of 0 to 3 with a maximum total score of 12. These indices are: 1) Bowel Frequency, 2) Bleeding, 3) Physician's Global Assessment and 4)

Endoscopy/Sigmoidoscopy Findings. Mildly to moderately active ulcerative colitis was defined as a MMDAI score between 6 to 10, a rectal bleeding score of at least 2, and an endoscopy/sigmoidoscopy score of at least 2. See the table below.

**Modified Mayo Disease Activity Index (MMDAI) or Ulcerative Colitis Symptom Score (UCSS)**

Bowel Frequency	Bleeding	Physician’s Global Assessment	Endoscopy/Sigmoidoscopy Findings
0 = Normal number of stools per day for this subject	0 = No blood seen	0 = Normal	0 = Normal or inactive disease
1 = 1 to 2 more stools than normal	1 = Streaks of blood with stool less than half the time	1 = Mild disease	1 = Mild disease (erythema, decreased vascular pattern)
2 = 3 to 4 more stools than normal	2 = Obvious blood with stool most of the time	2 = Moderate disease	2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = 5 or more stools than normal	3 = Blood alone passed	3 = Severe disease	3 = Severe disease (spontaneous bleeding, ulceration)

For the bowel frequency calculation, a reference point of the normal number of daily bowel movements was obtained. A MMDAI bowel frequency grade from 0 to 3 was assigned on each day over the 3 days prior to the study visit. The average score over the previous 3 days was the overall MMDAI bowel frequency subscale score.

**Secondary Endpoints:** Key secondary endpoints were: (1) clinical remission at week 8, defined as a score of 0 for rectal bleeding and a combined score of at least 2 for bowel frequency and physician assessment; (2) mucosal healing at week 8, defined as endoscopy score of 0 or 1; (3) improvement (from baseline) in bowel frequency; (4) improvement in rectal bleeding; (5) improvement in physicians assessment; and (6) complete remission at week 8, defined as an MMDAI score no larger than 1.

**Sample Size Calculation:**

A total of 250 male and non-pregnant women ages 18 and older from 55 centers were included in this study. Of these, 167 subjects were randomized to Balsalazide tablets and 83 to placebo.

Sample size calculation was based on showing a statistically significant difference in the proportion of subjects with clinical improvement and improvement in rectal bleeding in the two treatment arms after 8 weeks; assuming 50% success in the Balsalazide arm and 30% success in placebo arm to show clinical improvement with improvement in rectal bleeding at the end of the treatment period. With a two-sided significant level 0.05, 80% power and a 2:1 randomization ratio (Balsalazide: placebo), a total of 150 subjects were randomized to the active arm and 75 to placebo.

**Statistical Methodology:**

For the primary statistical analysis and primary comparison, the Cochran-Mantel-Haenszel (CMH) test was used stratifying by analysis center. For labeling purposes, a total of six selected secondary endpoints were analyzed using a hierarchical procedure. In order to assess center effects, the sponsor pooled the centers with insufficient number of subjects with the geographically nearest center in order to create “analysis centers” of sufficient size. This pooling was specified in the SAP.

The sponsor did not plan to adjust for covariates such as baseline characteristics or disease history. The sponsor considered subjects who dropped out of the study as treatment failures, and this was the pre-specified primary analyses.

**Multiple Comparison/Multiplicity:**

Statistical testing of the multiple secondary endpoints was performed in a hierarchical step down manner, which controlled the overall type I error at .05.

**Analysis Population:**

The primary statistical analysis was done using the Intent-to-Treat (ITT) population. The ITT population was defined as all randomized subjects who took at least 1 dose of the study drug.

**3.2 Efficacy Results**

**Patient Disposition, Demographics and Baseline Characteristics:**

Of the 167 subjects in the Balsalazide tablets arm the sponsor excluded one subject from the ITT analyses because all MMDAI scores were missing for that subject. Therefore, a total of 166 Balsalazide subjects were used for the analysis of the ITT. All 83 subjects in placebo group were included in the ITT analysis. A total of 155 subjects (62%) completed the study as shown in the table below:

<b>Patient Disposition</b>			
	<b>BSZ Tablets (n=167)</b>	<b>Placebo (n=83)</b>	<b>Total (n=250)</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>N (%)</b>
Subjects randomized	167 (100.0)	83 (100.0)	250 (100.0)
Subjects completed the study	111 (66.5)	44 (53.0)	155 (62.0)
Subjects withdrawn early	56 (33.5)	39 (47.0)	95 (38.0)
<b>Reasons for withdrawal</b>			
Adverse event	15 (9.0)	10 (12.0)	25 (10.0)
Lost to follow-up	1 (0.6)	3 (3.6)	4 (1.6)
Lack of efficacy	27 (16.2)	24 (28.9)	51 (20.4)
Subject request to withdraw	4 (2.4)	1 (1.2)	5 (2.0)
Noncompliance	2 (1.2)	1 (1.2)	3 (1.2)
Other	7 (4.2)	2 (2.4)	9 (3.6)

Ref: slightly modified from Sponsor's Table 5, Module 5, vol. 16

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A total of 121 (48.4%) male and 129 (51.6%) female subjects participated in this study. The majority (93.2%) of the subjects were older than 65 years old. More than eighty-three percent of the subjects were White. The table below illustrates the demographic characteristics. There was a baseline imbalance for BMI. There was no imbalance in baseline disease characteristics.

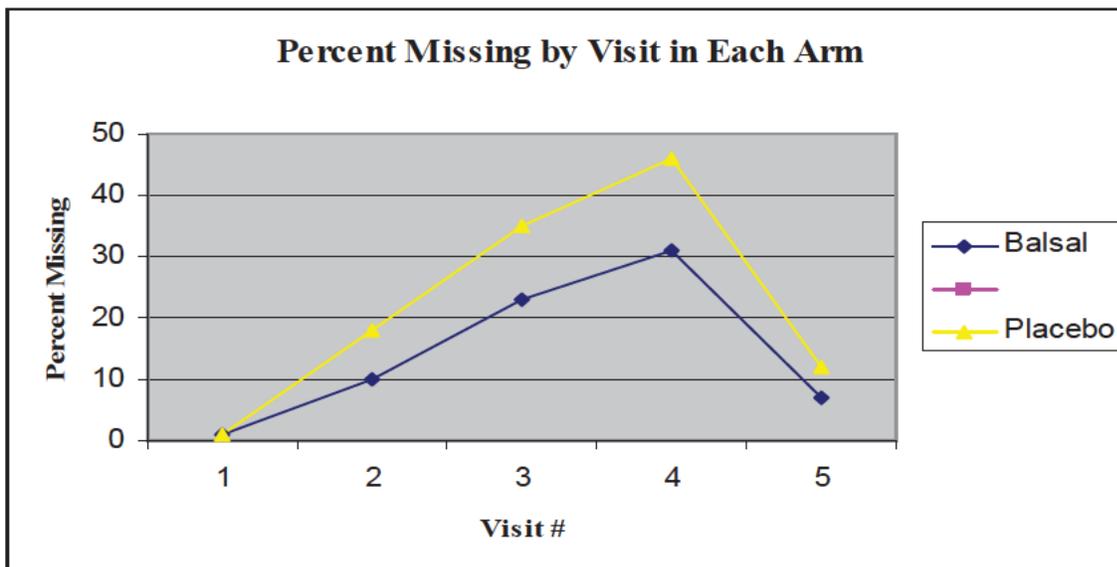
## Demographic Characteristics

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Parameter/Statistic	BSZ Tablets 6.6 g/day (N=166)	Placebo (N=83)	Total (N=249)	P-value <sup>a</sup>
<b>Age (years): n (%)<sup>b</sup></b>				
N	166	83	249	0.3128
Mean (SD)	43.6 (13.4)	45.4 (13.0)	44.2 (13.2)	
Median	42.0	48.0	43.0	
Range (Min, Max)	19, 78	21, 80	19, 80	
<b>Age group (years)</b>				0.7967
<65: n (%)	154 (92.8)	78 (94.0)	232 (93.2)	
≥65: n (%)	12 (7.2)	5 (6.0)	17 (6.8)	
<b>Sex: n (%)</b>				1.0000
Male	81 (48.8)	40 (48.2)	121 (48.6)	
Female	85 (51.2)	43 (51.8)	128 (51.4)	
<b>Race: n (%)<sup>c</sup></b>				0.3158
Asian	5 (3.0)	0 (0)	5 (2.0)	
Black or African American	22 (13.3)	11 (13.3)	33 (13.3)	
Native Hawaiian or Pacific Islander	3 (1.8)	0 (0)	3 (1.2)	
White	135 (81.8)	72 (86.7)	207 (83.5)	
<b>Ethnicity: n (%)</b>				1.0000
Hispanic or Latino	19 (11.4)	9 (10.8)	28 (11.2)	
Not Hispanic or Latino	147 (88.6)	74 (89.2)	221 (88.8)	
<b>BMI (kg/m<sup>3</sup>)</b>				0.0224
N	166	82	248	
Mean (SD)	27.4 (5.8)	29.3 (6.6)	28.0 (6.1)	
Median	26.9	27.8	27.4	
Range (Min, Max)	11, 51	20, 53	11, 53	

Ref. Sponsor's Table 8, Module 5 vol. 16

The Figure below shows the missing rate by visit for each treatment group. This illustrates that the placebo group had a consistently higher percent missing than the active treatment.



**Analyses of the Primary and Secondary Endpoints:**

Table 1 shows the primary and secondary endpoints compared across treatment groups. Subjects who had a missing values at week 8 were classified as treatment failures.

**Table 1: Number of Subjects Responding for Primary and Key Secondary Endpoints**  
(ITT population)

	Balsalazide (n=166)	Placebo (n=83)	P-Value
Primary Efficacy Endpoint	92 ( 55%)	33 (40%)	<b>.024</b>
Key Secondary Endpoints			
Clinical Remission	64 (39%)	19 (23%)	0.096
Mucosal Healing	88 (53%)	27 (33%)	0.004
Bowel Frequency	82 (49%)	31 (37%)	0.075
Rectal Bleeding	98 (59%)	35 (42%)	0.013*
Physician’s Assessment	99 (60%)	30 (36%)	<0.001*
Complete Remission	34 (20%)	11 (13%)	0.096*

\* not formally testable since bowel frequency endpoint failed hierarchical testing.

Reviewer’s table, results for secondary endpoints modified from sponsor table 2.7.3-13

As can be observed in the above table, the primary efficacy endpoint showed a statistically significant difference between Balsalazide and Placebo (p=0.02). Results of the primary analysis using the per protocol population was similar: (b) (4) (58%) vs. (b) (4) (41%) p = .019.

In the hierarchy of secondary endpoints, clinical remission and mucosal healing showed treatment benefit; however the difference in improved bowel frequency is not statistically significant. Accordingly, the remaining secondary endpoints could not be formally tested for significance, and those p values in the table are shown for exploratory purposes.

Additional sensitivity analyses were performed by the reviewer using all available, non-missing data (completer’s analysis) and a worst-case scenario was applied where the missing data were replaced by a worst possible scale value. These results did not change the efficacy conclusions in both of these cases.

There were some questions regarding the integrity of the data from study Site 216. This reviewer repeated the efficacy analyses with this center excluded. The results did not alter the conclusions.

**Additional Analyses of Secondary Endpoints:**

Tables 2 through 5 show each index of the MMDAI (bleeding, bowel frequency, physician assessment and sigmoidoscopy finding) for baseline, the end of the treatment, and the change from baseline, by severity. Comparisons were made with the Chi-square test. The p-values are presented for exploratory purposes only. These findings are generally consistent with those in Table 1.

**Table 2: Bleeding**

Treatment Arm/ Efficacy	Balsalazide	Placebo	P-Value
<b>Baseline</b>	(n=165)	(n=81)	0.96
Normal	5 (3%)	2 (2%)	
Mild	9 (5%)	4 (5%)	
Moderate	145 (88%)	71 (88%)	
Severe	6 (4%)	4 (5%)	
<b>Endo of Treatment</b>	(n=156)	(n=73)	0.08
Normal	78 (50%)	24 (33%)	
Mild	29 (19%)	15 (21%)	
Moderate	45 (29%)	32 (44%)	
Severe	4 (3%)	2 (3%)	
<b>Change from Baseline</b>	(n=156)	(n=73)	0.10
Normal	50 (32%)	32 (44%)	
Mild	28 (18%)	18 (25%)	
Moderate	72 (46%)	21 (29%)	
Severe	2 (1%)	0 (0%)	
Worse	4 (3%)	2 (3%)	

**Table 3: Bowel Frequency**

Treatment Arm/ Efficacy	Balsalazide	Placebo	P-Value
<b>Baseline</b>	(n=165)	(n=81)	0.22
Normal	11 (7%)	1 (1%)	
Mild	48 (29%)	20 (25%)	
Moderate	54 (33%)	30 (37%)	
Severe	52 (32%)	30 (37%)	
<b>Endo of Treatment</b>	(n=156)	(n=73)	0.48
Normal	50 (32%)	22 (30%)	
Mild	49 (31%)	17 (23%)	
Moderate	32 (21%)	19 (26%)	
Severe	25 (16%)	15 (21%)	
<b>Change from Baseline</b>	(n=156)	(n=73)	0.8
Normal	49 (31%)	27 (37%)	
Mild	49 (31%)	17 (23%)	
Moderate	30 (19%)	13 (18%)	
Severe	8 (5%)	6 (8%)	
Worse	20 (13%)	10 (14%)	

**Table 4: Physician Assessment**

Treatment Arm/ Efficacy	Balsalazide	Placebo	P-Value
<b>Baseline</b>	(n=165)	(n=81)	0.86
Normal	1 (1%)	0 (0%)	
Mild	19 (12%)	10 (12%)	
Moderate	139 (84%)	67 (83%)	
Severe	6 (4%)	4 (5%)	
<b>Endo of Treatment</b>	(n=154)	(n=73)	0.004
Normal	46 (30%)	11 (15%)	
Mild	59 (38%)	21 (29%)	
Moderate	44 (29%)	35 (48%)	
Severe	5 (3%)	6 (8%)	
<b>Change from Baseline</b>	(n=154)	(n=73)	0.002
Normal	48 (31%)	34 (47%)	
Mild	63 (41%)	23 (32%)	
Moderate	38 (25%)	7 (10%)	
Severe	0 (0%)	1 (1%)	
Worse	5 (3%)	8 (11%)	

**Table 5: Endoscopy/Sigmoidoscopy**

Treatment Arm/ Efficacy	Balsalazide	Placebo	P-Value
<b>Baseline</b>	(n=165)	(n=81)	0.22
Normal			
Mild	10 (6%)	1 (1%)	
Moderate	135 (82%)	69 (85%)	
Severe	20 (12%)	11 (14%)	
<b>Endo of Treatment</b>	(n=142)	(n=68)	0.005
Normal	40 (28%)	6 (9%)	
Mild	51 (36%)	23 (34%)	
Moderate	40 (28%)	31 (46%)	
Severe	11 (8%)	8 (12%)	
<b>Change from Baseline</b>	(n=142)	(n=68)	0.02
Normal	48 (34%)	31 (46%)	
Mild	50 (35%)	27 (40%)	
Moderate	39 (27%)	6 (9%)	
Severe	2 (1%)	0 (0%)	
Worse	3 (2%)	4 (6%)	

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age and Other Special/Subgroup Populations

Table 6, below, shows the overall efficacy results of the study are largely due to treatment response in the Male subgroup. Women were observed to have a high response rate in the Placebo arm, and consequently no effect was seen for the Female subgroup. The sponsor could not provide satisfactory explanation for the high placebo response for the Female subgroup.

**Table 6: Subgroup Analyses of the Primary Endpoint Variable (MMDAI)**

	Balsalazide (b) (4)	Placebo (b) (4)	P-Value
Whole Population	(b) (4)=55%	(b) (4)=40%	0.02
Sex			
Male	(b) (4)=57%	(b) (4)=20%	<0.001 (b) (4)
Female			
Age			
<65 years	86/154=56%	29/78=37%	0.007
≥65 years	6/12=50%	4/5=80%	0.25
Race			
White	74/135=55%	4/11=36%	0.05
Non-White	18/31=58%	29/72=40%	0.22
Baseline Total MMDAI			
<8 (mild disease)	36/68=53%	9/26=35%	0.11
≥8 (moderate disease)	56/98=57%	24/57=42%	0.07
Time Since Diagnosis			
Newly Diagnosed	15/25=60%	5/11=45%	0.42
Not Newly Diagnosed	77/141=55%	28/72=39%	0.03
Smoking History			
Current Smoker	12/22=36%	3/11=27%	0.14
Current Non-Smoker	80/144=56%	30/72=42%	0.05
Prior 5-ASA Treatment			
Yes	65/125=52%	26/64=41%	0.14
No	27/41=66%	7/19=37%	0.03

This reviewer performed additional subgroup analyses as shown in Tables 8 and 9 below. These results illustrate the gender effect for two of the secondary endpoints that the medical reviewer indicated as clinically important. Additional analyses by gender and center do not show that any particular center contributed to the gender effect. In twelve out of sixteen centers, males had no response to placebo, however, in all the centers, females showed at least one response to placebo

**Table 7: Clinical Remission\* By Gender**

	Balsaladize (b) (4)	Placebo (b) (4)	P-Value
Male	28/81=34.6%	5/40=12.5%	0.01
Female	(b) (4)		

\*Clinical Remission was defined as a score of 0 for rectal bleeding and combined score of <=2 for bowel frequency and physician's assessment

**Table 8: Mucosal Healing\* By Gender**

	Balsaladize (b) (4)	Placebo (b) (4)	P-Value
Male	42/81=51.9%	8/40=20.0%	<0.001
Female	(b) (4)		

\*Mucosal healing was defined endoscopy/sigmoidoscopy score of 0 or 1 at the end of treatment

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The primary efficacy endpoint comparison showed a statistically significant difference between Balsalazide Disodium tablets and Placebo (p=0.02). In addition, when the analyses were repeated to compare all the components of the primary endpoint between the two treatment groups, significant results were observed throughout, except for complete remission and the bowl frequency. However, a p-value of .02 may not be considered as showing substantial evidence of efficacy for a single study. Achieving a p-value of less than .001 would provide clearer evidence that the study results could in fact be replicated.

However, for a single study, it is expected that efficacy results are consistent across subgroups, In this study, the efficacy results are largely driven by the Male subgroup. Women were observed to have had a high response rate in the Placebo arm which results in a numerically higher response rate in placebo compared to the Balsalazide group. This effect has not been adequately explained by the sponsor.

### 5.2 Conclusions and Recommendations

Based on data from a single study and from a statistical perspective, data reported in this submission demonstrated that Balsalazide taken three tablets two times a day for a total of 6.6 g for 8 weeks does not present a compelling evidence to be efficacious in subjects with mildly to moderately active Ulcerative Colitis (UC). It is recommended that the sponsor provide one additional study to confirm the efficacy results for Balsalazide.

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Mike Welch

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BIOMETRICS

Submitting to DFS for Shahla Farr. Concur with review.

**Screening of New NDA for Statistical Filing  
Division of Biometrics 3**

**NDA #:** 22-205

**Applicant:** Salix Pharmaceuticals

**Trade/Generic Name:** Balsalazide Disodium Tablets

**Indication:** Treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older

**Date of Submission:** July 16, 2007

**Filing Meeting:** August 27, 2007

**User Fee Goal Date:** May 18, 2008

**Project Manager (Division):** Kristen Everett, RN (DGP)

**Medical Team:** Fathia Gibril, MD, Ruyi He, MD (TL)

**Statistical Reviewer:** Shahla Farr

**Filed by:** M. Welch

**Filing Decision:** This application can be filed.

**Background**

This is a 505(b)(1) application for balsalazide disodium 1100 mg tablets for treatment of mildly to moderately active ulcerative colitis (UC) in adults. The balsalazide capsule formulation, Colazal Capsules, 750 mg, was approved under NDA 20610 in July, 2000. A single study has been submitted to support the efficacy and safety for the new formulation, and additional safety data are provided from an ongoing open-label study.

**Overview of studies**

The principle efficacy study is BZUC3002, a multi-center, randomized, double blind, placebo controlled study of 250 subjects with mildly to moderately active UC. Subjects were randomized 2:1 to receive the test product or placebo at three tablets two times daily for a total daily dose of 6.6 g for eight weeks. (The corresponding daily dose for the capsule formulation is 6.75 g /day for eight weeks.) The primary analysis endpoint was the proportion of subjects who at end of study, experienced both clinical improvement (defined as a 3 point or greater decrease from baseline in the Modified Mayo Disease Activity Index (MMDAI)) and improvement in the rectal bleeding subscale of the MMDAI defined as a decrease of at least 1 point in the rectal bleeding score. Secondary endpoints were also based on combined MMDAI subscale scores including physician's assessment, mucosal healing and bleeding. The primary statistical analysis used the CMH test stratified by analysis center and shows a p-value of about .02 for the primary comparison. Secondary endpoints were tested in a hierarchical fashion. Only the first two secondary endpoints showed statistical significance.

**Potential Review Issues**

At the August 8, 2005 End of Phase 2 meeting and the August 27, 2007 pre-NDA meeting, the sponsor was advised that two adequate and well-controlled studies were recommended and that if a single study were submitted, it would be expected to show substantial evidence of efficacy. The level of evidence and data quality will be a review issue; it will be expected that efficacy results across centers, subgroups and other factors, and multiple secondary endpoints demonstrate consistent findings. The Colazol studies may provide some supportive evidence for efficacy. Other review issues include sensitivity of results to dropouts, imputation and center-pooling strategies. The reviewer should also investigate if type I error control was clearly pre-specified for both primary and secondary endpoints.

Checklist for Filing	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Study data and reports submitted to EDR according to Ectd Guidance	Access to EDR data files OK
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups	OK

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