CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022205Orig1s000

MEDICAL REVIEW(S)

Division Director Summary Review

Date	April 27, 2010
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA/BLA #	NDA 022205
Applicant Name	Salix Pharmaceuticals, Inc.
Date of Submission	October 26, 2009; Received October 27, 2009
PDUFA Goal Date	April 27, 2010
Proprietary Name / Established (USAN) Name	Giazo Balsalazide disodium
Dosage Forms / Strength	Tablet for oral administration Each tablet contains 1.1g balsalazide disodium
Proposed Indication(s)	Treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older
Recommended Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christopher Leptak, MD, PhD/John Hyde, Ph.D., MD
Statistical Review	Shahla Farr, MS/Mike Welch, PhD
CDTL Review	John Hyde, Ph.D., MD
Clinical Pharmacology	Insook Kim, PhD/ Sue-Chih Lee, PhD
CMC	Marie Kowblansky, PhD/Moo-Jhong Rhee, PhD
DMEPA	Diane Smith, PharmD/Irene Chan, PharmD, BCPS/Todd Bridges, RPh/Melina Griffis, RPh, Denise Toyer, PharmD, Carol Holquist RPh.

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
DMEPA = Division of Medication Error Prevention and Analysis

Division Director Summary Review

1. Introduction

This is the second resubmission of NDA 022205. The NDA was not approved in its original July 17, 2007, submission because the Clinical and Statistical reviewers determined that the Applicant had not established the efficacy of the product. An Approvable letter was issued by FDA on May 16, 2008. The first resubmission, on June 30, 2008, resulted in a CR letter, dated December 22, 2008, after FDA's Clinical and Statistical reviewers again determined that the Applicant had not adequately established product efficacy. The Applicant resubmitted a second time (the third and current review cycle) on October 26, 2009. Although the reviewers have recommended approval in this review cycle, the NDA cannot be approved because the Office of Compliance has recommended a "Withhold Approval" due to manufacturing issues at the finished dosage manufacturer (Nexgen Pharma Inc.).

The original NDA submission included a single placebo-controlled clinical study (BZUC3002) to support the proposed indication "treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older." The Applicant submitted an additional clinical study during the course of the first review cycle, but the study was not reviewed in that cycle. The NDA was not approved because the reviewers determined that the single study submitted in the original NDA submission (Study BZU3002) did not provide adequate evidence of efficacy. The Division cited both the lack of a statistically persuasive finding of treatment effect and the lack of consistency in treatment effect between the subsets of men and women within the single study as the deficiencies that precluded approval in the May 16, 2008 Approvable Letter. The letter stated that approval would be dependent on "review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis."

Dr. Hyde, the Cross Disciplinary Team Leader (CDTL) for the first resubmission, noted that the Division's guidance in the pre-NDA meeting before the original submission emphasized the requirements of a single study for evidence of effectiveness delineated in section II.C.3 of the "Evidence Document" (*Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* 1998), which demands that the study be statistically very persuasive with a "very low p-value" (conventionally viewed as being a p-value that provides a strength of evidence comparable to two studies with $p < 0.05$). This position was reiterated in the original in the Approvable letter. Dr. Hyde considered this position arguably too stringent, in light of the fact that the product is an oral balsalazide product. Oral balsalazide has previously been shown to be efficacious for the indication proposed in this NDA. He did not agree that a statistically highly persuasive p-value should be required for an application that seeks marketing approval for a new dosing format for balsalazide (tablets administered twice a day) when the product is already marketed as capsules (three times a day dosing), and is a pro-drug for a drug, mesalamine, which has been shown to be effective for the same indication in multiple other marketing applications. This conclusion is supported by the standard delineated in the Evidence Document, in section

II.C.2.a, which allows taking into account related study data when considering the strength of evidence provided by the single trial.

However, Dr. Hyde also concluded in his review of the first resubmission that the large and unexplained difference in treatment effect observed between genders in that single trial was an important deficiency that rendered the trial inadequate as a stand alone trial to support marketing approval of Giazo, as proposed by the Applicant. The female subset represented half the study population. The Statistical and Clinical reviewers concluded that the noninferiority trial BZUC3003 submitted for review in the second cycle did not establish the efficacy of Giazo and could not resolve the issue of the inconsistent treatment effects observed between genders in BZUC3002. The FDA issued a CR letter at the completion of the review.

The Applicant has submitted no new studies in this second resubmission. The submission includes the Applicant's arguments to support their conclusion that Giazo is effective in both men and women with mildly to moderately active ulcerative colitis, based on data from the previously submitted trials BZUC3002 and BZUC3003. The reviewers have completed their review and have concluded that this balsalazide product can be marketed if the indication is narrowed to treatment of men:

"GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older; effectiveness in female patients was not demonstrated in clinical studies. Safety and effectiveness of GIAZO therapy beyond 8 weeks have not been established."

2. Background

This is an application for a new oral formulation of balsalazide disodium, a tablet containing 1.1 g balsalazide disodium that the Applicant proposes will be dosed twice daily – three tablets twice daily, for a total dose of 6.6g – for up to 8 weeks, for the following proposed indication:

> GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. Safety and effectiveness of GIAZO beyond 8 weeks in adults have not been established.

There are currently other balsalazide formulations on the market, but this would be the first product dosed twice daily. The other approved products include one marketed by the Applicant, Colazal (a capsule formulation dosed three times a day, for total dose of 6.75 g). Balsalazide is a prodrug of mesalamine (5-amino salicylic acid, 5-ASA), and there are multiple mesalamine products on the market for treatment of mild to moderately severe ulcerative colitis, including products that are dosed once a day, three times a day and four times a day, in mesalamine total doses that range 2.4 g – 4.8 grams per day.

The Applicant was told in response to a question about providing a single induction study to support approval at their August 8, 2005 End of Phase 2 meeting that two studies were recommended "unless results from a single study are robust (or adequate justification is provided as to why two are not necessary)." Similarly at the April 27, 2007 Pre-NDA

Meeting the Division stated that "approvability of your new dosage form will ultimately be based on the robustness of the data and the consistency of effect seen in the primary and secondary endpoints" in response to the Applicant's proposal to submit the single study, BZUC3002, to support efficacy in their NDA . The Division further clarified that, "Also, since study BZUC3002 is intended to be a single principle [sic] study for efficacy, results are expected to be internally consistent and robust, demonstrating substantial efficacy with a p-value considerably smaller than .05."

In the original NDA submission, the Applicant submitted the single trial BZUC3002, which demonstrated a significant inconsistency in treatment effect between males and females. Females treated with placebo in the study had a similar outcome as females treated with Giazo, and the primary efficacy outcome was actually numerically better with placebo. The approvable letter stated the following deficiency and means for addressing the deficiency:

> "Your placebo controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study.
>
> The issuance of an approval is dependent upon the review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis."

After taking an Approvable action on May 16, 2008, the Division met with the Applicant in a June 9, 2008 Post-Action Meeting. In that meeting the Division told the Applicant that clinical Study BZUC3003, which the Applicant had submitted during the initial review cycle but was not reviewed by the FDA, appeared to be a study that would constitute a response to the Approvable Letter. The Division, however, qualified that response by saying that the adequacy of the second study would be a review issue.

The Applicant's first Complete Response resubmission, which was dated June 30, 2008, contained the clinical study discussed at the Post-Action Meeting (BZUC3003), additional clinical safety data, and stability data to extend the expiration date. The Division notified the Applicant in early November 2008 that the Division had identified deficiencies that precluded initiating labeling. Those deficiencies were explained and discussed in a teleconference between the FDA Clinical and Statistical reviewers and the Applicant on 11/13/08. The reviewers noted that the active controlled study comparing Giazo to Asacol was inadequate to establish the efficacy of Giazo because Giazo was not found to be superior to Asacol, and the study did not establish that Giazo is noninferior to Asacol. In addition, the Applicant had not adequately addressed the gender discrepancy in treatment effect observed in the originally reviewed study. The second study, BZUC3003, was inadequate to address this issue.

The Complete Response (CR) letter dated December 22, 2008, cited two major deficiencies:

1) Inadequate justification of the (b) (4) non-inferiority margin for Study BZUC3003.
2) Inability of the results of Study BZUC3003 to address the deficiencies of the May 16, 2008, Approvable letter.

The letter further stated:

> "Future approval of BD tablets for the treatment of mildly to moderately active UC will be dependent upon the review of additional efficacy data from an adequate and well-controlled study that demonstrates substantial evidence of effectiveness and has the ability to resolve the questions about differences between men and women regarding the treatment effect of BD tablets in active UC. Before initiating such a study, we recommend that you obtain input from us regarding the study design."

The Applicant met with FDA on March 16, 2009, after receiving the CR letter. The Applicant presented additional analyses to explain the gender differences. The Applicant also proposed a (b) (4) for the noninferiority study to show (b) (4) The FDA responded that the proposed (b) (4) could not be used to establish (b) (4). The FDA advised the Applicant that additional clinical data would be best, but that the Applicant could consider submitting the additional analyses and additional external information, including comparative PK between genders, to help explain the gender difference.

In the current resubmission, no new study was submitted.

3. CMC

In the original review cycle, the CMC Reviewer found that sufficient information was provided to assure the identity, strength, purity, and quality of the drug product. The stability data supported a 24-month expiration date. In the first resubmission, additional stability data were submitted that supported a 36-month expiration.

In this submission, the CMC reviewers found that all labels and labeling have the required CMC information and are acceptable.

The Office of Compliance issued an "Acceptable" overall recommendation on 3/17/08 for all the facilities involved; however, during this review cycle, on April 12 2010, the Office of Compliance issued a new overall recommendation of Withhold, after completion of an inspection of the finished dosage manufacturer (Nexgen Pharma Inc.). The District Office noted that the inspection revealed "widespread GMP deficiencies and the marketing of at least 20 potential unapproved drugs." The CMC reviewers recommend that the application cannot be approved until the acceptability of the manufacturing site has been established.

4. Nonclinical Pharmacology/Toxicology

There were no new Pharmacology/Toxicology data in this resubmission. Dr. Ke Zhang recommended approval from the preclinical standpoint in his review of the original submission.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewers recommended approval of the original NDA submission. There were no new clinical pharmacology data in this resubmission, however, the Applicant submitted their analyses of available pharmacokinetic data (by gender) in an effort to address the observed inconsistent treatment effect between men and women in Study BZU3002. Dr. Kim noted the Applicant's argument using comparable systemic exposure to balsalazide and its metabolites between men and women cannot address the observed inconsistency. Dr. Kim stated in her review that, "The equivalent therapeutic efficacy in different subpopulations (men vs. women) may be expected based on the equivalent systemic exposure when one can reasonably assume similar disease progression and similar response to treatment between these subpopulations. However, one can not reasonably assume similar disease progression and similar response to treatment between men and women especially in this case with the identified inconsistent placebo effect between men and women. As such, the similar systemic exposure to balsalazide and mesalamine can not be used to support similar therapeutic effect between men and women."

Dr. Kim recommended a post marketing study requirement to characterize the pharmacokinetics of balsalazide, mesalamine and N-acetyl aminosalicylic acid in pediatric patients. She also recommended a post marketing commitment study of the in vivo effect of concomitant antibiotics on conversion of balsalazide to mesalamine by gut-flora.

I concur with her recommendations.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Please refer to Dr. John Hyde's excellent summary of the clinical and statistical review findings in his CDTL review.

The primary endpoint of the clinical trials Study BZUC3002 and Study BZUC3003 was based on the Modified Mayo Disease Activity Index, MMDAI. This index is comprised of 4 subscores (bowel frequency, rectal bleeding, endoscopic appearance and physician's global assessment), which range from 0-3 (higher score representing more severe disease). Totaling the subscores yields a score that can range from 0-12. The primary endpoint, <u>clinical improvement</u> at the end of the treatment period, was defined by at least a 3 point improvement in MMDAI, associated with an improvement in rectal bleeding score of at least 1 point.

The single clinical study BZUC3002, which was submitted and reviewed in the original review cycle, was a randomized, double-blind, placebo-controlled study of Giazo that enrolled 250 patients with mildly to moderately active UC from 55 U.S. centers. The primary endpoint was assessed at 8 weeks. Primary efficacy endpoint results are summarized in the table below. The table includes the important subgroup analysis by gender.

Proportion of Patients with Clinical Improvement at Week 8 in Study BZUC3002

	Giazo 6.6 g/day % (# response/N)	Placebo % (# response/N)	Difference (Giazo – Asacol)	P-value
Total Population	**55%** (b) (4)	**40%** (b) (4)	**15%**	0.024
Males	**57%** (b) (4)	**20%** (b) (4)	**37%**	<0.001
Females	**54%** (b) (4)	**58%** (b) (4)	**-4%**	(b) (4)

Despite the statistically significant difference favoring Giazo in the overall study population, the outcome was not consistent between genders. In fact, females actually appeared to do better on placebo than Giazo. A nominally statistically significant difference between treatment effects by gender (37% vs. -4%, nominal $p < 0.003$ by M-H Chi-square test for homogeneity) was noted.

Two key secondary efficacy endpoints were Clinical Remission and Mucosal Healing. Clinical Remission was defined as a score of 0 for rectal bleeding plus a combined score of ≤ 2 for bowel frequency and physician's global assessment (MMDAI); the endoscopic sub-score was not considered in this definition. This endpoint definition differed from the primary endpoint "clinical improvement" not only in its deletion of the endoscopy component, but it also required a rectal bleeding score of zero (compared to a reduction in rectal bleeding by at least one point in the primary endpoint) and set a total remaining score for the remaining two components (physican global and bowel frequency) that can't be exceeded. (Clinical improvement defined the total shift downward in score that was considered an improvement.) Mucosal Healing was defined as an endoscopy/sigmoidoscopy score of 0 or 1, where a score of 1 could include signs of erythema or decreased vascular pattern; by definition, the presence of friability indicated a score of 2 or 3.

The following table, reproduced and modified from the CDTL review, summarizes the outcomes by gender that were observed for the secondary endpoints Clinical Remission and Mucosal Healing. It also summarizes outcomes for the bowel frequency and rectal bleeding subscores of the MMDAI. Dr. Hyde points out in his review that no nominally statistically significant outcomes in females were observed in any of these additional analyses, and that there were lower rates of improvement (as defined for responder analysis) in rectal bleeding and bowel frequency with Giazo than placebo in the females who participated in this trial.

Secondary Endpoint Results in Study 2 by Gender

Variables	Giazo n/N (%)	Placebo n/N (%)	Difference	p-value for Difference	p-value for Inhomo-geneity
Clinical Remission					(b) (4)
Males	28/81 (**35**)	5/40 (**13**)	**22%**	0.01	
Females	(b) (4)				
Mucosal Healing					
Males	42/81 (**52**)	8/40 (**20**)	**32%**	<0.001	
Females	(b) (4)				
Bowel Frequency					
Males	43/81 (**53**)	12/40 (**30**)	**23%**	0.02	
Females	(b) (4)				
Rectal Bleeding					
Males	51/81 (**63**)	13/40 (**33**)	**30%**	0.002	
Females	(b) (4)				

The second study (reviewed in the second review cycle), BZUC3003, was a randomized, double-blind, active-controlled study in patients with mildly to moderately active UC. Patients were randomized between Giazo (balsalazide) or Asacol (mesalamine). Treatment duration was six weeks. The dose of Asacol (mesalamine) was 0.8g TID (total 2.4 g/D), the approved dose. The Giazo dose was the dose proposed for marketing, 3.3g BID (total 6.6 g/D). Like Study BZU3002, the primary endpoint was defined as a reduction of at least 3 points in MMDAI and a reduction of at least 1 point in the rectal bleeding score. In BZU3003, however, the end of study assessment was made at Week 6 instead of Week 8. The objective was to establish noninferiority of Giazo to Asacol. The Applicant's proposed noninferiority margin was (b) (4). The design features, including duration of treatment, dose, method of assessment, schedule of assessments, and eligibility criteria, were carefully evaluated by the Clinical and Statistical reviewers, in order to determine whether suitable previously conducted studies had been utilized to establish an appropriate noninferiority margin for analysis of the primary endpoint.

Although the initial BZU3003 protocol specified the primary analysis would utilize the ITT population, the first protocol amendment (approximately 3 months after initiating the study) changed the population for analysis to the per-protocol population. As part of these changes, the definition of the ITT population was modified. The ITT population became all patients who met the following criteria: 1) took at least one dose of study drug, 2) baseline MMDAI score is between 6 and 10, inclusive, 3) MMDAI bleeding score is at least 2 or greater, and 4) MMDAI endoscopy score is at least 2 or greater. This revised ITT population definition was referred to by the FDA reviewers as the modified ITT population, or mITT. The per protocol population of the primary efficacy analysis was defined as the patients in the mITT population who had no major protocol deviation and had at least one post-baseline assessment of the primary efficacy endpoint. The changes made in the analysis population were a significant review issue for the Statistical reviewer, Shahla Farr, MS, and prompted her to conduct a number of exploratory analyses utilizing differing definitions of the primary analysis population. These analyses are described in detail in her second cycle Statistical review.

Of the total of 410 patients randomized in this study, 351 qualified for inclusion in the per protocol population. The population was nearly evenly split between males and females – 48% were males. The table below summarizes the outcome observed for the primary endpoint in the overall ITT population ("All Randomized"), the per-protocol population, as defined above, and the modified ITT population (mITT), as defined above. The Applicant concluded that Giazo is noninferior to Asacol because the lower bound of the 95% interval of the difference between Giazo and Asacol in the per protocol population analysis was (b) (4).

Percentages of Patients with Clinical Response at Week 6/EOT in Study BZUC3003

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference (Giazo – Asacol) (95% C.I.)
Per-Protocol	**61.7%** (b) (4)	**60.8%** (b) (4)	**0.9%** (b) (4)
mITT	**56.3%** (b) (4)	**56.2%** (b) (4)	**0.1%** (b) (4)
All Randomized*	**53.3%** (b) (4)	**54.6%** (b) (4)	**-1%** (b) (4)

*Statistical Reviewer's analysis (second review cycle), with all dropouts coded as failures.

The FDA Statistical reviewer determined that the Applicant hadn't adequately justified the (b) (4) noninferiority (NI) margin. She found that only one study in the Applicant's meta-analysis of 16 placebo-controlled studies (Sninski, et al.) was suitable to determine an NI margin. The other studies differed substantively in their design from Study BZUC3003 (different primary endpoints, duration of treatment and patient populations). The noninferiority margin derived from the Sninski study, -3%, was much smaller than that used by the Applicant. The treatment effect for Asacol in the Sninski study was estimated to be 26%, with a 95% confidence interval of (6%, 45%). Halving of the lower bound of the confidence interval resulted in the 3% margin. Using the 3% margin, the Statistical reviewer concluded that Study BZUC3003 did not establish that Giazo is noninferior to Asacol.

Given the differences in outcome by gender observed in Study BZUC3002, the response rates by gender were of particular interest in Study BZCU3003. The analyses of the primary endpoint by gender are summarized in the table below.

Analysis of Efficacy by Gender, mITT Population Study BZU3003

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference (Giazo – Asacol) (95% C.I.)
Males	**51%** (b) (4)	**49%** (b) (4)	**2%** (b) (4)
Females	(b) (4)		

The reviewers noted that the lack of a placebo arm renders this study unable to address the gender issue raised in the review of Study BZCU3002. The lower limit of the confidence intervals for the comparison of Giazo and Asacol is lower in females than males in this study, (b) (4) It is unclear whether this observed difference is meaningful. The Statistical reviewer explored pooling the data from Studies BZCU3002 and BZCU3003 and found that the pooled female response rate for Giazo remained indistinguishable from the placebo from BZCU3002.

The first resubmission received a CR, and the Applicant resubmitted again on October 26, 2010. In the current submission the Applicant has attempted to address the noninferiority margin issue from BZCU3003 through re-derivation of the noninferiority margin, and they have argued that reanalysis of both Studies BZCU3002 and BZU3003 showed that females with mildly to moderately active ulcerative colitis have a disease response to Giazo therapy. The Applicant presented a reanalysis of BZCU3003 using an endpoint from a historical study to show that a (b) (4) noninferiority margin was met. The reviewers did not find this reanalysis persuasive. With regard to the gender discrepancy in efficacy, the Applicant provided an analysis of the placebo controlled trial, Study BZU3002, and continued to argue that the absence of observed treatment effect in females was secondary to a spuriously high placebo response for the primary endpoint. The Applicant argued that there was a consistent treatment effect observed in females in the secondary efficacy endpoints and that the gender difference was driven by the MMDAI subcomponent stool frequency. However, the Clinical reviewer noted that the post hoc analysis of each MMDAI subcomponent revealed a consistent gender disparity.

The Clinical reviewer investigated trials that supported approval of other mesalamine related products for ulcerative colitis looking for previously documented evidence of gender disparity in this drug class. He noted that in most of the trials in which he found apparent differences between genders, the differences appeared to be compatible with subgroup variability. However, the results of the four-week placebo controlled study of the balsalazide formulation Colazal were considered particularly noteworthy, in that they also suggest a discrepancy in balsalazide efficacy based on gender (see Table below, which is reproduced from the CDTL review). The endpoints for which differences are most apparent are stool frequency, abdominal pain and patient functional assessment.

Results of Placebo-Controlled Trial of Colazal in UC (Study CP069101)

Efficacy Endpoints		Colazal 6.75 g/day Men (n=46) Women (n=26)	Placebo Men (n=19) Women (n=16)	Difference Giazo - Placebo
Stool Blood	Men	33%	21%	12%
	Women	54%	44%	10%
Stool Frequency	Men	42%	26%	16%
	Women	27%	31%	-4%
Patient Functional Assessment	Men	44%	16%	28%
	Women	35%	38%	-3%
Abdominal Pain	Men	22%	16%	6%
	Women	27%	44%	-17%
Symptom Assessment	Men	30%	21%	9%
	Women	39%	38%	1%
Sigmoidoscopy	Men	48%	47%	1%
	Women	39%	37%	2%
Physician's Global Assessment	Men	35%	47%	-12%
	Women	39%	50%	-11%

Adapted from Table 22 of Clinical Review for the second review cycle, which was modified from Colazal Applicant's NDA 20-610 submission, 1988, Vol 7.1, p. 164. Missing values are counted as failures.

The Clinical and Statistical reviewers concluded that the gender analysis from this placebo controlled trial of the previously approved balsalazide product, Colazol, also suggested discrepant gender effects. This additional information provided some support for limiting the indication of Giazo to males.

I concur with the CDTL's summary comments regarding the evidence of efficacy of Giazo presented in this NDA. That discussion can be found in Section 11. Other Relevant Regulatory Issues of his CDTL review. I agree with the reviewers that Study BZCU3003 did not demonstrate noninferiority to Asacol with a margin that could be supported. I agree with Dr. Hyde's position that this second study is not critical for approval and that his position is supported by section II.C.2.a of the Evidence Document. Oral balsalazide has previously been shown to be efficacious for the indication proposed in this NDA. A statistically highly persuasive p-value should not be required for BZCU3002 since it is for a new dosing format for balsalazide (tablets administered twice a day), a product already marketed as capsules (three times a day dosing), and a pro-drug for a drug, mesalamine, which has been shown to be effective for the same indication in multiple other marketing applications.

I agree that the striking gender discrepancy in efficacy observed in Study BZCU3002 remains unexplained, but that it also remains difficult to take the position that Giazo is not efficacious, in light of the favorable outcome for the primary endpoint for the overall study population and that balsalazide has been shown to be effective for treatment of ulcerative colitis in the past. I believe that the reviewers' recommendation to limit product labeling to treatment of men can be supported in light of the discrepant efficacy outcome in females treated in BZCU3002, and the gender analysis of the placebo controlled trial for the approved balsalazide product Colazol, which also suggests the presence of disparity of treatment effect by gender. I agree

that the indication statement in the product label should include the language, "effectiveness in female patients was not demonstrated in clinical studies." The reviewers have recommended a post marketing commitment (PMC) placebo controlled trial of female patients with active ulcerative colitis to assess the efficacy of an eight week course of Giazo therapy for the treatment of active disease in this patient population. The design of this trial will include three treatment arms for comparison: Giazo, Colazal, and placebo. Before initiating the study, the protocol will be submitted to the FDA for comment regarding the study design. The Applicant agreed to this post marketing commitment.

8. Safety

The total safety data base was comprised of 565 patients treated with Giazo, of whom 430 had been exposed for more than eight weeks, 331 for at least six months, and 140 for at least a year. I concur with the Clinical reviewers' previous conclusion that the overall safety profile of Giazo is similar to that of the approved capsule dosage form of balsalazide. The Clinical reviewer assessed the adverse event data based on gender and found that a lower proportion of males had adverse events than females.

I concur with the Clinical reviewers' recommendations that the adverse reaction information from postmarketing experience with the other balsalazide formulation, Colazal, and important adverse reaction information from postmarketing experience with mesalamine products should be included in the Giazo label. Those recommendations are reflected in labeling negotiated with the Applicant.

9. Advisory Committee Meeting

There was no Advisory Committee to discuss this resubmission.

10. Pediatrics

The Applicant requested full waiver of the PREA requirement for pediatric studies because Giazo doesn't represent a meaningful benefit over existing available therapy for the pediatric population. The Applicant's balsalazide disodium product, Colazal, which is formulated in a capsule, is approved for treating active UC in pediatric patients ages 5 through 17 years. The capsules can be opened to sprinkle on food. The Pediatric Research Committee (PeRC), on October 29, 2008 (in the second review cycle), agreed with waiving requirements under the age of 12 years, but felt that the BID dosing option (vs. TID with Colazal capsules) should be available to pediatric patients who can take tablets. The PeRC told the reviewers that if they believed that adequate information already exists to permit labeling for children aged 12 and over, a waiver could be granted. They deferred to the review team as to whether additional studies would be needed.

In the current review cycle, in response to negotiations with the FDA review team, the Applicant proposed a pediatric plan to conduct a PK study in male patients ages 12 through 17 years. The application was presented to PeRC on April 14, 2010, and the committee

concurred with the plan but suggested considering including children of even younger ages who still might be able to swallow the tablet.

11. Other Relevant Regulatory Issues

DSI inspected sites from both BZUC3002 and BZUC3003. The clinical data from BZUC3002 were found to be acceptable in the first review cycle. The Clinical Inspection Summary memo from DSI for BZUC3003, in the second review cycle, concluded that the data from both inspected sites could be used in support of the NDA.

I concur with the Clinical reviewers' conclusion that a QT evaluation for Giazo is not necessary because nonclinical studies do not indicate that there is a potential for QT prolongation and because the clinical trial and postmarketing experience with balsalazide and mesalamine products has not indicated that there may be an issue with QT prolongation.

I agree with the CDTL's analysis and conclusions regarding the duration of studies that support marketing approval for this NDA for the proposed indication. Although the Division has been advising sponsors of products intended to treat UC that NDAs for products that will be utilized for chronic management of this disease should be supported by studies of one year duration, the Applicant reached agreement with the Division in an end of phase 2 meeting in 2005 that they would only need to complete induction studies to support an NDA. The CDTL concluded that this agreement should stand, and I concur. I agree that labeling should explicitly state the limitations of the clinical studies upon which the approval was based. The Indications and Usage section of the product label will state, "Safety and effectiveness of Giazo therapy beyond 8 weeks have not been established." The Dosage and Administration section will state (b) (4)

12. Labeling

Please see Dr. John Hyde's CDTL review for a detailed discussion of the labeling issues. The reviewers' recommendations regarding labeling were incorporated in label negotiations. I concur with the plan to limit the indication to male patients, and to state in the indication that "effectiveness in female patients was not demonstrated in clinical studies." In addition, I agree with including the statement in the indication that "Safety and effectiveness of Giazo therapy beyond 8 weeks have not be established." I agree with the plan to only include the results of the placebo controlled trial in the product label, and that for the primary endpoint, the efficacy outcomes for both males and females should be presented so that prescribers may better understand why the product is indicated only for men.

With regard to the proprietary name, in the initial review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) reviewer objected to the Applicant's proposed trade name, "Giazo" because it represented a dual trade name. During the review of this resubmission DMEPA reexamined the previously identified issues surrounding use of the name "Giazo" for a tablet form of balsalazide by an Applicant who has another balsalazide

product marketed under a different name, the capsule formulation Colazol. They examined the Applicant's submission of results from a Failure Mode Effect Analysis and their arguments to justify the trade name "Giazo". The final DMEPA recommendation is that the proposed trade name is acceptable; however, the NDA will not be approved this cycle. DMEPA's recommendations regarding labeling, including container and carton labeling, were incorporated and addressed in labeling negotiations.

DDMAC's recommendations for labeling revisions were incorporated in labeling negotiations.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response.

I concur with the recommendations of the Clinical reviewer, the Statistical reviewers and the CDTL, that the Applicant has provided sufficient information to support approval of this balsalazide product for the indication:

GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older; effectiveness in female patients was not demonstrated in clinical studies. Safety and effectiveness of GIAZO therapy beyond 8 weeks have not been established.

However, due to the Office of Compliance's recommendation to Withhold approval due to manufacturing issues identified at the finished dosage manufacturer, the CMC reviewers have recommended that the application not be approved. Based on cGMP issues, this resubmission will receive a CR action.

- Risk Benefit Assessment

I concur with the CDTL that the risk characteristics of Giazo appear similar to those of the currently marketed oral balsalazide product. The reviewers have determined that efficacy of Giazo has been established in male patients only, based on the results of the single, placebo controlled trial submitted in support of this application, Study BZU3002. The product will be indicated for male patients with mildly to moderately active ulcerative colitis (b) (4)

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

When the manufacturing issues are resolved and the application is approved in a future review cycle, the following post marketing commitments should be included in the approval letter. These were discussed with the Applicant in this review cycle and the Applicant agreed to these commitments on April 2, 2010 (PREA required study) and April 21, 2010 (PMCs).

1) A PK study in pediatric patients ages 12 through 17 will be a PREA requirement, because it has been determined that such a study is needed to support pediatric labeling for that age range.

2) A placebo-controlled clinical trial in female active ulcerative colitis patients to assess the efficacy of an eight week course of Giazo therapy for the treatment of active disease in this patient population. The design of this trial will include three treatment arms for comparison: Giazo, Colazal, and placebo. Before initiating the study, the protocol will be submitted to the FDA for comment regarding the study design.

3) A pharmacokinetic study in patients to evaluate the effect of concomitant therapy with antibiotics commonly used in ulcerative colitis on the metabolism of balsalazide following administration of Giazo.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22205	ORIG-1	SALIX PHARMACEUTICALS INC	BALSALAZIDE DISODIUM TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA J GRIEBEL
04/27/2010

Cross-Discipline Team Leader Review

Date	April 27, 2010
From	John E. Hyde, Ph.D., M.D., Clinical Team Leader, DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 22-205 N-000
Applicant	Salix Pharmaceuticals, Inc.
Date of Submission	October 26, 2009; Received October 27, 2009
PDUFA Goal Date	April 27, 2010
Proprietary Name / **Established (USAN) names**	GIAZO Balsalazide disodium
Dosage forms / Strength	Tablet for oral administration; each tablet contains 1.1 g balsalazide disodium.
Proposed Indication	Treatment of mildly to moderately active ulcerative colitis in patients 18 year of age and older.
Recommended:	Complete Response

1. Introduction

This submission, received October 27, 2009, is the second resubmission (i.e., third review cycle) for this NDA. It was submitted in response to a Complete Response letter issued by the FDA on 12/22/08. This application is for a new oral formulation of balsalazide disodium. The product is a tablet containing 1.1 g balsalazide disodium.

The Applicant proposed the following indication:

> GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. Safety and effectiveness of GIAZO beyond 8 weeks in adults have not been established.

The proposed dosing is three tablets twice daily (b) (4) (for a total daily dose of 6.6 g) for up to eight weeks. The Applicant proposed labeling with a contraindication for hypersensitivity to salicylates or any component of Giazo tablets, and with warnings about the potential for exacerbations of ulcerative colitis, the possibility of prolonged gastric retention in patients with pyloric stenosis, the risk of renal toxicity, and the need for caution when used in hepatic impairment. The proposed pregnancy category is B.

Previous review cycles identified a marked difference between genders in the response to Giazo, with females showing a much smaller treatment effect compared to males in the one placebo-controlled study. Females tended to have a higher placebo response rate, but no clear explanation has been found for the relative lack of benefit over placebo. Review of a placebo-controlled study submitted for the earlier approval of the other balsalazide product, Colazal, also showed greater benefit for males than females, whereas several trials of mesalamine products did not show a consistent gender effect. The review team

recommended approval of the product with the indication limited to males, and the Applicant has agreed.

Failure to pass inspection at the Nexgen Pharma, Inc., facility has led to a withhold recommendation from the Office of Compliance, so the current recommended action is a Complete Response. All of the review disciplines have recommended approval apart from the facility inspection issue; with the labeling negotiated with the Applicant and submitted on 4/26/10, the application is otherwise approvable.

Selected sections of the CDTL Review dated 12/21/08 from the previous review cycle are summarized or reproduced in condensed form in this review to provide adequate context. The reader is referred to that previous review for more complete background, description of previous cycle reviews, and certain discussions.

2. Background

General Background

See the previous CDTL review for background on ulcerative colitis and its drug therapy.

Related Approved Products

The other approved balsalazide disodium product, Colazal capsules, has the following indication:

> COLAZAL is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older. Safety and effectiveness of COLAZAL beyond 8 weeks in children (ages 5-17 years) and 12 weeks in adults have not been established.

The recommended dosing is 2.25 g (as three 750 mg capsules) TID for a total daily dose of 6.75 g, for up to 8 weeks. Pediatric dosing can be the same as adult dosing or 750 mg TID (total daily dose 2.25 g); capsules may be opened to sprinkle on applesauce. For comparison, the approved dose of oral mesalamine to treat active UC ranges from 2.4 to 4.8 g/day, in single or divided doses, depending on formulation. (Each gram of balsalazide disodium is considered equivalent to about 350 mg mesalamine, so the proposed daily dose of 6.6 g Giazo corresponds to about 2.3 g mesalamine.) The approved dose of oral mesalamine for maintenance of remission is 1.6 g/day divided into BID dosing for Asacol and 1.5 g once daily for Apriso.

Colazal is contraindicated in patients with hypersensitivity to salicylates. The labeling has warnings that Colazal may exacerbate UC symptoms, that patients with pyloric stenosis may have prolonged gastric retention of the capsules, and that Colazal should be administered with caution in patients with renal dysfunction or renal disease history). The pregnancy category is B.

The elements of the Colazal labeling are similar to those of approved mesalamine products. Apriso (mesalamine granules) was approved in October 2008 with labeling that also contains a warning regarding risks of use in patients with pre-existing liver disease. Postmarketing

reports of renal injury with mesalamine and related products have been uncommon; renal injury appears to be an idiopathic reaction to mesalamine when given to humans in the therapeutic dose range.

Presubmission Activities

The reader is referred to the CDTL review for the previous cycle for additional background on presubmission activities leading up to the second review cycle. Highlights from that review are presented here along with a description of subsequent activities.

Giazo was developed under IND 38,492, which was the same IND used to develop the Colazal capsule. Colazal was approved 7/18/00, and three postmarketing commitments from that approval remain outstanding according to the PMC annual report of 9/18/2009: 1) conduct in vivo drug interaction studies in animals and discuss the need for additional studies based on the outcome, 2) compare PK data on balsalazide to PK data on mesalamine in renal impairment in the literature and determine the need for additional studies, and 3) evaluate PK of balsalazide in hepatic impairment if clinically relevant results are obtained in renal impairment. No timelines were included in the wording of these commitments.

<u>End-of-Phase-2 Meeting</u>
The Applicant held an End-of-Phase-2 (EOP2) meeting for the tablet formulation on August 8, 2005. The Applicant proposed to provide only a single induction study to support approval. The FDA responded that two studies are recommended but noted that an NDA could be filed with a single study. The FDA made additional recommendations to make the treatment duration eight weeks, to add an active control arm, such as Asacol, to include patients 12 to 18 years if pediatric labeling is being contemplated, and to obtain additional safety data. Of note, the FDA did not state that a long-term efficacy study would be required.

<u>Pre-NDA Meeting</u>
A pre-NDA meeting was held 4/27/07. The Applicant proposed to submit only a single placebo-controlled study (Study 2, as presented below) for efficacy. The FDA repeated the recommendations of the EOP2 meeting, but stated approvability would depend on the robustness of the data. The FDA added that, with Study 2 providing the only evidence of efficacy, “results are expected to be internally consistent and robust, demonstrating substantial efficacy with a p-value considerably smaller than .05.”

<u>First Review Cycle</u>
The original NDA, received on 7/17/07, included the report of Study 2 to support efficacy. The Applicant also submitted a report of an active-controlled clinical study (Study 3) during the review cycle, but the Division had not solicited it and elected not to review it in that cycle.

Although Study 2 showed a statistically significant difference overall, the review team did not feel it provided adequate evidence of efficacy on its own. They also identified a marked gender difference in the treatment effect, with females showing essentially no benefit. The Division issued an Approvable Letter on 5/16/08 citing the following deficiencies (quoted from the letter):

> Your placebo controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study.
>
> The issuance of an approval is dependent upon the review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis.

Post-Action Meeting

A post-action meeting was held 6/9/08 at the Applicant's request. The FDA stated that Study 3, an active-control study, might constitute a response to the Approvable Letter, but its adequacy would be a review issue, and the adequacy of the non-inferiority margin would be a review concern.

Second Review Cycle

The resubmission in response to the Approvable Letter was received on June 30, 2008. It was classified as a Type 2 resubmission and given an action date of 12/31/08. It consisted essentially of only the addition of Study 3 as evidence of efficacy.

The Clinical and Statistical Reviewers did not agree with the Applicant's justification of the proposed non-inferiority margin, and did not conclude that Study 3 contributed toward substantial evidence of efficacy. Further, the submission did not address the gender disparity in treatment effect explicitly, and Study 3 was not viewed by the review team as adequate to address it, because the study lacked a placebo group. The Statistical Reviewer concluded that the resubmission did not present evidence of efficacy. The Clinical Reviewer concluded that concerns of the previous review cycle were not addressed adequately, and he recommended a Complete Response action.

On December 22, 2008, the Division issued a Complete Response Letter citing the following deficiencies in need of resolution:

1. Inadequate justification of the (b) (4) non-inferiority margin for Study 3.

2. Inability of the results of Study 3 to address the deficiencies of the previous approvable letter [namely, failure to address the questions about the gender differences in treatment effect].

See the CR Letter for the full text of the deficiencies. The CR Letter recommended that the Applicant obtain additional efficacy data from an adequate and well controlled study to address the second deficiency.

Post-Action Meeting

Following the Complete Response action, a meeting was held on March 16, 2009, at the Applicant's request. At the meeting (but not as part of the meeting package), the Applicant presented additional analyses of the data from Study 2 to explain the gender differences; the FDA responded that they could not provide conclusions about the acceptability of the

analyses without an opportunity to review them. The Applicant also proposed a (b) (4) for Study 3 showing (b) (4); the FDA responded that that method could not be used from the regulatory standpoint to establish (b) (4) The FDA advised the Applicant that additional clinical data would be best, but that the Applicant could consider submitting the additional analyses and additional external information, possibly including PK comparing mesalamine release between genders, to help explain the gender difference. The FDA stated it was not possible at the time of the meeting to determine whether it would find the newly presented analyses acceptable.

Submission and Review

The NDA Complete Response resubmission was dated October 26, 2009, and was received on October 27, 2009. It was classified as a Type 2 resubmission and given an action date of April 27, 2010. The NDA resubmission contained 1) a re-derivation of a non-inferiority margin for Study 3 together with supporting articles from the literature, 2) re-analysis of Studies 2 and 3 to show a responses in females, 3) re-analysis of PK and dissolution data with a comparison of PK for males and females, 4) discussion of the advantages of Giazo over Colazal, 5) safety update, and 6) proposed labeling. The application consisted of a single volume in paper. A 120-day safety update was not provided; however, as noted in Section 8 below, all clinical trials had been closed, and all related safety data had been submitted during the second review cycle.

In a telecon on March 23, 2010, the Applicant was notified by the Division that concerns about the efficacy in females still remained, and the review team inquired whether the Applicant would consider an indication limited to males. A few days later the Applicant notified the Division that such a limitation was acceptable. Following further negotiations, labeling was agreed upon as reflected in the submission on 4/26/10.

No Advisory Committee meeting was held to discuss this application.

The relevant review disciplines have all written review documents for this resubmission. The new primary review documents relied upon are the following:

Clinical Review by C. Leptak, dated 4/27/10.
Memorandum of Statistical Review by M. Welch, dated 4/26/10.
Review of Clinical Pharmacology by I. Kim, dated 4/7/10.
CMC Review by M. Kowblansky, dated 4/14/10.
DMEPA Proprietary Name Review by I. Chan, dated 4/1/10.
DMEPA Label and Labeling Review by I. Chan, dated 4/1/10.
DDMAC Labeling Review by K. Klemm, dated 4/12/10.

These reviews, along with the primary and supervisory review documents from the previous review cycles, should be consulted for more specific details of the application and review conclusions. This memorandum summarizes selected information from the primary review documents.

3. CMC

Conclusions and Recommendations from Previous Review Cycles
The processes and controls for the drug substance are the same as those for the drug substance used in the production of the capsule under approved NDA 20-610.

In the first review cycle, the CMC Reviewer found that sufficient information was provided to assure the identity, strength, purity, and quality of the drug product. The stability data supported a 24-month expiration date. The Office of Compliance issued an "Acceptable" overall recommendation on 3/17/08 for all the facilities involved. The Chemistry Reviewer recommended the NDA for approval with no Phase 4 commitments recommended. The Reviewer recommended that the Applicant be informed of the need to change the font of the established name and the locations of the strength, 1.1g, in the labels for the carton and the immediate label.

In the second cycle, the Reviewer concluded that additional stability data supported a 36-month expiration dating. The deficiencies in labels noted on the first review cycle were still pending. The Reviewer recommended the NDA for approval, pending corrections to the labels. No Phase 4 commitments were recommended.

Current Review Cycle Conclusions and Recommendations
The Reviewer concluded that all labels and labeling as revised during this resubmission had the required information from the CMC perspective, which addressed the deficiencies from previous review cycles. However, inspection of a proposed manufacturing facility (Nexgen Pharma, Inc.) found the site to be out of compliance with cGMP, and the Office of Compliance issued a WITHHOLD recommendation on 4/12/10. The CMC Reviewer concluded that the NDA is not recommended for approval until the acceptability of all manufacturing sites is established.

4. Nonclinical Pharmacology/Toxicology

There were no new Pharmacology/Toxicology data in the resubmission, and no additional review of nonclinical data was performed in this review cycle. The reader is referred to the Pharmacology/Toxicology review by K. Zhang, dated 1/10/08, from the initial review cycle.

Conclusions and Recommendations from Previous Review Cycles
A nonclinical review was conducted only for the initial NDA submission, as no new nonclinical data were submitted for the second review cycle. In his review, the Nonclinical Reviewer noted that renal toxicities had been seen in rats and recommended that the labeling include the statement: "Treatment with Colazal increased the incidence of pelvic and corticomedullary mineralization in kidney and urothelial hyperplasia in rats at oral doses of 600 mg/kg/day (about 0.7 fold the recommended human dose based on body surface area) or higher. Therefore, caution should be exercised when administering Colazal [sic] to patients with known renal dysfunction or a history of renal disease."

The Reviewer recommended approval from the preclinical standpoint. The Reviewer did not recommend any Phase 4 commitments.

Current Review Cycle
No new nonclinical data were provided in the resubmission, and there was no additional Nonclinical Review.

Additional Pharmacology/Toxicology Considerations
To help address a request from the clinical review team, the Supervisory Pharmacologist, D. Joseph, provided a summary of toxicology information from two previous NDAs (see Attachment 1). In NDA 20,610 (Colazal), the 2000 mg/kg/day dose of balsalazide disodium (~equivalent to 700 mg/kg/day of the mesalamine moiety of the compound) was not nephrotoxic in the 12-month oral study in dogs. Although PK was not done in that study, the same dose in a 28-day dog study produced an average AUC of 172 mcg•hr/mL. From NDA 18,651 (Asacol) 40 mg/kg/day of mesalamine was not nephrotoxic in a 12-month oral toxicity study in dogs, but 80 mg/kg/day was. The average AUC for the 40 mg/kg/day dose was 150 mcg•hr/mL in males and 164 mcg•hr/mL in females.

CDTL Comment:
Thus, in the dog studies, the systemic mesalamine exposure from balsalazide disodium was only about 6% of the systemic exposure that would be obtained by giving the equivalent amount of the mesalamine moiety alone, and the 2000 mg/kg/day dose of balsalazide did not produced a mesalamine exposure associated with nephrotoxicity in dogs. In contrast, humans administered Giazo had about 2/3 the systemic mesalamine exposure in terms of AUC (see table at end of Section 5) as those given therapeutic doses of commercial mesalamine formulations. Thus, there is reason to conclude that any nonclinical findings suggesting better safety of balsalazide compared to mesalamine in animal studies may be a reflection of the much lower related mesalamine exposures in animals and cannot be readily translated to humans. In internal discussions during labeling negotiations, the nonclinical review team was in agreement with removing descriptions of negative nonclinical studies relating to overdosage (acute toxicity) and renal toxicity.

5. Clinical Pharmacology/Biopharmaceutics

Conclusions and Recommendations from the Previous Review Cycles
(See the CDTL review dated 12/21/08 for a more detailed summary of clinical pharmacology results from previous review cycle.)

In the first review cycle, the Clinical Pharmacology Reviewer found the information in the application acceptable from a clinical pharmacology standpoint, but deferred labeling recommendations in light of the pending Approvable action for the original review cycle. The Reviewer recommended that administration of Giazo should take meals into account, but noted that Giazo was given without regard to food in the clinical studies. No Phase 4 commitments were recommended.

No additional clinical pharmacology data were submitted for the second review cycle, and no clinical pharmacology review was conducted for that cycle.

Current Review Cycle

The clinical pharmacology component of the current submission consisted of analyses and arguments based on existing clinical pharmacology data with the objective of addressing the question of gender differences. From a re-analysis of PK Study BZPK1003, the Applicant concluded that the pharmacokinetics were not significantly different between men and women. The Clinical Pharmacology Reviewer noted that her previous analysis of that study had shown systemic exposure after repeated dosing to be higher in females than males: the ratios (female/male) of average C_{max} values were 1.15 for balsalazide, 1.23 for mesalamine, and 0.99 for N-Ac-mesalamine; for average AUC the ratios (female/male) were 1.05 for balsalazide, 1.40 for mesalamine, and 1.10 for N-Ac-mesalamine. Urinary excretion of all analytes was also higher in females. The Reviewer interpreted this as suggesting that the systemic/local availability of mesalamine in females was likely no less than in males. She considered this to be a qualitative, rather than quantitative, evaluation due to the small number of subjects in the study (8 female, 10 male).

The Clinical Pharmacology Reviewer noted that Colazal and Giazo showed equivalence in the dissolution profile. The Applicant also provided an analysis of relative bioavailability of mesalamine comparing the two drug products, showing that the geometric mean ratio for AUC (Colazal/Giazo) was 103%, with a 90% CI of 85% to 125%. The Reviewer commented that this could be used for a qualitative comparison of systemic exposures, but that it was not acceptable as evidence of pharmacokinetic equivalence because the design was not adequate (it used repeated dosing with different regimens) and because systemic exposure of mesalamine did not support efficacy even if equivalent systemic exposure were demonstrated between genders.

Current Review Cycle Conclusions and Recommendations

The Clinical Pharmacology Reviewer recommended that the Applicant's argument using PK could not be used to address the deficiency of inconsistent treatment effect between men and women.

The Reviewer recommend changes to the proposed labeling to relocate certain information to more appropriate sections of the labeling, to limit the data in the table of PK parameters to key metabolites, to include protein binding data, and to eliminate data from different dosage forms or dosing regimens. She recommended several specific changes to the text of Section 12 (Clinical Pharmacology). See the review of 4/7/10 for details of the labeling recommendations.

The Reviewer recommended a Phase 4 requirement to study the PK of balsalazide and metabolites in the applicable pediatric population, either as alone or as part of a pediatric efficacy and safety trial. She also recommended a Phase 4 commitment for a drug interaction study to evaluate the effect of concomitant antibiotics on the conversion of balsalazide to mesalamine by gut flora.

Additional Clinical Pharmacology Considerations
In response to a question from the clinical team about systemic exposures from mesalamine-related products, the Clinical Pharmacology Reviewer (e-mail of 4/8/10) compiled PK data from the current labeling of mesalamine products (Asacol labeling did not contain PK data):

Comparative Exposure Data

	Mesalamine		N-Ac-5-ASA	
Daily Dose (regimen)	C_{max}	AUC_T	C_{max}	AUC_T
Lialda 2.4 g* (QD)	1.6	21	NA	NA
Lialda 4.8 g * (QD)	2.1	44.8	NA	NA
Apriso 1.5 g (QD)	2.7	17 ± 6	3.4	37 ± 9
Asacol HD 4.8 g (TID)	5 ± 4	20 ± 14	4.6 ± 2.5	25 ± 11
Giazo 6.6 g (BID)	1.5 ± 0.6	13 ± 6	2.2 ± 0.6	21 ± 6.4

* Single-dose PK

CDTL Comment:
Although the systemic mesalamine exposure from Giazo is at the low end of the range for mesalamine-related products, it is still roughly comparable (e.g., AUC for Giazo is about 2/3 or more of the AUC of the others, excluding high dose Lialda). Thus, it is reasonable that the warning on mesalamine products regarding renal effects and use in renal insufficiency be applied to Giazo as well (based on the presumption that the renal effects are mediated through systemic mesalamine exposure). See also CDTL Comment at the end of Section 4.

6. Clinical Microbiology

This section does not apply because Giazo is not an antimicrobial agent.

7. Clinical/Statistical- Efficacy

Clinical Data and Conclusions from the Previous Review Cycles

MMDAI
The clinical studies in this application measured UC disease activity using the modified Mayo disease activity index (MMDAI). This index is a sum of four subscores based on stool frequency, rectal bleeding, mucosal appearance on endoscopy, and physician's rating of disease activity. Each subscore can range from 0 to 3 (with higher scores representing more severe disease), so the highest total possible MMDAI score is 12. See the Clinical Review for a more complete description of the MMDAI scoring system.

Study 2
A single clinical study (BZUC3002, Study 2) was included at the time of the original NDA submission. Study 2 was a randomized, double-blind, placebo-controlled study of Giazo in mildly to moderately active UC. The study enrolled 250 patients from 55 U.S. centers. Patients were randomized 2:1 to Giazo 3.3g BID or placebo and treated for eight weeks. The primary endpoint was "Clinical Improvement" at eight weeks as defined by at least a 3-point

improvement in MMDAI with an improvement in rectal bleeding score of at least 1 point. Primary endpoint efficacy results are shown below for the primary analysis and for subgroup analysis by gender (table adapted from first cycle Team Leader Review):

Proportion of Patients with Clinical Improvement at Week 8 in Study 2

	Giazo 6.6 g/day % (# response/N)	Placebo % (# response/N)	Difference (Giazo – Asacol)	P-value
Total Population	**55%** (b) (4)	**40%** (b) (4)	**15%**	0.024
Males	**57%** (b) (4)	**20%** (b) (4)	**37%**	<0.001
Females	**54%** (b) (4)	**58%** (b) (4)	**-4%**	(b) (4)

Although the study found a statistically significant difference overall, there was a striking gender effect. Females appeared to do worse with Giazo than placebo, and there was a nominally statistically significant difference between treatment effects by gender (37% vs. -4%, nominal $p < 0.003$ by Mantel-Haenszel Chi-square test for inhomogeneity of the odds ratio in 2x2 tables).

In the analysis of secondary endpoints for the total population, the difference in clinical remission rate of 16% and the difference in mucosal healing rates of 20.5% were statistically significant overall, but the remaining results in the hierarchical testing procedure were considered exploratory due to a statistically non-significant finding for bowel frequency [although the p-value for clinical remission is given as 0.096 in the first cycle Statistical Review, the Reviewer has noted that there was a typographical error, and the correct value should be shown as 0.01 (~ 0.0096)]. In the analysis of secondary endpoints by gender, males showed nominally statistically significant results for clinical remission, mucosal healing, bowel frequency, rectal bleeding, and complete remission, but females showed no nominally significant differences for any of those variables, and they had lower improvement rates on Giazo than on placebo for rectal bleeding and bowel frequency.

Secondary Endpoint Results in Study 2 by Gender

Variables	Giazo n/N (%)	Placebo n/N (%)	Difference	p-value for Difference	p-value for Inhomogeneity
Clinical Remission					(b) (4)
Males	28/81 (**35**)	5/40 (**13**)	**22%**	0.01	
Females	(b) (4)				
Mucosal Healing					
Males	42/81 (**52**)	8/40 (**20**)	**32%**	<0.001	
Females	(b) (4)				
Bowel Frequency					
Males	43/81 (**53**)	12/40 (**30**)	**23%**	0.02	
Females	(b) (4)				
Rectal Bleeding					
Males	51/81 (**63**)	13/40 (**33**)	**30%**	0 002	
Females	(b) (4)				
Complete Remission					
Males	12/81 (**15**)	**0**	**15%**	0 01	
Females	(b) (4)				

Adapted from Table on p.26 of first cycle Clinical Review as provided by Statistical Reviewer.
Difference and p-values for Mantel-Haenszel test for inhomogeneity in 2x2 tables added by this reviewer.
Includes one additional female omitted from primary analysis due to all missing values-treated as failure.

CDTL Comment:
It is worth noting that a substantial gender disparity was seen in the relatively objective endoscopic endpoint of mucosal healing, and was therefore not limited only to endpoints depending on patient reporting.

Conclusions from the First Review Cycle
Although Study 2 showed a statistically significant difference overall, the Statistical Reviewer and Clinical Reviewer did not feel that the study, on its own, provided adequate evidence of efficacy. They also noted a marked gender difference in the treatment effect, with females showing essentially no benefit.

Study 3
The submission for the second review cycle contained the report of Study 3 (BZUC3003), a randomized, double-blind, active-controlled study in patients with mildly to moderately active UC. The study enrolled 410 patients from 79 U.S. centers. Patients were randomized with equal probability to Giazo 3.3 g BID or Asacol 0.8 g TID, using a double dummy design, and treated for six weeks. As in Study 2, the primary endpoint ("Clinical Improvement") was defined by at least a 3-point improvement in MMDAI with an improvement in rectal bleeding score of at least 1 point).

The initial protocol specified that the primary analysis was to be done using the ITT population but was changed to a per-protocol population in an amendment. (See the Statistical Review and Evaluation from the second review cycle.) The Applicant proposed to determine evidence of efficacy using a (b) (4) non-inferiority (NI) margin, and a last-observation-carried-forward (LOCF) rule was to be used for missing values.

The Applicant defined the "ITT" population as all patients who took at least one dose of study drug, who had MMDAI of 6 through 10 (per eligibility criteria), and who had baseline scores of at least 2 points for rectal bleeding and 2 points for endoscopy. This will be referred to here as a modified ITT (mITT) population. The Applicant defined the per-protocol (PP) population as those in the mITT population without major protocol deviations and with at least one post-baseline efficacy assessment.

The table below present results adapted from the Statistical Review from the second cycle:

Proportion of Patients with Clinical Improvement at Week 6/EOT in Study 3

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference (Giazo – Asacol) (95% C.I.)
Per-Protocol	**61.7%** (b) (4)	**60.8%** (b) (4)	**0.9%** (b) (4)
mITT	**56.3%** (b) (4)	**56.2%** (b) (4)	**0.1%** (b) (4)
All Randomized*	**53.3%** (b) (4)	**54.6%** (b) (4)	**-1%** (b) (4)

* Statistical Reviewer's analysis (second review cycle), all with all dropouts coded as failures.

Because the lower limit of the confidence interval in the PP population was smaller in magnitude than the designated NI margin of (b) (4) the Applicant concluded that the study showed Giazo was non-inferior to Asacol.

The Statistical Reviewer did not agree that the (b) (4) NI margin was justified. From the placebo-controlled study used for the approval of Asacol, she determined that the NI margin should not exceed -3%. The Clinical Reviewer also reviewed the literature and concluded that only one study (Sninsky et al.) provided a suitable basis for determination of an NI margin consistent with the ICH 10 Guidance; the others were deemed unsuitable due to their differences from the study design of BZUC3003. From the Sninsky study it also was determined that the NI margin should be -3%. Therefore, the Reviewers concluded that the study in this submission did not support the non-inferiority of Giazo compared to Asacol.

The response rates for this study by gender are shown in the following table (adapted from the Statistical Review from the second cycle):

Clinical Improvement by Gender in Study 3, mITT Population

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference Giazo – Asacol (95% C.I.)
Males	**51%** (b) (4)	**49%** (b) (4)	**2%** (b) (4)
Females	(b) (4)		

Numerically, the response rates for each gender were similar for the two treatment arms. With the smaller sample sizes, the confidence intervals for the differences within subgroups were wider that the confidence interval for the study overall, and the lower limits of the intervals were (b) (4). This study did not include a placebo group that could directly address the question of the size of any treatment effect in women.

In other subgroup analyses, there were too few non-whites and too few patients over 65 years to provide meaningful conclusions about those subgroups. See the second cycle Statistical and Clinical Reviews for details.

For the secondary endpoints, the two treatment groups appeared numerically similar, and none of the differences in secondary endpoints was statistically significant using the mITT population.

Conclusions and Recommendations from the Second Review Cycle

The Statistical Reviewer found that the NI margin the Applicant chose was not appropriate, and that Study 3 did not show clear evidence of efficacy. She concluded that the data in the resubmission did not present compelling evidence that Giazo is efficacious in patients with mildly to moderately active UC.

The Clinical Reviewer concluded that: 1) the Applicant's NI margin was inappropriate and Study 3 did not achieve success using a more appropriate NI margin, 2) the gender discrepancy was not addressed because the study lacked a placebo group, 3) evidence from the approval of Colazal and published data did not help explain the gender discrepancy, and

4) the submission did not have the ability to provide adequate labeling guidance regarding differential efficacy between men and women. The Clinical Reviewer did not believe that the concerns from the previous review cycle were addressed adequately, and he recommended that a Complete Response action be taken.

Clinical and Statistical Reviews for Current Review Cycle

The submission did not include new clinical data, but the Applicant provided a re-derivation of a non-inferiority margin for Study 3 with supporting articles from the literature together with a re-analysis of that Study. The Applicant also provided re-analyses of Studies 2 and 3 to argue that they showed a response in females.

Justification of the Non-inferiority Margin

The Applicant presented a re-analysis of Study 3 using the endpoint from an historical study to show that a NI margin of (b) (4) could be met, which, the Applicant argued, could be justified if the 50% discount were not used. The Applicant also presented additional analyses to argue that a (b) (4) NI margin was supportable. The Statistical Reviewer did not find the argument for a (b) (4) margin convincing, and concluded that a satisfactory NI margin for this situation remained to be determined. The Clinical Reviewer noted the Applicant had not provided any new clinical studies to serve as the basis for an NI margin, and he also did not find the Applicant's arguments persuasive.

Gender discrepancy

The Applicant provided analyses of secondary endpoints by gender and argued that the finding of a lesser effect in females was due to a spuriously high placebo response for the primary endpoint, but that there was a consistent treatment effect in females across secondary endpoints.

The Statistical Reviewer did not find the new analyses by gender to be convincing and noted that the high placebo response in females was seen in both primary and secondary endpoints.

The Clinical Reviewer felt that the Applicant had not provided substantially new arguments to address the gender issue. He was not persuaded by the Applicant's assertion that gender difference was driven by the subcomponent of stool frequency, and observed that in the Applicant's own post hoc analysis, a gender disparity was noted for each of the MMDAI subcomponents.

The Clinical Reviewer took the initiative to investigate gender disparity in other approved mesalamine–related products for UC. Although some studies showed differences between genders, for the most part he felt they appeared to be compatible with normal subgroup variability (See Clinical Review for study data tabulations). The Reviewer also examined the placebo-controlled study that used the balsalazide formulation Colazal. Although the study was small and not considered conclusive, the results of that four-week placebo-controlled study are noteworthy, in that they also suggested a substantial gender disparity with lack of effect in certain endpoints, most notably stool frequency, patient functional assessment, and abdominal pain:

Results of Placebo-Controlled Trial of Colazal in UC (Study CP069101)

Efficacy Endpoints		Colazal 6.75 g/day Men (n=46) Women (n=26)	Placebo Men (n=19) Women (n=16)	Difference Giazo - Placebo
Stool Blood	Men	33%	21%	12%
	Women	54%	44%	10%
Stool Frequency	Men	42%	26%	16%
	Women	27%	31%	-4%
Patient Functional Assessment	Men	44%	16%	28%
	Women	35%	38%	-3%
Abdominal Pain	Men	22%	16%	6%
	Women	27%	44%	-17%
Symptom Assessment	Men	30%	21%	9%
	Women	39%	38%	1%
Sigmoidoscopy	Men	48%	47%	1%
	Women	39%	37%	2%
Physician's Global Assessment	Men	35%	47%	-12%
	Women	39%	50%	-11%

Adapted from Table 22 of Clinical Review for the second review cycle, which was modified from Applicant's NDA 20-610 submission, 1988, Vol 7.1, p. 164. Missing values are counted as failures.

CDTL Comment:
The finding of no effect by sigmoidoscopy in this study could be a consequence of the study's short duration (four weeks), since endoscopic findings often lag clinical improvement in studies of active UC. Six or eight weeks is more commonly used when looking for an endoscopic response.

The Clinical Reviewer concluded that the deficiency regarding gender differences remained inadequately addressed.

Conclusions and Recommendations from the Current Review Cycle

The Clinical Reviewer was not convinced by the Applicant's non-inferiority arguments. He was not persuaded by the Applicant's analysis that the gender difference question had been adequately addressed, and therefore could not be ignored. From his review of the data, and in view of the lack of demonstrated efficacy in adult female patients, he felt that he could support an approval of Giazo for adult male UC patients only. He recommended considering a Phase 4 commitment to study efficacy in adult women with UC.

The Statistical Reviewer was not persuaded by the arguments justifying the Applicant's non-inferiority analysis and did not feel the analysis by gender was convincing. The Statistical Reviewer commented that resolution of the gender disparity did not seem likely without an additional placebo-controlled study. The Statistical Reviewer felt the studies in the submission supported efficacy of balsalazide for use in the male population.

8. Safety

Safety Data from Previous Review Cycles
In the safety database submitted for the original review cycle, 168 patients were treated with BD tables in the controlled study, and 130 patients (some the same) participated in an open-label extension study. Median exposure overall was 85.5 days. The Clinical Reviewer concluded that the safety assessment was adequate and that the safety profile of Giazo was similar to that of the approved capsule formulation of balsalazide disodium.

In addition to the eight-week (Study 2) and six-week (Study 3) efficacy studies above, the Applicant conducted an open-label extension study, Study BZUC3005 (Study 5), which accepted patients who successfully completed Study 2 or Study 3 and offered treatment for up to two years. See the CDTL Review or the Clinical Review from the previous review cycle for summary of safety findings.

Conclusions and Recommendations from the Second Review Cycle
The Clinical Reviewer concluded that there were no new safety signals and that the overall safety profile of Giazo was similar to that of the approved capsule dosage form (Colazal). He expressed some concern about finding more SAEs with Giazo than with Asacol (although the rates for both were less than for placebo). He noted that no thorough QT evaluation has been conducted for balsalazide disodium, but, based on current information, did not recommend that one be required for this product.

Current Review Cycle
All of the clinical trials with Giazo, including the extension study, were closed by 4/15/08, and all related clinical data had been provided to the NDA as of the safety update submitted 10/28/08, during the second review cycle. There were no new clinical trial data in the current submission. The safety update provided for the current review cycle consisted of a brief update on postmarketing data for Colazal and a review of safety literature for mesalamine products. The information appeared generally consistent with the previously submitted data regarding balsalazide safety and the known safety of mesalamine.

Although there were no new clinical trial data, the Clinical Reviewer requested additional analysis of the existing trial data and conducted a review of the data to assess the safety profile for a revised target population limited to males. He found that a lower proportion of males had adverse events (66% vs. 76% for females). He recommended that the labeling include the following table of common adverse events in male patients:

Adverse Reactions Experienced by at Least 2% of GIAZO –Treated Male Patients and at a Rate Greater than Placebo in a Placebo-Controlled Phase 3 Study

Adverse Reaction	GIAZO 6.6 g/day N=82	PLACEBO N=37
Anemia	3.7%	0%
Diarrhea	3.7%	0%
Pharyngolaryngeal Pain	3.7%	0%
Urinary Tract Infection	3.7%	0%
Arthralgia	2.4%	0%
Insomnia	2.4%	0%
Pain	2.4%	0%

In labeling negotiations, the Clinical Reviewer also recommended including adverse reaction information from postmarketing experience with the other balsalazide formulation, Colazal, as well as important adverse reaction information that he considered relevant from postmarketing experience with mesalamine products. The Reviewer also noted there had been six patients that had transient liver enzyme elevations. Although they had not met Hy's law and there was no evidence of irreversible liver damage, he recommended that the liver warning for Giazo be harmonized with the warning found in recently approved labeling for mesalamine products. The Reviewer's recommendations are reflected in labeling negotiated with the Applicant as submitted 4/26/09.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

Due to the low incidence of ulcerative colitis in pediatric patients below age 5 years, the Division has previously waived requirements for pediatric studies of ulcerative colitis treatment for that age group. The Division also has taken the position that there is sufficient similarity between adult and pediatric ulcerative colitis that efficacy in pediatrics can be extrapolated from adult findings, but that there is still a need for dose finding and for assessment of effectiveness and safety in pediatric populations. Colazal, the Applicant's capsule formulation of balsalazide, is indicated down to the age of 5 years and can reasonably be viewed as an age-appropriate pediatric formulation of balsalazide.

PeRC for Second Review Cycle

The application was presented to the Pediatric Research Committee (PeRC) on October 29, 2008. The committee agreed with waiving requirements under the age of 12 years, but felt that the option of BID dosing (vs. TID with Colazal) should be available to the older pediatric patients who can take the tablet formulation. The committee deferred to the Review Team as to whether additional studies (such as PK) would be needed, in which case pediatric studies should be a postmarketing requirement under PREA.

Current Review Cycle

In negotiations during the current review cycle, the Applicant proposed a pediatric plan to conduct a PK study in male patients 12 through 17 years, and proposed an agreement for a PREA-required PK study on 4/2/10. The application was presented again to PeRC on April 14, 2010. The committee concurred with the plan but suggested considering including younger ages that still might be able to swallow the tablet.

11. Other Relevant Regulatory Issues

Standard of Evidence for Efficacy

See also the discussion in the CDTL review dated 12/21/08 from the previous review cycle. This Reviewer feels that the appropriate standard is the one reflected in section II.C.2.a of the Evidence Document, in which related study data are taken into account and extraordinary statistical persuasiveness is not required. The Applicant's balsalazide capsule formulation (Colazal) is approved, the PK of Giazo and Colazal are similar (although not demonstrating similarity to a standard required for PK bioequivalence), but the relationship of blood concentration and response is not well understood. Thus, the conditions of II.C.2.a appear to be satisfied. For this Reviewer, the lack of very low p-value is not a critical deficiency of Study 2, and that study should be accepted as showing Giazo has an effect in treating UC.

However, the unexplained difference between genders in the treatment effect, accompanied by the unusually high placebo response rate in females, presents an important imperfection. The result runs contrary to what is seen with approved mesalamine products and remains unexplained. The gender difference is much more striking that the sorts of differences often seen in the face of the reduced sample sizes that accompany subgroup analyses: in Study 2 the gender difference was numerically large, clinically significant (a negative treatment effect in females vs. an almost tripling of response rate in males), and associated with quite a small nominal p-value. Whether Giazo has efficacy for females, and what treatment effect can be expected for females, are facts that need to be known before Giazo can be recommended for that subgroup.

The Clinical Reviewer and Statistical Reviewer for the previous and current review cycles concluded that Study 3 was not adequate to address the deficiencies cited in the May 2008 Approvable Letter. This Reviewer concurs with that conclusion. Because the results did not demonstrate non-inferiority to Asacol with a margin the Reviewers found supportable, it does not provide evidence of the efficacy of Giazo, and, as a corollary, is not able to address the question of efficacy in females. Even if it could have been argued that the results showed non-inferiority overall, the lack of a placebo control would have made it extremely difficult to make reliable inferences regarding the difference in the treatment effect between genders.

From the Clinical Reviewer's analysis of the other placebo-controlled study of balsalazide (using Colazal), there is evidence to suggest that the gender disparity in Study 2 might not be just an extreme case of a sporadic subgroup variation. For several endpoints (but not all) in the Colazal study, females responded differently than males and actually appeared to do worse with balsalazide than placebo.

It is difficult to argue that Giazo does not have efficacy, given the approval of Colazal and the overall positive result of Study 2. But it is also difficult to argue that the product should be recommended for women given the striking difference between gender responses seen in Study 2 and the consistency of that finding with the previous placebo-controlled study of Colazal suggesting lower, or a lack of, activity in the female subgroup. The course of action of approving the product but limiting the recommendation to use in male is admittedly unusual for this pharmacologic class, but it is reasonably supported by the aggregate of the relevant clinical data, and is arguably a more prudent course than including in the

recommend population a subgroup for which there remains important doubt about its efficacy.

Length of the Efficacy Studies
(See CDTL Review of 12/21/08 for additional discussion of this topic.) For the past several years the Division has been advising sponsors of products to treat UC that an NDA should include an evaluation of treatment strategies for the chronic management of UC for one year. However, at the time that the EOP2 meeting was held for this product (August 2005), the Division agreed that efficacy studies only of induction would be adequate for the NDA. Because there is no new substantial scientific issue that would require concluding that agreement is unacceptable, the agreement at the EOP2 meeting should stand. The length of the pivotal efficacy studies should not be an issue in the approval decision for this particular application, given the prior EOP2 agreement.

Given that there is a reasonable chronic safety database and an adequate basis to state the risks of chronic use appear to be generally similar to those of the 5-ASA products that are approved for chronic use in UC, there are no grounds to require a specific statement in the Warning and Precautions section warning against such use. However, it would be appropriate for the labeling to include explicit statements in Dosage and Administration and Clinical Studies to identify the limitations of the clinical data on which the approval is based.

Lack of QT Evaluation
There was no thorough QT assessment for this product, and the clinical studies did not incorporate collection of ECG data. Mesalamine products have been approved and marketed since 1987, and balsalazide has been marketed since 2000. Preclinical studies have not pointed to any problems with QT prolongation due to mesalamine or balsalazide, and postmarketing experience with balsalazide and mesalamine products have not identified a concern regarding QT prolongation. This Reviewer concurs with the Clinical Reviewer's recommendation that QT evaluation need not be required for approval of this application.

Division of Scientific Investigations (DSI) audits
The clinical data from Study 2 were found to be acceptable in the first review cycle. Following the submission of the Study 3 for the second review cycle, clinical site inspections for that study were conducted at Littleton, CO (Dr. Hansen), and Anderson, IN (Dr. Nowak). The Clinical Inspection Summary memo from DSI for the second review cycle, dated 12/10/08, reported interim classifications of NAI for the Anderson site and VAI for the Littleton site, but final classifications were outstanding at the time of the CR action. The DSI Reviewer had concluded in that review that the data from both inspected sites could be used in support of the NDA. The interim classifications were affirmed in the DSI letters sent to the two investigators on 3/27/09, following the second cycle action.

12. Labeling

Proprietary name
DMEPA had initially raised objections to using a trade name other than Colazal for the Applicant's alternative formulation of balsalazide disodium. The Applicant submitted

additional information in September 2008 in support of using a new trade name. Upon review of that information, DMEPA found the trade name "Giazo" to be acceptable from the standpoints of medication error an promotion in a review dated 4/13/09 (subsequent to the CR letter). The name remained acceptable as of the DMEPA review of 4/1/10.

Labeling Consults

DMEPA reviewed the proposed labeling and recommended that the package insert include description of the tablet shape in Sections 3 and 16 and the recommendation to take with food in under patient counseling information. DMEPA also provided specific recommendations for carton and container labels.

DDMAC reviewed the proposed package insert and made recommendations to improve clarity and reduce potential for promotional abuse, including the deletion of (b) (4)

Labeling issues

- Indication
  The lack of effect in females in Study 2 and confirmed in the review of the previous placebo controlled study with Colazal provides justification for labeling with an indication that does not include women, although the reasons for the findings remain obscure. Since the effect of Giazo in women was actually investigated and found to be lacking, wording that efficacy in women "was not seen in controlled studies" is preferable (b) (4)

- Warnings and Precautions
  Giazo should have same renal warning as other mesalamines. Although systemic mesalamine exposures are at low end of the range of mesalamine products, they are still of a similar magnitude. The negative studies in animals should not be interpreted as suggesting better renal safety of balsalazide vs. mesalamine. (See also CDTL Comments in Sections 4 and 5). The renal warning for Giazo should be substantially the same as that for other mesalamine products.

  Because Giazo results in systemic mesalamine exposures similar to that of other approved mesalamine products, and there have been reports of liver failure in patients with liver disease who received mesalamine, the labeling for Giazo also should include a liver warning similar to that used for recently labeled mesalamine products (e.g., as found in the labeling for Apriso).

- Clinical Pharmacology
  Section 12 (Clinical Pharmacology) should be extensively revised along the lines recommended by the Clinical Pharmacology Reviewer. Also, the proposed labeling contained a statement that bacterial action released mesalamine (b) (4) The Applicant was unable to provide data that specifically localized the release to that segment of the GI tract, so the term "gut" for site of release is more appropriate for labeling, pending further data.

(b) (4)

[redacted]

- Clinical Trial Data
  Study 3 should not be included, because the review team does not concur with the Applicant on the significance of the findings in Study 3, and because Study 2 is adequate and more definitive regarding efficacy. Further, since there has been no replication of a comparative study vs. Asacol, Study 3 should not be used for making any comparative claims. The description of Study 2 should include the overall results, as well as primary endpoint results by gender to help illustrate the reason for the limited indication. Since Study 2 shows a numerically negative effect in women, it is unlikely inclusion of the primary endpoint data on females in this specific case could be used to facilitate promotion of off-label use in females. Because the first two secondary endpoint results were positive overall by the pre-specified analysis, and because they are nominally statistically significant in the male subgroup, the secondary endpoint results for males can be included in the trial description.

  Because a variety of UC endpoints with similar names have been used in pharmaceutical trials of UC, the labeling should include at least some description of how endpoints were defined, and a reference for the scoring system should be provided.

- Labels
  The issues regarding carton and container labels identified by the CMC review in previous cycles have been resolved, per the CMC Reviewer.

- Other Labeling Issues
  No patient labeling or Medication Guide was proposed, and the review team did not feel that either needed to be required.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The CMC Reviewer did not recommend the application for approval due to failure of a manufacturing site to pass inspection. The application is otherwise approvable, and the labels and labeling negotiated with the Applicant and as submitted on 4/26/10 are currently

acceptable. Unless the WITHHOLD recommendation from the Office of Compliance is reversed by the action date, the recommended action is Complete Response due to deficiencies found during the inspection of Nexgen Pharma, Inc.

Risk Benefit Assessment

The risk characteristics for Giazo for treating UC appear similar to those of the already approved and marketed oral balsalazide product (Colazal), as well as approved mesalamine products. The outstanding benefit issue with this application is the significant uncertainty about the effectiveness of this product for female UC patients. The review team has recommended limiting the indication to male UC patients (b) (4)

Recommendation for Postmarketing Risk Evaluation and Management Strategies

No special postmarketing risk evaluation and management strategies (REMS) are recommended for this Application.

Recommendation for other Postmarketing Study Commitments or Requirements

As discussed above in Section 10, above, a PK study in pediatric patients ages 12 through 17 should be made a PREA requirement, because it was determined by the review team that such a study is needed to support pediatric labeling for that age range. The Applicant agreed to such a requirement on 4/2/10.

The Clinical Reviewer recommended a postmarketing commitment to conduct a study to evaluate efficacy in female patients, and the Clinical Reviewer and Clinical Pharmacology Reviewer recommended a commitment to conduct a study of antibiotic interaction. None of the other primary review disciplines had recommendations for additional postmarketing commitments or requirements.

There are unanswered questions regarding balsalazide disodium due to the Phase 4 commitments for Colazal (NDA 20-610) that remain outstanding. The review team considered whether similar commitments should be attached to the approval for Giazo as a means to providing a timeline for the commitments. The team concluded that it would not be necessary to restate the same commitments for Giazo. However (as above), the team felt that a drug-interaction study to investigate the effect of antibiotic therapy was of value, given the dependence of balsalazide metabolism on gut flora. Since the previous drug interaction commitment for Colazal did not address this concern directly, the team felt that an explicit commitment for an antibiotic interaction study was appropriate.

Commitments were negotiated and agreed upon with the Applicant as reflected in their submission on 4/21/10. However, given that a Complete Response action is contemplated because of manufacturing site problems, formalization and assignment of dates for these commitments, as well as for the PREA-required PK study, will need to be deferred until the application can be approved.

Recommended Comments to Applicant

None.

Attachment 1: Nonclinical PK data summary, provided by D. Joseph

Balsalazide Toxicity and Toxicokinetics (from Pharm/tox review of NDA 20,610 (Colazal))

12-Month Oral Study in Dogs:

Maximum dose of 2000 mg/kg/day balsalazide (equivalent to 700 mg/kg/day mesalamine) was NOT nephrotoxic; AUC values were not measured

Mesalamine AUC values are available from a 28-day oral toxicity study of balsalazide in dogs, in which 2000 mg/kg/day balsalazide was administered.

Day 1 Mesalamine AUC = 1113 nmol•hr/ml = 170 μg•hr/ml
Day 28 Mesalamine AUC = 1135 nmol•hr/ml = 174 μg•hr/ml

Mean Mesalamine AUC = 172 μg•hr/ml

Mesalamine Toxicity and Toxicokinetics (from Pharm/tox review of NDA 19,651 (Asacol))

12-Month Oral Study in Dogs:

40 mg/kg/day mesalamine was NOT nephrotoxic; toxicokinetics are shown in table below.

	Mesalamine AUC at 40 mg/kg/day	
	AUC (μg•hr/ml)	**AUC (μg•hr/ml)**
Day	**Males**	**Females**
1	137	168
6	128	164
29	133	153
189	177	193
370	177	144
Mean	150	164

80 mg/kg/day day mesalamine produced nephrotoxicity.
AUC range in males was 218-360 in males, mean = 295
AUC range in females was 273-430, mean = 353

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22205	ORIG-1	SALIX PHARMACEUTICALS INC	BALSALAZIDE DISODIUM TABLETS

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/s/

JOHN E HYDE
04/27/2010

CLINICAL REVIEW

Application Type	Complete Response Resubmission
Submission Number	NDA 22-205
Submission Review Cycle	Third
Letter Date	October 26, 2009
Stamp Date	October 27, 2009
PDUFA Goal Date	April 27, 2010
Reviewer Name	Christopher Leptak, M.D., Ph. D.
Review Completion Date	April 26, 2010
Established Name	Balsalazide Disodium
(Proposed) Trade Name	Giazo
Therapeutic Class	Locally-Acting Aminosalicylate (Anti-inflammatory)
Applicant	Salix Pharmaceuticals, Inc.
Priority Designation	Standard
Formulation	Tablet (1.1g)
Dosing Regimen	3.3g BID
Indication	Mildly to moderately active UC
Intended Population	18 years of age and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends that Giazo (NDA 22-205) can be approved for the treatment of adult male UC patients. However, given that facilities proposed for the manufacture of this product were found not to be in compliance with cGMP and the Office of Compliance (OC) issued an overall Withhold recommendation, the NDA is not recommended for approval until the manufacturing site deficiencies are resolved and the OC finds all sites acceptable. Therefore, this reviewer recommends that a Complete Response regulatory action be taken on the current complete response resubmission.

For the original submission, the review team concluded that the Applicant's single placebo-controlled study, BZUC3002, was inadequate to support effectiveness of BD tablets and an Approvable action was taken. BZUC3002 failed to demonstrate a statistically persuasive and consistent finding of treatment effect between men and women, subpopulations that were equally represented in the study. The observed superiority of BD tablets over placebo was driven by a subpopulation's finding, namely, male patients. A substantial therapeutic gain was demonstrated among men (37%), but none among women (-4%). Since therapeutic effect in women was indeterminate secondary to the unexplained high placebo response rate in this subgroup, efficacy of BD tablets was not established in female patients. In the Executive Summary of her clinical review dated 4 April, 2008, Dr. Fathia Gibril recommended that the issuance of a future approval be dependent upon the review of additional efficacy data from an adequate and well-controlled study that would demonstrate substantial evidence of effectiveness and consistent finding across important subgroups, namely, males and females.

For the second review cycle, BZUC3003, a non-inferiority trial was submitted and reviewed, This reviewer did not believe that the concerns of the previous review team have been adequately addressed. In summary, the following deficiencies were found: 1) the non-inferiority (NI) margin of success chosen by the Applicant was not appropriate and the study did not achieve success when a more representative NI margin was employed, 2) the lack of a placebo arm in the study did not address the gender response discrepancy found in BZUC3002, 3) additional evidence from the published literature and from the approval of Colazal, a capsule formulation of BD marketed by the Applicant, did not resolve the unexpected outcome of differential treatment response between men and women, and 4) the inability to provide adequate labeling guidance to the medical community regarding the observed differential efficacy between men and women with ulcerative colitis.

For this third review cycle, no additional clinical data was submitted. In an attempt to address the deficiencies identified in the first two review cycles, the Applicant submitted several post-hoc analyses of the original data from BZUC3002 and BZUC3003. Upon

review of this information and the Applicant's proposal for why BD should be approved, this reviewer concludes that the previously described deficiencies remain inadequately addressed. Should the product be approved for adult male UC patients only, given the lack of demonstrated efficacy in adult female patients, I could support this decision based on the Guidance for Industry "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" (Section II, C, 2, a).

1.2 Recommendation on Postmarketing Actions

Risk Management Activity

Should this NDA be approved in the future, an assessment of appropriate risk management would need to take into account updated information at that time. At present, given the low frequency of serious adverse events and the lack of specific active safety concerns, this reviewer does not recommend a risk management plan for balsalazide disodium for the treatment of adult patients with mildly to moderately active UC.

Required Phase 4 Commitments

The Sponsor requested waiver for pediatric studies required under the Pediatric Research Equity Act (PREA). On 29 October, 2008, this recommendation for full waiver of pediatric studies with the BD tablet formulation was presented before the PERC committee. The outcome of the discussion was: 1) full waiver of studies for pediatric UC patients under 12 years of age, 2) should the product be approved, the label should include information for adolescent UC patients between 12 and 17 years of age, and 3) the Division has the discretion to determine if additional studies are required to adequately label BD for this adolescent UC patient population. For this review cycle, a second PERC committee meeting was held on 8 April, 2010. The outcome of that discussion was consistent with the prior PERC recommendations with the following suggestion for the Division's consideration: labeling of the product for children under the age of twelve for those patients able to swallow the adult tablet formulation.

Other Phase 4 Requests

Should the product be approved, the following Phase 4 commitments should be considered:

- Efficacy study in adult women with UC should the product be approved for adult male UC patients
- Pediatric PK study in adolescent pediatric UC patients aged 12 to 17 years of age
- Clinical pharmacology study evaluating potential drug interaction between Giazo and commonly prescribed antibiotics for the treatment of UC

1.3 Summary of Clinical Findings

Brief Overview of Clinical Program

In support of the proposed indication for use in ulcerative colitis patients, the sponsor previously submitted the results from two clinical trials:

- BZUC3002 was a Phase 3, double-blind, randomized, multi-center, parallel-group, placebo-controlled study that was conducted in the US. Eligible patients (n=250) were randomized to receive either BD tablets or placebo in a 2:1 ratio for eight weeks.
- BZUC3003 is a Phase 3, double-blind, double-dummy, randomized, multi-center, active-controlled study conducted in the US. Eligible patients were randomized 1:1 to receive either BD tablets or Asacol, an approved mesalamine drug product used as the active comparator, for six weeks.

No new clinical study data was submitted as part of this third review cycle. When appropriate, prior review cycle findings and conclusions are incorporated as part of this review for ease of reference and to provide background for the discussion.

Efficacy

The efficacy of BD tablets was evaluated in a two Phase 3 clinical trials. BZUC3002 was a placebo-controlled, eight-week evaluation of BD tablets in patients with mildly to moderately active UC and was reviewed during the first submission of NDA 22-205. BZUC3003 was a six-week evaluation comparing BD tablets to Asacol as an active comparator in an analogous patient population and was reviewed as part of the second review cycle resubmission.

For both studies, efficacy was assessed using the Modified Mayo Disease Activity Index (MMDAI) which has a maximum total score of 12. The MMDAI evaluated four indices (stool frequency, rectal bleeding, physician's global assessment [PGA], and endoscopic findings; See Section 6.1.2 Figure 1) each on a scale from 0 to 3, with 3 being severe disease. A daily diary was kept by patients to record stool frequency, rectal bleeding, and other symptoms. End of treatment (EOT) assessments occurred if a patient did not complete the study regardless of reason. A complete MMDAI score was calculated at screening/baseline in both clincial studies; final MMDAI assessments occurred at Week 8/EOT for BZUC3002 and at Week 6/EOT for BZUC3003.

For both studies, the pre-specified primary efficacy endpoint was the proportion of subjects who achieved clinical improvement and improvement in rectal bleeding (RB) by the end of the clinical trial. Clinical improvement was defined as a $\geq$ 1 point improvement in the total MMDAI score, and improvement in RB was defined as a $\geq$ 1 point improvement in the RB sub-score component.

BZUC3002

The findings of Dr. Fathia Gibril's review are presented below:

Primary Endpoint Analysis

Compared to placebo, a significantly larger proportion of ITT subjects treated with BD tablets achieved clinical improvement and improvement in RB: (b) (4) (55%) vs (40%) (b) (4) p=0.024. Similar results were observed in analysis of PP population: (b) (4) (57.6%) vs (40.6%) (b) (4); p=0.019.

In a gender-specific subgroup analysis, BD tablet was superior over placebo in male patients (57% (b) (4) vs 20% (b) (4); p<0.001). By contrast, the treatment difference was insignificant in female patients (54% (b) (4) vs 58% (b) (4); p= (b) (4)). Of note, female patients (n=128) comprised 51% of the ITT population. In summary, a substantial therapeutic gain was demonstrated among males (37%), but none among females (-4%).

The reason for the observed discrepancy in the placebo response rates across gender was not clear and additional information provided by the Applicant upon Dr. Gibril's request was found to be non-contributory.

Secondary Endpoint Analysis

In the hierarchical secondary endpoint analysis, a significantly larger proportion of ITT subjects in the BD tablets group experienced clinical remission and mucosal healing compared with the placebo group: 64/166 (38.6%) vs (22.9%) 19/83; p=0.0096 and 88/166 (53.0%) vs (32.5%) 27/83; p=0.0035, respectively. The third key secondary endpoint in the hierarchy (improvement in bowel frequency) failed to reach statistical significance, therefore, the analysis for this endpoint and the subsequent secondary endpoints were considered exploratory in nature as pre-specified in the statistical analysis plan.

To further investigate the observed discrepancy in results across gender, a post-hoc gender-specific sub-group analysis of secondary endpoints was conducted by the Division's statistician, Dr Shahla Farr. The results were consistent with the primary endpoint analysis. In men, a significantly larger proportion of subjects in the BD tablet group than in the placebo group experienced clinical remission (p=0.01), mucosal healing (p<0.001), improvement in bowel frequency (p=0.02), improvement in rectal bleeding (p=0.002) and complete remission (p=0.01). By contrast, the treatment differences were insignificant for all secondary endpoint variables in women (p-values: (b) (4) respectively). This is not surprising since secondary endpoint variables were subsets of the composite primary endpoint.

Based upon a comprehensive review of efficacy data generated from a single placebo controlled study, the reviewer concluded that the observed superiority of BD tablets over placebo was driven by a subpopulation's finding, namely, male patients. Conversely, the efficacy of BD tablets had not been established in female patients. The lack of therapeutic effect in female patients was due to the unexplained high placebo response rate.

BZUC3003

The proportion of subjects in the PP population who achieved clinical improvement and improvement in rectal bleeding at Week 6/EOT was similar for the BD cohort (61.7%) and the Asacol cohort (60.8%). The difference in the proportions of the patients who achieved this primary endpoint was 0.85%, allowing the lower bound of the 95% confidence interval for the treatment difference to be greater than the pre-specified, non-inferiority margin of (b) (4) (95% CI: - (b) (4) From these results, the Applicant concluded that balsalazide disodium tablets were not inferior to the active comparator Asacol, using the Applicant's criterion.

Evaluating efficacy in the ITT population as a sensitivity assessment revealed the proportion of subjects in the ITT population who achieved clinical improvement and improvement in rectal bleeding were similar for the BD cohort (56.3%) and the Asacol cohort (56.2%). The non-inferiority analysis revealed that balsalazide disodium tablets were not inferior to Asacol (0.13%; 95% CI: (b) (4) using the Applicant's criterion.

The superiority of BD to Asacol was also evaluated in the ITT population using a CMH test, adjusted for analysis center. No statistically significant difference (0.13%, p=0.4666) was observed between the two treatment groups. (b) (4)

This reviewer and the other members of the second review cycle resubmission team concluded that the NI margin chosen by the Applicant was inappropriate. Upon review of both the literature submitted by the Applicant as well as applicable placebo-controlled studies with Asacol, a NI margin of less than 3% was calculated to be more appropriate, making the comparison of therapeutic effect between BD and Asacol indeterminate and non-supportive (b) (4) Since this study did not have a placebo treatment arm, the gender discrepancy in treatment effect identified in the original review cycle was not addressed.

Safety

Safety data were previously submitted and analyzed from three sources: BZUC3002 (reviewed as part of the original submission), BZUC3003 (reviewed as part of second review cycle), and BZUC3005, an open-label, safety study of patients who previously participated in BZUC3002 and BZUC3003 (reviewed during both previous review cycles). No new additional safety data was collected or submitted during this review cycle.

For BZUC3002, of the 250 randomized patients, 247 were included in the safety population: 168 (99.4%) patients in the BD tablet group and 79 (97.5%) patients in the placebo group. Of a total of 410 patients randomized in BZUC3003, 408 patients were included in the safety population analysis: 210 (99%) patients in the BD-treatment group and 198 (100%) patients in the Asacol-treatment group. A total of 565 unique patients

received BD tablets either as a result of randomization to a BD cohort in one of the Phase 3 studies or as open-label treatment in the ongoing safety study BZUC3005; the analysis of this pooled data constituted the comprehensive safety population.

Regarding deaths, none occurred during conduct of BZUC3002 or BZUC3003. One patient enrolled in BZUC3005 died of metastatic malignant melanoma and was determined to be unlikely related to BD drug treatment.

Serious adverse events (SAEs) were reported in 5% of the comprehensive safety population. Worsening UC was the only SAE reported by >1% of patients and occurred at a frequency of 2% of the total patients exposed to BD treatment. In a comparison of the SAEs reported for BZUC3002 and BZUC3003 by treatment arm, both more types of SAEs and greater numbers of patients experienced an SAE in association with BD treatment compared to treatment with Asacol. The one exception was for the preferred term arthritis (one patient treated with Asacol and none treated with BD). The most frequent AE leading to discontinuation from BD therapy was worsening UC for all treatment arms in all studies (5% of BD-treated patients, 2% of Asacol-treated patients, and 11% of placebo-treated patients).

Comparing adverse events (AEs) in the treatment arms of the two Phase 3 studies, the proportion of patients reporting at least one AE were similar between the BD-treated (59%) and Asacol-treated (55%) cohorts, but higher in the placebo-treated (70%) patients. Overall, events related to gastrointestinal (GI) disorder were the most frequently reported AE (29% of BD-, 25% of Asacol-, and 38% of placebo-treated patients) for those events occurring in more than 2% of total patients. Worsening of UC was the most common GI-related event in all treatment cohorts (7% of BD-, 2% of Asacol-, and 15% of placebo-treated patients). The only GI events that occurred in ≥ 2% of patients in the BD-treated group and not in the placebo-treated group were abdominal distension (2%), flatulence (2%), and hemorrhoids (< 1%). Outside of GI-associated disorders, headache was the most commonly reported AE with a frequency of 8% in BD-, 10% in Asacol-, and 14% of placebo-treated patients. There were no clinically meaningful changes in laboratory parameters or vital signs in the Phase 3 studies. The interim report from an ongoing long-term, open-label, safety extension study (BZUC3005) including 443 patients showed a similar safety profile compared to the two Phase 3 studies. For the comprehensive safety population, the most frequent AEs were worsening UC (10%) and abdominal pain (4%).

Overall, for the double-blind studies, the proportion of patients who experienced drug-related TEAEs was comparable across the treatment groups (10% of BD-treated patients, 11% of Asacol-treated patients, and 9% of placebo-treated patients). Drug-related AEs that occurred in >1% of BD-treated were worsening UC (1% BD-, 0% Asacol-, and 3% placebo-treated patients), diarrhea (1% BD-, 2% Asacol-, and 1% placebo-treated patients), nausea (3% BD-, 4% Asacol-, and 0% placebo-treated patients), and headache (1% BD-, 3% Asacol-, and 1% placebo-treated patients).

Of note, a thorough QT study was not completed for either the BD capsule or tablet formulations. This reviewer does not recommend such a study be completed at this time for the following reasons. As a class of compounds, the 5-ASA drugs have been marketed for 16 years without any known cardiac toxicity risks identified to date. In addition, the bioavailability of BD is very small given that most of the drug and its metabolites remain in the gut with only a small fraction systemically absorbed. Should a cardiac signal emerge in the future, a thorough QT study could be considered at that time.

The overall safety profile of the tablet formulation is comparable to the approved capsule formulation Colazal, including data available from post-marketing reports. However, based upon the cumulative data from the clinical development program, there is concern that 5% of the comprehensive safety population reported at least one SAE and that both more types of SAEs and greater numbers of patients experienced an SAE in the BD-treated patients compared to those treated with Asacol. In addition, more BD-treated (5%) patients withdrew from the studies because of worsening UC compared to Asacol (2%). Finally, regarding the Applicant's proposed warning of use in patients with hepatic impairment, six patients treated with BD had transient transaminase elevations without evidence of irreversible liver damage.

Dosing Regimen and Administration

The recommended total daily dose is 6.6g to be taken in two divided doses (three 1.1g tablets BID) for up to 8 weeks.

It should be noted that no separate dose-response trial was conducted with the new BD tablet formulation. The rationale was that the proposed total daily dose (6.6g/day) for new tablet formulation is similar to that of the capsule formulation (6.75g/day), Colazal, which was approved in July 18, 2000 for the same indication. The goal of the clinical program was to offer patients with a more convenient daily dosing regimen with the new tablet formulation (BID vs TID).

Drug-Drug Interactions

Drug interaction studies have not been conducted with BD tablets. Given that there are no known drug interactions with mesalamine drug or pro-drug formulations, this reviewer does not foresee potential complications arising from drug-drug interactions with BD tablets. The local action of the drug and limited systemic absorption reduces the likelihood of significant hepatic or blood-associated drug interactions with other compounds that act through systemic mechanisms. Of note, as stated in the Colazal label, an *in vitro* study using human liver microsomes demonstrated that balsalazide and its metabolites (5-ASA, N-Ac-5-ASA, 4-ABA, and N-Ac-4-ABA) were not shown to inhibit the major CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) evaluated. Therefore, balsalazide and its metabolites are not expected to inhibit the metabolism of other drugs that are substrates for these CYP enzymes.

As a pro-drug that requires metabolism by gut flora to release mesalamine, medications that alter the composition of intestinal bacteria could affect, in theory, the activity of BD

treatment. To date, patients enrolled in BZUC3002, BZUC3003, and BZUC3005 had very limited concomitant exposure to antibiotics during the clincial trials. This theoretical concern remains unanswered at this time.

Special Populations

Gender disparity in treatment effect was one of the deficiencies identified in the original review cycle for Study BZUC3002. Study BZUC3003 failed to show non-inferiority to Asacol when a more appropriate NI margin was used, making a sub-analysis by gender noncontributory. In addition, BZUC3003 failed to address the observed large placebo-response rate in women enrolled in BZUC3002; BZUC3003 was a NI study design without a placebo arm for comparison. Unless the issue of gender disparity can be resolved, this reviewer agrees with the concerns of Dr. Gibril that the observed superiority of BD tablets over placebo in BDUC3002 was driven by a sub-population's finding, namely, male patients. Conversely, the efficacy of BD tablets has not been established in women. This gender disparity in treatment effect needs to be adequately addressed before the future approval of BD tablets.

Regarding other special populations, all the patients enrolled in BZUC3002 and BZUC3003 were adults with evidence of active UC disease. Safety and effectiveness of BD tables in the pediatric UC population have not been studied. There have been no studies with BD tablets in patients with renal or hepatic impairment. Pregnant women and nursing mothers were excluded from clinical trials with BD tablets. The clinical program did not include sufficient number of patients aged 65 and older (<10%) to determine whether they respond differently than younger patients. The majority of the patients were Caucasian (BZUC3002 83% and BZUC3003 86%) limiting the ability to study potential differences in safety and effectiveness among different racial groups. Like the capsule formulation of BD, Pregnancy Class B has been recommended for the tablet formulation with no impaired fertility or harm to the fetus noted in both rat and rabbit studies; excretion of BD in breast milk is not known.

2 INTRODUCTION AND BACKGROUND

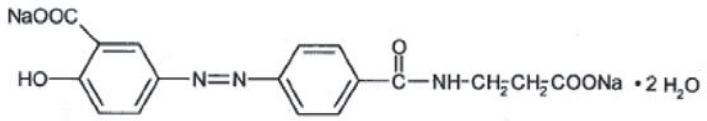
2.1 Product Information

The applicant seeks approval for BD tablet (1.1 g) for use in mildly to moderately active UC at a total daily dose of 6.6 g to be administered BID (three tablets BID) for up to eight weeks.

Proposed Trade Name: Giazo
Generic Name: balsalazide disodium
Code Name: BD
Drug Form: Pro-drug
Released Active Drug Product: 1.1g of BD is enzymatically cleaved in the colon to produce mesalamine (5-aminosalicylic acid, also referred to as 5-ASA), an anti-inflammatory drug. Each tablet of BD, upon enzymatic breakdown, yields (b) (4) of mesalamine.

Chemical Name: (E)-5-[[-4-[[(2-carboxyethyl) amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate.

Structural formula:



Therapeutic Class: Anti-inflammatory
Formulation: Tablet

The exact mechanism of action of mesalamine is not fully understood, but appears to be local in the colon rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by inhibiting cyclooxygenase and lipooxygenase activity as well as prostaglandin production in the colon.

2.2 Currently Available Treatment for the Indication

The following oral mesalamine or mesalamine pro-drug preparations are currently marketed in the US for use in UC medical management. The dosages and indications are listed below:

- Lialda (1.2 g tablet) at a total daily dose of 2.4 g or 4.8 g once daily. Induction of remission in mildly to moderately active UC.
- Colazal (750 mg capsule) at a total daily dose of 6.75 g in three divided doses. Treatment of mildly to moderately active UC.
- Asacol (400 mg tablet) at a total daily dose of 2.4 g in three divided doses. Treatment of mildly to moderately active UC and maintenance of remission.
- Pentasa (250 mg or 500 mg capsule) at a total daily dose of 4 g in four divided doses. Treatment of mildly to moderately active UC and induction of remission.
- Sulfasalazine (500 mg tablet) at a total daily dose of 3 g in three divided doses. Treatment of mildly to moderately active UC.
- Dipentum (250 mg capsule) at a total daily dose of 1 g in two divided doses. Maintenance of remission in UC patients intolerant to sulfasalazine.
- Asacol HD (800 mg tablet) at a total daily dose of 2.4 g in three divided doses. Treatment of moderately active UC.
- Apriso (0.375 g capsule) at a total daily dose of 1.5 g in a single morning dose. Maintenance of remission for UC.

In additional to the oral mesalamine class of agents, other approved products for the treatment of UC include oral and systemic steroids and Remicade, a biologic TNF blocker. Although approved for other disease indications, other immunosuppressants (b) (4) are widely used off-label for the treatment of UC.

2.3 Availability of Proposed Active Ingredient in the United States

Balsalazide disodium is the active ingredient of Colazal, a capsule formulation of BD. Colazal is marketed in the US for the treatment of mildly to moderately active UC in patients aged five years and older. There are no known concerns of limited product availability.

2.4 Important Issues With Pharmacologically Related Products

The BD pro-drug is enzymatically cleaved to produce mesalamine, the active ingredient and a member of the 5-ASA class. Therefore, BD is contraindicated in patients with a hypersensitivity to salicylates. Patients with pyloric stenosis may have prolonged gastric retention of BD tablets, reducing the efficacy of the product as the pro-drug requires delivery to the colon where it is locally active.

Renal toxicity has been observed in animals and patients given mesalamine or pro-drugs that are converted to mesalamine; caution should be exercised when administering BD to patients with known renal dysfunction or a history of renal disease. Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease; symptoms include cramping, acute abdominal pain,

and bloody diarrhea, sometimes in association with fever, headache, or rash. Mesalamine has also been associated with reports of hepatic failure in patients with pre-existing liver disease.

2.5 Pre-submission Regulatory Activity

Reference to meetings between the Agency and Applicant are filed under IND 38,492 for BD. Pertinent discussions and agreements are summarized below:

End of Phase 2 Meeting (8 August, 2005) Clinical Discussion Summary:

1) Per the Applicant's intent to submit a single study in support of approval of BD for the treatment of mildly or moderately active UC in adult patients, the Agency clarified that approvability would be based on robustness of the data and consistency of effect seen in primary and secondary endpoints.
2) Regarding the proposed dosing regimen, the Agency shared that treatment with 3.3 g BID appeared acceptable as long as adequate safety and efficacy can be demonstrated using this new dose and dosing regimen.
3) Regarding study length, the Agency recommended treatment duration of eight weeks. (b) (4) . The Agency emphasized that it would be difficult to compare the results of shorter duration clinical trials with the outcomes that led to the finding of safety and efficacy for Colazal capsules.
4) For the proposed placebo-controlled study (later to become BZUC3002), in addition to the use of a placebo control, the Agency recommended adding a third treatment arm as an active, approved comparator.
5) If a non-inferiority study were to be conducted and Asacol be used as the active comparator (later to become BZUC3003), the Agency emphasized that the Applicant needed to clarify the study design and the dose regimen to be used.

Pre-NDA Meeting (27 April, 2007) Clinical Discussion Summary:

1) The Agency reemphasized that submission of a single clinical trial in support of approval would require that the study be statistically robust and that the data show consistency of effect seen in primary and secondary endpoints.
2) The Agency agreed to the proposed scope of the safety database.
3) The Agency asked for clarification if BZUC3003 was to be completed and submitted as part of the data to support NDA 22-205.
4) The Agency indicated that a full submission of BZUC3005 safety data was required.
5) The Agency requested the CRFs for all patients who discontinued study participation for any reason.

Approvable Action for Initial Submission of NDA 22-205 (16 May, 2008):

As stated in the Approvable Letter, before the application may be approved, the Applicant needed to resolve the following issues:

> "Your placebo-controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study."
>
> "The issuance of an approval is dependent upon the review of an additional adequate and well-controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis."

Post-Approvable Action Meeting with Applicant (9 June, 2008):

1) The submission of BZUC3003 was agreed upon to constitute a Complete Response to the Approvable action.
2) The Agency reiterated that gender subgroup data would not be interpreted in a confirmatory manner, but should be consistent with results based on the entire study population.
3) The Agency is interested in the derivation and justification for the Applicant's NI margin and that adequacy of the margin will be a review concern.
4) An integrated safety update is required for resubmission and a new 120-Day Safety Update would be expected as well.
5) The Agency stressed that the safest way to minimize medication errors is to manage both BD formulations under one proprietary name, Colazal.
6) The Applicant will submit updated stability data with the resubmission.

Complete Response Action for Second Review Cycle of NDA 22-205 (22 December, 2008):

1. Inadequate Justification of the (b) (4) Non-Inferiority for Study BZUC3003

Your non-inferiority (NI) margin was not appropriately justified. In support of the (b) (4) NI margin, you cite input from clinicians with experience in the treatment of active ulcerative colitis (UC) and make reference to several studies in the published literature. You conducted a meta-analysis of 16 placebo-controlled trials (between years 1967 to 1989), of which 11 studies were for induction in UC. All these studies included patients with mildly to severely active UC.

However, we do not agree that all these studies support your choice of the (b) (4) NI margin. The choice of NI margin should be based on data from 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. Only one study (Sninsky et al.) of the 11 you cited exemplifies the appropriate choice of a reference trial for NI margin assessment as outlined in the ICH E10 Guidance. Although not identical in efficacy endpoint selection, Study BZUC3003 and the Sninsky article used analogous composite disease activity indices for efficacy determination.

The Sninsky article reports that the six-week combined treatment outcomes of patients classified as "in remission" or "improved" were: 10/44 (23%) patients in the Asacol 2.4 g/day treatment arm and 21/43 (49%) patients in the placebo treatment arm achieved clinical improvement (an endpoint similar to the primary efficacy endpoint assessment in Study BZUC3003). Thus, a treatment effect for Asacol (Asacol treatment response minus placebo treatment response) can be estimated as 26%, with a 95% Confidence Interval of (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 statistical practice, that *smallest* effect is estimated as 50% of the lower confidence bound, which would be 3% based on the Sninsky study. Thus, as judged from your reference literature, the study that adheres acceptably to the ICH E10 criteria results in a substantially lower NI margin (3%) than the margin (b) (4) used in your study. The choice of a 3% NI margin is also supported by a study used for Agency approval of Asacol.

2. Inability of the Results of Study BZUC3003 to Address the Deficiencies of the May 16, 2008, Approvable Letter

With the NI margin taken to be 3%, Study BZUC3003 fails to demonstrate non-inferiority of BD tablets compared to Asacol. Therefore, Study BZUC3003 cannot be considered to provide additional evidence of the efficacy of BD tablets. Because Study BZUC3003 fails to provide evidence of efficacy, a gender sub-analysis of this study does not contribute information to resolve the question about the differences between men and women regarding the efficacy of BD tablets. Further, without a placebo comparison, this study cannot provide reliable estimates of the treatment effect, and, consequently, cannot convincingly address questions about the difference in treatment effect between men and women. Therefore, the deficiencies identified in the May 16, 2008, Approvable letter have not been addressed by Study BZUC3003 and your Complete Response submission, and those deficiencies remain to be resolved.

Future approval of BD tablets for the treatment of mildly to moderately active UC will be dependent upon the review of additional efficacy data from an adequate and well-controlled study that demonstrates substantial evidence of effectiveness and has the ability to resolve the questions about differences between men and women regarding the treatment effect of BD tablets in active UC. Before initiating such a study, we recommend that you obtain input from us regarding the study design.

Post-Regulatory Type A Action Meeting with Applicant (16 March, 2009) summarized below:

1) The Applicant must directly address the observed gender discrepancy in treatment effect observed in BZUC3002.
2) The Agency did not agree with a (b) (4) treatment arm for BZUC3003.
3) The Agency stated that PK data for the BD tablet and capsule formulations could not be compared to infer efficacy since the dosing regimens for the two products differ.
4) The Agency stressed that a 3% NI margin is the appropriate choice for BZUC3003.

2.6 Other Relevant Background Information

BD tablets are not marketed in any country. Colazal, the capsule formulation, was approved in the U.S. on 18 July, 2000, for the treatment of mildly to moderately active ulcerative colitis (UC) in patients 18 years of age and older. In December 2006, the indication was expanded to include use in children 5 to 17 years of age for the same indication. The labeling states that safety and effectiveness of balsalazide beyond 8 weeks in children (ages 5 to 17 years) and 12 weeks in adults have not been established.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review staff for the initial submission of NDA 22-205 made the following conclusions and recommendations: 1) the NDA provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product; 2) expiration dating was determined to be 36 months, 3) but facilities proposed for the manufacture of this product were found not to be in compliance with cGMP and the Office of Compliance (OC) issued an overall Withhold recommendation. Therefore, from a CMC prospective, the NDA is not recommended for approval until the manufacturing site deficiencies are resolved and the OC finds all sites acceptable. For details, please see Dr. Marie Kowblansky's CMC review dated April 15, 2010.

3.2 Animal Pharmacology/Toxicology

No new animal studies were conducted under NDA 22-205. The conclusions and recommendations from the Pharmacology/Toxicology review staff for the initial submission of NDA 22-205 were as follows:

1. From a preclinical standpoint, an approval action was recommended.
2. Labeling recommendations suggesting caution in use in patients with known renal function or a history of renal disease. This concern was based on an observed increased incidence of pelvic and corticomedullary mineralization in kidney and urothelial hyperplasia in rats at oral doses approximately 0.7 fold the recommended human dose based on body surface area.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The studies were submitted as the primary sources of clinical efficacy and safety data for NDA 22-205. The first was a single placebo-controlled study (BZUC3002) conducted by the Applicant in the U.S. and included in the initial submission of this NDA. The second was a non-inferiority study (BZUC3003) conducted by the Applicant in the U.S. and submitted for review with the second resubmission Complete Response. In addition, safety data was collected as part of a long-term, open-label safety and tolerability study (BZUC3005). Studies were submitted as a paper version in the Common Technical Document format (CTD).

4.2 Tables of Clinical Studies

Table 1: Summary of Clinical Studies

Study ID	Number of Study Centers and Locations	Design	Study Drug Dose, Regimen, and Route	Study Objectives	No. of Patients by Arm:	Duration of Treatment
BZUC3002	55 Centers All U.S.	Multi-center, Randomized, Double-blind, placebo-controlled, parallel-group	BD 3.3 g (1.1 g X 3) BID Oral	Primary: Evaluate the safety and efficacy of BD in patients with active UC	Placebo: 83 BD: 167 (n = 250)	8 weeks
BZUC3003	79 Centers All U.S.	Randomized, Double-blind, Double-dummy, active-controlled, parallel-group	BD: 3.3 g BID Asacol: 0.8 g TID Both Oral	Primary: Evaluate the safety and efficacy of BD in patients with active UC	BD: 212 Asacol: 198 (n= 410)	6 weeks
BZUC3005	All U.S.	Multi-center, open-label	BD: 3.3 g BID or 4.4 g BID Oral	Long-term safety and tolerability of BD	Goal 500 443 Enrolled at time of submission	2 year minimum

5 CLINICAL PHARMACOLOGY

Balsalazide disodium (BD) is a pro-drug that is designed to release an active moiety 5-aminosalicylic acid (5-ASA) and an inactive carrier moiety 4-amino benzoyl-β-alanine (4-ABA) upon enzymatic degradation by gut microflora. The 5-ASA and 4-ABA are further metabolized to N-acetyl-5-ASA and N-acetyl-4-ABA respectively. For complete details, please see the Clinical Pharmacology review of Insook Kim, Ph.D. dated 7 April, 2010.

The exact mechanism of action of mesalamine, the biologically active compound of the BD pro-drug, is not fully understood, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by inhibiting cyclooxygenase and lipooxygenase activity, and prostaglandin production in the colon.

Included in the original submission of NDA 22-205 were two new pharmacokinetic studies: 1) a study that assessed the relative bioavailability of the new BD tablet formulation compared to the previously approved capsule formulation and 2) a food effect study. To summarize the clinical pharmacology review findings:

1) The clinical pharmacology data were reviewed and found to be acceptable.
2) Although there was a higher amount of drug delivered per dose with the tablet formulation, the Cmax of balsalazide for systemic exposure is somewhat higher for the capsule formulation. After a single dose, however, the Cmax for mesalamine and the primary metabolite are somewhat higher for the tablet compared to the capsule formulation. The tablet's multi-dosing AUC for both mesalamine and the primary metabolite were higher than that observed with the capsule formulation. By gender, the Cmax of mesalamine in females was 123% of that in males, and the AUC in females relative to males was 140%.
3) A high fat diet influenced the systemic exposure of both mesalamine and the primary metabolite. For mesalamine, the Cmax was reduced by 66%, and the AUC was reduced by 15%. Absorption was delayed by a high fat diet as well; Tmax was increased from 0.5 hour to 2.0 hours.

5.1 Pharmacokinetics

In response to the lack of consistency of treatment effect between male and female patients, the Applicant cited available pharmacokinetic (PK) data to address this concern. In summary, this analysis demonstrated that the rate and extent of bio-conversion of BD to mesalamine was comparable between men and women. In addition, when BD tablets are compared to the marketed product Colazal, the results show that both formulations have 1) equivalent 24-hour exposures, 2) demonstrate very similar PK between men and

women with no differences in the rate and extent of pro-drug conversion, and 3) equivalence in the *in vitro* dissolution profile, confirming that no relevant differences exist between the immediate release formulations.

However, Dr. Kim does not recommend that this data and analysis support consistency of treatment effect between men and women. Since no evidence was provided to support a pattern of comparable disease progression between the genders and the placebo response rates widely differed between men and women, she concluded that similar systemic exposure cannot be used to support similar therapeutic effect between male and female patients.

5.2 Pharmacodynamics

No pharmacodynamic study was conducted for this application, possibly because mesalamine, the active moiety of the BD pro-drug, is thought to have a local action in the colon rather than systemic action.

5.3 Exposure-Response Relationships

No dose-response study was conducted for this application.

6 EFFICACY

6.1 Indication

Balsalazide tablets are proposed "***for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. Safety and effectiveness of Giazo beyond 8 weeks in adults have not been established."***

Methods

The Applicant seeks approval for balsalazide disodium (BD) tablets for treatment of mildly to moderately active UC. The BD tablet contains 1.1g of BD, a pro-drug that is enzymatically cleaved in the colon by local gut flora to release mesalamine, the active drug product. Although the exact mechanism of action of mesalamine is not fully understood, it appears to have anti-inflammatory properties and to act locally in the colonic mucosa. To date, seven oral agents that act through either local delivery or local release of mesalamine have been approved for use in mildly to moderately active UC: Asacol (delayed-release tablet), Lialda (delayed-release tablet), Apriso (delayed-release capsule), Pentasa (controlled-release capsule), Sulfasalazine tablet (pro-drug), Colazal capsule (balsalazide disodium, pro-drug), and Dipentum capsule (olsalazine, sodium pro-drug).

In support of the proposed indication, the Applicant submitted efficacy data from two clinical studies during the previous two review cycles. The first study BZUC3002 was submitted for evaluation as part of the original NDA submission and was reviewed by Dr. Fathia Gibril (Clinical Reviewer) dated 4 April, 2008, and Dr. Ruyi He (Medical Team Leader) dated 9 May, 2008. The second study BZUC3003 was reviewed during the second review cycle by this reviewer and Dr. John Hyde (Medical Team Leader); please see respective reviews dated 20 December, 2008 and 21 December, 2008.

For this third cycle review, no new clinical study data was provided. *In lieu* of such information, the Applicant completed several post-hoc analyses of the data from BZUC3002 and BZUC3003 in an attempt to address the deficiencies identified in the first two review cycles' Complete Response letters.

The goal of the balsalazide clinical development program was to provide a more convenient dosing regimen, since BD tablets are dosed BID compared to Colazal capsules, which are dosed TID.

General Discussion of Endpoints

BZUC3002 and BZUC 3003 used the Modified Mayo Disease Activity Index (MMDAI) to compare baseline and end of study (six weeks) disease activity assessments. The MMDAI is a composite score consisting of four sub-scores (i.e., bowel frequency, rectal bleeding, physician's global assessment, and endoscopy findings). The MMDAI evaluates these four indices, each on a scale of 0 to 3 (3 being severe disease). The maximal total score is 12.

Figure 1: Modified Mayo Disease Activity Index (MMDAI)

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

* The modification that has been made to the Mayo index is the deletion of "friability" from an endoscopy sub-score equal to "1". With this modification, the presence of friability is indicative of an endoscopy sub-score of 2 or 3.

The pre-specified primary efficacy endpoint for both BZUC3002 and BZUC3003 was the proportion of patients who achieved clinical improvement and improvement in rectal bleeding subscale of the Modified Mayo Disease Activity Index (MMDAI) at the end of six weeks of therapy. Clinical improvement was defined as a ≥ 3 point improvement from baseline in the MMDAI total score; improvement in the rectal bleeding subscale was defined as a ≥ 1 point improvement from baseline in the rectal bleeding score.

In all efficacy analyses of proportions, patients who terminated early from the study due to lack of efficacy or UC-related AEs were considered to be treatment failures regardless of the MMDAI scores. If post-baseline components of the MMDAI score were missing, the last available MMDAI individual subscore(s) was/were carried forward.

Reviewer's comment:

There is currently no universally accepted and validated measure of disease activity in UC patients. The MMDAI used by the Applicant has been supported by the Agency as an acceptable scoring index in clinical UC trials. Measurement of disease activity is critical in evaluating new therapies in UC clinical trials. The proposed MMDAI has been widely used in UC clinical trials and is a reasonable scoring index for ulcerative colitis because it allows for an adequate, overall assessment of a patient's disease activity state.

Key secondary efficacy endpoints, in hierarchical order for formal statistical analysis and testing, were as follows:

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

Reviewer's Comment:

At the End of Phase 2 meeting held on 8 August, 2005, the meeting minutes reflect that, in general, the proposed primary and secondary endpoints appeared to be acceptable.

6.1.1.1 Outstanding identified efficacy deficiencies from prior review cycles

1. Non-Inferiority Margin for BZUC3003

The Applicant provided the following information related to the choice of the NI margin for BZUC3003 as part of this most recent resubmission:

- Resubmission of the previously submitted published literature articles stating that the totality of the evidence supports the choice of a (b) (4) NI margin
- If one assumes a (b) (4) NI margin and applies the response definitions of the Sninsky article to the BZUC3003 data, this post-hoc analysis provides evidence for the non-inferiority of BD compared to Asacol

Reviewer's Comment

1. Is the non-inferiority margin appropriate?

Since the cited literature was previously examined during the second review cycle, the team response is provided below. For a complete discussion of the statistical analyzes performed and of the justification of non-inferiority margin (NI) chosen, please see the statistical review by Dr. Mike Welch dated 21 December, 2008. In summary, the Applicant chose the (b) (4) NI margin based on the following approach. The Applicant

performed a meta-analysis of 16 placebo-controlled trials conducted between 1967 and 1989; the placebo-controlled trials were identified as part of a literature search. Of the 16 trials, 11 studies were identified that chose induction of remission of UC as there primary efficacy endpoint. The study populations for these 11 studies focused on mildly to moderately active UC patients. In addition to the literature references, the Applicant also justified the NI margin based on input from clinicians with experience in the treatment of active UC. Driven by the literature analysis and clinical input, the Applicant concluded that the (b) (4) *NI margin was justified.*

This reviewer, however, does not agree with the process by which the (b) (4) *NI margin was chosen. The guidance ICH Topic E 10: Choice of Control Group in Clinical Trials (CPMP/ICH/364/96) was adopted for approval January 2001. Section* ***1.5.1 Assay Sensitivity in Non-inferiority or Equivalence Trials*** *states, in part, that the presence of assay sensitivity in a NI clinical study may be deduced from historical evidence of sensitivity to drug effects, namely that similarly designed trials conducted in the past can be used to determine effective treatments from less effective or ineffective treatments. Specifically, appropriately designed and conducted clinical trials that tested a specific active therapy reliably showed a treatment effect. Optimally, the demonstrated treatment effect of the active therapy intended for use as the active comparator in the NI trial was reliably found to be superior to placebo. The NI trial should be similar in design to that of the reference trials for the active comparator (e.g. analogous entry criteria, allowable concomitant therapy. Based on this ICH guidance, this reviewer concludes that studies that support the choice of a NI margin should have been conducted under placebo-controlled conditions with the active comparator. And such studies should be analogous to the design of the NI trial of interest (i.e., similar patient population, inclusion/exclusion criteria, treatment dose and duration of the active comparator, and efficacy endpoints to be assessed).*

Applying these specifications to the literature references submitted by the Applicant in support of the (b) (4) *NI margin, this reviewer finds that all but one of the studies fall short of the guidance's "similarity" definition. Study design deviations from the NI trial of interest include:*

- *Different active treatments; only one study tested Asacol, the active comparator for BZUC3003*
- *Differing durations of treatment, ranging from 14 to 42 days*
- *Different inclusion/exclusion criteria*
- *Different efficacy endpoint assessments*

The one study referenced by the Applicant that did have a similar design to BZUC3003 was by Sninsky, et al. (Annals Int Med. 1991; 115:350-355). As best could be determined from the Methods section of the referenced article, the patient population, inclusion/exclusion criteria, and treatment dose and duration of Asacol therapy was similar to BZUC3003. The primary efficacy endpoint was clinical response based on a scoring system similar to the MMDAI with the main difference being the inclusion of an additional sub-score for a Patient's Functional Assessment. So, although not identical to

BZUC3003, this reviewer feels that the Sninsky publication, from all those submitted by the Applicant, best exemplifies the appropriate choice of a reference trial for NI margin assessment as outlined in the ICH E10 guidance.

The Sninsky study found that the proportion of patients achieving clinical improvement after six-weeks of treatment was 49% for the 2.4 Asacol-treatment arm and 23% for the placebo-treatment arm. The difference in the treatment responses between these two arms was statistically significant (p=0.003). The authors subdivided the Asacol-treatment responders into four groups:

- *"In remission" was defined as a complete resolution of all symptoms, with all assessment scores determined to be zero*
- *"Improved" was defined as a reduction in the physician's global assessment (PGA) score and in at least one other component score, with no score increased in severity*
- *"Maintained" was defined as no change in the PGA score and other component scores might be reduced by no score could increase in severity*
- *"Worsened" was defined as an increase in any individual component score*

The "in remission" and "improved" Asacol-treatment response subgroups, when combined, would most closely mimic the clinical improvement primary efficacy endpoint for BZUC3003. This reviewer acknowledges that this generalization is not based on a rigorous assessment of the Sninsky study data (not available to the reviewer). However, based on the information provided in the article, this determination allows for the NI margin calculation to be calculated and compared with the Applicant's chosen NI margin of (b) (4)

The six-week combined treatment outcomes of patients classified as "in remission" or "improved" yields: 10/44 (23%) patients in the Asacol 2.4 treatment arm and 21/43 (49%) patients in the placebo-treatment arm (as determined from the data presented in Table 4 of the Sninsky article). Next, a treatment effect (Asacol treatment-response minus placebo-treatment response) for Asacol was determined to be 26% (95%CI: 6%, 45%). Then, following the NI margin determination procedures followed by the statisticians, the lower CI margin is reduced by 50% to reduce the effect of "bio creep" to yield an NI margin of 3%. Thus, as judged from the Applicant's own reference literature, the study that best adheres to the criteria of the ICH E10 guidance results in a substantially lower NI margin (3%) than the one determined by the Applicant (b) (4)

Is a 3% NI margin reasonable? To see if other data could support a 3% NI margin, this reviewer and the statisticians reviewed the original studies submitted under NDA 19-651 for the original Asacol approval in 1991. The placebo-controlled study submitted with this NDA was similar in design to BZUC3003 (similar patient population, treatment dose and duration). Like the Sninsky article, there was a difference in primary efficacy endpoint. But, like Sninsky, the "clinical improvement" assessment was based on a composite score similar to the MMDAI used in BZUC3003. Although the Applicant for NDA 19-651 did a post-hoc correction of some of the data (see the Statistical Review by

Dr. Farr for details), the corrected data were used in the approval of the NDA and showed the following results.

Table 2: NDA 19-651 Improvement Rate at Week 6: Post-hoc Corrected Data

Study C14	Asacol 2.4 g/day n/N (%) (95% CI)	Placebo n/N (%) (95% CI)	Treatment Difference % (95% CI)	p-value
ITT Population	22/53 (42) (28%, 56%)	11/51 (21) (11%, 35%)	20% (2%, 37%)	0.03
PP Population	21/43 (49%) (33%, 65%)	10/44 (23) (11%, 38%)	26% (6%, 45%)	0.01

If one accepts the "corrected" data at face value (again, the corrected data was used for the approval action for Asacol), the treatment differences range from 20% to 26% with the lower limits of the 95% CI ranging from 2% to 6%. Thus, reducing the lower CI by 50% as above, the calculated NI margin should range from 1% to 3% for patients with mildly to moderately active UC treated for six-weeks of therapy with Asacol, providing additional support that a more appropriate NI margin should not exceed 3%.

This reviewer concludes, therefore, that the Applicant has not provided convincing data in support of the (b) (4) *NI margin. And when the more appropriate 3% NI margin is imputed, the study does not support non-inferiority of BD compared to Asacol for the treatment of mildly to moderately active UC in adult patients. This conclusion was shared with the Applicant in the Complete Response letter dated 22 December, 2008 and as well as the post-regulatory Type A action meeting.*

2. Post-hoc analysis of BZUC3003 using the Sninsky response definitions.

The Applicant states in the submission that the Agency agreed to a NI margin of (b) (4) based on discussions at the post-regulatory action meeting 16 March, 2009. As reflected in the Agency's meeting minutes (DAARTS document 4 May, 2008), the Agency shared that given only one study could be used for the NI margin calculation (as the other studies did not meet the criteria outlined in ICH E10 discussed above, the more likely margin might have been (b) (4) if two studies had been found applicable. In further clarification discussion with Dr. Mike Welch, the Agency may have accepted a (b) (4) NI margin given the circumstance of only a single study if this NI margin had been pre-specified as part of the clinical study design; this was not the case.

Assuming a (b) (4) NI margin to be acceptable, the Applicant applied the response definition (i.e., subjects in "remission" or "improved") in the Sninsky study to the data from

BZUC3003 according to comparative disease activity definitions for the two studies as described in the table below:

BZUC3003 (PP Population) and Sninsky Publication: Comparison of Disease Activity at Baseline and Definition of Efficacy Endpoints (Applicant's Table 4, p. 9).

Activity at Baseline and Definition of Efficacy Endpoints

	BZUC3003 Study*		Sninsky Study**		
Assessments	Balsalazide Disodium N=206	Mesalamine (2.4 g/d) N=194	Placebo N=52	Mesalamine (1.6 g/d) N=53	Mesalamine (2.4 g/d) N=53
Baseline Demographic Variables					
Physician's Global Assessment	2.0 ±0.32	1.9 ±0.34	1.53 ±0.54	1.51 ±0.50	1.53 ±0.58
Stool frequency	1.9 ±0.78	1.9 ±0.83	1.49 ±1.16	1.30 ±0.99	1.53 ±1.05
Rectal bleeding	2.1 ±0.30	2.1 ±0.24	1.41 ±0.91	1.25 ±0.87	1.17 ±0.80
Sigmoidoscopy	2.2 ±0.42	2.2 ±0.39	1.60 ±0.53	1.60 ±0.57	1.66 ±0.65
Primary Efficacy Endpoints					
Clinical Improvement; improvement in rectal bleeding	A ≥ 3 point improvement from baseline in the MMDAI and a ≥ 1 point improvement in the rectal bleeding score from baseline				
Remission			Complete resolution of all symptoms with all assessment scores determined to be zero		
Improved			Reduction in the physician's global assessment score and in at least one other component score, with no score increased in severity		
Maintained			No change in the physician's global assessment score, component scores might be reduced, but no score could increase in severity		
Worsened			Increase in an increase in any individual component score		

* The BZUC3003 study utilized the Modified Mayo Disease Activity Index (MMDAI).
** The Sninsky study utilized the Mayo Disease Activity Index (MDAI).

Using this comparative definition assessment, the Applicant applied the Sninsky definitions to the study outcome data for BZUC3003 to calculate the treatment response difference between BD and Asacol. The data are presented in the Applicant's Table 1, p. 6 and modified below:

Treatment Outcome Using BZUC3003 Data (PP Population) and Sninsky Efficacy Endpoint at End of Treatment

Treatment Outcome	Treatment Group BD (n=180)	Asacol (n=171)	Rate Difference (Asacol – Giazo)	95% CI for Diff
In remission or improved	**110 (61%)**	**96 (56%)**	**-5.0%**	**(-15.3%, 5.3%)**

From this data, the Applicant concluded that BD is shown to be non-inferior to Asacol for this study based on the upper limit of the 95% CI for treatment difference yielding 5.3% for the PP population and 5.9% for the ITT population (data not shown).

Reviewer's Comment:

The Applicant selected a pre-specified NI margin of (b) (4) *based on data that upon previous review the Agency did not agree supported this choice. The Applicant did not provide additional literature references and the Agency, thereby, concludes that a 3% NI Margin remains to be the appropriate choice. In addition, post-hoc changes to study outcome definitions, knowing the desired result, is not an acceptable approach.*

6.1.1.1.1 Discrepancy in Gender Response Identified in BZUC3002

BZUC3002

In her review of the original submission, Dr. Gibril made the following observations and conclusions. In BZUC3002, there was an observed gender disparity in treatment effect between male and female patients with UC. The findings of the previous review team are summarized first to enable comparisons with the BZUC3003 analysis. While the BD treatment-response rate was comparable between males and females (57% and 54%, respectively) in BZUC3002, the placebo-response was markedly different between male and female patients (20% vs 58%, respectively). As a result, a substantial treatment effect (BD treatment-response rate minus the placebo-response rate) was observed in men (37%), but none in women (-4%). The basis for the difference in placebo response rates was not clear. Additional information provided by the sponsor upon reviewer's request was non-contributory. Review of relevant published literature did not suggest gender as a factor for differences in placebo response rate in the population of interest. In a meta-analysis study recently published (Su et al., Gastroenterol 2007;132:516-526), the authors reported that placebo patients with higher mean disease activity scores at baseline were associated with lower placebo response rates. In the Applicant's study, the mean baseline disease activity scores were comparable across treatment groups as well as across gender: male patients had mean MMDAI scores of 8 in both BD- and placebo-treatment groups while female patients had mean MMDAI scores of 7.6 vs 8 for BD- and placebo-treatment groups respectively.

Table 3: BZUC3002 Results of Primary Endpoint Analysis by Sub-groups

	BD n/N (%)	Placebo n/N (%)	p-value
Total Population	(b) (4) (55)	(b) (4) (40)	**0.02**
Sex			
Male	(b) (4) (57)	(b) (4) 20)	<0.001 (b) (4)
Female	(54)	(58)	

To further investigate the observed discrepancy in the primary endpoint analysis across gender, a post-hoc secondary endpoint analysis by gender was conducted. The findings were consistent with the primary endpoint findings; statistically significant differences in treatment responses were seen in men but not women. This observation was not surprising since the secondary endpoint variables were subsets of the primary composite endpoint.

In summary, based on the observed gender discrepancy in treatment effect for BZUC3002 and the inability to explain the high placebo-response rate in women, the reviewers concluded that this issue required resolution before BD tablets could be approved at a future date.

Table 4: BZUC3002 Results of Secondary Endpoints Analysis by Gender

Variables	**BD n/N (%)**	**Placebo n/N (%)**	**p-value**
Clinical Remission			
Males	28/81 (35)	5/40 (13)	0.01
Females	(b) (4)		
Mucosal Healing			
Males	42/81 (52)	8/40 (20)	<0.001
Females	(b) (4)		
Bowel Frequency			
Males	43/81 (53)	12/40 (30)	0.02
Females	(b) (4)		
Rectal Bleeding			
Males	51/81 (63)	13/40 (33)	0.002
Females	(b) (4)		
Complete Remission			
Males	12/81 (15)	0	0.01
Females	(b) (4)		

BZUC3003

Since this study did not have a placebo treatment arm, the review team concluded that the previously identified deficiency from the original review cycle had not been adequately addressed.

Reviewer's Comment from second review cycle:

1. Given the concerns of gender from the BZUC3002 study, BZUC3003 fails to address the lack of evidence to support a treatment effect in women. The absence of a placebo arm for comparison as part of the BZUC3003 study design does not help to resolve the concerns. In an attempt to impute an appropriate placebo group, the statistical reviewer pooled the data from BZUC3002 and BZUC3003 and compared the results among the three different treatment arms. Of note, this reviewer acknowledges that the two clinical studies are not identical (different durations of treatment); however, the patient populations, inclusion/exclusion criteria, and primary efficacy endpoint were similar enough to justify pooling the data to allow for a surrogate placebo arm for the BZUC3003 study.

Table 5: Combined BZUC3002/BZUC3003 Results of Primary Endpoint Analysis by Gender: ITT Population

	BD n/N (%) (95% CI)	**Asacol** n/N (%) (95% CI)	**Placebo** n/N (%) (95% CI)	% Difference BD vs Placebo (95% CI)	% Difference Asacol vs Placebo (95% CI)	Difference BD vs Asacol (95% CI)
Male	(b) (4) (53%) (b) (4)	(b) (4) (49%) (b) (4)	(b) (4) (20%) (b) (4)	33% (b) (4)	29% (b) (4)	4% (b) (4)
Female	(b) (4)					

With the imputed placebo arm from BZUC3002, the proportion of female patients with a BD-treatment response compared to placebo-response was (b) (4) *with a 95% CI of* (b) (4) *leaving the gender treatment effect disparity still unresolved.*

To address this concern in greater depth, this reviewer looked at two additional sources of information to determine if they might assist in helping to explain the observed large placebo-treatment effect observed in women in BZUC3002. First, like Dr. Gibril, this reviewer completed a search of the medical literature for descriptions of differential placebo-response between male and female UC patients. Like her, this reviewer did not

find specific references related to this topic. However, a meta-analysis was identified that assessed the efficacy of 5-ASA compounds for the treatment of active UC. In the publication by Kane, et. al. (Reviews in Gastroenterological Disorders. 2003; 3(4), 210-218), of 31 studies identified, 19 met the entry criteria:

1) *Randomized trials with a parallel group design*
2) *Study population of adults with mild or moderate active UC*
3) *Comparison of oral 5-ASA compounds to placebo, sulfasalazine, or non-oral 5-ASA agents*
4) *Evaluation of clinical improvement or remission*
5) *Studies on rectal preparations, combination therapies, maintenance of remission, or therapy for Crohn's disease were excluded.*

Although the referenced studies in this meta-analysis did not do sub-population analyses for gender, a survey of those studies that were placebo-controlled showed placebo-response rates (including both male and female patients) ranging from 9% to 50%. This reviewer acknowledges that the studies vary greatly in their design including duration of treatment; the data are therefore strictly intended to give a reference range only. Thus, although the placebo-response rate in women in the BZUC3002 study (58%) is greater than the highest identified placebo-response rates reported in the meta-analysis, the response rate is not out of the range of reasonable possibility. If there was not supporting evidence for a placebo-response rate as high as that seen in BZUC3002, then this reviewer would be more inclined to question the importance of the finding and perhaps consider the finding a statistical outlier of possibility. However, the study findings from published literature suggest otherwise.

Second, this reviewer looked at the studies submitted under NDA 20-610, the original NDA for the approval of Colazal, to determine if a gender disparity in treatment effect was found. The two main studies that lead to the approval of Colazal were of a non-inferiority study design without placebo-treatment arms. In addition, the Applicant submitted one placebo-controlled study. CP069101 was a Phase 3, randomized, placebo-controlled, double-blind, dose-response study designed to compare Colazal 4.5 g and 6.75 g with placebo in patients with mildly to moderately active UC. Unlike BZUC3002, the treatment period was for four-weeks instead of eight-weeks. Both studies used a composite primary efficacy endpoint. None of the primary or secondary endpoints showed statistical significant differences between Colazal 6.75- and placebo-treated patients. The reviewers agreed with the Applicant that the lack of response in CP069101 was likely secondary to too short of a treatment duration.

As part of the study's evaluation, a subgroup analysis by gender was completed. This analysis showed significantly higher improvement rates in stool bleeding in female patients compared with male patients treated with either Colazal or placebo. The results of the gender sub-population analysis are shown in the table below.

For many of the efficacy endpoints, there is an observed trend of improved responses in women versus men in both treatment groups. However, in the placebo-treatment arm,

women have a greater efficacy response than men in six of the seven endpoints and the differences are more pronounced. Since not all of the data are available, calculated p-values would have to be inferred and would therefore not be reliable. That said, there does appear to be a trend towards a greater placebo-response in women than men. The Applicant for NDA 20-610 concluded that there was no evidence of statistically significant, gender-related differences for any of the efficacy endpoints, that determination was based on pooled data between the two Colazal treatment arms.

Although not conclusive, the gender sub-analysis for CP069101 provides additional concerns that there may, indeed, be a gender-specific response difference between men and women with UC treated with Colazal and also with placebo. The reasons for this potential gender disparity are unclear. However, until shown otherwise, this reviewer agrees with the concerns of Dr. Gibril and the original submission's review team and recommends that such discrepancies be adequately addressed before the future approval of BD tablets.

Table 6: CP069101 Clinical Efficacy Results: ITT-1 (missing values counted as failures)

Efficacy Endpoints	Colazal 6.75 g/day Men (n=46)	Colazal 6.75 g/day Women (n=26)	Placebo Men (n=19)	Placebo Women (n=16)
Stool Blood	33%	54%	21%	44%
Stool Frequency	42%	27%	26%	31%
Patient Functional Assessment	44%	35%	16%	38%
Abdominal Pain	22%	27%	16%	44%
Symptom Assessment	30%	39%	21%	38%
Sigmoidoscopy	48%	39%	47%	37%
Physician's Global Assessment	35%	39%	47%	50%

Modified from Applicant's NDA 20-610 submission, 1988, Vol 7.1, p. 164

Third, this reviewer evaluated the additional materials provided by the Applicant provided on 11 November, 2008, to address the gender imbalance in the placebo-response rates observed for BZUC3002. The evidence submitted was previously shared with the Agency 11 March, 2008, in response to an Agency Information Request during

the original NDA submission. The Applicant noted that one critical factor, based on a review of the literature, that has a profound effect on placebo-response in UC clinical trials is the number and frequency of study visits. In a published review (Ilnyckyj et al., Gastroenterology, 112(6):1854-8,1997) of 38 clinical trials in active UC patients, the variable that most significantly modified the placebo-response rate was the number of study visits. Notably, more frequent study visits (i.e., >3 vs <3) had a direct correlation with a greater placebo-treatment response. Ilnyckyj et al. concluded that a higher number of clinic visits resulting in patient interaction with a physician and subsequent physician assessments provide an added therapeutic benefit for patients and contribute to the placebo effect. Applying this observation to the BZUC3002 study, the Applicant noted that more placebo-treated female patients compared to placebo-treated male patients completed the study (70.0% vs 35.0%, respectively). This observation, together with a greater number of study visits by placebo-treated female patients, led the Applicant to conclude that these findings may have influenced an increased placebo-response in female patients, with repeated physician assessments at clinic visits having a positive therapeutic effect on the patients' health. This reviewer finds this line of reasoning questionable since BZUC3002 achieved success (p=0.02) secondary to a large drop-out rate among placebo-treated male patients by inference. Conversely, if one agrees with the Applicant's rationale for the observed gender discrepancy in placebo-treated patients, the study would likely have failed if more placebo-treated male patients had completed the study, thus likely increasing the overall placebo-response arm, thereby decreasing the overall BD-treatment effect.

The Applicant's information for the disparity in gender treatment effect for this resubmission cycle

The Applicant provided the following post-hoc analyses to address the gender disparity issue:

- Differences in number of clinical site visits and duration in the study for men and women
- Variability in response to the subject-derived stool frequency subcomponents of the MMDAI **(**see table below**)**

From these analyses, the Applicant concludes that the high placebo response rate for BZUC3002 was a spurious result and should be ignored.

BZUC3002 Gender Sub-analysis for MMDAI subcomponents at Week 8/EOT

	BD	Placebo	P-value for Treatment Diff
Baseline Change in Mean MMDAI score			(b) (4)
Women			
Men	-3.31	-0.97	<0.0001
Improvement in Rectal Bleeding			(b) (4)
Women			
Men	53 (65%)	11 (28%)	0.0001
Improvement in Stool Frequency			(b) (4)
Women			
Men	41 (51%)	8 (20%)	0.0015
Endoscopy Score of 0 or 1			(b) (4)
Women			
Men	40 (49%)	7 (18%)	0.0007
Improvement in PGA			(b) (4)
Women			
Men	46 (57%)	7 (18%)	<0.0001

Modified from Applicant's Tables 10, 11, 12, 13, and 14

Reviewer's Comment:

1. Dr. Gibril evaluated the Applicant's prior claims that number of clinical site visits and duration in the study contributed to the differences in gender placebo response. No new arguments were provided during this review cycle.

2. Regarding the potential of an MMDAI sub-score driving the gender disparity, this reviewer disagrees with the Applicant's conclusion that the difference in gender-specific placebo response was driven by the MMDAI subcomponent stool frequency. Based on the Applicant's own post-hoc analysis, the gender disparity remains evident for each of the MMDAI score subcomponents.

3. Generalizability of differential gender response for other mesalamine class products. This reviewer evaluated the impact of gender on treatment response for other approved products in the mesalamine class, regardless of formulation or drug delivery methodology. In summary, the data suggest that:

- *Of all the mesalamine class products, BD formulations (Giazo and Colazal) are the only products that have a consistent difference in treatment response between male and female patients.*
- *There is inconsistency in gender-specific treatment responses for those clinical trials which contained a placebo treatment arm. (No difference seen for Pentasa; placebo-treated women responded better than men for Giazo and Lialda; placebo-treated men responded better for Apriso, especially if of Russian decent).*
- *For those clinical trials which compared different drug doses, a gender-specific treatment response was not always found and did not appear to correlate with gender.*

- *Many of the clinical trial analyses conducted by the Sponsors or the FDA did not include sub-analyses by gender with respect to disease activity subscores for composite efficacy outcome measures.*
- *Even for placebo-treated patients, improvements in "hard endpoints" (i.e. endoscopic scores) were sometimes found.*

Below are summarizes of the gender-specific information that is known for each of the mesalamine products:

- ***Asacol.*** *NDA 19-651. Approved 1991 (400 mg tablet) for: Treatment of mildly to moderately active UC and maintenance of remission. Modified from Dr. Fan's stats review (February 26, 1991):*

Gender sub-analysis of percentage of patients who had improvement in sigmoidoscopic score

	Placebo	Asacol 1.6 g/day	Asacol 2.4 g/day
Women	6/25 (24%)	10/28 (36%)	11/29 (38%)
Men	6/27 (22%)	10/25 (40%)	11/24 (46%)

Of note, from this data, there is improvement in "hard endpoints" (i.e., endoscopy) even in placebo-treated patients; this observation is seen for both men and women. There appears to be a slight dose response for both genders.

- ***Asacol HD.*** *NDA 21-830. Approved 2008 for: Treatment of moderately active UC. Modified from Dr. Anil Rajpal's clinical review, p. 26. Three clinical trials, all compared 4.8 to 2.4 dose, no placebo arms.*

  Study 2006444: Gender sub-analysis of percentage of patients who achieved treatment response

	Asacol 2.4 g/day	Asacol 4.8 g/day	Difference in Success Rate btn two treatment groups
Women	65.9%	71.5%	5.6 (-4.2, 15.5)
Men	65.3%	69.1%	3.8 (-5.0, 12.7)

No significant differences seen between gender response rates. Both genders show evidence of trend in dose response.

Study 2000083: Gender sub-analysis of percentage of patients who achieved treatment response (modified from statistical review, p. 9).

	Asacol 2.4 g/day	Asacol 4.8 g/day	Difference in Success Rate btn two treatment groups
Women	32/52 (62%)	26/44 (59%)	-3% (-22.1, 17.2)
Men	21/44 (48%)	29/40 (73%)	25% (4.58, 45.0)

Study 2000082: Gender sub-analysis of percentage of patients who achieved treatment response (modified from statistical review, p. 9).

	Asacol 2.4 g/day	Asacol 4.8 g/day	Difference in Success Rate btn two treatment groups
Women	48/77 (62%)	49/75 (65%)	3% (-12.3, 18.3)
Men	29/62 (47%)	40/54 (74%)	27% (10.2, 44.4)

Studies 2000082 and 2000083 suggested that 4.8 dose might not provide additional efficacy over 2.4 in women; there does appear to be a dose response in men.

- ***Apriso.*** *NDA 22-301. Approved 2008 for: Maintenance of remission of UC. Two clinical studies data combined. Modified from Dr. Farr's statistical review, p. 14*

Country or gender sub-analysis of percentage of patients who achieved remission.

	Placebo	Apriso	p-value
Country			
USA	48/91 (53%)	130/172 (75.5%)	<0.001
Russia	71/98 (72%)	166/201 (82.6%)	0.042
Gender			
Women	50/88 (57%)	165/207 (79%)	<0.001
Men	69/101 (68%)	132/166 (80%)	0.039

On a further sub-analysis by both country and gender of percentage of patients who achieved remission

	Placebo	Apriso	p-value
USA			
Women	18/40 (45%)	68/90 (76%)	0.03

Men	30/51 (56%)	62/82 (76%)	0.04
Russia			
Women	32/48 (67%)	96/117 (82%)	0.03
Men	39/50 (78%)	70/84 (83%)	**0.44**

Of note, the data indicate that efficacy in Russian men was not established due to high placebo response in this sub-group.

- ***Lialda**. NDA 22-000. Approved 2007 for: Induction of remission in mildly to moderately active UC. Modified from Dr. Gross's statistical review, p. 16*

Gender sub-analysis of percentage of patients who achieved remission

	Placebo	Lialda 2.4g/day	Lialda 4.8 g/day
Women	21%	45%	41%
Men	14%	29%	29%

Of note, from this data, across all treatment groups, women had a greater tendency to achieve remission. For both men and women, there was not a dose response component to this observation. Also, women had a higher placebo-treatment response than men.

- ***Colazal**. NDA 20-610. Approved 2000 for: Treatment of mildly to moderately active UC. Two Clinical Trials compared two doses of Colazal(6.75g/day vs 2.25 g/day); no placebo treatment arms in pivotal clinical trials. No gender analysis found in reviews.*

- ***Pentasa**. NDA 20-049. Approved 1993 for: Treatment of mildly to moderately active UC and induction of remission. Modified from Dr. Gallo Torre's review, p. 127. "Gender was a significant covariate for Stool Consistency, Rectal Bleeding, and Urgency. Women manifested a better response than men for all three variables." However, for second clinical trial, gender not found to impact primary efficacy variables (PGA, treatment failure, sigmoidoscopic index).*

Efficacy Conclusions Summaried

6.1.1.2 Study BZUC3002

In the sponsor's single placebo-controlled study (n=249, 166 in the BD-treatment arm), there was an unexplained difference in results between male and female patients. Identified during the original submission and prior review of BZUC3002, a sub-group analysis by gender showed that while both male and female patients responded similarly on BD therapy (57% of men and 54% of women were identified as responders in the primary endpoint efficacy analysis), there was a marked difference in placebo response (20% of men and 58% of women). When compared to placebo response, the treatment effect of BD therapy was superior to placebo in male patients ($p<0.001$) but the treatment difference was insignificant in females (b) (4) Consequently, a substantial therapeutic gain was demonstrated among men (37%), but none among women (-4%). The observed superior efficacy of BD tablets in the study was largely driven by a subpopulation's finding, namely, males. Conversely, the efficacy of BD tablets was not established in women with UC.

6.1.1.3 Study BZUC3003

In this non-inferiority, active-controlled study comparing BD tablets to Asacol, the Applicant's cited literature and rationale do not support the choice of a (b) (4) NI margin. Placebo-controlled studies of Asacol, the active comparator in BZUC3003, dosed comparably, in a similar patient population, for an analogous length of time, and with comparable efficacy endpoints, support a NI margin no greater than 3%. When this 3% NI is employed, the study fails to support that BD tablets are non-inferior to Asacol. In addition, since this study did not have a placebo-controlled cohort, the previously outstanding question regarding gender discrepancy in treatment response remains unanswered. And review of the literature and the studies that led to approval of Colazal are inconclusive to help address this observation, impeding the ability to adequately label the product for use in both gender patient populations.

6.1.1.4 Overall Efficacy Assessment

Based upon review of the information generated during the previous submission cycles as well as the new post-hoc analyses submitted by the Applicant during the current review cycle, this reviewer finds that the totality of the data does not demonstrate cohesive and conclusive evidence supporting efficacy of Giazo in the treatment of female patients with UC.

Should Giazo be approved for only male patients with UC, this reviewer suggests that a post-marketing study be completed in female UC patients to provide additional data to (b) (4) This study should be placebo-controlled and should strongly consider a Colazal comparative arm

given that both products share the BD active ingredient and there is a suggestion of a gender disparity in treatment effect for Colazal in the single placebo-controlled study.

7 INTEGRATED REVIEW OF SAFETY

Current Contraindications, Warnings, and Precautions for Colazal

In the context of background safety information for the active moiety balsalazide disodium, Colazal, the capsule formulation of BD approved in 2000, has a safety profile consistent with other members of the 5-ASA class of compounds. The current labeling for Colazal has the following information regarding safety concerns:

Contraindications

Patients with hypersensitivity to salicylates. Hypersensitivity reactions may include, but are not limited to, the following: anaphylaxis, bronchospasm, and skin reaction.

Warnings and Precautions

1. Exacerbations of Ulcerative Colitis. In adult clinical trials, 3 out of 259 patients reported exacerbation of UC symptoms. In pediatric clinical trials, 4 out of 68 patients reported symptoms of UC exacerbation.
2. Pyloric Stenosis: Patients with pyloric stenosis may have prolonged gastric retention of Colazal capsules.
3. Renal: Renal toxicity has been observed in animals and patients given other mesalamine products. Caution should be exercised with patients with known renal dysfunction or a history of renal disease.

Common Adverse Events in Adult UC Patients

In four controlled clincial studies, patients who received Colazal 6.75 g/day most frequently reported the following AEs: headache (8%), abdominal pain (6%), diarrhea (5%), nausea (5%), vomiting (4%), respiratory infection (4%), and arthralgia (4%). Some AEs (abdominal pain, fatigue, and nausea) were reported more frequently in women than in men. AEs reported by 1% or more of patients who participated in the four controlled clinical trials are presented in Table 7.

Table 7: AEs Occurring in ≥1% of Adult Colazal Patients in Phase 3 Clinical Trials

Adverse Reaction	Colazal 6.75 g/day N=259	Placebo N=35
Abdominal pain	16 (6%)	3 (1%)
Diarrhea	14 (5%)	3 (1%)
Arthralgia	9 (4%)	0 (0%)
Rhinitis	6 (2%)	0 (0%)
Insomnia	6 (2%)	0 (0%)
Fatigue	6 (2%)	0 (0%)
Flatulence	5 (2%)	0 (0%)
Fever	5 (2%)	0 (0%)
Dyspepsia	5 (2%)	0 (0%)
Pharyngitis	4 (2%)	0 (0%)
Coughing	4 (2%)	0 (0%)
Anorexia	4 (2%)	0 (0%)
Urinary tract infection	3 (1%)	0 (0%)
Myalgia	3 (1%)	0 (0%)
Flu-like disorder	3 (1%)	0 (0%)
Dry mouth	3 (1%)	0 (0%)
Cramps	3 (1%)	0 (0%)
Constipation	3 (1%)	0 (0%)

Modified from Colazal labeling Table 1.

Note: AEs occurring in at least 1% of Colazal patients which were less frequent than placebo for the same event were not included in the table.

Key safety findings from previous review cycle

Safety data were submitted and analyzed from three sources: BZUC3002 (reviewed as part of the original submission), BZUC3003 (reviewed as part of the second review cycle), and BZUC3005, an ongoing, open-label, safety study of patients who previously

participated in BZUC3002 and BZUC3003 (reviewed during both the first and the second review cycles).

For BZUC3002, of the 250 randomized patients, 247 were included in the safety population: 168 (99.4%) patients in the BD tablet group and 79 (97.5%) patients in the placebo group. Two patients in the placebo group and one patient in the BD tablet group did not have a post-baseline safety assessment and were excluded from the safety population. Of a total of 410 patients randomized in BZUC3003, 408 patients were included in the safety population analysis: 210 (99%) patients in the BD-treatment group and 198 (100%) patients in the Asacol-treatment group. Two patients randomized to the BD cohort, received study drug, but had no post-baseline safety assessment and were excluded from the safety population. A total of 565 unique patients received BD tablets either as a result of randomization to a BD cohort in one of the Phase 3 studies or as open-label treatment in the safety study BZUC3005; the analysis of this pooled data constituted the comprehensive safety population.

Regarding deaths, none occurred during conduct of BZUC3002 or BZUC3003. One patient enrolled in BZUC3005 died of metastatic malignant melanoma and was determined to be unlikely related to BD drug treatment.

Serious adverse events (SAEs) were reported in 5% of the comprehensive safety population. Worsening UC was the only SAE reported by >1% of patients and occurred at a frequency of 2% of the total patients exposed to BD treatment. In a comparison of the SAEs reported for BZUC3002 and BZUC3003 by treatment arm, both more types of SAEs and greater numbers of patients experienced an SAE in association with BD treatment compared to treatment with Asacol. The one exception was for the preferred term arthritis (one patient treated with Asacol and none treated with BD). The most frequent AE leading to discontinuation from BD therapy was worsening UC for all treatment arms in all studies (5% of BD-treated patients, 2% of Asacol-treated patients, and 11% of placebo-treated patients).

Comparing adverse events (AEs) in the treatment arms of the two Phase 3 studies, the proportion of patients reporting at least one AE were similar between the BD-treated (59%) and Asacol-treated (55%) cohorts, but higher in the placebo-treated (70%) patients. Overall, events related to gastrointestinal (GI) disorder were the most frequently reported AE (29% of BD-, 25% of Asacol-, and 38% of placebo-treated patients) for those events occurring in more than 2% of total patients. Worsening of UC was the most common GI-related event in all treatment cohorts (7% of BD-, 2% of Asacol-, and 15% of placebo-treated patients). The only GI events that occurred in ≥ 2% of patients in the BD-treated group and not in the placebo-treated group were abdominal distension (2%), flatulence (2%), and hemorrhoids (< 1%). Outside of GI-associated disorders, headache was the most commonly reported AE with a frequency of 8% in BD-, 10% in Asacol-, and 14% of placebo-treated patients. There were no clinically meaningful changes in laboratory parameters or vital signs in the Phase 3 studies. The final report from the long-term, open-label, safety extension study (BZUC3005) included 443 patients showed a similar safety profile compared to the two Phase 3 studies. For the comprehensive

safety population, the most frequent AEs were worsening UC (10%) and abdominal pain (4%).

Overall, for the double-blind studies, the proportion of patients who experienced drug-related TEAEs was comparable across the treatment groups (10% of BD-treated patients, 11% of Asacol-treated patients, and 9% of placebo-treated patients). Drug-related AEs that occurred in >1% of BD-treated were worsening UC (1% BD-, 0% Asacol-, and 3% placebo-treated patients), diarrhea (1% BD-, 2% Asacol-, and 1% placebo-treated patients), nausea (3% BD-, 4% Asacol-, and 0% placebo-treated patients), and headache (1% BD-, 3% Asacol-, and 1% placebo-treated patients).

Of note, a thorough QT study was not completed for either the BD capsule or tablet formulations. This reviewer does not recommend such a study be completed at this time for the following reasons. As a class of compounds, the 5-ASA drugs have been marketed for 16 years without any known cardiac toxicity risks identified to date. In addition, the bioavailability of BD is very small given that most of the drug and its metabolites remain in the gut with only a small fraction systemically absorbed. Should a cardiac signal emerge in the future, a thorough QT study could be considered at that time.

The overall safety profile of the tablet formulation is comparable to the approved capsule formulation Colazal, including data available from post-marketing reports. However, based upon the cumulative data from the clinical development program, there is concern that 5% of the comprehensive safety population reported at least one SAE and that both more types of SAEs and greater numbers of patients experienced an SAE in the BD-treated patients compared to those treated with Asacol. In addition, more BD-treated (5%) patients withdrew from the studies because of worsening UC compared to Asacol (2%). Finally, regarding the Applicant's proposed warning of use in patients with hepatic impairment, six patients treated with BD had transient transaminase elevations without evidence of irreversible liver damage.

7.1 Methods and Findings

For the current review cycle, no new safety data were generated since the submission of the last safety update dated 27 June, 2008 per the Applicant. No new data were submitted for review and there are no on-going or planned safety assessment studies in the future.

For the comprehensive safety population, of the 565 patients treated with BD tablets, no SAE preferred term was experienced by >2% of patients and only worsening UC (2%) occurred in 1% or more of balsalazide-treated patients.

Table 8: Treatment-Emergent SAEs for the Comprehensive Safety Population (BZUC3002, BZUC3003, and BZUC3005)

Preferred Term	Comprehensive Safety Population N=565 n (%)
Patients with at least one SAE	28 (5)
Colitis ulcerative	10 (2)
Abdominal pain	4 (<1)
Cellulitis	3 (<1)
Anemia	2 (<1)
Intervertebral disc protrusion	2 (<1)
Abortion spontaneous	1 (<1)
Ankle fracture	1 (<1)
Bronchitis	1 (<1)
Cardiac failure congestive	1 (<1)
Chest pain	1 (<1)
Cholecystitis	1 (<1)
Clostridial infection	1 (<1)
Clostridial colitis	1 (<1)
Convulsion	1 (<1)
Dehydration	1 (<1)
Deep vein thrombosis	1 (<1)
Dyspnea	1 (<1)
Influenza	1 (<1)
Lower limb fracture	1 (<1)
Lymphedema	1 (<1)
Metastatic malignant melanoma	1 (<1)
Pancreatic enzymes increased	1 (<1)
Pneumonia	1 (<1)
Pyrexia	1 (<1)
Thrombophlebitis	1 (<1)
Weight decreased	1 (<1)

Note: All patients received BD treatment, either through randomization to the BD cohorts in BZUC3002 or BZUC3003 or as part of open-label treatment in BZUC3005

7.1.1.1 Common Adverse Events

7.1.1.2 Common adverse event tables

Table 9: Summary of TEAEs Reported by ≥ 2% of Patients in Phase 3, Double-blind Studies (BZUC3002 and BZUC3003; both genders represented)

SOC/Preferred Term	ARSS BD[a] N=378 % (n)	Asacol N=198 % (n)	Placebo N=79 % (n)
Number of patients with at least one AE	59% (223)	55% (108)	70% (55)
Gastrointestinal Disorders	29 (109)	25 (50)	38 (30)
Colitis ulcerative	7 (26)	2 (4)	15 (12)
Nausea	6 (21)	7 (14)	5 (4)
Abdominal Pain	4 (15)	6 (12)	4 (3)
Vomiting	3 (12)	5 (10)	3 (2)
Diarrhea	3 (10)	3 (2)	3 (5)
Flatulence	2 (8)	3 (6)	0 (0)
Abdominal distension	2 (9)	2 (4)	0 (0)
Dyspepsia	2 (6)	3 (5)	3 (2)
Constipation	<1 (3)	1 (2)	5 (4)
Abdominal pain upper	1 (4)	0 (0)	3 (2)
Hemorrhoids	<1 (3)	2 (3)	0 (0)
Cardiac Disorders	2 (8)	2 (4)	3 (2)
Chest pain	2 (6)	2 (3)	1 (1)
General Disorders and Administration Site Conditions	9 (34)	6 (12)	14 (11)
Fatigue	3 (10)	3 (5)	5 (4)
Pyrexia	2 (8)	<1 (1)	1 (1)
Edema peripheral	1 (4)	<1 (1)	4 (3)
Pain	1 (4)	0 (0)	4 (3)
Asthenia	<1 (1)	<1 (1)	3 (2)
Infections and Infestations	19 (70)	15 (30)	18 (14)
Nasopharyngitis	4 (15)	4 (8)	5 (4)
Urinary tract infection	3 (12)	5 (9)	1 (1)
Influenza	3 (10)	2 (3)	4 (3)
Upper respiratory tract infection	3 (10)	2 (3)	3 (2)
Sinusitis	3 (10)	2 (3)	1 (1)
Herpes simplex	<1 (3)	0 (0)	3 (2)
Metabolism and nutrition disorders	2 (6)	1 (2)	6 (5)
Hypokalemia	<1 (2)	0 (0)	3 (2)
Hyperlipidemia	0 (0)	0 (0)	3 (2)
Musculoskeletal And Connective Tissue Disorders	10 (38)	12 (24)	8 (6)
Back pain	3 (12)	3 (6)	4 (3)
Arthralgia	2 (8)	2 (4)	1 (1)
Muscle spasms	2 (7)	2 (3)	0 (0)
Myalgia	1 (5)	2 (4)	1 (1)
Pain in extremity	2 (6)	1 (2)	1 (1)
Arthritis	0 (0)	2 (3)	0 (0)

Nervous System Disorders	11 (41)	14 (27)	15 (12)
Headache	8 (31)	10 (20)	14 (11)
Dizziness	1 (4)	2 (4)	0 (0)
Psychiatric Disorders	4 (14)	1 (2)	4 (3)
Insomnia	3 (10)	1 (2)	1 (1)
Renal and Urinary Disorders	8 (29)	4 (7)	3 (2)
Hematuria	<1 (1)	2 (3)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders	8 (29)	4 (7)	3 (2)
Pharyngolaryngeal pain	3 (12)	2 (3)	1 (1)
Cough	1 (5)	2 (3)	0 (0)
Skin and Subcutaneous Tissue Disorders	5 (20)	4 (8)	3 (2)
Rash	2 (7)	3 (5)	1 (1)

AEs were recorded in MedDRA version 8.1

[a] ARSS BD population are all patients who received BD-treatment in either BZUC3002 or BZUC3003

Should BD be approved only for male UC patients, a more appropriate common AE table for the purpose of labeling should focus only on BZUC3002 since this was the only placebo-controlled study. Given the small number of patients in this sub-analysis, a single reported AE would result in an incidence >1%. Therefore, the data are presented for AEs occurring in >2% of male patients and at a rate greater than placebo. The most common AEs occurring in male patients in this study are listed in the following table:

Adverse Reactions Experienced by at Least 2% of GIAZO-Treated Male Patients and at a Rate Greater than Placebo in a Placebo-Controlled Phase 3 Study

Adverse Reaction	GIAZO 6.6 g/day N=82	PLACEBO N=37
Anemia	3.7%	0%
Diarrhea	3.7%	0%
Pharyngolaryngeal Pain	3.7%	0%
Urinary Tract Infection	3.7%	0%
Arthralgia	2.4%	0%
Insomnia	2.4%	0%
Pain	2.4%	0%

7.1.1.3 Additional analyses and explorations

Based on the mechanism of action of BD and other compounds which act through release or delivery of 5-ASA, an analysis of AEs by pancreatic, renal, and hepatic organ systems was conducted. For the cumulative analysis of the data from the two Phase 3 studies, BD-treated patients developed TEAEs that involved the renal system (nine patients) and hepatic system (six patients); no TEAEs for the pancreatic system were reported. The findings are shown in Table 10 below.

Reviewer's Comment:

1. Renal toxicity has been noted with other members of the 5-ASA drug class and is included in the warnings section of the Colazal labeling for BD capsules. This reviewer recommends that a warning be included in Giazo's labeling to address this potential risk and the language should reflect that found in other mesalamine class products.

2. The Applicant has proposed adding the following to the "Warnings and Precautions" of the labeling for BD tablets: (b) (4)

For the six patients that developed elevated liver enzymes in the Phase 3 studies of BD tablets, none of them met the criteria for Hy's Law (transaminase elevations combined with increased bilirubin in the absence of increased alkaline phosphatase). In addition, these patients did not have evidence of irreversible liver damage; the transaminase elevations resolved to baseline levels. In the context of post-marketing safety reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine, the patients in the BD studies did not have pre-existing liver disease and did not develop liver failure.

Should BD tablets be approved in the future, attention should be paid to Applicant's proposal of a hepatic warning to the labeling. To address the issue in greater depth, a thorough post-marketing evaluation of safety reports for members of the 5-ASA class of compounds could be of benefit. If the data indicate that a true hepatic signal exists, a class warning should be considered for Colazal and other members of the 5-ASA class.

Table 10: TEAEs Experienced by BD-Treated Patients Related to Renal and Hepatic Systems (BZUC3002 and BZUC3003 Studies)

SOC/PT	BD N=378 n (%)	Asacol N=378 n (%)	Placebo N=378 n (%)
Hepatic Function			
ALT increased	2 (<1)	0 (0)	0 (0)
AST increased	3 (<1)	0 (0)	0 (0)
Albumin	1 (<1)	0 (0)	0 (0)
Renal Function			
Bacteria urine	1 (<1)	0 (0)	1 (1)
Blood urine present	1 (<1)	0 (0)	1 (1)
Creatinine renal clearance decreased	1 (<1)	0 (0)	0 (0)
Hypokalemia	2 (<1)	0 (0)	2 (3)
Hematuria	1 (<1)	3 (2)	3 (2)
Renal failure	1 (<1)	0 (0)	0 (0)
White blood cells urine positive	2 (<1)	0 (0)	0 (0)

7.1.1.4 Explorations for drug-demographic interactions

Comprehensive safety population for second review cycle submission

Regarding gender, women reported TEAEs more frequently than did men (76% and 66%, respectively). TEAEs occurring in at least 5% of female patients and at least twice as frequent as in male patients were nausea (9% vs. 3%), back pain (5% vs. 2%), sinusitis (6% vs. 2%), and urinary tract infection (8% vs. 3%). Rectal hemorrhage was the only TEAE occurring in at least 5% of men and at least twice as often as women (6% vs. 2%). A similar number of men (13%) and women (12%) treated with BD tablets experienced a worsening of their UC symptoms.

The most common AE that led to study withdrawal was worsening of UC symptoms; no definitive trends were observed when a sub-population analysis was performed.

8 ADDITIONAL CLINICAL ISSUES

8.1 Special Populations

As identified during the original submission and prior review of BZUC3002, a sub-group analysis by gender showed that while both male and female patients responded similarly on BD therapy (57% of men and 54% of women were identified as responders in the primary endpoint efficacy analysis), there was a marked difference in placebo response (20% of men and 58% of women). When compared to placebo response, the treatment effect of BD therapy was superior to placebo in male patients ($p<0.001$) but the treatment difference was insignificant in females (b) (4) Consequently, a substantial therapeutic gain was demonstrated among men (37%), but none among women (-4%). While a small sample size could be a potential factor for such a disparity, it is not likely in this case as women made up 51% of the evaluated patients. This gender disparity in treatment response was consistent in that evaluation of the secondary efficacy endpoints revealed a statistically significant response in male patients; the treatment differences were insignificant for all secondary endpoint variables in female patients. This finding is not surprising since secondary endpoint variables were subsets of the composite primary endpoint.

Although the gender disparity in treatment effect was one of the deficiencies identified in the original review cycle, the Applicant's submission of BZUC3003 in this Complete Response did not resolve this concern. In BZUC3003, a sub-group analysis by gender showed a consistent response rate between men and women for both BD- and Asacol-treatment (BD: 51% of men and (b) (4) of women; Asacol: 49% of men and (b) (4) of women). However, BZUC3003 failed to address the observed large placebo-response rate in women enrolled in BZUC3002; BZUC3003 was a NI study design without a placebo arm for comparison.

The Applicant postulated that a possible explanation for the gender disparity may be linked to a correlation between number of study visits completed and placebo response. In the reference cited by the Applicant, Ilnyckyj et al. concluded that a higher number of clinic visits, resulting in more frequent patient interaction with a physician and subsequent physician assessments, provide an added therapeutic benefit for patients and contribute to the placebo effect. Applying this observation to the BZUC3002 study, the Applicant noted that more placebo-treated female patients compared to placebo-treated male patients completed the study (70.0% vs 35.0%, respectively). This observation, together with a greater number of study visits by placebo-treated female patients, led the Applicant to conclude that the increased number of study visits by women may have influenced an increased placebo-response rate in female patients. The Applicant postulated that repeated physician assessments at clinic visits had a positive therapeutic effect on the patients' health. This reviewer finds this line of reasoning questionable

since, by inference, BZUC3002 achieved success (p=0.02) secondary to a large drop-out rate among placebo-treated male patients. Conversely, if one agrees with the Applicant's rationale for the observed gender discrepancy in placebo-treated patients, the study would likely have failed if more placebo-treated male patients had completed the study, thus likely increasing the overall placebo-response arm, thereby decreasing the overall BD-treatment effect.

Since the reason for the observed discrepancy in the placebo response rates across gender was not clear, this reviewer looked at other sources for potential explanations. Review of relevant published literature did not suggest gender as a potential factor for differences in placebo response in the population of interest. A review of study CP-69101, a placebo-controlled study of Colazal (BD capsule formulation) submitted as part of NDA 20-610, showed a trend of improved responses in women versus men in both Colazal- and placebo-treated patients. In the placebo-treatment arm, women had a greater efficacy response than men in six of the seven endpoints. Although not conclusive, the gender sub-analysis for CP069101 provides additional concerns that there may, indeed, be a gender-specific response difference between men and women with UC. The reasons for this potential gender disparity are unclear.

Unless the issue of gender disparity can be resolved, this reviewer agrees with the concerns of Dr. Gibril that the observed superiority of BD tablets over placebo in BDUC3002 was driven by a sub-population's finding, namely, male patients. Conversely, the efficacy of BD tablets has not been established in women. This gender disparity in treatment effect needs to be adequately addressed before the future approval of BD tablets.

Regarding other special populations, safety and effectiveness of BD tables in pediatric patients have not been studied. There have been no studies with BD tablets in patients with renal or hepatic impairment. Pregnant women and nursing mothers were excluded from clinical trials with BD tablets. The clinical program did not include sufficient number of patients aged 65 and older (<10%) to determine whether they respond differently than younger patients.

8.2 Pediatrics

The NDA did not include patients less than 18 years old. The Sponsor requested waiver for pediatric studies required under the Pediatric Research Equity Act (PREA), and provided the following justification: 1) Balsalazide Disodium has been granted orphan drug designation status for pediatric patients with UC indicating that the number of pediatric patients with UC is small, and 2) the new tablet formulation contains the same active ingredient as in the capsule formulation Colazal, which is already approved for use in pediatric patients with UC aged five years and above. Although only Colazal has been approved for this indication, both formulations would be intended for the treatment of mildly to moderately active UC at a similar total daily dose. Colazal capsules can be opened and sprinkled on applesauce as a pediatric administrative alternative; while the

tablets may be more difficult to administer to pediatric population because of difficulty to swallow. Therefore, the implementation of the tablet formulation does not represent a meaningful benefit over the existing capsule formulation in terms of treatments (dosage and ability to administer) for pediatric patients.

The BD tablet (1100 mg), the subject of this NDA, contains the same active ingredient as the product Colazal capsule (750 mg), which is approved for a pediatric population (aged 5 years and older). Although only Colazal has been approved for this indication, both formulations would be intended for the treatment of mildly to moderately active ulcerative colitis. The tablet drug product is proposed to be administered for a total daily dose of 6.6 g/day (three 1100 mg tablets BID) whereas the capsule dose is a total of 6.75 g/day (three 750 mg capsules TID). An advantage of the Colazal capsules is that they can be opened and sprinkled on applesauce as a pediatric administrative alternative; the tablets may be more difficult to administer to the pediatric population because of the difficulty to swallow as well as the inability to more easily adjust for weight-based dosing of the product. A tablet formulation of balsalazide disodium would provide a slight clinical benefit (BID versus TID dosing) over the approved Colazal capsule formulation. But, that advantage would apply only to patients old enough to be able to swallow tablets and in whom weight-based dosing would be feasible given the tablet's dosage strength. Since an already approved pediatric product formulation of balsalazide disodium is currently marketed, the limited benefit of BID versus TID dosing in a small subset of the pediatric ulcerative colitis patient population is negligible. This reviewer therefore recommended full waiver, for consideration by the PERC committee, of pediatric studies for the balsalazide tablet formulation.

On 29 October, 2008, this recommendation for full waiver of pediatric studies with the BD tablet formulation was presented before the PERC committee. The outcome of the discussion was: 1) full waiver of studies for pediatric patients with UC under the age of 12, 2) should the product be approved, the label should include information for adolescent patients with UC aged 12 to 17, and 3) the Division has the discretion to determine if additional studies are required to adequately label for this adolescent UC patient population.

On 8 April, 2010, a second meeting before the PERC committee transpired. The outcome of that discussion was consistent with the prior PERC recommendations with the following suggestion for the Division's consideration: labeling of the product for children under the age of twelve for those patients able to swallow the adult tablet formulation.

If the BD tablet formulation is approved in the future, additional PK studies are required in the adolescent UC patient population. These studies need to be presented before the PERC committee for additional input and guidance. Should labeling for the tablet formation product more forward, this reviewer agrees with the PERC committee recommendations and concurs that instructions for use in adolescent UC patients should be included in the product label.

8.3 Literature Review

The published literature the Applicant submitted in paper format was reviewed. In addition, this reviewer conducted an independent review of the literature with respect to the observed gender disparity in BD treatment effect between men and women with UC. This information and the conclusions drawn from it can be found in Section 6.1.4.4.4 of this review.

For the non-inferiority (NI), the Applicant submitted the results of a literature search to justify the NI used for BZUC3003. Upon review of the studies included in the second cycle resubmission, the review team concluded that only one literature reference closely approximated the ICH E.10 guideline for appropriate NI trial design.

8.4 Postmarketing Risk Management Plan

Colazal, the capsule formulation of BD, does not have a risk map or REMs; there is no postmarketing risk management plan for the BD tablet formation.

9 OVERALL ASSESSMENT

9.1 Conclusions

For the original submission, the review team concluded that the Applicant's single placebo-controlled study, BZUC3002, was inadequate to support effectiveness of BD tablets. As stated in the approvable letter, BZUC3002 "did not demonstrate a statistically persuasive finding of treatment effect" and there was a "lack consistency of treatment effect between men and women, subsets that were equally represented in the study." While the response rate was comparable between men and women in the BD-treatment group (57% and 54%, respectively), it was markedly different in the placebo group (20% in men compared to 58% in women). Consequently, a substantial therapeutic gain was demonstrated among male patients (37%), but none among female patients (-4%). The observed superiority of BD tablets over placebo was driven by a subpopulation's finding, namely, male patients. Conversely, the efficacy of BD tablets was not established in female patients and the therapeutic effect in women was indeterminate secondary to the unexplained high placebo response rate in this subgroup. In the Executive Summary of her clinical review dated 4 April, 2008, Dr. Fathia Gibril recommended that the issuance of a future approval be dependent upon the review of additional efficacy data from an adequate and well-controlled study that would demonstrate substantial evidence of effectiveness and consistent finding across important subgroups, namely, male and female patients. In her Division Director review dated 17 May, 2008, Dr. Donna Griebel stated that although the primary efficacy endpoint analysis of BD tablets was found to be statistically significantly superior to placebo, the p-value was not persuasive, the finding was not consistent in an important subset analysis (gender) that represented half the study population, and the additional prospectively defined secondary endpoints that were found to significantly favor treatment with BD vs. placebo were not independent endpoints, but were linked to the primary endpoint and each other. She concluded that an additional study that supports the efficacy of BD tablets for mildly to moderately active UC should be submitted by the Applicant to support future approval.

For the second review cycle, BZUC3003, a non-inferiority trial using Asacol as an active comparator, was submitted. Upon review of this study, this reviewer did not believe that the concerns of the previous review team had been adequately addressed. In summary, the following deficiencies were found: 1) the non-inferiority (NI) margin of success chosen by the Applicant was not appropriate and the study did not achieve success when a more representative NI margin was employed, 2) the lack of a placebo arm in the study did not address the gender response discrepancy found in BZUC3002, 3) additional evidence from the published literature and from the approval of Colazal, a capsule formulation of BD marketed by the Applicant, did not resolve the unexpected outcome of differential treatment response between men and women, and 4) the inability to provide

adequate labeling guidance to the medical community regarding the observed differential efficacy between men and women with ulcerative colitis.

For this third review cycle, no additional clinical trial data was submitted. In an attempt to address the deficiencies identified in the first two review cycles, the Applicant submitted several post-hoc analyses of the original data from BZUC3002 and BZUC3003. Upon review of this information and the Applicant's proposal for why BD should be approved, this reviewer concludes that the previously described deficiencies remain inadequately addressed.

Following a teleconference between FDA and the Applicant on March 29, 2010, the Applicant notified FDA that it wished to pursue labeling approval for male patients only. In follow-up, the Applicant submitted draft labeling for Giazo for a male-only indication on April 6, 2010. Given that the prior submissions had identified a lack of evidence to support efficacy in female patients and there was no such concern of lack of effectiveness in male patients, this reviewer can support the approval of Giazo for male UC patients.

9.2 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends that Giazo can be approved for the treatment of adult male UC patients. However, given that facilities proposed for the manufacture of this product were found not to be in compliance with cGMP and the Office of Compliance (OC) issued an overall Withhold recommendation, the NDA is not recommended for approval until the manufacturing site deficiencies are resolved and the OC finds all sites acceptable. Therefore, this reviewer recommends that a Complete Response regulatory action be taken on the current complete response resubmission.

For the original submission, the review team concluded that the Applicant's single placebo-controlled study, BZUC3002, was inadequate to support effectiveness of BD tablets and an Approvable action was taken. BZUC3002 failed to demonstrate a statistically persuasive and consistent finding of treatment effect between men and women, subpopulations that were equally represented in the study. The observed superiority of BD tablets over placebo was driven by a subpopulation's finding, namely, male patients. A substantial therapeutic gain was demonstrated among men (37%), but none among women (-4%). Since therapeutic effect in women was indeterminate secondary to the unexplained high placebo response rate in this subgroup, efficacy of BD tablets was not established in female patients. In the Executive Summary of her clinical review dated 4 April, 2008, Dr. Fathia Gibril recommended that the issuance of a future approval be dependent upon the review of additional efficacy data from an adequate and well-controlled study that would demonstrate substantial evidence of effectiveness and consistent finding across important subgroups, namely, males and females.

For the second review cycle, BZUC3003, a non-inferiority trial was submitted and reviewed, This reviewer did not believe that the concerns of the previous review team

have been adequately addressed. In summary, the following deficiencies were found: 1) the non-inferiority (NI) margin of success chosen by the Applicant was not appropriate and the study did not achieve success when a more representative NI margin was employed, 2) the lack of a placebo arm in the study did not address the gender response discrepancy found in BZUC3002, 3) additional evidence from the published literature and from the approval of Colazal, a capsule formulation of BD marketed by the Applicant, did not resolve the unexpected outcome of differential treatment response between men and women, and 4) the inability to provide adequate labeling guidance to the medical community regarding the observed differential efficacy between men and women with ulcerative colitis.

For this third review cycle, no additional clinical data was submitted. In an attempt to address the deficiencies identified in the first two review cycles, the Applicant submitted several post-hoc analyses of the original data from BZUC3002 and BZUC3003. Upon review of this information and the Applicant's proposal for why BD should be approved, this reviewer concludes that the previously described deficiencies remain inadequately addressed. Should the product be approved for adult male UC patients, given the lack of demonstrated efficacy in adult female patients, this reviewer could support this decision based on the Guidance for Industry "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" (Section II, C, 2, a). In brief, since Colazal, the capsule formulation of BD, has been approved and marketed, the additional clinical study (BZUC3002) provides additional support for the approval of Giazo, the tablet formulation of BD, for male UC patients.

9.3 Recommendation on Postmarketing Actions

Risk Management Activity

Should this NDA be approved in the future, an assessment of appropriate risk management would need to take into account updated information at that time. At present, given the low frequency of serious adverse events and the lack of specific active safety concerns, this reviewer does not recommend a risk management plan for balsalazide disodium for the treatment of adult patients with mildly to moderately active UC.

Required Phase 4 Commitments

The Sponsor requested waiver for pediatric studies required under the Pediatric Research Equity Act (PREA). On 29 October, 2008, this recommendation for full waiver of pediatric studies with the BD tablet formulation was presented before the PERC committee. The outcome of the discussion was: 1) full waiver of studies for pediatric UC patients under 12 years of age, 2) should the product be approved, future approval for adolescent UC patients between 12 and 17 years of age should be considered, and 3) the Division has the discretion to determine if additional studies are required to adequately label BD for this adolescent UC patient population. For this review cycle, a second

PERC committee meeting was held on 8 April, 2010. The outcome of that discussion was consistent with the prior PERC recommendations with the following suggestion for the Division's consideration: labeling of the product for children under the age of twelve for those patients able to swallow the adult tablet formulation.

Other Phase 4 Requests

Should the product be approved the following Phase 4 commitments should be considered:

- Efficacy study in adult women with UC should the product be approved for adult male UC patients
- Pediatric PK study in adolescent pediatric UC patients aged 12 to 17 years of age
- Clinical pharmacology study evaluating potential drug interaction between Giazo and commonly prescribed antibiotics for the treatment of UC

9.4 Labeling Review

Should BD tablets be approved at a future date, this reviewer recommends consideration of the following:

1) To harmonize existing mesalamine-class warnings, consideration should be made to include language from other approved mesalamine products for the following warnings: mesalamine intolerance syndrome, renal impairment, and hepatic impairment.
2) Consideration should be made to the recommendations put forth by Ann Corken Mackey in her OSE consult dated 14 January, 2008. Namely, DDRE recommends class labeling for all 5-ASA products to include the following warnings: myocarditis, pericarditis, vasculitis, pruritus, pleural effusion, pneumonia with and without eosinophilia, alveolitis, renal failure, interstitial nephritis, and pancreatitis. Although evidence is limited (based on postmarketing reports), the following adverse events have been reported for other 5-ASA drugs and should be considered for inclusion in the BD label: interstitial lung disease, urticaria, pulmonary fibrosis, hemolytic uremic syndrome, angioedema, toxic epidermal necrolysis, pericardial effusion, leukopenia, and thrombocytopenia.
3) The concomitant use of antibiotics with BD tablets should be addressed since such therapy may effect the composition of gut flora and thereby the effectiveness of BD given its pro-drug form. If necessary, a study addressing this topic may need to be conducted as part of a post-marketing commitment.
4) Consideration of additional language for special populations, namely pediatric and geriatric patients. For the former, consider labeling the product for pediatric patients capable of swallowing the adult tablet formation of BD.

The following is a labeling draft for Giazo that has been negotiated and agreed upon by FDA and the Applicant at the conclusion of this third resubmission review cycle:

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22205	ORIG-1	SALIX PHARMACEUTICALS INC	BALSALAZIDE DISODIUM TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER L LEPTAK
04/27/2010

JOHN E HYDE
04/27/2010
Concur with recommendation on regulatory action.

Division Director Summary Review

Date	December 22, 2008
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 22-205 N-000
Applicant Name	Salix Pharmaceuticals, Inc.
Date of Submission	June 30, 2008
PDUFA Goal Date	December 31, 2008
Proprietary Name / **Established (USAN) Name**	Giazo Balsalazide disodium
Dosage Forms / Strength	Tablet for oral administration Each tablet contains 1.1g balsalazide disodium
Proposed Indication(s)	Treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older
Recommended Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christopher Leptak, MD, PhD/John Hyde, MD, PhD
Statistical Review	Shahla Farr, MS/Mike Welch, PhD
CMC	Maria Ysern, MS
DSI	Roy Blay, PhD/ Constance Lewin, MD, MPH
CDTL Review	John Hyde, MD PhD
OSE/DMEPA	Todd Bridges, RPh/Diane Smith, PharmD

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention Assessment
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This is the first resubmission of this NDA in response to the Approvable letter issued by FDA on May 16, 2008. The original NDA, received by FDA on 7/17/07, included a single placebo-controlled clinical study (BZUC3002) to support the proposed indication "treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older". The Applicant submitted an additional clinical study during the course of the first review cycle, but the Division did not review that study as it was not a component of the NDA submission that had been filed.

The NDA was not approved because the clinical and biostatistical reviewers did not determine that the single study submitted in the original NDA submission (Study BZU3002) had provided adequate evidence of efficacy. There was an important discrepancy in treatment effect observed between the males and females in the study, and no clinical benefit was established in females. In the May 16, 2008, Approvable Letter the Division cited both the lack of a statistically persuasive finding of treatment effect and the lack of consistency in treatment effect between the subsets of men and women within the single study as the deficiency that precluded approval of the NDA. The letter stated that approval would be dependent on "review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis".

Please refer to Dr. John Hyde's thorough Cross Disciplinary Team Leader (CDTL) Review of this resubmission. He was not the CDTL for the first NDA submission, but has in the context of his review, summarized the original review findings of the FDA reviewers in the original review cycle. He has carefully evaluated the findings of the biostatistical and clinical review team from the original study and their ultimate recommendation to issue an approvable action in the first cycle. He has summarized his own conclusions regarding the strength of the data provided by the original study (BZUC3002) in Section 11. Other Relevant Regulatory Issues of his CDTL review. Dr. Hyde notes that the Division's guidance in the pre-NDA meeting included an emphasis on the requirements of a single study for evidence of effectiveness delineated in section II.C.3 of the "Evidence Document" (*Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* 1998), which demands that the study be statistically very persuasive with a "very low p-value" (conventionally viewed as being a p-value that provides a strength of evidence comparable to two studies with $p < 0.05$). He expresses concern regarding the appropriateness of giving emphasis to the persuasiveness of the observed p-value from a single study, not only in the pre-NDA meeting but the Approvable letter, for an NDA that proposes marketing of an oral balsalazide product. He does not agree that a statistically highly persuasive p-value should be required for an application that seeks marketing approval for a new dosing format for balsalazide (tablets administered twice a day) when the product is already marketed as capsules (three times a day dosing), and is a pro-drug for a drug, mesalamine, which has been

shown to be effective for the same indication in multiple other marketing applications. He notes that the pharmacokinetics of the basalazide tablet and capsule products are very similar. This conclusion is also supported by the standard delineated in the Evidence Document, in section II.C.2.a, which allows taking into account related study data when considering the strength of evidence provided by the single trial.

I concur with Dr. Hyde's conclusion that study BZUC3002's p value <0.02 itself is not sufficient to argue that the evidence from that single trial was inadequate to establish that Giazo is effective in the treatment of mildly to moderately active ulcerative colitis, given the existing evidence that balsalazide is effective for treatment of mildly to moderately active ulcerative colitis. I also concur, however, with his additional conclusion that the unexplained difference in treatment effect observed between genders in that single trial, was an important deficiency, that rendered the trial inadequate as a stand alone trial to support marketing approval of Giazo. He notes that the difference in treatment effect between genders was quite large, and despite the fact that the subset of females represented half the study population and a negative treatment effect was observed in that subset, a nominally significant outcome favoring balsalazide was still observed. This positive outcome resulted from a near tripling of response rate in males. I agree with Dr. Hyde that it is important to understand what treatment effect can be expected in females before the product can be approved. This lack of consistent treatment effect between genders was listed in the Approvable letter as a reason for not approving the product in the first review cycle.

In my review I will focus on the salient review issues that the reviewers have identified in their evaluation of the evidence provided by the second study, BZUC3003, submitted for review in this review cycle.

2. Background

This application is for a new oral formulation of balsalazide disodium, a tablet containing 1.1 g balsalazide disodium that the applicant proposes will be dosed twice daily – three tablets twice daily, for a total dose of 6.6g – for up to 8 weeks, for the following proposed indication:

> GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. Safety and effectiveness of GIAZO beyond 8 weeks in adults have not been established.

There are currently other balsalazide formulations on the market, but this would be the first product dosed twice daily. The other approved products include one marketed by the applicant, Colazal (a capsule formulation dosed three times a day, for total dose of 6.75 g), and multiple generics. Balsalazide, however, is a prodrug of mesalamine (5-amino salicylic acid, 5-ASA), and there are multiple mesalamine products on the market for treatment of mild to moderately severe ulcerative colitis, including products that are dosed once a day, three times a day and four times a day, in mesalamine total doses that range 2.4g – 4.8 grams per day. As Dr. Hyde notes in his review, since balsalazide disodium is "considered equivalent to about (b) (4) mesalamine… the proposed daily dose of 6.6 g balsalazide disodium is comparable to about (b) (4) mesalamine", which falls in the range of the approved mesalamine doses.

With regard to the regulatory history of the development of the Giazo balsalazide table, the applicant was told in response to a question about providing a single induction study to support approval at their August 8, 2005 End of Phase 2 meeting that two studies were recommended "unless results from a single study are robust (or adequate justification is provided as to why two are not necessary)." Similarly at the April 27, 2007 Pre-NDA Meeting the Division stated that "approvability of your new dosage form will ultimately be based on the robustness of the data and the consistency of effect seen in the primary and secondary endpoints" in response to the Applicant's proposal to submit the single study, BZUC3002, to support efficacy in their NDA . The Division further clarified that, "Also, since study BZUC3002 is intended to be a single principle [sic] study for efficacy, results are expected to be internally consistent and robust, demonstrating substantial efficacy with a p-value considerably smaller than .05."

As stated above in the Introduction section of this summary review, the FDA took an Approvable action on the original NDA submission. The single trial contained a significant inconsistency across subsets, the clinical benefit demonstrated in the overall study findings was only observed in the males who participated in the study. Females treated with placebo in the study had a similar outcome as females treated with Giazo, and in fact, the primary efficacy outcome was actually numerically higher in women treated with placebo. The approvable letter stated the following deficiency and means for addressing the deficiency:

> "Your placebo controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study.
>
> The issuance of an approval is dependent upon the review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis."

After taking an approvable action on May 16, 2008, the Division met with the applicant in a June 9, 2008 Post-Action Meeting. As Dr. Hyde notes in his review, in that meeting the Division told the applicant clinical study BZUC3003, which the applicant had submitted during the initial review cycle but was not reviewed by the FDA, appeared to be a study that would constitute a response to the Approvable Letter. The Division, however, qualified that response by saying that the adequacy of the second study would be a review issue.

The Applicant's Complete Response resubmission, which was dated 6/30/08, contained the clinical study discussed at the Post-Action Meeting (BZUC3003), additional clinical safety data, and stability data to extend the expiration date. The Division notified the Applicant in early November 2008 that the Division had identified deficiencies that precluded initiating labeling. Those deficiencies were explained and discussed in a teleconference between the FDA clinical and biostatistical reviewers and the Applicant on 11/13/08. The reviewers noted that the active controlled study comparing Giazo to Asacol was inadequate to establish the

efficacy of Giazo because Giazo was not found to be superior to Asacol, and the study did not establish that Giazo is noninferior to Asacol. In addition, the applicant had not adequately addressed why females had not experienced a treatment benefit from Giazo in the original study. The second study submitted in this complete response was inadequate to address the issue of gender effect.

My review will focus on the clinical and statistical reviewers' critical evaluation of the strength of evidence provided by the second study, BZUC3003.

3. CMC

The resubmission contained additional stability data. In the original review cycle, the CMC Reviewer found that sufficient information was provided to assure the identity, strength, purity, and quality of the drug product. The stability data supported a 24-month expiration date, and the Office of Compliance issued an "Acceptable" overall recommendation on 3/17/08 for all the facilities involved. The reviewer did note that the font of the established name and the locations of the strength, 1.1g, in the labels for the carton and the immediate label, need to be changed.

In this review cycle, I concur with the CMC Reviewer's conclusion that the additional stability data supported a 36-month expiration dating. Since the deficiencies in labels noted on the first review cycle are still pending, I concur with the CMC Reviewer's recommendation that for this NDA to be approved in the future, the pending corrections to the labels will need to be completed.

4. Nonclinical Pharmacology/Toxicology

Please see Dr. John Hyde's CDTL review. There were no new Pharmacology/Toxicology data in this resubmission. Dr. Ke Zhang recommended approval from the preclinical standpoint in his review of the original submission.

5. Clinical Pharmacology/Biopharmaceutics

Please see Dr. John Hyde's CDTL review. There were no new clinical pharmacology data in this resubmission. Dr. Insook Kim, PhD dated 5/6/08, recommended approval in her review of the original NDA submission, but deferred making labeling recommendations, given the Approvable action.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Please refer to Dr. John Hyde's excellent summary of the clinical and statistical review findings in his CDTL review.

The primary endpoint of the clinical trial submitted in the initial NDA submission, BZUC3002, and the clinical trial submitted in this first resubmission, BZUC3003, was based on the Modified Mayo Disease Activity Index, MMDAI. This index is comprised of 4 subscores, which range from 0-3 (higher score representing more severe disease). Totaling the subscores yields a score that can range from 0-12. The primary endpoint, clinical improvement at the end of the treatment period, was defined by at least a 3 point improvement in MMDAI, associated with an improvement in rectal bleeding score of at least 1 point.

The single clinical study BZUC3002 reviewed in the previous review cycle was a randomized, double-blind, placebo-controlled study of Giazo that enrolled 250 patients with mildly to moderately active UC from 55 U.S. centers. The primary endpoint was assessed at 8 weeks in this study. Primary efficacy endpoint results are summarized in the table (reproduced from Dr. John Hyde's CDTL review) below, which also includes the important subgroup analysis by gender (data adapted from previous cycle Team Leader Review). The disparity in treatment effect between men and women lead to the Approvable action in the first review cycle.

Proportion of Patients with Clinical Response at Week 8 in Study BZUC3002

	Giazo 6.6 g/day % (# response/N)	Placebo % (# response/N)	Difference (Giazo – Asacol)	P-value
Total Population	**55%** (b) (4)	**40%** (b) (4)	**15%**	0.024
Males	**57%** (b) (4)	**20%** (b) (4)	**37%**	<0.001
Females	**54%** (b) (4)	**58%** (b) (4)	**-4%**	(b) (4)

Despite the statistically significant difference overall favoring treatment with Giazo, the outcome was not consistent between genders. In fact, females actually appeared to do better on placebo than Giazo. As Dr. Hyde points out in his CDTL review, "there was a nominally statistically significant difference between treatment effects by gender (37% vs. -4%, nominal $p < 0.003$ by M-H Chi-square test for homogeneity)". Secondary endpoint analyses performed by gender did not allay concerns that the drug effect differed by gender.

The study submitted in this NDA resubmission, BZUC3003, was a randomized, double-blind, active-controlled study in patients with mildly to moderately active UC. Patients were randomized between treatment with Giazo (balsalazide) or Asacol (mesalamine) for six weeks. The dose of Asacol (mesalamine) used in this study was 0.8g TID (total 2.4 g/D), which is the approved dose. The Giazo dose was the dose proposed for marketing, 3.3g BID (total 6.6 g/D). Blinding was accomplished by a double-dummy design. The objective of the study was to establish that Giazo is noninferior to Asacol for treatment of this patient population. The

design features, including duration of treatment, dose, method of assessment, schedule of assessments, and eligibility criteria, were carefully evaluated by the clinical and statistical reviewers, in order to determine whether suitable previously conducted studies had been utilized to establish an appropriate noninferiority margin for analysis of the primary endpoint.

Similar to study BZU3002, the primary endpoint clinical response in BZU3003 was defined as a reduction of at least 3 points in MMDAI and a reduction of at least 1 point in the rectal bleeding score. In BZU3003, however, the end of study assessment was made at Week 6 instead of Week 8, and the primary efficacy analysis was a noninferiority analysis, (b) (4) . The Applicant's proposed noninferiority margin was (b) (4) Protocol-specified major secondary endpoints were identified and analyzed in hierarchical order.

Although the initial BZU3003 protocol specified the primary analysis would utilize the ITT population, the first protocol amendment (approximately 3 months after initiating the study) changed the population for analysis to the per-protocol population. As part of these changes, the definition of the ITT population was modified. The ITT population became all patients who met the following criteria: 1) took at least one dose of study drug, 2) baseline MMDAI score is between 6 and 10, inclusive, 3) MMDAI bleeding score is at least 2 or greater, and 4) MMDAI endoscopy score is at least 2 or greater. This revised ITT population definition is referred to by the FDA reviewers as the modified ITT population, or mITT. The per protocol population of the primary efficacy analysis was defined as the patients in the mITT population who had no major protocol deviation and had at least one post-baseline assessment of the primary efficacy endpoint. The changes made in the analysis population were a significant review issue for the biostatistical reviewer, Shahla Farr, MS, and prompted her to conduct a number of exploratory analyses utilizing differing definitions of the primary analysis population. These analyses are described in detail in her biostatistical review.

Of the total of 410 patients randomized in this study, 351 qualified for inclusion in the per protocol population. The population was nearly evenly split between males and females – 48% were males. The table below (reproduced from Dr. John Hyde's CDTL review) summarizes the outcome observed for the primary endpoint for the overall ITT population ("All Randomized"), the per-protocol population, as defined above, and the modified ITT population (mITT), as defined above. Given the Applicant's defined noninferiority margin of (b) (4) the Applicant concluded that Giazo is noninferior to Asacol, since the lower bound of the 95% interval of the difference between Giazo and Asacol in the per protocol population analysis was (b) (4)

Percentages of Patients with Clinical Response at Week 6/EOT in Study BZUC3003

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference (Giazo – Asacol) (95% C.I.)	P-value
Per-Protocol	**61.7%** (b) (4)	**60.8%** (b) (4)	**0.9%** (b) (4)	(b) (4)
mITT	**56.3%** (b) (4)	**56.2%** (b) (4)	**0.1%** (b) (4)	
All Randomized	**54.7%** (b) (4)	**55.1%** (b) (4)	**-0.3%** (b) (4)	

However, Shahla Farr, MS, the FDA Biostatistical Reviewer, did not find that the Applicant had adequately justified their selection of the (b) (4) noninferiority (NI) margin. She found in her review of the Applicant's meta-analysis of 16 placebo-controlled studies, that only one study (Sninski, et al.) was suitable for use to determine an NI margin. The other studies were not appropriate to include in the meta-analysis because they differed substantively in their design from study BZUC3003 (different primary endpoints, varying durations of treatment and different patient populations). Five of the 16 studies were not studies of induction treatment.

The Sninski study permitted determination of a much smaller noninferiority margin than that used by the Applicant, -3%. Please refer to the FDA Biostatistical Review for a detailed explanation of how this margin was derived. Given that the treatment effect for Asacol in that study was estimated to be 26%, with a 95% confidence interval of (6%, 45%), halving of the lower bound of the confidence interval resulted in the 3% margin. The biostatistical reviewer identified an additional placebo-controlled study, not included in the meta-analysis submitted by the applicant, which was used for the approval of Asacol. Based on this study, she found again that the NI margin for the comparison to Asacol should not exceed -3%. She concluded that study BZUC3003 did not support that Giazo is noninferior to Asacol, and as such, does not establish that Giazo is effective for the treatment of patients with mildly to moderately severe ulcerative colitis.

Given the differences in outcome by gender observed in the study submitted in the original NDA submission, study BZUC3002, the response rates by gender were of particular interest in study BZCU3003. The analyses of the primary endpoint by gender in the noninferiority study are summarized in the table below, which is reproduced from the CTDL review by Dr. John Hyde, who adapted it for the biostatistical reviewer's review.

Analysis of Efficacy by Gender, mITT Population Study BZU3003

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference (Giazo – Asacol) (95% C.I.)
Males	**51%** (b) (4)	**49%** (b) (4))	**2%** (b) (4) (b) (4)
Females			

The clinical and statistical reviewers note in their reviews that the lack of a placebo arm in this study does not allow it to clearly address the question regarding treatment effect in women raised in the review of study BZCU3002. The lower limit of the confidence intervals for the comparison of Giazo and Asacol is lower in females than males in this study, (b) (4) It is unclear whether this observed difference is meaningful. The biostatistical reviewer, Shahla Farr, MS, did conduct an exploratory analysis by pooling the data from studies BZCU3002 and BZCU3003, and found that despite the higher female response rate observed in BZCU3003, the pooled female response rate with Giazo remained indistinguishable from the placebo BZCU3002.

I concur with the conclusions of the biostatistical and clinical reviewers that the data in this resubmission do not provide compelling evidence that Giazo is efficacious in patients with mildly to moderately active UC for the following reasons: 1) when an appropriately derived noninferiority margin is applied, the result of the noninferiority study, BZCU3003, did not establish that Giazo is noninferior to Asacol and 2) the Applicant has not provided evidence to explain the discrepancy in efficacy between males and females observed in the superiority study BZCU3003. I concur with the reviewers' recommendation that this resubmission should receive a CR.

8. Safety

The total safety data base in the submission was comprised of 565 patients treated with Giazo, of whom 430 had been exposed for more than eight weeks, 331 for at least six months, and 140 for at least a year. I concur with the clinical reviewers' conclusion that the overall safety profile of Giazo is similar to that of the approved capsule dosage form of balsalazide. Dr. Leptak noted that there has been no thorough QT evaluation of balsalazide disodium, but he did not recommend that a thorough QT evaluation be conducted in the future. Please refer to the CDTL review of this issue in Section 11. Other Regulatory Issues. I concur with the conclusions of Dr. Leptak and Dr. Hyde that it is not necessary to require the applicant to conduct a thorough QT study of balsalazide, based on the reasons stated in Dr. Hyde's CDTL review.

9. Advisory Committee Meeting

There was no Advisory Committee to discuss this resubmission.

10. Pediatrics

Please see Dr. John Hyde's thorough discussion in his CDTL. The Applicant requested full waiver of the PREA requirement for pediatric studies because Giazo did not represent a meaningful benefit over existing available therapy for the pediatric population. The Applicant's balsalazide disodium product, Colazal, which is formulated in a capsule, is approved for treating active UC in pediatric patients ages 5 through 17 years. The capsules can be opened to sprinkle on food. The Pediatric Research Committee (PeRC), on October 29, 2008, agreed with waiving requirements under the age of 12 years, but felt that the BID dosing option (vs. TID with Colazal capsules) should be available to pediatric patients who can take tablets. The PeRC told the Division reviewers that if they believed that adequate information already exists to permit labeling for children aged 12 and over, a waiver could be granted. The clinical reviewers plan to work with the clinical pharmacology reviewers to determine whether additional pharmacokinetic studies are needed in the ≥ 12 years of age pediatric group. If they determine that pharmacokinetic studies are needed, the waiver will not be granted in this group. I concur with this plan.

11. Other Relevant Regulatory Issues

In the Clinical Inspection Summary entered in DFS on December 11, 2008, Dr. Blay noted that two sites that participated in BZUC3003 were inspected, one in Colorado (enrolled 16 subjects) and one in Indiana (enrolled 11 subjects). The observations in both studies, which in the review are summarized as "data appear acceptable in support of the relevant application", were qualified by Dr. Blay. He noted that the observations were based on verbal communication with the field investigator and that an addendum review will be generated if the conclusions change upon "receipt and review of the EIR".

Dr. Christopher Leptak reviewed the financial disclosure report for the investigators from study BZUC3003 and found that one investigator held equity interest, 25,000 shares of stock in Salix Pharmaceuticals, Inc. This investigator only enrolled (b) patients in the study.

Please see Dr. John Hyde's detailed discussion of the additional regulatory issues he identified in the course of his review of the current resubmission and the prior approvable action. Please see Section 1. Introduction of my review for my concurrence with the concerns he raised regarding applying *the Guidance of Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998*, to the assessment of the evidence provided in an NDA that proposes marketing balsalazide. I also agree with his analysis and conclusions regarding the duration of studies that the applicant should be asked to complete to support marketing approval for the proposed indication.

12. Labeling

Please see Dr. John Hyde's CDTL review for a detailed discussion of the labeling issues. I concur with his decision to not enter label negotiations with the applicant this review cycle, given that an approval action is not planned this review cycle. For the same reason, I concur with the decision to not send the label to DDMAC for review this review cycle and his decision to not review the applicant's submission of the proposed container label for the professional sample bottle this review cycle.

With regard to the Proprietary name, in the initial review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) reviewer objected to the applicant's proposed trade name, "Giazo" because it represented a dual trade name. During the review of this resubmission DMEPA reexamined the previously identified issues surrounding use of the name "Giazo" for a tablet form of balsalazide by an applicant who has another balsalazide product marketed under a different name, the capsule formulation Colazol. They examined the Applicant's submission of results from a Failure Mode Effect Analysis and their arguments to justify the trade name "Giazo." The final DMEPA recommendations remain pending at the time of my review. The NDA will not be approved this submission, so the final recommendation from DMEPA regarding the acceptability of the name is not critical at this time.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action – Complete Response. I concur with the recommendations of the clinical reviewer, the biostatistical reviewers' and the CDTL, Dr. John Hyde, for a CR action. I concur with their assessment that the Applicant's Complete Response submission has not adequately addressed the deficiencies cited in the May 18, 2008 Approvable letter. An additional adequate and well controlled trial will need to be submitted to establish the effectiveness of Giazo for the treatment of mildly to moderately active ulcerative colitis. Given the fact the Applicant has been unable to explain the disparate treatment effect between genders observed in the initial placebo controlled trial reviewed by the FDA, the reviewers believe that the additional study will need to be a placebo controlled trial. Although the CMC, Pharmacology, and Clinical Pharmacology Reviewers recommended approval of the NDA in the initial review cycle, and those recommendations have not changed, this does not represent a conflict because the deficiencies cited by the clinical and biostatistical reviewers are specific to the data reviewed by those two disciplines.

I agree with Dr. John Hyde that despite the lack of a final determination from DMEPA regarding the acceptability of the proposed trade name, Giazo, at the time of the completion of the clinical and biostatistical reviews, this should not preclude taking a CR action prior to receipt of DMEPA's final recommendation. We are not recommending approval of the product for marketing at this time. DMEPA's final recommendations can be conveyed to the applicant in a subsequent discipline review letter. The product name would need to be evaluated again at the time of future submission, in any case, given the planned CR action. Similarly, I concur that the CR action can be taken without receipt of the final field office reports from the DSI audits, given the fact that the noninferiority study BZUC3003 was not

found to provide evidence of efficacy, even without finding unacceptable site deficiencies. The DSI reviewers here in the Washington area have entered a preliminary review in DFS that indicates, based on their verbal communications with the field office, the data obtained at the two sites investigated were acceptable for consideration in the NDA review.

Dr. Hyde has recommended that the following comments should be conveyed in a separate letter to the Applicant:

1) The CMC Reviewer's comment regarding the format of the label
2) A recommendation that the Applicant investigate the potential for antibiotics to interfere with balsalazide metabolism.
3) DMEPA's decision regarding the trade name "Giazo."

- Risk Benefit Assessment

I concur with the CDTL that the risk characteristics of Giazo appear similar to those of the currently marketed oral balsalazide product (Colazal capsules). The outstanding issue remains the uncertain effectiveness of this product in female patients with ulcerative colitis, which significantly hinders our ability to provide adequate instructions for the use of this product.

- Recommendation for Postmarketing Risk Management Activities

Not applicable. I do not recommend approval at this time.

- Recommendation for other Postmarketing Study Commitments

I concur with Dr. Hyde that if this application is approved in a future review cycle, a pharmacokinetic study may be required in pediatric patients aged 12 through 17. A decision regarding the need for this study will be based on further evaluation by the clinical pharmacology and clinical reviewers.

I also agree with Dr. Hyde that the unanswered questions regarding balsalazide disodium that were to be addressed as Phase 4 commitments for Colazal (NDA 20-610) but remain outstanding eight years after its initial approval, could be addressed as phase 4 commitments in a future approval of Giazo, with specific timelines.

Dr. Hyde has recommended that the Applicant be asked to evaluate the potential for drug-drug interaction with concurrent antibiotics, to determine whether the antibiotic therapy interferes with mesalamine release, diminishing the treatment effect of Giazo. I concur with this recommendation.

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/s/

Donna Griebel
12/22/2008 04:45:09 PM
DIRECTOR

Cross-Discipline Team Leader Review

Date	December 21, 2008
From	John E. Hyde, Ph.D., M.D., Clinical Team Leader, DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 22-205 N-000
Applicant	Salix Pharmaceuticals, Inc.
Date of Submission	June 30, 2008; Received June 30, 2008
PDUFA Goal Date	December 31, 2008
Proprietary Name / **Established (USAN) names**	GIAZO Balsalazide disodium
Dosage forms / Strength	Tablet for oral administration; each tablet contains 1.1 g balsalazide disodium.
Proposed Indication	Treatment of mildly to moderately active ulcerative colitis in patients 18 year of age and older.
Recommended:	Complete Response

1. Introduction

This submission, received June 30, 2008, is the first resubmission of this NDA in response to an Approvable letter issued by FDA on May 16, 2008. This application is for a new oral formulation of balsalazide disodium. The product is a tablet containing 1.1 g balsalazide disodium.

The proposed indication is:

> GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. Safety and effectiveness of GIAZO beyond 8 weeks in adults have not been established.

The proposed dosing is three tablets twice daily (b) (4) (for a total daily dose of 6.6 g) for up to eight weeks. The Applicant proposed labeling with a contraindication for hypersensitivity to salicylates or any component of Giazo tablets, and with warnings about the potential for exacerbations of ulcerative colitis, the possibility of prolonged gastric retention in patients with pyloric stenosis, the risk of renal toxicity, and the need for caution when used in hepatic impairment. The proposed pregnancy category is B.

Balsalazide disodium was first approved July 18, 2000, as a 750 mg capsule formulation under the trade name Colazal in NDA 20-610, from the same Applicant as the current NDA. There are no other approved formulations of balsalazide disodium in the U.S.; however, several oral formulations of mesalamine, a closely related drug, have been approved for treating ulcerative colitis.

2. Background

General Background

Ulcerative Colitis

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology. Peak age of onset is in the early twenties, but it can vary widely. UC is more common in whites vs. non-whites, but the incidence is fairly similar for men and women. The disease is manifest as mucosal inflammation and mucosal ulceration that occur in the colon in a continuous segment beginning with the rectum. Extent of involvement varies from proctitis to pancolitis. Involved areas classically show inflammatory changes limited to the mucosa, and there may be extensive, broad-based ulceration in severe cases. Clinically, UC presents as a chronic, relapsing disease with variable-length bouts of bloody mucoid diarrhea and lower abdominal pain. There may be long quiescent periods between attacks. There may also be systemic manifestations involving joints, eyes, skin, or the hepatobiliary system. Potential serious complications include severe bleeding, toxic megacolon, and perforation. There is a significant risk of colon cancer with longstanding disease: pancolitis for 10 years or longer has a 20- to 30-fold increased risk of cancer compared to the general population.

Ulcerative Colitis Therapy

Approved therapies for UC include corticosteroids to "tide the patient over a critical period" of UC, and aminosalicylates, which are available in rectal formulations (Canasa and Rowasa [mesalamine]) and oral formulations (Azulfadine [sulfasalazine]; Asacol, Pentasa, and Lialda [mesalamine]; Dipentum [olsalazine]; and Colazal [balsalazide]) as limited-term therapy to treat mildly or moderately active UC. The aminosalicylates Azulfadine, Asacol, Apriso (mesalamine), and Dipentum are approved as chronic therapy to maintain remission in UC. Colazal is approved for pediatric use in patients 5 years and older. Also used, but unapproved, therapies for ulcerative colitis include (b) (4) (b) (4). Use of any of the preceding has come to be considered part of "conventional therapy." Remicade (infliximab), a TNF blocker, is approved for induction and maintenance of remission in moderately to severely active UC for patients with an inadequate response to conventional therapy.

Balsalazide disodium is considered to be a prodrug for mesalamine. It is cleaved by intestinal flora into mesalamine (5-aminosalisylic acid, or 5-ASA) and a second compound (4-aminobenzoyl-β-alanine, or 4-ABA) that is thought to be inactive. Both of these metabolites also have N-acetylated metabolites. Oral formulations of mesalamine are designed to have delayed- and/or extended-release characteristics in an attempt to target delivery to colon. Typically, a third or less of orally administered mesalamine is systemically absorbed. Giazo is not a delayed-release formulation of balsalazide; rather, it is designed to achieve delivery of mesalamine to the target site through its prodrug characteristic by remaining intact until it is metabolized to mesalamine by intestinal flora.

Mesalamine's specific mechanism of action is unknown, but it is thought to act primarily topically in the colon by blocking cyclooxygenase and 5-lipoxygenase, thereby inhibiting production of arachidonic acid metabolites and diminishing inflammation. Mesalamine may also act as a reactive oxygen metabolite scavenger. Nonclinical studies identified the kidney and GI tract as targets of toxicity of mesalamine when given in high doses.

Related Approved Products

The other approved balsalazide disodium product, Colazal capsules, has the following indication:

> COLAZAL is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older. Safety and effectiveness of COLAZAL beyond 8 weeks in children (ages 5-17 years) and 12 weeks in adults have not been established.

The recommended dosing is 2.25 g (as three 750 mg capsules) TID for a total daily dose of 6.75 g, for up to 8 weeks. Pediatric dosing can be the same as adult dosing or 750 mg TID (total daily dose 2.25 g); capsules may be opened to sprinkle on applesauce.

The approved dose of oral mesalamine to treat active UC ranges from 2.4 to 4.8 g/day, in single or divided doses, depending on formulation. (Each gram of balsalazide disodium is considered equivalent to about (b) (4) mesalamine, so the proposed daily dose of 6.6 g balsalazide disodium is comparable to about (b) (4) mesalamine.) The approved dose of oral mesalamine for maintenance of remission is 1.6 g/day divided into BID dosing for Asacol and 1.5 g once daily for Apriso.

Colazal is contraindicated in patients with hypersensitivity to salicylates. The labeling has warnings that Colazal may exacerbate UC symptoms, that patients with pyloric stenosis may have prolonged gastric retention of the capsules, and that Colazal should be administered with caution in patients with renal dysfunction or renal disease history). The pregnancy category is B.

The elements of the Colazal labeling are very similar to those of approved mesalamine products. Apriso (mesalamine granules) was approved in October 2008 with labeling that also contains a warning regarding risks of use in patients with pre-existing liver disease. Postmarketing reports of renal injury with mesalamine and related products have been uncommon; renal injury appears to be an idiopathic reaction to mesalamine when given to humans in the therapeutic dose range.

Presubmission Activities

Giazo was developed under IND 38,492, which was opened on 6/22/92. This is the same IND used to develop the Colazal capsule and under which pediatric studies for Colazal were done.

With the approval of Colazal, the Applicant made nine postmarketing commitments (PMCs), of which four remain outstanding according to the PMC annual report of 9/17/2008. It should be noted that no timelines were included in the wording of these four commitments. The remaining commitments are (quoted from the 7/18/00 AP letter):

PMC 4 (Status: submitted)

> Regarding requested *in vitro* drug interaction studies, you have committed to conducting *in vitro* drug interaction studies to evaluate the potential for commonly co-administered drugs to interact with balsalazide.

PMC 5 (Status: pending)

With respect to requested *in vivo* drug interaction studies, based on the results of the *in vitro* drug interaction studies, you have agreed to conduct *in vivo* drug interaction studies in appropriate animal species and evaluate the PK (as deemed necessary). Based on the outcome of these studies, you will discuss with the Agency the need for any additional studies.

PMC 6 (Status: pending)

Regarding the requested renal impairment study, you have agreed to compare the PK data from the multiple-dose PK study to that obtained from literature on patients with varying degrees of renal impairment that are receiving mesalamine or related prodrugs. Based on the outcome of the analysis of the multiple-dose PK study, it will be decided whether an additional study is needed to assess PK of balsalazide in patients with varying degrees of renal impairment.

PMC 7 (Status: pending)

Regarding the hepatic impairment study, you have agreed to evaluate the PK of balsalazide in hepatically-impaired patients if clinically-relevant results are obtained in the renal impairment study.

<u>End-of-Phase-2 Meeting</u>

The Applicant held an End-of-Phase-2 (EOP2) meeting with the FDA on August 8, 2005. The Applicant proposed to provide only a single induction study to support approval. The FDA responded that two studies are recommended "unless results from a single study are robust (or adequate justification is provided as to why two are not necessary)," but noted that an NDA could be filed with a single study. The FDA agreed that the proposed pharmacology and toxicology information was adequate, but advised the Applicant that PK studies would be needed to evaluate multiple-dose PK of the proposed product and the relative bioavailability vs. Colazal. The FDA made several additional recommendations, including the following:

- Make the treatment duration eight weeks to facilitate comparisons to the original Colazal trial data.
- Add an active control arm, such as Asacol.
- Include patients 12 to 18 years if pediatric labeling is being contemplated.
- Obtain additional safety data on the tablet formulation, because the dosing differs from that of the marketed capsule formulation, in that the amount per dose is 50% greater.

The FDA stated that the application would be subject to PREA requirements for a pediatric plan. The FDA also informed the Applicant that a formal response to the Phase 4 commitments regarding renal impairment was still required.

<u>Pre-NDA Meeting</u>

A pre-NDA meeting was held April 27, 2007. The Applicant proposed to submit a single study, BZUC3002, for efficacy, as well as PK studies that responded to the requests made at the EOP2 meeting. The FDA repeated the recommendations of the EOP2 meeting regarding number of clinical studies, and stated that "approvability of your new dosage form will ultimately be based on the robustness of the data and the consistency of effect seen in the primary and secondary endpoints." The FDA added, "Also, since study BZUC3002 is intended to be a single principle [sic] study for efficacy, results are expected to be internally consistent and robust, demonstrating substantial efficacy with a p-value considerably smaller

than .05." The FDA remarked that the proposed safety database was adequate for filing, with adequacy for approval being a review issue.

First Review Cycle

The original NDA was dated 7/16/07 and received on 7/17/07. The submission included the report of a single placebo-controlled clinical study (BZUC3002) to support efficacy. During the review, the Applicant also submitted a report of an additional clinical study (BZUC3003). However, the Division had not solicited that report and elected not to review it as part of that review cycle.

Although Study BZUC3002 showed a statistically significant difference overall, the Statistical Reviewer and Clinical Reviewer did not feel that the study, on its own, provided adequate evidence of efficacy. They also identified a marked gender difference in the treatment effect, with females showing essentially no benefit. On May 16, 2008, the Division issued an Approvable Letter citing the following deficiencies in need of resolution (quoted from the letter):

> Your placebo controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study.
>
> The issuance of an approval is dependent upon the review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis.

That was followed on May 22, 2008, by a letter to the Applicant denying the trade name "Giazo" on the grounds that it was confusing and misleading. The letter recommended use of the single trade name "Colazal" for both the capsule and tablet formulations. The letter also included CMC comments regarding required changes to the carton and container labels.

Post-Action Meeting

Following the Approvable action, a meeting was held on June 9, 2008, at the Applicant's request. The FDA stated that the second clinical study (BZUC3003, which had been submitted during the review cycle but not reviewed) appeared to be a study that would constitute a response to the Approvable Letter, but its adequacy would be a review issue. The FDA expressed its interest in the derivation and justification of the non-inferiority margin and stated that adequacy of the margin would be a review concern. The Applicant was instructed to provide an updated ISS and to submit a safety update 120 days after the Complete Response submission. The FDA agreed to accept updated stability data with the complete response submission.

The Applicant also presented arguments for retaining the proposed trade name "Giazo." The FDA recommended that the Applicant provide a Failure Mode Effect Analysis of the effect of using one vs. two trade names.

Submission and Review

The NDA Complete Response resubmission was dated 6/30/08 and was also received on that date. It was classified as a Type 2 resubmission and given an action date of December 31, 2008. The application contained a clinical study, additional clinical safety data, and stability data to extend the expiration date. The application was submitted as paper copies with electronic data sets (as was the original submission). A 120-day safety update was received 10/29/08. In early November 2008, the Applicant was notified by the Division that deficiencies in the application precluded commencing labeling negotiations, and the deficiencies were explained further in a teleconference between the FDA and the Applicant on 11/13/08.

No Advisory Committee meeting was held to discuss this application.

The relevant review disciplines have all written review documents for this resubmission. The new primary review documents relied upon are the following:

Clinical Review by C. Leptak, dated 12/20/08.
Statistical Review and Evaluation by S. Farr, (draft version of 12/19/08).
CMC Review by M. Ysern, dated 10/14/08 & finalized 11/21/08
Clinical Inspection Summary (interim) by K. Malek, dated 12/10/08.

These reviews, along with the primary and supervisory review documents from the original review cycle, should be consulted for more specific details of the application and review conclusions. This memorandum summarizes selected information from the primary review documents.

3. CMC

The resubmission contained additional stability data. The reader is referred to the review from the previous review cycle and to the review by M. Ysern, dated 10/14/08.

<u>Conclusions and Recommendations from Original Review Cycle</u>
The processes and controls for the drug substance are [redacted] (b) (4) The CMC Reviewer found that sufficient information was provided to assure the identity, strength, purity, and quality of the drug product. The stability data supported a 24-month expiration date.

The Office of Compliance issued an "Acceptable" overall recommendation on 3/17/08 for all the facilities involved.

The Chemistry Reviewer recommended the NDA for approval. No Phase 4 commitments, agreements, or risk management steps were recommended. The Reviewer recommended that the Applicant be informed of the need to change the font of the established name and the locations of the strength, 1.1g, in the labels for the carton and the immediate label.

Current Review Cycle Conclusions and Recommendations
The Reviewer concluded that the additional stability data supported a 36-month expiration dating. The deficiencies in labels noted on the first review cycle were still pending. The Reviewer recommended the NDA for approval, pending corrections to the labels. No Phase 4 commitments, agreements, or risk management steps were recommended. The Reviewer recommended the Applicant be sent a comment regarding revisions to the label.

4. Nonclinical Pharmacology/Toxicology

There were no new Pharmacology/Toxicology data in the resubmission, and no additional review of nonclinical data was performed in this review cycle. The reader is referred to the Pharmacology/Toxicology review by K. Zhang, dated 1/10/08, from the initial review cycle.

Conclusions and Recommendations from Original Review Cycle
The Reviewer noted that renal toxicities had been seen in rats and recommended that the labeling include the statement: "Treatment with Colazal increased the incidence of pelvic and corticomedullary mineralization in kidney and urothelial hyperplasia in rats at oral doses of 600 mg/kg/day (about 0.7 fold the recommended human dose based on body surface area) or higher. Therefore, caution should be exercised when administering Colazal [sic] to patients with known renal dysfunction or a history of renal disease."

The Reviewer recommended approval from the preclinical standpoint. The Reviewer did not recommend any Phase 4 commitments.

5. Clinical Pharmacology/Biopharmaceutics

There were no new clinical pharmacology data in the resubmission, and no additional review of clinical pharmacology data was conducted in this review cycle. The reader is referred to the Office of Clinical Pharmacology Review by I. Kim, dated 5/6/08, from the initial review cycle.

Conclusions from the Original Review Cycle
After a single dose of Giazo, the T_{max} is 0.5 hours for balsalazide and 12 hours for mesalamine. The $t_{1/2}$ is 1.9 hours for balsalazide and 9.5 hours for mesalamine. With repeated dosing, steady state is reached in about three days, and the AUC for balsalazide increases by a factor 1.2-fold, but the AUC is more significantly increased (4- to 9-fold) for the metabolites, including mesalamine. The AUC for balsalazide and metabolites after repeated dosing is 5% to 40% higher in females compared to males. The relative bioavailability in terms of AUC for tablets compared to capsules (Colazal) was 87% for balsalazide, 123% for mesalamine, and 93% for N-Ac-mesalamine. Accumulation degree was similar for tablets and capsules despite the different dosing frequency; the Reviewer felt that was consistent with the short half-file of balsalazide. A high fat diet significantly attenuated the rate of absorption of mesalamine and N-Ac-mesalamine. The Reviewer

recommended that administration of Giazo should take meals into account, but noted that Giazo was given without regard to food in the clinical studies.

No drug interactions studies were done; however, the Applicant has conducted *in vitro* interaction studies, as described in the current Colazal labeling, that showed balsalazide and its metabolites did not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

No QT assessments were submitted in the NDA.

The Reviewer found the clinical pharmacology information acceptable from a clinical pharmacology standpoint, but deferred labeling recommendations in light of the pending Approvable action for the original review cycle. No Phase 4 commitments were recommended.

6. Clinical Microbiology

This section does not apply because Giazo is not an antimicrobial agent.

7. Clinical/Statistical- Efficacy

The reader is referred to the Clinical Review by C. Leptak, dated 12/20/08, and the Statistical Review by S. Farr, (draft as of 12/19/08), for complete information.

MMDAI

The clinical studies in this application measured UC disease activity using the modified Mayo disease activity index (MMDAI). This index is a sum of four subscores based on stool frequency, rectal bleeding, mucosal appearance on endoscopy, and physician's rating of disease activity. Each subscore can range from 0 to 3 (with higher scores representing more severe disease), so the highest total possible MMDAI score is 12. See the Clinical Review for a more complete description of the MMDAI scoring system.

Clinical Data and Conclusions from the Previous Review Cycle

A single clinical study (BZUC3002, Study 2) was included at the time of the original NDA submission. A second clinical study (Study 3, see below) was submitted later and was not reviewed in the original cycle. Study 2 was a randomized, double-blind, placebo-controlled study of Giazo in mildly to moderately active UC. The study enrolled 250 patients from 55 U.S. centers. Patients were randomized 2:1 to Giazo 3.3g BID or placebo and treated for eight weeks. The primary endpoint was clinical improvement at eight weeks as defined by a 3-point improvement in MMDAI with an improvement in rectal bleeding score of at least 1 point. Primary endpoint efficacy results are shown below for the primary analysis and for subgroup analysis by gender (data adapted from previous cycle Team Leader Review):

Proportion of Patients with Clinical Response at Week 8 in Study 2

	Giazo 6.6 g/day % (# response/N)	Placebo % (# response/N)	Difference (Giazo – Asacol)	P-value
Total Population	**55%** (b) (4)	**40%** (b) (4)	**15%**	0.024
Males	**57%** (b) (4)	**20%** (b) (4)	**37%**	<0.001
Females	**54%** (b) (4)	**58%** (b) (4)	**-4%**	(b) (4)

Although the study found a statistically significant difference overall, there was a striking gender effect. Females appeared to do worse with Giazo than placebo, and there was a nominally statistically significant difference between treatment effects by gender (37% vs. -4%, nominal $p < 0.003$ by M-H Chi-square test for homogeneity).

In the analysis of secondary endpoints for the total population, the difference in clinical remission rate of 16% and the difference in mucosal healing rates of 20.5% were statistically significant, but the remaining results in the hierarchical testing procedure were considered exploratory due to a statistically non-significant finding for bowel frequency. In the analysis of secondary analysis by gender, males showed nominally statistically significant results for clinical remission, mucosal healing, bowel frequency, rectal bleeding, and complete remission, but females showed no nominally significant differences for any of those variables, and they had lower improvement rates on Giazo than on placebo for rectal bleeding and bowel frequency.

In the safety review of the original review cycle, 168 patients were treated with BD tables in the controlled study, and 130 patients (some the same) participated in an open-label extension study. Median exposure overall was 85.5 days. The Clinical Reviewer concluded that the safety assessment was adequate and that the safety profile of Giazo was similar to that of the approved capsule formulation of balsalazide disodium.

Current Submission: Phase 3 Study – BZUC3003 (Study 3)

The NDA resubmission contained the report of a randomized, double-blind, active-controlled study in patients with mildly to moderately active UC conducted at 79 U.S. centers. Patients were treated with Giazo or Asacol for six weeks and evaluated for clinical response.

Eligibility

To be eligible, patients needed to be adults with UC extending at least 20 cm from the rectum on screening endoscopy and with mildly to moderately active disease as determined by a modified Mayo disease activity index (MMDAI) score of 6 through 10. Patients were excluded for the following: recent failure to respond to balsalazide, creatinine > 1.5 times upper limit of normal, creatinine clearance ≤ 60 mL/min, liver enzyme or bilirubin elevation more than twice normal, history of major bowel surgery, other GI disease, significant medical conditions, or allergy to salicylates. Patients could not have received recent treatment with corticosteroids, immunosuppressants or immunosuppressive biologic agents. See the Clinical Review for additional details of the eligibility criteria.

Treatment

Patients were randomized with equal probability to oral dosing with either Giazo 3.3 g (three tablets) BID, for a total daily dose 6.6 g, or Asacol 0.8 g (two tablets) TID, for a total daily dose of 2.4 g. Treatment assignment was blinded with a double-dummy design using over-encapsulated Asacol tablets. Patients were instructed to take three tablets and two capsules in the morning, two capsules in the afternoon, and three tablets and two capsules in the evening. Treatment continued for six weeks. (The Asacol dosing of 0.8 g TID for six weeks is consistent with the labeled dosing recommendations for Asacol for active UC.) Concomitant therapy could not include immunosuppressants, alternative UC therapy, systemic or topical corticosteroids, diarrhea preparations, or intestinal regulators. NSAID therapy for more than one week was allowed only for low dose aspirin. Antibiotics were only allowed as a seven to 10 day course for conditions unrelated to UC. Anticoagulant therapy was not allowed due to safety concerns.

Assessments

Patients recorded stool frequency, presence of blood in stool, and UC symptoms in daily diaries. Office study visits were conducted at the ends of Weeks 1, 2, and 6. Laboratory testing was done at Weeks 2 and 6. A repeat endoscopy was scheduled at Week 6, and was optional at Week 2. MMDAI (excluding endoscopy score if endoscopy not done) was collected at all three visits. Patients who had worsening symptoms had an unscheduled visit involving endoscopy, if possible, and treatment was discontinued if the investigator considered the patient to have worsened. Patients who completed the study could receive continuing therapy with Giazo in an open-label extension if the site was participating; those who did not enroll in the extension had a follow-up visit at Week 8.

Endpoints and Analysis

The primary endpoint was clinical response as defined by a reduction of at least 3 points in MMDAI and a reduction of at least 1 point in the rectal bleeding score, based on the assessment at Week 6, or at end of treatment (EOT) if terminated early. The initial protocol specified that the primary analysis was to be done using the ITT population. This was changed to a per-protocol population in an amendment. (See the Statistical Review and Evaluation for a discussion of that and other protocol amendments.) The Applicant proposed to determine evidence of efficacy using a (b) (4) non-inferiority (NI) margin. A last observation carried forward (LOCF) rule was to be used for missing values.

Protocol-specified major secondary endpoints were: 1) clinical remission (rectal bleeding score of 0 and MMDAI ≤ 2 excluding endoscopy); 2) mucosal healing; 3) improvement in physician's assessment;, 4) improvement in rectal bleeding; 5) improvement in bowel frequency; and 6) complete remission (MMDAI ≤ 1). The secondary endpoint assessments all were based on status at Week 6/EOT in a (modified) ITT population, and they were to be analyzed in hierarchical order to control for multiplicity.

Results

A total of 410 patients from 79 centers were randomized in Study 3. The median age was 41 years, and 5% were 65 or older, proportion of males was 48%, and proportion Caucasian was 86%. Median duration of diagnosis was 5.4 years, and the fraction of newly diagnosed cases was 9%. The median baseline MMDAI was 8 points. Overall, 82% of patients completed

the study; the most common reason for early withdrawal in both treatment groups was lack of efficacy. The Applicant defined the "ITT" population as all patients who took at least one dose of study drug, who had MMDAI of 6 through 10 (per eligibility criteria), and who had baseline scores of at least 2 points for rectal bleeding and 2 points for endoscopy. This will be referred to as a modified ITT (mITT) population in this review. The Applicant defined the per-protocol (PP) population as those in the mITT population without major protocol deviations and with at least one post-baseline efficacy assessment. Of the 410 randomized, 400 were in the mITT population, and 351 were in the PP population.

The tables below present results adapted from tables in the Statistical Review:

Percentages of Patients with Clinical Response at Week 6/EOT in Study 3

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference (Giazo – Asacol) (95% C.I.)
Per-Protocol	**61.7%** (b) (4)	**60.8%** (b) (4)	**0.9%** (b) (4)
mITT	**56.3%** (b) (4)	**56.2%** (b) (4)	**0.1%** (b) (4)
All Randomized*	**53.3%** (b) (4)	**54.6%** (b) (4)	**-1%** (b) (4)

* Statistical Reviewer's analysis, all with all dropouts coded as failures.

Because the lower limit of the confidence interval in the PP population was greater than the designated NI margin of (b) (4) the Applicant concluded that the study showed Giazo was non-inferior to Asacol and thus provided evidence of efficacy of Giazo. (b) (4) . The Statistical Reviewer did not agree that the (b) (4) NI margin was justified by the publications and other arguments provided by the Applicant. From the placebo-controlled study used for the approval of Asacol, she determined that the NI margin should not exceed -3%. The Clinical Reviewer also reviewed the literature and concluded that only one study (Sninsky et al.) provided a suitable basis for determination of an NI margin consistent with the ICH 10 Guidance; the others were deemed unsuitable due to their differences from the study design of BZUC3003. From the Sninsky study it also was determined that the NI margin should be -3%. Therefore, the Reviewers concluded that the study in this submission did not support the non-inferiority of Giazo compared to Asacol.

The response rates by gender are shown in the following table (adapted from the Statistical Review):

Analysis of Efficacy by Gender, mITT Population

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference (Giazo – Asacol) (95% C.I.)
Males	**51%** (b) (4)	**49%** (b) (4)	**2%** (b) (4) (b) (4)
Females	(b) (4)		

Numerically, the response rates for each gender were similar for the two treatment arms. With the smaller sample sizes of these subgroups, the confidence intervals for the differences were wider that the one for the study overall, and the lower limits of the interval were (b) (4) This study did not include a placebo group that could directly address the question of the size of any treatment effect in women.

In other subgroup analyses, there were too few non-whites and too few patients over 65 years to provide meaningful conclusions about those subgroups. See the Statistical and Clinical Reviews for details.

For the secondary endpoints, the two treatment groups appeared numerically similar, and none of the differences in secondary endpoints was statistically significant using the mITT population.

Conclusions and Recommendations from the Current Review Cycle

The Statistical Reviewer found that the NI margin the Applicant chose was not appropriate, and that the additional study did not show clear evidence of efficacy. She concluded that the data in the resubmission did not present compelling evidence that Giazo is efficacious in patients with mildly to moderately active UC.

The Clinical Reviewer concluded that: 1) the Applicant's NI margin was inappropriate and the study did not achieve success using a more appropriate NI margin, 2) the gender discrepancy was not addressed because the study lacked a placebo group, 3) evidence from the approval of Colazal and published data did not help explain the gender discrepancy, and 4) the submission did not have the ability to provide adequate labeling guidance regarding differential efficacy between men and women. The Clinical Reviewer did not believe that the concerns of the previous review team were addressed adequately, and he recommended that a Complete Response regulatory action be taken.

8. Safety

In addition to the eight-week (Study 2) and six-week (Study 3) efficacy studies above, the Applicant conducted an open-label extension study, Study BZUC3005 (Study 5). Study 5 accepted patients who successfully completed Study 2 or Study 3. Patients were treated with Giazo 3.3 g BID, but dosing could be increased to 4.4 g BID at the investigator's discretion.

Visits were scheduled at Months 1 and 3, and every three months thereafter. Treatment duration could be up to two years.

The total safety data base in the submission was comprised of 565 patients treated with Giazo, of whom 430 had been exposed for more than eight weeks, 331 for at least six months, and 140 for at least a year.

There was one death in a 63-year old male diagnosed with malignant melanoma during the open-label extension study. The death was due to complications of brain lesions. There were 10 patients treated with Giazo who developed one or more SAEs, half of these patients had SAEs related to ulcerative colitis. A table of common adverse events is presented in the Clinical Review. In general, the type and frequency of AE were similar to those of other 5-ASA products, and, in the active-control study (Study 3), Giazo AEs were similar to those of Asacol, although there was a trend toward more UC symptoms and nausea than Asacol, but less abdominal pain and vomiting.

Conclusions

The Clinical Reviewer concluded that there were no new safety signals and that the overall safety profile of Giazo was similar to that of the approved capsule dosage form. He expressed some concern about finding more SAEs with Giazo than with Asacol (although the rates for both were less than for placebo). He noted that no thorough QT evaluation has been conducted for balsalazide disodium, but, based on current information, did not recommend that one be required for this product.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

Due to the low incidence of ulcerative colitis in pediatric patients below age 5 years, the Division has previously waived requirements for pediatric studies of ulcerative colitis treatment for that age group. The Division also has taken the position that there is sufficient similarity between adult and pediatric ulcerative colitis that efficacy in pediatrics can be extrapolated from adult findings, but that there is still a need for dose finding and for assessment of effectiveness and safety in pediatric populations.

The Applicant requested that the PREA requirement for pediatric studies be waived in full on the grounds that Giazo did not represent a meaningful benefit over existing available therapy for the pediatric population. The Applicant's other formulation of balsalazide disodium, Colazal capsules, is approved for treating active UC in pediatric patients ages 5 through 17 years. The capsule can be opened to sprinkle on food and represents a reasonable pediatric formulation.

The application was presented to the Pediatric Research Committee (PeRC) on October 29, 2008. The committee agreed with waiving requirements under the age of 12 years, but felt that the option of BID dosing (vs. TID with Colazal) should be available to the older pediatric patients who can take the tablet formulation. The committee deferred to the Review Team as to whether there was already adequate information to permit labeling for that age group, in which case a waiver could be granted, or whether additional studies (such as PK) would be needed, in which case pediatric studies should be a postmarketing requirement under PREA.

The Clinical Reviewer agreed with the PeRC recommendations. He proposed that, should Giazo be approved in a future review cycle, the Clinical Pharmacology staff be asked to determine whether PK studies of Giazo in the age range 12 through 17 years would be needed to support labeling for those pediatric patients.

11. Other Relevant Regulatory Issues

Standard of Evidence for Efficacy

Implicit in the statistical and clinical reviews from the initial review cycle is the sentiment that the results of Study 2 should meet the requirements of a single study for evidence of effectiveness as elaborated in section II.C.3 of the "Evidence Document" (*Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* 1998). That section demands that the study be statistically very persuasive with a "very low p-value" (conventionally viewed as being a p-value that provides a strength of evidence comparable to two studies with $p < 0.05$). This is also essentially the message conveyed to the Applicant at the pre-NDA meeting.

In contrast, this Reviewer feels that the appropriate standard is the one reflected in section II.C.2.a of the Evidence Document, in which related study data are taken into account and extraordinary statistical persuasiveness is not required. The Applicant's balsalazide capsule formulation (Colazal) is approved, the PK of Giazo and Colazal are similar (although not demonstrating similarity to a standard required for PK bioequivalence), but the relationship of blood concentration and response is not well understood. Thus, the conditions of II.C.2.a appear to be satisfied. In this Reviewer's mind, the lack of very low p-value is not a critical deficiency of Study 2.

However, the Evidence Document also states that "… reliance on a single study of a given use … leaves little room for study imperfections or contradictory (nonsupportive) information." The document further states that the need "… to otherwise know what needs to be known about a drug before it is marketed …" may result in basing an effectiveness determination on more than one study. To this Reviewer, the unexplained difference between genders in the treatment effect, accompanied by the unusually high placebo response rate in females, presents an important imperfection. The result runs contrary to that seen with approved 5-ASA products and remains unexplained. The gender difference is much more striking that the sorts of differences often seen in the face of the reduced sample sizes that accompany subgroup analyses: in Study 2 the gender difference was numerically large, clinically significant (a negative treatment effect in females vs. an almost tripling of

response rate in males), and associated with quite a small nominal p-value. Whether Giazo has efficacy for females, and what treatment effect can be expected for females, are facts that need to be known before Giazo is marketed. Therefore, this Reviewer is in agreement with the conclusion that Study 2 is insufficient for approval.

The Clinical Reviewer and Statistical Reviewer for the current review cycle concluded that Study 3 was not adequate to address the deficiencies cited in the May 2008 Approvable Letter. This Reviewer concurs with that conclusion. Because the results did not demonstrate non-inferiority to Asacol with a margin the Reviewers found supportable, it does not provide evidence of the efficacy of Giazo, and, as a corollary, is not able to address the question of efficacy in females. Even if it could have been argued that the results showed non-inferiority overall, the lack of a placebo control would have made it extremely difficult to make reliable inferences regarding the difference in the treatment effect between genders. The clearest course to resolving the deficiencies in the application would be to conduct an additional placebo-controlled study that is adequately powered to confirm or refute the previous finding of a differential treatment effect between the genders.

Length of the Efficacy Studies

In recent years the Division has been advising sponsors of drug products to treat UC at End-of-Phase-2 (EOP2) meetings that, in addition to investigating efficacy for induction of response or remission, they should propose and evaluate treatment strategies for how the product is to be used in the chronic management of UC (such as re-induction for flare or chronic maintenance therapy for prevention of relapse), and they should evaluate that use in pivotal studies in ulcerative colitis for a duration of one year. At the time that the EOP2 meeting was held for this product (August 2005), the Division agreed that efficacy studies only of induction would be adequate for an NDA. Because there is no new substantial scientific issue essential to determining the safety or effectiveness of the drug that would require concluding that agreement is not acceptable, the agreement at the EOP2 meeting should stand. The length of the pivotal efficacy studies should not be an issue in the approval decision for this particular application.

Given that safety data for chronic treatment with Giazo were collected on over 300 patients for at least six months and over 100 patients beyond one year, there is a reasonable chronic safety database and an adequate basis to state the risks of chronic use appear to be similar to those of 5-ASA products that are approved for chronic use in UC. There are no grounds to require a specific warning against such use. However, it would be appropriate for the labeling to include an explicit statement concerning the limitations of the clinical trials on which the approval is based. Similar to what the Applicant already proposed in labeling, this Reviewer recommends that such information appear in the Clinical Studies section of the labeling and be reflected in the recommendations in the Dosage and Administration section.

Lack of QT Evaluation

There was no thorough QT assessment for this product, and the clinical studies did not incorporate collection of ECG data. Mesalamine products have been approved and marketed since 1987, and balsalazide has been marketed since 2000. Preclinical studies have not pointed to any problems with QT prolongation due to mesalamine or balsalazide, and postmarketing experience with balsalazide and mesalamine products have not identified a

concern regarding QT prolongation. This Reviewer concurs with the Clinical Reviewer's recommendation that QT evaluation need not be required for approval of this application.

Division of Scientific Investigations (DSI) audits
Clinical site inspections for Study 3 were conducted at Littleton, CO (Dr. R. N. Hansen), and Anderson, IN (Dr. T. V. Nowak). Minor documentation and protocol deviations were found at the Littleton site and no violations were found at the Anderson site. The interim classification memo from DSI by K. Malek, dated 12/10/08, concluded that the data from both inspected sites can be used in support of the NDA. The final DSI classifications are pending as of the date of this CDTL Review.

12. Labeling

Proprietary name
From the initial review cycle review by D. Smith, dated 5/20/08, the Division of Medication Error Prevention and Analysis (DMEPA) objected to the proposed trade name of "Giazo" on the grounds that it represented a dual trade name. DMEPA believed that the different strengths and dosing frequencies could be managed under one proprietary name.

In the resubmission, the Applicant provided the results of a Failure Mode Effect Analysis and presented arguments to justify use of the trade name "Giazo." The final DMEPA recommendations are pending as of the date of this CDTL Review.

Labeling issues
Given that an Approval action is not being planned for this review cycle and there were no labeling negotiations with the Applicant, considerations regarding specific labeling issues are being deferred until the application is otherwise approvable. No DDMAC comments have been provided on labeling. The reviewers did not recommend that the product needed patient labeling or a Medication Guide.

In an amendment dated September 19, 2008, the Applicant submitted the proposed container label for the professional sample bottle. That submission was not reviewed in this cycle in light of the anticipated Complete Response action.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
The recommended action is Complete Response (CR). The CMC, Pharmacology, and Clinical Pharmacology Reviewers recommended this NDA for approval in the initial review cycle, and those recommendations have not changed. However, the Statistical Reviewer and Clinical Reviewer for the current review cycle recommend a CR action, because they concluded that the Applicant's Complete Response submission did not adequately address the clinical and statistical deficiencies cited in the 5/18/08 Approvable Letter. There is no conflict in the various discipline recommendations because the concerns raised in the statistical and clinical reviews are issues specific to those two disciplines. This Reviewer

concurs with taking a CR action stating that the deficiencies previously identified have not be resolved adequately by the Applicant's Complete Response resubmission.

At the time of this CDTL Review, DMEPA has not provided a final determination regarding the acceptability of the proposed trade name, Giazo. Also, the DSI memo regarding audits of the clinical sites reflects interim, not final, classifications. Nevertheless, this Reviewer recommends proceeding with a CR action. Because this is not an Approval action, even a currently acceptable name could be subject to rejection in a subsequent review cycle; and if "Giazo" is determined to be unacceptable shortly after the CR Letter is issued, that fact could be conveyed in a subsequent Discipline Review Letter. Because Study 3 was not considered to provide evidence of efficacy, a change in DSI's classification of the study sites would not affect the conclusions about Study 3 that lead to a CR action. It would be best practice to identify any serious study site deficiencies in the CR Letter, but given that the chances appear to be remote that there would be a change in the final DSI classification, and given that the currently identified deficiencies and recommended action would not be altered by a change in DSI classification, it would be reasonable under the circumstances not to delay the action only for a final DSI classification.

Risk Benefit Assessment

The risk characteristics for Giazo for treating UC appear similar to those of the already approved and marketed oral balsalazide product (Colazal). The outstanding benefit issue with this application is the significant uncertainty about the effectiveness of this product for female UC patients, and the difficulty in providing adequate instructions for use until that uncertainly is resolved.

Recommendation for Postmarketing Risk Management Activities

No special postmarketing risk management activities are recommended for this Application.

Recommendation for other Postmarketing Study Commitments or Requirements

None of the primary review disciplines had recommendations for additional postmarketing commitments or requirements. As discussed above in section 10, Pediatrics, if this application is approved in a future review cycle, a PK study in pediatric patients ages 12 through 17 might become a requirement if it is determined that such a study is needed to support pediatric labeling for that age range.

There are several unanswered questions regarding balsalazide disodium due to the Phase 4 commitments for Colazal (NDA 20-610) that remain outstanding eight years after its initial approval. This Reviewer recommends that, if Giazo is approved in a future review cycle, any of the Phase 4 commitments for Colazal outstanding at that time should also be made Phase 4 commitments for Giazo, and specific timelines should be added to those commitments.

Given the role of intestinal flora in the production of the active metabolite, mesalamine, this Reviewer feels the Applicant should be asked to evaluate the potential for a drug-drug interaction with antibiotics, namely, whether concurrent antibiotic therapy interferes with mesalamine release, which might diminish the treatment effect. Should Giazo come to approval, this Reviewer recommends that the Division negotiate a Phase 4 commitment to investigate the potential for antibiotics to interfere with the action of balsalazide. This might take the form of a PK study to assess the effect of concurrent antibiotics on the

pharmacokinetics of balsalazide and its metabolites. In the meantime, this Reviewer proposes that a comment be sent to the Applicant recommending the Applicant plan to investigate such a drug-drug interaction.

Recommended Comments to Applicant

The CMC Reviewer's comment regarding the format of the label should be sent to the Applicant.

A comment should be sent recommending the Applicant investigate the potential for antibiotics to interfere with balsalazide metabolism.

DMEPA's decision regarding the trade name "Giazo" should be communicated to the Applicant once DMEPA's review is finalized.

Because it anticipated that the trade name determination will not be made until after the Division takes an action on this resubmission, the trade name decision and the other comments can be sent in a separate Discipline Review Letter following the issuance of the Complete Response letter.

The comments to the Applicant should be substantially similar to the following:

Carton and Container Labels

1. Revise the format of the nomenclature in the labels as follows:

Giazo [or replaced by "Trade Name," if Giazo is not acceptable]
(balsalazide disodium) tablets
1.1 g

Drug-drug Interactions

2. Because the action of balsalazide disodium is assumed to be dependent on the release of mesalamine through the action of intestinal flora, it will be important to understand what impact concomitant systemic antibiotic therapy could have on the effectiveness of your product, and to provide that information in labeling. We ask that you make plans to conduct drug-drug interaction studies to investigate this issue, and we recommend that you present a proposal to us for consideration and discussion.

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/s/

John Hyde
12/21/2008 04:36:55 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	Complete Response Resubmission
Submission Number	NDA 22-205
Submission Code	N-000
Letter Date	June 30, 2008
Stamp Date	June 30, 2008
PDUFA Goal Date	December 31, 2008
Reviewer Name	Christopher Leptak, M.D., Ph. D.
Review Completion Date	December 20, 2008
Established Name	Balsalazide Disodium
(Proposed) Trade Name	Giazo
Therapeutic Class	Locally-Acting Aminosalicylate (Anti-inflammatory)
Applicant	Salix Pharmaceuticals, Inc.
Priority Designation	Standard
Formulation	Tablet (1.1g)
Dosing Regimen	3.3g BID
Indication	Mildly to moderately active ulcerative colitis
Intended Population	18 years of age and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that a Complete Response regulatory action be taken on the Applicant's resubmission of marketing application (NDA 22-205) for balsalazide disodium (BD) tablets intended for use in mildly to moderately active ulcerative colitis (UC).

For the original submission, the review team concluded that the Applicant's single placebo-controlled study, BZUC3002, was inadequate to support effectiveness of BD tablets and an Approvable action was taken. BZUC3002 failed to demonstrate a statistically persuasive finding of treatment effect and lacked consistency of treatment effect between men and women, subpopulations that were equally represented in the study. The observed superiority of BD tablets over placebo was driven by a subpopulation's finding, namely, male patients. A substantial therapeutic gain was demonstrated among men (37%), but none among women (-4%). Since therapeutic effect in women was indeterminate secondary to the unexplained high placebo response rate in this subgroup, efficacy of BD tablets was not established in female patients. In the Executive Summary of her clinical review dated 4 April, 2008, Dr. Fathia Gibril recommended that the issuance of a future approval be dependent upon the review of additional efficacy data from an adequate and well-controlled study that would demonstrate substantial evidence of effectiveness and consistent finding across important subgroups, namely, males and females.

After review of BZUC3003, a non-inferiority trial and the only study included for review in this resubmission application, this reviewer does not believe that the concerns of the previous review team have been adequately addressed. In summary, the following deficiencies were found: 1) the non-inferiority (NI) margin of success chosen by the Applicant was not appropriate and the study did not achieve success when a more representative NI margin was employed, 2) the lack of a placebo arm in the study did not address the gender response discrepancy found in BZUC3002, 3) additional evidence from the published literature and from the approval of Colazal, a capsule formulation of BD marketed by the Applicant, did not resolve the unexpected outcome of differential treatment response between men and women, and 4) the inability to provide adequate labeling guidance to the medical community regarding the observed differential efficacy between men and women with ulcerative colitis.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Should this NDA be approved in the future, an assessment of appropriate risk management would need to take into account updated information at that time. At present, given the low frequency of serious adverse events and the lack of specific active safety concerns, this reviewer

does not recommend a risk management plan for balsalazide disodium for the treatment of adult patients with mildly to moderately active UC.

1.2.2 Required Phase 4 Commitments

The Sponsor requested waiver for pediatric studies required under the Pediatric Research Equity Act (PREA). On 29 October, 2008, this recommendation for full waiver of pediatric studies with the BD tablet formulation was presented before the PERC committee. The outcome of the discussion was: 1) full waiver of studies for pediatric UC patients under 12 years of age, 2) should the product be approved, the label should include information for adolescent UC patients between 12 and 17 years of age, and 3) the Division has the discretion to determine if additional studies are required to adequately label BD for this adolescent UC patient population.

1.2.3 Other Phase 4 Requests

Unless there is consensus that additional pediatric studies are needed to label BD for use in adolescent patients with UC, this reviewer does not recommend any additional Phase 4 commitments for this NDA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In support of the proposed indication for use in ulcerative colitis patients, the sponsor previously submitted the results from a single Phase 3, double-blind, randomized, multi-center, parallel-group, placebo-controlled study (BZUC3002) that was conducted in the US. Eligible patients (n=250) were randomized to receive either BD tablets or placebo in a 2:1 ratio for eight weeks. As part of this resubmission of NDA 22-205, a second clinical trial is submitted for review. BZUC3003 is a Phase 3, double-blind, double-dummy, randomized, multi-center, active-controlled study conducted in the US. Eligible patients were randomized 1:1 to receive either BD tablets or Asacol, an approved mesalamine drug product used as the active comparator, for six weeks.

1.3.2 Efficacy

The efficacy of BD tablets was evaluated in a two Phase 3 clinical trials. BZUC3002 was a placebo-controlled, eight-week evaluation of BD tablets in patients with mildly to moderately active UC and was reviewed during the first submission of NDA 22-205. BZUC3003 was a six-week evaluation comparing BD tablets to Asacol as an active comparator in an analogous patient population and was reviewed as part of this Complete Response resubmission.

For both studies, efficacy was assessed using the Modified Mayo Disease Activity Index (MMDAI) which has a maximum total score of 12. The MMDAI evaluated four indices (stool

frequency, rectal bleeding, physician's global assessment [PGA], and endoscopic findings; See Section 6.1.2 Figure 1) each on a scale from 0 to 3, with 3 being severe disease. A daily diary was kept by patients to record stool frequency, rectal bleeding, and other symptoms. End of treatment (EOT) assessments occurred if a patient did not complete the study regardless of reason. A complete MMDAI score was calculated at screening/baseline in both clincial studies; final MMDAI assessments occurred at Week 8/EOT for BZUC3002 and at Week 6/EOT for BZUC3003.

For both studies, the pre-specified primary efficacy endpoint was the proportion of subjects who achieved clinical improvement and improvement in rectal bleeding (RB) by the end of the clinical trial. Clinical improvement was defined as a ≥ 1 point improvement in the total MMDAI score, and improvement in RB was defined as a ≥ 1 point improvement in the RB sub-score component.

Efficacy Results for BZUC3003

All efficacy analyses were performed using the Per Protocol (PP) population, which consisted of all patients included in the ITT population who did not have a major protocol deviation and who had at least one post-baseline primary efficacy assessment. The intent-to-treat (ITT) population served as a sensitivity assessment, although the original ITT definition was amended after initiation of the clinical trial. The original definition was conventional and consisted of all randomized subjects who received at least one dose of study drug; the amended ITT definition restricted the population to those that met the MMDAI inclusion criteria.

For Study BZUC3003, 400 (97.6%) of the total 410 study patients randomized were included in the ITT population. A total of 351 (85.6%) patients were included in the PP population. Overall, both the reasons for exclusion and the percentage of patients not included in a given population were comparable between the two study treatment cohorts. The change in the ITT definition and by association, the PP definition as well, raises concerns regarding assessment of the study's success. In addition, concerns are also raised with respect to the study's conduct in general as the amended definition draws attention to the fact that patients who did not meet the inclusion criteria were enrolled and received study drug.

<u>Primary Endpoint Analysis</u>
The proportion of subjects in the PP population who achieved clinical improvement and improvement in rectal bleeding at Week 6/EOT was similar for the BD cohort (61.7%) and the Asacol cohort (60.8%). The difference in the proportions of the patients who achieved this primary endpoint was 0.85%, allowing the lower bound of the 95% confidence interval for the treatment difference to be greater than the pre-specified, non-inferiority margin (NI) of (b) (4) (95% CI: (b) (4) From these results, the Applicant concluded that balsalazide disodium tablets were not inferior to the active comparator Asacol. As a sensitivity assessment, a similar analysis was conducted on the amended ITT population; results for the two treatment cohorts were again similar with 56.3% of the BD- and 56.2% of the Asacol-treated patients achieving both clinical improvement and improvement in rectal bleeding. The non-inferiority analysis for the amended ITT population also led the Applicant to conclude that balsalazide disodium tablets were not inferior to Asacol (0.13%; 95% CI: (b) (4)

However, upon review of both the literature submitted by the Applicant as well as applicable placebo-controlled studies with Asacol, a NI margin of less than 3% was calculated to be more appropriate, making the comparison of therapeutic effect between BD and Asacol indeterminate and non-supportive (b) (4)

1.3.3 Safety

Safety data were submitted and analyzed from three sources: BZUC3002 (reviewed as part of the original submission) and BZUC3003 (reviewed as part of this Complete Response resubmission) were two Phase 3 studies and BZUC3005 is an ongoing, open-label, safety study of patients who previously participated in BZUC3002 and BZUC3003.

For BZUC3002, of the 250 randomized patients, 247 were included in the safety population: 168 (99.4%) patients in the BD tablet group and 79 (97.5%) patients in the placebo group. Two patients in the placebo group and one patient in the BD tablet group did not have a post-baseline safety assessment and were excluded from the safety population. Of a total of 410 patients randomized in BZUC3003, 408 patients were included in the safety population analysis: 210 (99%) patients in the BD-treatment group and 198 (100%) patients in the Asacol-treatment group. Two patients randomized to the BD cohort, received study drug, but had no post-baseline safety assessment and were excluded from the safety population. A total of 565 unique patients received BD tablets either as a result of randomization to a BD cohort in one of the Phase 3 studies or as open-label treatment in the ongoing safety study BZUC3005; the analysis of this pooled data constituted the comprehensive safety population.

Regarding deaths, none occurred during conduct of BZUC3002 or BZUC3003. One patient enrolled in BZUC3005 died of metastatic malignant melanoma and was determined to be unlikely related to BD drug treatment.

Serious adverse events (SAEs) were reported in 5% of the comprehensive safety population. Worsening UC was the only SAE reported by >1% of patients and occurred at a frequency of 2% of the total patients exposed to BD treatment. In a comparison of the SAEs reported for BZUC3002 and BZUC3003 by treatment arm, both more types of SAEs and greater numbers of patients experienced an SAE in association with BD treatment compared to treatment with Asacol. The one exception was for the preferred term arthritis (one patient treated with Asacol and none treated with BD). The most frequent AE leading to discontinuation from BD therapy was worsening UC for all treatment arms in all studies (5% of BD-treated patients, 2% of Asacol-treated patients, and 11% of placebo-treated patients).

Comparing adverse events (AEs) in the treatment arms of the two Phase 3 studies, the proportion of patients reporting at least one AE were similar between the BD-treated (59%) and Asacol-treated (55%) cohorts, but higher in the placebo-treated (70%) patients. Overall, events related to gastrointestinal (GI) disorder were the most frequently reported AE (29% of BD-, 25% of Asacol-, and 38% of placebo-treated patients) for those events occurring in more than 2% of total patients. Worsening of UC was the most common GI-related event in all treatment cohorts (7% of BD-, 2% of Asacol-, and 15% of placebo-treated patients). The only GI events that occurred in ≥ 2% of patients in the BD-treated group and not in the placebo-treated group were abdominal

distension (2%), flatulence (2%), and hemorrhoids (< 1%). Outside of GI-associated disorders, headache was the most commonly reported AE with a frequency of 8% in BD-, 10% in Asacol-, and 14% of placebo-treated patients. There were no clinically meaningful changes in laboratory parameters or vital signs in the Phase 3 studies. The interim report from an ongoing long-term, open-label, safety extension study (BZUC3005) including 443 patients showed a similar safety profile compared to the two Phase 3 studies. For the comprehensive safety population, the most frequent AEs were worsening UC (10%) and abdominal pain (4%).

Overall, for the double-blind studies, the proportion of patients who experienced drug-related TEAEs was comparable across the treatment groups (10% of BD-treated patients, 11% of Asacol-treated patients, and 9% of placebo-treated patients) as shown in Table 32. Drug-related AEs that occurred in >1% of BD-treated were worsening UC (1% BD-, 0% Asacol-, and 3% placebo-treated patients), diarrhea (1% BD-, 2% Asacol-, and 1% placebo-treated patients), nausea (3% BD-, 4% Asacol-, and 0% placebo-treated patients), and headache (1% BD-, 3% Asacol-, and 1% placebo-treated patients).

Of note, a thorough QT study was not completed for either the BD capsule or tablet formulations. This reviewer does not recommend such a study be completed at this time for the following reasons. As a class of compounds, the 5-ASA drugs have been marketed for 16 years without any known cardiac toxicity risks identified to date. In addition, the bioavailability of BD is very small given that most of the drug and its metabolites remain in the gut with only a small fraction systemically absorbed. Should a cardiac signal emerge in the future, a thorough QT study could be considered at that time.

The overall safety profile of the tablet formulation is comparable to the approved capsule formulation Colazal, including data available from post-marketing reports. However, based upon the cumulative data from the clinical development program, there is concern that 5% of the comprehensive safety population reported at least one SAE and that both more types of SAEs and greater numbers of patients experienced an SAE in the BD-treated patients compared to those treated with Asacol. In addition, more BD-treated (5%) patients withdrew from the studies because of worsening UC compared to Asacol (2%). Finally, regarding the Applicant's proposed warning of use in patients with hepatic impairment, six patients treated with BD had transient transaminase elevations without evidence of irreversible liver damage.

1.3.4 Dosing Regimen and Administration

The recommended total daily dose is 6.6g to be taken in two divided doses (three 1.1g tablets BID) for up to 8 weeks.

It should be noted that no separate dose-response trial was conducted with the new BD tablet formulation. The rationale was that the proposed total daily dose (6.6g/day) for new tablet formulation is similar to that of the capsule formulation (6.75g/day), Colazal, which was approved in July 18, 2000 for the same indication. The goal of the clinical program was to offer patients with a more convenient daily dosing regimen with the new tablet formulation (BID vs TID).

1.3.5 Drug-Drug Interactions

Drug interaction studies have not been conducted with BD tablets. Given that there are no known drug interactions with mesalamine drug or pro-drug formulations, this reviewer does not foresee potential complications arising from drug-drug interactions with BD tablets. The local action of the drug and limited systemic absorption reduces the likelihood of significant hepatic or blood-associated drug interactions with other compounds that act through systemic mechanisms. Of note, as stated in the Colazal label, an *in vitro* study using human liver microsomes demonstrated that balsalazide and its metabolites (5-ASA, N-Ac-5-ASA, 4-ABA, and N-Ac-4-ABA) were not shown to inhibit the major CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) evaluated. Therefore, balsalazide and its metabolites are not expected to inhibit the metabolism of other drugs that are substrates for these CYP enzymes.

As a pro-drug that requires metabolism by gut flora to release mesalamine, medications that alter the composition of intestinal bacteria could affect, in theory, the activity of BD treatment. To date, patients enrolled in BZUC3002, BZUC3003, and BZUC3005 had very limited concomitant exposure to antibiotics during the clincial trials. This theoretical concern remains unanswered at this time.

1.3.6 Special Populations

Gender disparity in treatment effect was one of the deficiencies identified in the original review cycle. In the Applicant's Complete Response resubmission, the new study BZUC3003 failed to show non-inferiority to Asacol when a more appropriate NI margin was used, making a sub-analysis by gender noncontributory. In addition, BZUC3003 failed to address the observed large placebo-response rate in women enrolled in BZUC3002; BZUC3003 was a NI study design without a placebo arm for comparison. Unless the issue of gender disparity can be resolved, this reviewer agrees with the concerns of Dr. Gibril that the observed superiority of BD tablets over placebo in BDUC3002 was driven by a sub-population's finding, namely, male patients. Conversely, the efficacy of BD tablets has not been established in women. This gender disparity in treatment effect needs to be adequately addressed before the future approval of BD tablets.

Regarding other special populations, all the patients enrolled in BZUC3002 and BZUC3003 were adults with evidence of active UC disease. Safety and effectiveness of BD tables in the pediatric UC population have not been studied. There have been no studies with BD tablets in patients with renal or hepatic impairment. Pregnant women and nursing mothers were excluded from clinical trials with BD tablets. The clinical program did not include sufficient number of patients aged 65 and older (<10%) to determine whether they respond differently than younger patients. The majority of the patients were Caucasian (BZUC3002 83% and BZUC3003 86%) limiting the ability to study potential differences in safety and effectiveness among different racial groups. Like the capsule formulation of BD, Pregnancy Class B has been recommended for the tablet formulation with no impaired fertility or harm to the fetus noted in both rat and rabbit studies; excretion of BD in breast milk is not known.

2 INTRODUCTION AND BACKGROUND

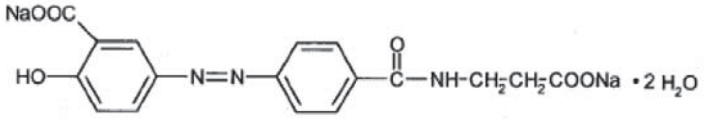
2.1 Product Information

In the current NDA 22-205 submission, the sponsor seeks approval for BD tablet (1.1 g) for use in mildly to moderately active UC at a total daily dose of 6.6 g to be administered BID (three tablets BID) for up to eight weeks.

Proposed Trade Name: Giazo
Generic Name: balsalazide disodium
Code Name: BD
Drug Form: Pro-drug
Released Active Drug Product: 1.1g of BD is enzymatically cleaved in the colon to produce mesalamine (5-aminosalicylic acid, also referred to as 5-ASA), an anti-inflammatory drug. Each tablet of BD, upon enzymatic breakdown, yields (b) (4) of mesalamine.

Chemical Name: (E)-5-[[-4-[[(2-carboxyethyl) amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate.

Structural formula:



Therapeutic Class: Anti-inflammatory
Formulation: Tablet

The exact mechanism of action of mesalamine is not fully understood, but appears to be local in the colon rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by inhibiting cyclooxygenase and lipooxygenase activity as well as prostaglandin production in the colon.

Subsequent information has shown that there are no (b) (4) in the formulation, suggesting that the potential safety concern which may be associated with these compounds is not an issue for BD tablets.

2.2 Currently Available Treatment for the Indication

The following oral mesalamine or mesalamine pro-drug preparations are currently marketed in the US for use UC medical management. The dosages and indications are listed below:

- Lialda (1.2 g tablet) at a total daily dose of 2.4 g or 4.8 g once daily. Induction of remission in mildly to moderately active UC.
- Colazal (750 mg capsule) at a total daily dose of 6.75 g in three divided doses. Treatment of mildly to moderately active UC.
- Asacol (400 mg tablet) at a total daily dose of 2.4 g in three divided doses. Treatment of mildly to moderately active UC and maintenance of remission.
- Pentasa (250 mg or 500 mg capsule) at a total daily dose of 4 g in four divided doses. Treatment of mildly to moderately active UC and induction of remission.
- Sulfasalazine (500 mg tablet) at a total daily dose of 3 g in three divided doses. Treatment of mildly to moderately active UC.
- Dipentum (250 mg capsule) at a total daily dose of 1 g in two divided doses. Maintenance of remission in UC patients intolerant to sulfasalazine.
- "Asacol 800" and Apriso have been recently approved as well.

In additional to the oral mesalamine class of agents, other approved products for the treatment of UC include oral and systemic steroids and Remicade, a biologic TNF blocker. Although approved for other disease indications, other immunosuppressants including (b) (4) (b) (4) are widely used off-label for the treatment of UC.

2.3 Availability of Proposed Active Ingredient in the United States

Balsalazide disodium is the active ingredient of Colazal, a capsule formulation of BD. Colazal is marketed in the US for the treatment of mildly to moderately active UC in patients aged five years and older. There are no known concerns of limited product availability.

2.4 Important Issues With Pharmacologically Related Products

The BD pro-drug is enzymatically cleaved to produce mesalamine, the active ingredient and a member of the 5-ASA class. Therefore, BD is contraindicated in patients with a hypersensitivity to salicylates. Patients with pyloric stenosis may have prolonged gastric retention of BD tablets, reducing the efficacy of the product as the pro-drug requires delivery to the colon where it is locally active.

Renal toxicity has been observed in animals and patients given mesalamine or pro-drugs that are converted to mesalamine; caution should be exercised when administering BD to patients with known renal dysfunction or a history of renal disease. Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease; symptoms include cramping, acute abdominal pain, and bloody diarrhea,

sometimes in association with fever, headache, or rash. Mesalamine has also been associated with reports of hepatic failure in patients with pre-existing liver disease.

2.5 Pre-submission Regulatory Activity

Reference to meetings between the Agency and Applicant are filed under IND 38,492 for BD. Pertinent discussions and agreements are summarized below:

End of Phase 2 Meeting (8 August, 2005) Clinical Discussion Summary:

1) Per the Applicant's intent to submit a single study in support of approval of BD for the treatment of mildly or moderately active UC in adult patients, the Agency clarified that approvability would be based on robustness of the data and consistency of effect seen in primary and secondary endpoints.
2) Regarding the proposed dosing regimen, the Agency shared that treatment with 3.3 g BID appeared acceptable as long as adequate safety and efficacy can be demonstrated using this new dose and dosing regimen.
3) Regarding study length, the Agency recommended treatment duration of eight weeks, (b) (4) The Agency emphasized that it would be difficult to compare the results of shorter duration clinical trials with the outcomes that led to the finding of safety and efficacy for Colazal capsules.
4) For the proposed placebo-controlled study (later to become BZUC3002), in addition to the use of a placebo control, the Agency recommended adding a third treatment arm as an active, approved comparator.
5) If a non-inferiority study were to be conducted and Asacol be used as the active comparator (later to become BZUC3003), the Agency emphasized that the Applicant needed to clarify the study design and the dose regimen to be used.

Pre-NDA Meeting (27 April, 2007) Clinical Discussion Summary:

1) The Agency reemphasized that submission of a single clinical trial in support of approval would require that the study be statistically robust and that the data show consistency of effect seen in primary and secondary endpoints.
2) The Agency agreed to the proposed scope of the safety database.
3) The Agency asked for clarification if BZUC3003 was to be completed and submitted as part of the data to support NDA 22-205.
4) The Agency indicated that a full submission of BZUC3005 safety data was required.
5) The Agency requested the CRFs for all patients who discontinued study participation for any reason.

Approvable Action for Initial Submission of NDA 22-205 (16 May, 2008):

As stated in the Approvable Letter, before the application may be approved, the Applicant needed to resolve the following issues:

> "Your placebo-controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study."
>
> "The issuance of an approval is dependent upon the review of an additional adequate and well-controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis."

Post-Approvable Action Meeting with Applicant (9 June, 2008):

1) The submission of BZUC3003 was agreed upon to constitute a Complete Response to the Approvable action.
2) The Agency reiterated that gender subgroup data would not be interpreted in a confirmatory manner, but should be consistent with results based on the entire study population.
3) The Agency is interested in the derivation and justification for the Applicant's NI margin and that adequacy of the margin will be a review concern.
4) An integrated safety update is required for resubmission and a new 120-Day Safety Update would be expected as well.
5) The Agency stressed that the safest way to minimize medication errors is to manage both BD formulations under one proprietary name, Colazal.
6) The Applicant will submit updated stability data with the resubmission.

2.6 Other Relevant Background Information

BD tablets are not marketed in any country. Colazal, the capsule formulation, was approved in the U.S. on 18 July, 2000, for the treatment of mildly to moderately active ulcerative colitis (UC) in patients 18 years of age and older. In December 2006, the indication was expanded to include use in children 5 to 17 years of age for the same indication. The label states that safety and effectiveness of balsalazide beyond 8 weeks in children (ages 5 to 17 years) and 12 weeks in adults have not been established.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review staff for the initial submission of NDA 22-205 made the following conclusions and recommendations: 1) the NDA provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product; 2) all facilities involved are in compliance with cGMP; and 3) a recommendation of approval pending some graphic and formatting changes to the label. For this resubmission of NDA 22-205, updated stability data was submitted for review; the CMC review by Maria Ysern concluded that the Applicant provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, and all facilities involved are in compliance with cGMP. Expiration dating was determined to be 36 months. An approval regulatory action was recommended from a CMC standpoint. Should BD tablets be approved in the future, the format of the labeling nomenclature needs to be revised as noted in the original CMC review.

3.2 Animal Pharmacology/Toxicology

No new animal studies were conducted under NDA 22-205. The conclusions and recommendations from the Pharmacology/Toxicology review staff for the initial submission of NDA 22-205 were as follows:

1. From a preclinical standpoint, an approval action was recommended.
2. Labeling recommendations suggesting caution in use in patients with known renal function or a history of renal disease. This concern was based on an observed increased incidence of pelvic and corticomedullary mineralization in kidney and urothelial hyperplasia in rats at oral doses approximately 0.7 fold the recommended human dose based on body surface area.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The studies were submitted as the primary sources of clinical efficacy and safety data for NDA 22-205. The first was a single placebo-controlled study (BZUC3002) conducted by the Applicant in the U.S. and included in the initial submission of this NDA. The second was a non-inferiority study (BZUC3003) conducted by the Applicant in the U.S. and submitted for review with this resubmission Complete Response. Both studies were submitted as a paper version in the Common Technical Document format (CTD).

4.2 Tables of Clinical Studies

Table 1: Summary of Clinical Studies

Study ID	Number of Study Centers and Locations	Design	Study Drug Dose, Regimen, and Route	Study Objectives	No. of Patients by Arm:	Duration of Treatment
BZUC3002	55 Centers All U.S.	Multi-center, Randomized, Double-blind, placebo-controlled, parallel-group	BD 3.3 g (1.1 g X 3) BID Oral	Primary: Evaluate the safety and efficacy of BD in patients with active UC	Placebo: 83 BD: 167 (n = 250)	8 weeks
BZUC3003	79 Centers All U.S.	Randomized, Double-blind, Double-dummy, active-controlled, parallel-group	BD: 3.3 g BID Asacol: 0.8 g TID Both Oral	Primary: Evaluate the safety and efficacy of BD in patients with active UC	BD: 212 Asacol: 198 (n= 410)	6 weeks
BZUC3005	All U.S.	Multi-center, open-label	BD: 3.3 g BID or 4.4 g BID Oral	Long-term safety and tolerability of BD	Goal 500 443 Enrolled at time of submission	2 year minimum

4.3 Review Strategy

The Applicant resubmitted NDA 22-205 in the CTD format as a paper version. In this resubmission Complete Response, efficacy and safety data of BD tablets were submitted for BZUC3003, a Phase 3 non-inferiority trial with Asacol as the active-comparator. The reviewer thoroughly reviewed this additional clinical study with equal regard to safety and efficacy and placed the findings and conclusions within the context of BZUC3002, the Phase 3 placebo-controlled study submitted for review with the initial submission of NDA 22-205. In addition, an interim safety report for an open-label, safety and tolerability extension study (BZUC3005) was submitted in this application and was reviewed as part of the integrated safety assessment.

The reviewer approached this submission first by focusing upon the concerns of the previous review team. Namely, 1) did the Applicant's new study adequately address the lack of statistical robustness which prevented product approval based upon the single clinical trial BZUC3002 and 2) did the Applicant provide adequate evidence and rationale to explain the observed gender discrepancy in treatment effect found in BZUC3002, thereby allowing for appropriate labeling of the product?

Within the context of these concerns, this reviewer evaluated BZUC3003 to determine to what extent this study addressed the previously identified deficiencies and provided support to the Applicant's claim and request for approval. The protocol was examined first, and then the study report was assessed for efficacy and safety. The reviewer's final judgment on safety and efficacy for the proposed indication was based on whether the stated primary objective of efficacy was achieved and if the safety profile of the drug was appropriately determined and described. Furthermore, additional information was sought from published clinical literature relevant to the proposed drug product and medical condition being treated. Finally, the data submitted in support of the approval of Colazal were examined and put into context with the findings from BZUC3002 and BZUC3003.

4.4 Data Quality and Integrity

The Division of Scientific Investigation (DSI) was consulted for this NDA and its two primary clinical studies.

Inspected during the previous review cycle, BZUC3002 was conducted at 55 centers in the US. Three sites (# 216, #547, and #675) were inspected and the DSI audit report was finalized on 3 April, 2008. The report audit concluded that although there were some violations at study sites 216 and 547, the violations would likely not affect the validity of the data and thus could be used in support of the NDA. There was no violation at site #675. The overall quality of data was discussed and reanalyzed for verification purpose by the Division's statistical reviewer Dr Shahla Farr and was found to be acceptable.

For BZUC3003, consults were requested for sites conducted by Dr. Richard Hansen (Littleton, CO) and Dr. Thomas Nowak (Anderson, IN). Although the report audits were not completed at

the time of this review, the preliminary report dated 10 December, 2008 did not find any significant violations.

4.5 Compliance with Good Clinical Practices

The Applicant documented that all studies were conducted in accordance with the current applicable regulations, International Conference on Harmonization (ICH), Good Clinical Practice (GCP) and local ethical and legal requirements. The Applicant also documented that the study was conducted in accordance with the principles of the Declaration of Helsinki.

The Applicant documented that patients were informed by the Investigator or an authorized staff member about the nature of the study prior to the start of the study. Each patient signed a study-specific consent form to serve as a participant in the study.

4.6 Financial Disclosures

Investigators for clinical study BZUC3003 submitted disclosure statements as required by the regulations 21 CRF Part 54. One investigator participated in financial arrangements or held financial interests requiring disclosure. (b) (6) held equity interest in the Applicant as defined by 21 CFR 54.2 (b) in that he holds 25,000 shares of stock in Salix Pharmaceuticals, Inc. In clinical study BZUC3003, (b) (6) enrolled (b) (6) patients out of the 410 participants. Although the final DSI site inspection audits are not yet completed, a sensitivity sub-analysis by site conducted by the statistical reviewer did not show any given site to preferentially alter the efficacy conclusions put forth by the Applicant. This analysis by the statistical reviewer was completed using sites that enrolled more than seven patients. Therefore, since (b) (6) only enrolled (b) (6) patients, excluding these patients from the efficacy analysis did not effect the efficacy outcome determination by the Applicant.

5 CLINICAL PHARMACOLOGY

Balsalazide disodium (BD) is a pro-drug that is designed to release an active moiety 5-aminosalicylic acid (5-ASA) and an inactive carrier moiety 4-amino benzoyl-β-alanine (4-ABA) upon enzymatic degradation by gut microflora. The 5-ASA and 4-ABA are further metabolized to N-acetyl-5-ASA and N-acetyl-4-ABA respectively. For complete details, please see the Clinical Pharmacology review of Insook Kim, Ph.D. dated 28 March, 2008.

The exact mechanism of action of mesalamine, the biologically active compound of the BD pro-drug, is not fully understood, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is possible

that mesalamine diminishes inflammation by inhibiting cyclooxygenase and lipooxygenase activity, and prostaglandin production in the colon.

Included in the original submission of NDA 22-205 were two new pharmacokinetic studies: 1) a study that assessed the relative bioavailability of the new BD tablet formulation compared to the previously approved capsule formulation and 2) a food effect study. To summarize the clinical pharmacology review findings:

1) The clinical pharmacology data were reviewed and found to be acceptable.
2) Although there was a higher amount of drug delivered per dose with the tablet formulation, the Cmax of balsalazide for systemic exposure is somewhat higher for the capsule formulation. After a single dose, however, the Cmax for mesalamine and the primary metabolite are somewhat higher for the tablet compared to the capsule formulation. The tablet's multi-dosing AUC for both mesalamine and the primary metabolite were higher than that observed with the capsule formulation. By gender, the Cmax of mesalamine in females was 123% of that in males, and the AUC in females relative to males was 140%.
3) A high fat diet influenced the systemic exposure of both mesalamine and the primary metabolite. For mesalamine, the Cmax was reduced by 66%, and the AUC was reduced by 15%. Absorption was delayed by a high fat diet as well; Tmax was increased from 0.5 hour to 2.0 hours.

5.1 Pharmacokinetics

There are no outstanding issues with Pharmacokinetics.

5.2 Pharmacodynamics

No pharmacodynamic study was conducted for this application, possibly because mesalamine, the active moiety of the BD pro-drug, is thought to have a local action in the colon rather than systemic action.

5.3 Exposure-Response Relationships

No dose-response study was conducted for this application.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Balsalazide tablets are proposed "***for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. Safety and effectiveness of [balsalazide disodium tablets] beyond 8 weeks in adults have not been established."***

6.1.1 Methods

The Applicant seeks approval for balsalazide disodium (BD) tablets for treatment of mildly to moderately active UC. The BD tablet contains 1.1g of BD, a pro-drug that is enzymatically cleaved in the colon by local gut flora to release mesalamine, the active drug product. Although the exact mechanism of action of mesalamine is not fully understood, it appears to have anti-inflammatory properties and to act locally in the colonic mucosa. To date, seven oral agents that act through either local delivery or local release of mesalamine have been approved for use in mildly to moderately active UC: Asacol (delayed-release tablet), Lialda (delayed-release tablet), Apriso (delayed-release capsule), Pentasa (controlled-release capsule), Sulfasalazine tablet (pro-drug), Colazal capsule (balsalazide disodium, pro-drug), and Dipentum capsule (olsalazine, sodium pro-drug).

In support of the proposed indication, the Applicant submitted the efficacy data from two clinical studies. The first study BZUC3002 was submitted for evaluation as part of the original NDA submission and was reviewed by Dr. Fathia Gibril (Clinical Reviewer) dated 4 April, 2008, and Dr. Ruyi He (Medical Team Leader) dated 9 May, 2008. The second study BZUC3003 is a new clinical trial that will be reviewed for the first time as part of the Applicant's resubmission to the Complete Response regulatory action taken for the original NDA submission.

For this efficacy review, a complete analysis of the new clinical study BZUC3003 will follow. In addition, the findings and recommendations from the previous review team for BZUC3002 will be summarized and included in Sections 6.1.1 Methods, 6.1.4 Efficacy Findings, and 6.1.6 Efficacy Conclusions.

Of note, a dose-response trial was not conducted with the Balsalazide tablet formulation. The rationale was that the proposed total daily dose (6.6 g/day) for new Balsalazide tablet formulation is similar to that of the existing Colazal capsule formulation (6.75 g/day), which was approved 18 July, 2000, for the same indication. The goal of the Balsalazide clinical development program was to provide a more convenient dosing regimen, since Balsalazide tablets are dosed BID compared to Colazal capsules, which are dosed TID.

6.1.1.1 BZUC3003

BZUC3003 is a Phase 3, double-blind, double-dummy, randomized, multi-center, parallel-group, actively-controlled study conducted in the US at 79 centers. A total of 410 eligible patients were randomized to receive balsalazide disodium (BD) tablets or mesalamine tablets (over-encapsulated Asacol) in a 1:1 ratio for six weeks.

6.1.1.2 BZUC3002

BZUC3002 is a Phase 3, double-blind, randomized, multi-center, parallel-group, placebo-controlled study conducted in the US at 55 centers. A total of 250 eligible patients were randomized to receive balsalazide disodium (BD) tablets or placebo in a 2:1 ratio for eight weeks.

6.1.1.3 BZUC3003 Protocol Amendments

Submission of original protocol to the Agency: 15 February, 2006
Study Initiated: 10 May, 2006 Study Completed: 10 August, 2007

Protocol Amendment 01: 8 August, 2006
Key changes study design changes were:

1) 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 ≥ 2 on the MMDAI bleeding component and ≥ 2 on the MMDAI endoscopy/sigmoidoscopy component of the clinical study protocol".
2) 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.
3) Clarification was added that the primary efficacy analysis was to be performed on the PP population and the analyses of baseline characteristics and efficacy sensitivity analyses were to be performed for the ITT.
4) 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.
5) The definition of treatment failure was clarified to include subjects who terminated early due to lack of efficacy including GI-associated AEs.

Protocol Amendment 02: 22 November, 2006

No significant changes affecting study design were made; changes were editorial in nature.

Protocol Amendment 03: 3 August, 2007

Key study design changes were:

1) Statistical analysis plan updated to clarify methods to be used.
2) Secondary efficacy endpoints were reorganized and subdivided to allow for hierarchical testing.

6.1.1.4 Efficacy Analysis

The primary efficacy analysis was performed on the per protocol (PP) population. The non-inferiority analysis was performed on the intent to treat population (ITT) as a sensitivity analysis. All other efficacy analyses were performed on the ITT population. Of note, the definition of the ITT population was amended after the initiation of the study; the amended ITT population consisted of all randomized patients who received at least one dose of study drug and who met and who met Inclusion Criterion #6 (see Reviewer's Comment below). The PP population was defined as the ITT population without major protocol deviations such as violation of any inclusion/exclusion criteria and wrongful drug allocation.

In all efficacy analyses of proportions, patients who terminated early from the study due to lack of efficacy or UC-related AEs were considered to be treatment failures regardless of the MMDAI scores. If post-baseline components of the MMDAI score were missing, the last available MMDAI individual subscore(s) was/were carried forward.

Non-inferiority was to be declared if the lower limit of the two-sided 95% confidence interval of the difference in combined endpoint rates between the treatment groups (rate of clinical and rectal bleeding improvement for BD tablets minus the rate of clinical and rectal improvement for the active comparator mesalamine tablets) is ≥ (b) (4) (i.e., (b) (4) points in favor of mesalamine tablets). The 95% confidence interval was calculated with use of the normal approximation to the binomial distribution. The non-inferiority analysis was performed for the PP population as part of the primary efficacy analysis. The non-inferiority analysis was also performed for the ITT population as a sensitivity analysis.

If the primary efficacy analysis demonstrated that BD tablets were non-inferior to mesalamine tablets, then the potential superiority of BD tablets to mesalamine tablets was to be evaluated using a Cochran-Mantel-Haenszel (CMH) test, adjusted for analysis center.

The statistical testing of the primary and key secondary endpoints was pre-specified and performed in a hierarchical fashion. Statistical testing was performed using two-sided tests with an alpha level of 0.05. These endpoints were tested in the order they are listed in Section 6.1.2 below. Significance tests were reported until a non-significant p-value was found ($p > 0.05$).

Once a non-significant p-value was calculated, all subsequent significance tests were considered exploratory in nature.

No interim analysis was planned or performed.

Reviewer's Comments:

1. Although the original protocol defined the ITT population as all randomized patients who received at least one dose of study drug, the ITT protocol definition was amended three months after the origination of the study. The amended ITT definition was changed to "all randomized subjects who took at least 1 dose of study drug ***and*** *who met inclusion criterion # 6". This inclusion criterion stated that to be enrolled in the study, "the subject had a baseline MMDAI score between 6 and 10, inclusive (i.e., mildly to moderately active UC). Additionally, subjects must have scored ≥ 2 on the MMDAI bleeding component and ≥ 2 on the MMDAI endoscopy/sigmoidoscopy component of the clinical study protocol."*

Since a patient should not have been enrolled and received study drug without meeting the necessary inclusion and exclusion criteria, this modification of the ITT definition while the study was in process raises some concerns regarding adherence to the good clinical study management. Since the PP population is a subset of the ITT population, the composition of both populations was altered by this change in the ITT definition. This reviewer believes that the original ITT definition is more appropriate, and the patients excluded by the amended ITT definition should be included as part of the efficacy assessments.

6.1.2 General Discussion of Endpoints

BZUC3003 used the Modified Mayo Disease Activity Index (MMDAI) to compare baseline and end of study (six weeks) disease activity assessments. The MMDAI is a composite score consisting of four sub-scores (i.e., bowel frequency, rectal bleeding, physician's global assessment, and endoscopy findings). The MMDAI evaluates these four indices, each on a scale of 0 to 3 (3 being severe disease). The maximal total score is 12.

Figure 1: Modified Mayo Disease Activity Index (MMDAI)

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

* The modification that has been made to the Mayo index is the deletion of "friability" from an endoscopy sub-score equal to "1". With this modification, the presence of friability is indicative of an endoscopy sub-score of 2 or 3.

The pre-specified primary efficacy endpoint for BZUC3003 was the proportion of patients who achieved clinical improvement and improvement in rectal bleeding subscale of the Modified Mayo Disease Activity Index (MMDAI) at the end of six weeks of therapy. Clinical improvement was defined as a ≥ 3 point improvement from baseline in the MMDAI total score; improvement in the rectal bleeding subscale was defined as a ≥ 1 point improvement from baseline in the rectal bleeding score.

In all efficacy analyses of proportions, patients who terminated early from the study due to lack of efficacy or UC-related AEs were considered to be treatment failures regardless of the MMDAI scores. If post-baseline components of the MMDAI score were missing, the last available MMDAI individual subscore(s) was/were carried forward.

Reviewer's comment:

1. There is currently no universally accepted and validated measure of disease activity in UC patients. The MMDAI used by the Applicant has been supported by the Agency as an acceptable scoring index in clinical UC trials. Measurement of disease activity is critical in evaluating new therapies in UC clinical trials. The proposed MMDAI has been widely used in UC clinical trials and is a reasonable scoring index for ulcerative colitis because it allows for an adequate, overall assessment of a patient's disease activity state.

In addition, as pointed out in Dr. Gibril's review of 4 April, 2008, there has been no formal attempt to define efficacy endpoints such as clinical improvement or remission in UC clinical trials. However, remission defined as complete relief of inflammatory symptoms has been generally considered to represent a higher level of clinical response than clinical improvement where a given point reduction in a total MMDAI score is usually selected at random. It is worth mentioning that while remission was the primary endpoint in clinical trials that led to approval of Lialda, clinical improvement is the proposed primary endpoint in the current application.

2. The Applicant classified only those patients who terminated the study early secondary to lack of efficacy or UC-related AEs as treatment failures; early withdrawal for other reasons was not considered a treatment failure. For a more appropriate sensitivity assessment, the statistical reviewer did a sub-analysis were all early withdrawal patients were considered to be treatment failures regardless of reason. The full discussion, including the impact of this assessment, is found in the reviewer's comment under Section 6.1.4.4.2.

Key secondary efficacy endpoints, in hierarchical order for formal statistical analysis and testing, were as follows:

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

Reviewer's Comment:

1. *As stated above in Section 6.1.1.3, the secondary endpoints were subdivided and reorganized as part of a protocol amendment after the initiation of the study.*
2. *At the End of Phase 2 meeting held on 8 August, 2005, the meeting minutes reflect that, in general, the proposed primary and secondary endpoints appeared to be acceptable.*

6.1.3 Study Design: BZUC3003

The Applicant's BZUC3003 study was titled "A Multi-center, Randomized, Double-Blind, Actively-Controlled, Parallel-Group Trial to Evaluate the Safety and Efficacy of a New Tablet Formulation and Dosing Regimen of Balsalazide Disodium (BD) 3.3 g BID versus Mesalamine (5-ASA) as Asacol 0.8 g TID in Mildly to Moderately Active Ulcerative Colitis."

Study Started: 10 May, 2006
Study completed: 10 August, 2007

BZUC3003 was a clincial study to evaluate the effectiveness and safety of a new tablet formulation of balsalazide disodium in patients with mildly to moderately active UC. This new formulation has a twice daily dosing regimen compared to the capsule formulation, which is dosed three times a day. Eligible patients were randomized 1:1 to receive either BD tablets or

Asacol (mesalamine) tablets, the active comparator. Some mesalamine products have been shown to be more efficacious than placebo and to be effective in inducing and maintaining remission in mildly to moderately active UC. Specifically, Asacol is currently the most prescribed mesalamine compound in the U.S., where it has been marketed for 16 years. As the active comparator for BZUC3003, Asacol has been approved and proven effective in the treatment of UC at the dosage used and in the population studied.

The pre-specified primary efficacy endpoint for BZUC3003 was the proportion of patients who achieved clinical improvement and improvement in rectal bleeding subscale of the Modified Mayo Disease Activity Index (MMDAI) at the end of six weeks of therapy. Clinical improvement was defined as a ≥ 3 point improvement from baseline in the MMDAI total score; improvement in the rectal bleeding subscale was defined as a ≥ 1 point improvement from baseline in the rectal bleeding score.

The study consisted of a screening phase (completed within seven days prior to randomization), a treatment phase (six weeks in duration), and a two-week post-treatment follow-up phase. The randomized design of the study was used to minimize bias by assigning patients to treatment groups using a randomization code.

6.1.3.1 Study Inclusion/Exclusion Criteria

Key inclusion criteria:

1. Signed and dated informed consent form completed prior to any study-related activities
2. Male or non-childbearing-potential female or fertile female using appropriate methods of birth control
3. ≥18 years of age
4. Patients with mildly to moderately active UC experiencing an acute flare
5. Patients who had not taken > 4.8 g QD Asacol, ≥ 6.75 g QD Colazal, or 2.4 g QD of mesalamine or equivalent daily dose using any other 5-ASA products at any time during the 14 days preceding the initiation of the study medication
6. Baseline MMDAI score between 6 and 10 inclusive, and a score of ≥ 2 on rectal bleeding and a score of ≥ 2 on endoscopy
7. Evidence of disease activity that extended at least 20 cm from the rectum on screening endoscopy

Key exclusion criteria:

1. Patient's UC worsened or failed to improve during chronic therapy (> seven days) with ≥ 6.6 g/day of balsalazide disodium within 30 days of screening
2. Patient received chronic (> 15 days) immunosuppressive therapy (AZA, 6-MP) or corticosteroids (oral or topical rectal) within #) days prior to screening
3. Treatment with intra-rectal aminosalicylates for ≥2 consecutive days within 7 days of screening
4. Treatment with infliximab, cyclosporine, natalizumab, or methotrexate for UC within the last 30 days prior to screening
5. Regular use of NSAIDS except cardio-protective aspirin

6. Use of anti-diarrheal therapy during screening and at any time during the study
7. Clinical or radiographic findings suggestive of serious UC complications
8. The patient had infectious, ischemic, or immunologic diseases involving the GI tract
9. Positive stool culture for ovum and parasites or *C. Difficile*
10. Prior bowel surgery, with the exception of appendectomy or cholecystectomy
11. Sclerosing cholangitis
12. History of HIV, Hepatitis B, or Hepatitis C infection
13. Unstable cardiovascular, coagulopathy, or pulmonary disease that was characterized by worsening in the disease condition that required a change in treatment or medical care within one month of randomization
14. Active malignancy (except basal cell carcinoma of the skin or *in situ* cervical carcinoma that was surgically excised) with the last five years
15. More than twice the ULN for any of the following LFTs: ALT, AST, AP, or TBili.
16. Uncontrolled, clinically significant renal disease as evidenced by 1.5 times ULN of serum creatinine
17. Calculated creatinine clearance level of ≤ 60 mL/min
18. Pregnant or lactating women

REVIEWER'S COMMENT: Since patients who previously failed balsalazide therapy within the previous 30 days prior to enrollment were excluded, a sub-analysis of patients with a prior history of balsalazide treatment was performed to determine the generalizability of any efficacy claims (see Section 6.1.4.4.4). Otherwise the inclusion and exclusion criteria are adequate.

6.1.3.2 Study Procedure

The study consisted of a screening period, a treatment period, and a follow-up period completed two weeks post-treatment (see Table 2 below). A daily diary was kept by the patient to record stool frequency, rectal bleeding, and symptoms. During the six-week treatment period, patients returned to the study site at four scheduled visits (Weeks 0, 1, 2, and 6) for study assessments and allocation of study drug and diary cards. Clinical laboratory testing included hematology, blood chemistry, urinalysis, and calculated creatinine clearance. Patients underwent a colonoscopy/sigmoidoscopy at or around the time of Screening and at Week 6; an optional endoscopy assessment occurred at Week 2 of treatment. Patients who discontinued prior to Week 6 underwent a colonoscopy/sigmoidoscopy, if possible, at their Early Termination visit. A complete MMDAI was calculated at Screening/Baseline visit, and at Week 6/Visit 4 (or the Early Termination visit, if applicable). In addition, an abbreviated MMDAI (excluding endoscopy) was calculated at Visits 2 through 4.

Asacol was the active comparator for BZUC3003. Approved for use in 1992, Asacol is indicated for treatment of mildly to moderately active UC, the same population studied in this NI clinical trial. The usual dosage in adults is two 400 mg tablets taken TID for a total daily dose of 2.4 g for a duration of six weeks; the same dose, frequency, and duration of treatment used for patients randomized to the Asacol cohort in this study.

To maintain blinding in the study, a double-dummy approach was utilized. Blinded study drug was packaged in blister cards, each containing a daily dose of either six active BD tablets and six placebo capsules or six over-encapsulated Asacol capsules and six placebo tablets. BD tablets were administered as three tablets BID, with each tablet containing 1.1 g BD. Asacol was administered as two over-encapsulated capsules TID, with each capsule containing 0.4 g of Asacol. Placebo tablets and placebo capsules were also administered to maintain the study blind. Patients were instructed to take three tablets and two capsules in the morning, two capsules in the afternoon, and three tablets and two capsules in the evening. This design allowed for appropriate dosing of the two study drugs despite differential dosage patterns (BID vs. TID).

Concomitant medications were permitted as long as they were pre-existing prior to study enrollment, they did not change during the course of the study, and they were not one of the following:

- Immunosuppressants: azathioprine, 6-mercaptopurine, cyclosporine, TNF-blocking agent, or natalizumab
- Experimental drugs
- NSAIDs as chronic treatment (> one week) except for cardioprotective, low dose aspirin
- Oral, rectal, or IV corticosteroids
- Oral antibiotics: metronidazole and ciprofloxacin were allowed for up to ten days of treatment for conditions unrelated to UC therapy
- Psyllium-containing bulk agents
- Loperamide, bismuth subsalicylate, and opioids
- Anticholinergics or sucralfate
- 5-ASA medications
- Anticoagulant therapy
- Diarrhea-inducing compounds
- Alternative or complementary therapies

Table 2: BZUC3003 Schedule of Study Assessments

Study Assessment	Visit 0/Screening (3 to7 days prior to randomization)	Visit 1 (Baseline/ Randomization) (Day 1)	Visit 2 (Day 7 ± 1 day)	Visit 3 (Day 14 ± 3 days)	Visit 4/EOT (Day 42 ± 3 days)	Visit 5/Follow-up[g] (Day 56 ± 2 days)
Informed consent	X					
Medical History/ Demographic information	X					
Physical Examination	X	X[a]	X[a]	X[a]	X	X[a]
Obtain VS measurements	X	X	X	X	X	
Serum Pregnancy test[b]	X				X	
Record concomitant meds	X	X	X	X	X	X
Clinical laboratory tests	X[d]			X	X	
Colonoscopy or Flexible Sigmoidoscopy[e]	X			X[f]	X	
IBD QoL questionnaire	X			X	X	
Dispense diary with complete instructions	X	X	X	X		
Dispense Study Drug		X	X	X		
Calculate MMDAI score	X	X	X[c]	X[f]	X	
Assess and record AEs		X	X	X	X	X
Retrieve/review AE and patient diary		X	X	X	X	
Collect study drug and determine compliance			X	X	X	
Confirm patient eligibility criteria	X	X				

[a] *symptom-directed physical exam only to be performed if necessary*
[b] *females of childbearing potential only*
[c] *Calculate abbreviated MMDAI, calculated using all subscores except sigmoidoscopy*
[d] *Stool culture added for Ova and Parasites and C. difficile at screening visit*
[e] *Minimum of 3 days had to elapse between endoscopic visit and the Baseline/ Randomization visit*
[f] *Endoscopic evaluation at Visit 3 was optional (if performed, complete MMDAI was calculated; if not, then abbreviated MMDAI was calculated)*
[g] *In person or via telephone*

Modified from Applicant's Table 3, Module 5.3.5.1.2, p. 38.

6.1.4 Efficacy Findings

6.1.4.1 Patient Disposition

A total of 410 patients from 79 U.S. clinical trial sites were randomly assigned to study treatment groups; 212 patients in the balsalazide (BD) treatment cohort and 198 patients in the mesalamine (5-ASA) treatment cohort. Of the 410 patients enrolled and randomized, a total of 338 (82.4%) patients completed the study: 82.5% of patients in the BD cohort and 82.3% of patients in the Asacol cohort. Overall, the most common reason for discontinuation was lack of efficacy (8.5%). Study withdrawal was comparable between the two treatment cohorts (17.5% BD vs. 17.7% Asacol). However, fewer patients administered BD compared to Asacol withdrew due to lack of efficacy (7.1% vs. 10.1% respectively).

Table 3: Patient Disposition in Study BZUC3003

	BD Cohort (n=212)	Asacol Cohort (n=198)	Total (n=410)
	% (n)	% (n)	% (N)
Patients randomized	100 (212)	100 (198)	100 (410)
Patients completed the study	82.5 (175)	82.3 (163)	82.4 (338)
Patients withdrawn early	17.5 (37)	17.7 (35)	17.6 (72)
Reasons for withdrawal			
Adverse event	4.7 (10)	3.0 (6)	3.9 (16)
Lost to follow-up	1.4 (3)	2.5 (5)	2.0 (8)
Lack of efficacy	7.1 (15)	10.1 (20)	8.5 (35)
Patient request to withdraw	4.2 (9)	1.0 (2)	2.7 (11)
Noncompliance	0.0 (0)	0.5 (1)	0.2 (1)
Other	0.0 (0)	0.5 (1)	0.2 (1)

Modified from Applicant's Table 5, Module 5.3.5.1.2, p.66
Note: Withdrawal reason of "other" due to subject not committed to completing study after seeing pill and breaking dose seal.

6.1.4.2 Patient Demographics

The demographic characteristics of age, sex, race, and ethnicity were comparable across treatment groups. For the amended ITT population presented by the Applicant, the mean age was 42.1 years (range, 18 to 79 years of age) and approximately 5% were ≥ 65 years. A little over half of all patients (51.8%) were female and most patients were white (86%).

Table 4: Baseline Demographic Characteristics in Study BZUC3003: Amended ITT population

	BD	5-ASA	Total
Patients randomized	206 n (%)	194 n (%)	400 n (%)
Sex			
Female	107 (51.9%)	100 (51.5%)	207 (51.8%)
Male	99 (48.1)	94 (48.5)	193 (48.3)
Race			
White	179 (86.9)	165 (85.1))	344 (86.0)
Black	20 (9.7)	23 (11.9)	43 (10.8)
Asian	4 (1.9)	3 (1.5)	7 (1.8)
American Indian/Alaskan Native	2 (1.0)	2 (1.0)	4 (1.0)
Other	1 (0.5)	1 (0.5)	2 (0.5)
Age (yrs)			
Median	42.0	40.0	41.0
BMI (kg/m^2)			
Median	26.31	26.43	26.36

Modified from Applicant's Table 9, Module 5.3.5.1.2, p. 72.

6.1.4.3 Baseline Disease Activity and other Characteristics

Baseline disease activity and other characteristics were comparable across treatment groups as summarized below and as shown in Table 5 and Table 6. To access disease activity and to identify patients with mildly to moderately active UC, the MMDAI was chosen. For the four subscores that comprise the total calculated MMDAI, the parameters suggest balance between the two treatment groups and are indicative of patients who would be experiencing an active UC flare. The mean MMDAI total score at baseline was 8.2 (range: 6 to 10). Most patients experienced obvious blood with their stools most of the time (mean 2.1; SD 0.28). The mean endoscopy score was 2.2 (SD 0.41). Very few patients had a normal number of stools per day (3%). The PGA median score of 2.0 (SD 0.32) indicated that from a physician's perspective, most patients fell into the moderate disease strata.

When the ITT and PP populations are compared, the summary baseline disease characteristics are almost identical.

Reviewer's Comment:

A smaller number of patients in the BD cohort (1%) compared to the Asacol cohort (5.2%) had normal daily stool frequency. Although the total number of patients that had normal daily stool frequency was small (12 patients out of 400), a post-hoc assessment shows that the comparison does represent a nominally statistically significant difference (p=0.028).

Table 5: MMDAI Baseline Disease Characteristics for Treatment Arms in Study BZUC3003: Amended ITT population

Assessed Parameter	BD Tablets	Asacol	Total
MMDAI Total Score			
N	206	194	400
Mean (SD)	8.2 (1.06)	8.1 (1.07)	8.2 (1.07)
Median	8.0	8.0	8.0
Range: Min, Max	6, 10	6, 10	6, 10
Disease Severity: % (n)			
< 8 (mild disease)	28.6% (59)	30.4% (59)	29.5% (118)
≥ 8 (moderate disease)	71.4% (147)	69.6% (135)	70.5% (282)
Rectal Bleeding Subscore: % (n)			
Mean (SD)	2.1 (0.30)	2.1 (0.25)	2.1 (0.28)
None seen	0% (0)	0% (0)	0% (0)
Streaks with stool < 50% of time	0% (0)	0% (0)	0% (0)
Obvious blood with stool most times	90.3% (186)	93.3% (181)	91.8% (367)
Blood alone	9.7% (20)	6.7% (13)	8.3% (33)
Endoscopy/Sigmoidoscopy Subscore: % (n)			
Mean (SD)	2.2 (0.42)	2.2 (0.40)	2.2 (0.41)
Normal or inactive disease	0% (0)	0% (0)	0% (0)
Mild disease	0% (0)	0% (0)	0% (0)
Moderate disease	77.2% (159)	79.9% (155)	78.5% (314)
Severe disease	22.8% (47)	20.1% (39)	21.5% (86)
Bowel Frequency: % (n)			
Mean (SD)	1.9 (0.79)	1.8 (0.85)	1.9 (0.82)
Normal # stools/day (SD)	2 (1.0)	10 (5.2)	12 (3.0)
1 to 2 more stools than normal	31.1% (64)	29.4% (57)	30.3% (121)
3 to 4 more stools than normal	40.8% (84)	41.2% (80)	41.0% (164)
5 or more stools than normal	27.2% (56)	24.2% (47)	25.8% (103)
Physician's Assessment: % (n)			
Mean (SD)	2.0 (0.30)	2.0 (0.34)	2.0 (0.32)
Normal	0% (0)	0% (0)	0% (0)
Mild disease	6.3% (13)	8.2% (16)	7.3% (29)
Moderate disease	90.8% (187)	88.1% (171)	89.5% (358)
Severe disease	2.9% (6)	3.6% (7)	3.3% (13)

Modified from Applicant's Table 10, Module 5.3.5.1.2, p. 74

As summarized below, other baseline characteristics were similar between the study treatment groups. Parameters assessed were mean time since initial diagnosis of UC, mean number of daily stools, time since most recent flare of UC, the number of newly diagnosed patients, and smoking history. Some differences to note: more time had passed since the onset of most recent

UC flare for patients in the BD- compared to the Asacol-treatment arms and more patients in the BD- compared to the Asacol-treatment arm had newly diagnosed UC.

Table 6: Other Baseline Characteristics by Treatment Arm in Study BZUC3003: Amended ITT population

Assessed Parameter	BD Tablets	Asacol	Total
Time since initial diagnosis of UC (years)			
N	206	194	400
Mean (SD)	8.0 (7.9)	8.1 (9.1)	8.0 (8.5)
Median	6.19	4.67	5.36
Range: Min, Max	0, 33.2	0, 39.3	0, 39.3
Normal number of daily stools			
Mean (SD)	1.8 (1.01)	1.8 (1.00)	1.8 (1.00)
Median	2.0	2.0	2.0
Range: Min, Max	1, 6	1, 6	1, 6
Time since onset of most recent flare (days)			
Mean (SD)	82 (167)	62 (91)	72 (136)
Median	34.0	30.5	33.0
Range: Min, Max	1, 1259	1, 746	1, 1259
Newly diagnosed UC: % (n)			
Yes	10.7% (22)	7.2% (14)	9.0% (36)
Smoking history: % (n)			
Never smoked	58.3% (120)	55.7% (108)	57.0% (228)
Ex-smoker	34.5% (71)	33.5% (65)	34.0% (136)
Smoker	7.3% (15)	10.8% (21)	9.0% (36)

Modified from Applicant's Table 11, Module 5.3.5.1.2, p. 77

Finally, the distribution of prior therapies to treat UC was analogous between the two study treatment cohorts (see Table 7 below).

Reviewer's Comment:

Of note, except for common concomitant therapies used to treat UC, the number of patients assigned to BD-treatment and exposed to any other given medication was less than 2% of the total number of patient in that treatment arm. This small number of patients with concomitant medication use outside those used to treat UC limits any conclusions that can be drawn regarding potential drug-drug interactions. However, additional data collected as part of the longitudinal safety study BZUC3005 may provide information to address that topic.

Table 7: Summary of Medications Used Previously to Treat UC by Treatment Group: Amended ITT population

Drug Class	BD Tablets N=206	Asacol N=194	Total N=400
Patients receiving any medication: % (n)	72.4% (152)	69.7% (138)	71.1% (290)
Anti-bacterials for systemic use	2.4 (5)	1.0 (2)	1.7 (7)
Anti-diarrhea/anti-infective agents	67.6 (142)	65.2 (129)	66.4 (271)
Anti-histamines for systemic use	0 (0)	0.5 (1)	0.2 (1)
Anti-neoplastic agents	1.9 (4)	4.0 (8)	2.9 (12)
Corticosteroids for systemic use	23.3 (49)	27.3 (54)	25.2 (103)
Digestives, including enzymes	0.5 (1)	0 (0)	0.2 (1)
Drugs for acid-related disorders	0.5 (1)	0.5 (1)	0.5 (2)
Drugs for functional gastrointestinal disorders	2.4 (5)	3.0 (6)	2.7 (11)
Immunosuppressive agents	5.7 (12)	3.0 (6)	4.4 (18)
Laxatives	1.0 (2)	0.5 (1)	0.7 (3)
Lipid modifying agents	0 (0)	0.5 (1)	0.2 (1)
Mineral supplements	0.5 (1)	0 (0)	0.2 (1)
Other nervous system drugs	0 (0)	0.5 (1)	0.2 (1)
Psycholeptics	0 (0)	0.5 (1)	0.2 (1)
Stomatological preparations	2.4 (5)	1.5 (3)	2.0 (8)
Unspecified herbal	1.0 (2)	1.0 (2)	1.0 (4)

Modified from Applicant's Table 12, Module 5.3.5.1.2, pp. 79, 80

For comparison, since the primary efficacy analysis was conducted in the PP population, the statistical reviewer did a similar analysis of key demographic and baseline characteristics for this population. As shown in Table 8 and Table 9 below, the outcomes are comparable with the Applicant's analysis in the amended ITT population.

Table 8: Baseline MMDAI Characteristics: Amended PP Population

	Balsalazide (N=180) Mean ± Std.	Mesalamine (N=171) Mean ± Std.
Baseline MMDAI Score	5.98 ± 0.92	5.86 ± 0.95
Baseline Bleeding	2.10 ± 0.30	2.06 ± 0.24
Baseline Bowel Frequency	1.91 ± 0.78	1.86 ± 0.83
Baseline Physician Ass.	1.97 ± 0.32	1.94 ± 0.34
Baseline Sigmoidoscopy	2.23 ± 0.42	2.18 ± 0.39

Table 9: Demographic and Baseline Characteristics: Amended PP population

	BD (N=180) n (%)	Asacol (N=171) n (%)	Total (N=351) n (%)
Sex			
Female	93 (52%)	87 (51%)	180 (51%)
Male	87 (48%)	84 (49%)	171 (49%)
Age Category			
< 65	171 (95%)	163 (95%)	334 (95%)
≥ 65	9 (5%)	8 (5%)	17 (8%)
Race			
White	157 (87%)	144 (84%)	301 (86%)
Non-White	23 (13%)	27 (16%)	50 (14%)
Baseline Disease			
Mild (< 8)	53 (29%)	52 (30%)	105 (30%)
Moderate ≥ 8)	127 (71%)	119 (70%)	246 (70%)
Newly Diagnosed			
Yes	20 (11%)	12 (7%)	32 (9%)
No	160 (89%)	159 (93%)	319 (91%)
Smoker			
Yes	13 (7%)	18 (11%)	31 (9%)
No	167 (93%)	153 (89%)	320 (91%)
Prior 5ASA Use			
Yes	139 (77%)	139 (81%)	278 (79%)
No	41 (23%)	32 (19%)	73 (21%)

6.1.4.4 Analyses of Efficacy

6.1.4.4.1 Analyses Populations

All randomized patients who received at least one dose of study drug and who met the MMDAI inclusion criteria specifications were included in the amended ITT population. The PP population consisted of all patients included in the ITT population who did not have a major protocol deviation and who had at least one post-baseline primary efficacy assessment. Major protocol deviations were: deviations from specific inclusion criteria, administration of prohibited medications, or wrongful allocation of study drug.

For Study BZUC3003, 400 (97.6%) of the total 410 study patients randomized were included in the ITT population. A total of 351 (85.6%) patients were included in the PP population. The distribution of the reasons for which patients were not included in the two populations analyzed

can be found in Table 12. Overall, both the reasons and the percentage of patients not included in a given population were comparable between the two study treatment arms.

Reviewer's Comment:

The definition of the ITT population was amended after the initiation of BZUC3003. The amended definition specified that patients must have receive at least one dose of study drug ***and*** *have met the inclusion criteria indicative of mildly to moderately active UC. The amended definition of the ITT population alters the intent of what constitutes a true ITT analysis.*

For the newly defined ITT population, the exclusion of 10 patients in total, secondary to not meeting one of the inclusion criteria, should not have significantly influenced the overall analysis, especially since the proportion of patients in a particular treatment cohort affected by the amended definition were comparable (BD 2.8% vs 5-ASA 2.0%). As discussed by Dr. Farr in her statistical review and presented in Table 10 below, the inclusion of these patients did not significantly affect the outcome of the primary efficacy endpoint variable assessment. Dr. Farr conducted a sensitivity analysis in which all randomized patients who received study drug (the original ITT definition) were included, and, for a conservative approach, these ten patients were coded as treatment failures. The results are comparable to the prior efficacy assessments of the amended ITT and PP populations.

Table 10: Proportion and 95% CI* of Subjects with Induction – Reviewer's Results (Study BZUC3003 – All Randomized Population)

Balsalazide (6.6 g) (95% CI)	**Asacol** (2.4 g) (95% CI)	Difference (95% CI)	P-Value
(b) (4)=54.7%	(b) (4)=55.1%	-0.3% (b) (4)	(b) (4)

However, since those patients were excluded for not meeting the MMDAI inclusion criteria specifications, there is concern that other protocol irregularities may have taken place. The MMDAI is a key component for both study enrollment and efficacy assessment so an evaluation of what study sites were involved was done to see if protocol irregularities at some sites may have inappropriately affected the overall efficacy assessment of the study. Of the ten patients excluded from the ITT population after the definition was amended, no more than two patients were enrolled at any given center (see Table 11 below). Since the inclusion of these patients as part of a sensitivity analysis did not significantly alter the efficacy assessment outcomes and the number of patients per site that were excluded was small, the concern of further deviations from protocol and good study management is lessened.

Table 11: Patients excluded from original ITT population by center

Center 1: N= 34	Patient 770-03
Center 2: N=40	Patients: 827-04 and 827-05
Center 3: N=29	Patient 821-04
Center 5: N=33	Patient 689-12
Center 7: N=49	Patients: 039-13 and 923-01
Center 10: N= 35	Patients: 517-02 and 517-04
Center 12: N=32	Patient 844-01

For the PP population, the majority of patients were excluded secondary to no post-baseline primary efficacy assessment. Per protocol, patients that were withdrawal from the study were supposed to have, at the time of study withdrawal, a complete efficacy assessment analogous to an end of study assessment. Given that 24 (11.3%) of patients in the BD-treatment cohort and 17 (18.6%) of patients in the Asacol-treatment cohort did not achieve this goal, the concern is raised about proper study management. Looking at the study centers were these patients did not have EOT post-baseline efficacy assessments, the largest number of patients (nine) were enrolled at Center 2 (N=40). Since almost a quarter of the patients at that site did not follow the guidelines of the protocol, an analysis of the impact of this site on success of the study was performed and discussed in the statistical review by Dr. Shahla Farr. For study sites with seven or more patients enrolled, an analysis of the primary efficacy endpoint, controlling for potential site-specific biases, showed those potential influences to be non-specific (p=0.12).

Table 12: Analysis Populations: Randomized Patients

Analysis Populations	BD Tablets N=212 % (n)	Asacol N=198 % (n)	Total N=410 % (n)
Patients in ITT population: Amended protocol definition	97.2% (206)	98.0% (194)	97.6% (400)
Patients excluded from ITT population: Original definition	2.8 (6)	2.0 (4)	2.4 (10)
Reason for exclusion			
Inclusion criterion #6 not met[1]	2.8 (6)	2.0 (4)	2.4 (10)
Patients in PP population: Amended protocol definition	84.9 (180)	86.4 (171)	85.6 (351)
Patients excluded from PP population: Original definition	15.1 (32)	13.6 (27)	14.4 (59)
Reason for exclusion			
Inclusion criterion #4 not met[2]	0.5 (1)	0 (0)	0.2 (1)
Inclusion criterion #6 not met	2.8 (6)	2.0 (4)	2.4 (10)
Took prohibited medications	2.4 (5)	4.0 (8)	3.2 (13)
No post-baseline 1° efficacy assessment	11.3 (24)	8.6 (17)	10.0 (41)

[1] Baseline MMDAI score between 6 and 10 inclusive, and a score of ≥ 2 on rectal bleeding and a score of ≥ 2 on endoscopy
[2] Patients with mildly to moderately active UC experiencing an acute flare
Modified from Applicant's Table 8, Module 5.3.5.1.2, p. 70

6.1.4.4.2 Primary Endpoint Analysis: Clinical Improvement and Improvement in Rectal Bleeding

The pre-specified primary efficacy endpoint for BZUC3003 was the proportion of patients who achieved clinical improvement and improvement in rectal bleeding subscale of the Modified Mayo Disease Activity Index (MMDAI) at the end of six weeks of therapy. Clinical improvement was defined as a ≥ 3 point improvement from baseline in the MMDAI total score; improvement in the rectal bleeding subscale was defined as a ≥ 1 point improvement from baseline in the rectal bleeding score. In all efficacy analyses of proportions, patients who terminated early from the study due to lack of efficacy or UC-related AEs were considered to be treatment failures regardless of the MMDAI scores. If post-baseline components of the MMDAI score were missing, the last available MMDAI individual subscore(s) was/were carried forward.

The proportion of subjects in the PP population who achieved clinical improvement and improvement in rectal bleeding at Week 6/EOT was similar for the BD cohort (61.7%) and the Asacol cohort (60.8%). The difference in the proportions of the patients who achieved this primary endpoint was 0.85%, allowing the lower bound of the 95% confidence interval for the treatment difference to be greater than the pre-specified, non-inferiority margin of (b) (4) (95% CI: (b) (4) From these results, the Applicant concluded that balsalazide disodium tablets were not inferior to the active comparator Asacol, using the Applicant's criterion.

Evaluating efficacy in the ITT population as a sensitivity assessment revealed the proportion of subjects in the ITT population who achieved clinical improvement and improvement in rectal bleeding were similar for the BD cohort (56.3%) and the Asacol cohort (56.2%). The non-inferiority analysis revealed that balsalazide disodium tablets were not inferior to Asacol (0.13%; 95% CI: (b) (4) using the Applicant's criterion.

The superiority of BD to Asacol was also evaluated in the ITT population using a CMH test, adjusted for analysis center. No statistically significant difference (0.13%, p=0.4666) was observed between the two treatment groups. (b) (4)

Table 13: Results of Primary Endpoint Analysis - ITT and PP Populations

Analysis of Primary Endpoint				
Population	BD n/N (%)	Asacol n/N (%)	Difference in proportion	95% CI
PP	(b) (4) (61.7)	(b) (4) (60.8)	0.85%	(b) (4)
ITT (sensitivity)	(b) (4) (56.3)	(b) (4) (56.2)	0.13%	

Modified from Applicant's Table 15, Module 5.3.5.1.2, p. 85

Reviewer's Comment:

1. Is the non-inferiority margin appropriate?

For a complete discussion of the statistical analyzes performed and of the justification of non-inferiority margin (NI) chosen, please see the statistical review by Dr. Shahla Farr. In summary, the Applicant chose the (b) (4) NI margin based on the following approach. The Applicant performed a meta-analysis of 16 placebo-controlled trials conducted between 1967 and 1989; the placebo-controlled trials were identified as part of a literature search. Of the 16 trials, 11 studies were identified that chose induction of remission of UC as there primary efficacy endpoint. The study populations for these 11 studies focused on mildly to moderately active UC patients. In addition to the literature references, the Applicant also justified the NI margin based on input from clinicians with experience in the treatment of active UC. Driven by the literature analysis and clinical input, the Applicant concluded that the (b) (4) NI margin was justified.

*This reviewer, however, does not agree with the process by which the (b) (4) NI margin was chosen. The guidance ICH Topic E 10: Choice of Control Group in Clinical Trials (CPMP/ICH/364/96) was adopted for approval January 2001. Section **1.5.1 Assay Sensitivity in Non-inferiority or Equivalence Trials** states, in part, that the presence of assay sensitivity in a NI clinical study may be deduced from historical evidence of sensitivity to drug effects, namely that similarly designed trials conducted in the past can be used to determine effective treatments*

from less effective or ineffective treatments. Specifically, appropriately designed and conducted clinical trials that tested a specific active therapy reliably showed a treatment effect. Optimally, the demonstrated treatment effect of the active therapy intended for use as the active comparator in the NI trial was reliably found to be superior to placebo. The NI trial should be similar in design to that of the reference trials for the active comparator (e.g. analogous entry criteria, allowable concomitant therapy. Based on this ICH guidance, this reviewer concludes that studies that support the choice of a NI margin should have been conducted under placebo-controlled conditions with the active comparator. And such studies should be analogous to the design of the NI trial of interest (i.e., similar patient population, inclusion/exclusion criteria, treatment dose and duration of the active comparator, and efficacy endpoints to be assessed).

Applying these specifications to the literature references submitted by the Applicant in support of the (b) (4) *NI margin, this reviewer finds that all but one of the studies fall short of the guidance's "similarity" definition. Study design deviations from the NI trial of interest include:*

- *Different active treatments; only one study tested Asacol, the active comparator for BZUC3003*
- *Differing durations of treatment, ranging from 14 to 42 days*
- *Different inclusion/exclusion criteria*
- *Different efficacy endpoint assessments*

The one study referenced by the Applicant that did have a similar design to BZUC3003 was by Sninsky, et al. (Annals Int Med. 1991; 115:350-355). As best could be determined from the Methods section of the referenced article, the patient population, inclusion/exclusion criteria, and treatment dose and duration of Asacol therapy was similar to BZUC3003. The primary efficacy endpoint was clinical response based on a scoring system similar to the MMDAI with the main difference being the inclusion of an additional sub-score for a Patient's Functional Assessment. So, although not identical to BZUC3003, this reviewer feels that the Sninsky publication, from all those submitted by the Applicant, best exemplifies the appropriate choice of a reference trial for NI margin assessment as outlined in the ICH E10 guidance.

The Sninsky study found that the proportion of patients achieving clinical improvement after six-weeks of treatment was 49% for the 2.4 Asacol-treatment arm and 23% for the placebo-treatment arm. The difference in the treatment responses between these two arms was statistically significant (p=0.003). The authors subdivided the Asacol-treatment responders into four groups:

- *"In remission" was defined as a complete resolution of all symptoms, with all assessment scores determined to be zero*
- *"Improved" was defined as a reduction in the physician's global assessment (PGA) score and in at least one other component score, with no score increased in severity*
- *"Maintained" was defined as no change in the PGA score and other component scores might be reduced by no score could increase in severity*
- *"Worsened" was defined as an increase in any individual component score*

The "in remission" and "improved" Asacol-treatment response subgroups, when combined, would most closely mimic the clinical improvement primary efficacy endpoint for BZUC3003. This reviewer acknowledges that this generalization is not based on a rigorous assessment of the Sninsky study data (not available to the reviewer). However, based on the information provided in the article, this determination allows for the NI margin calculation to be calculated and compared with the Applicant's chosen NI margin of (b) (4).

The six-week combined treatment outcomes of patients classified as "in remission" or "improved" yields: 10/44 (23%) patients in the Asacol 2.4 treatment arm and 21/43 (49%) patients in the placebo-treatment arm (as determined from the data presented in Table 4 of the Sninsky article). Next, a treatment effect (Asacol treatment-response minus placebo-treatment response) for Asacol was determined to be 26% (95%CI: 6%, 45%). Then, following the NI margin determination procedures followed by the statisticians, the lower CI margin is reduced by 50% to reduce the effect of "bio creep" to yield an NI margin of 3%. Thus, as judged from the Applicant's own reference literature, the study that best adheres to the criteria of the ICH E10 guidance results in a substantially lower NI margin (3%) than the one determined by the Applicant ((b) (4)

Is a 3% NI margin reasonable? To see if other data could support a 3% NI margin, this reviewer and the statisticians reviewed the original studies submitted under NDA 19-651 for the original Asacol approval in 1991. The placebo-controlled study submitted with this NDA was similar in design to BZUC3003 (similar patient population, treatment dose and duration). Like the Sninsky article, there was a difference in primary efficacy endpoint. But, like Sninsky, the "clinical improvement" assessment was based on a composite score similar to the MMDAI used in BZUC3003. Although the Applicant for NDA 19-651 did a post-hoc correction of some of the data (see the Statistical Review by Dr. Farr for details), the corrected data were used in the approval of the NDA and showed the following results.

Table 14: NDA 19-651 Improvement Rate at Week 6: Post-hoc Corrected Data

Study C14	Asacol 2.4 g/day n/N (%) (95% CI)	Placebo n/N (%) (95% CI)	Treatment Difference % (95% CI)	p-value
ITT Population	22/53 (42) (28%, 56%)	11/51 (21) (11%, 35%)	20% (2%, 37%)	0.03
PP Population	21/43 (49%) (33%, 65%)	10/44 (23) (11%, 38%)	26% (6%, 45%)	0.01

If one accepts the "corrected" data at face value (again, the corrected data was used for the approval action for Asacol), the treatment differences range from 20% to 26% with the lower limits of the 95% CI ranging from 2% to 6%. Thus, reducing the lower CI by 50% as above, the calculated NI margin should range from 1% to 3% for patients with mildly to moderately active

UC treated for six-weeks of therapy with Asacol, providing additional support that a more appropriate NI margin should not exceed 3%.

This reviewer concludes, therefore, that the Applicant has not provided convincing data in support of the (b) (4) *NI margin. And when the more appropriate 3% NI margin is imputed, the study does not support non-inferiority of BD compared to Asacol for the treatment of mildly to moderately active UC in adult patients.*

2. How does the amended ITT patient population definition affect the outcome of the primary efficacy analysis? Using data for the original ITT definition, a primary efficacy analysis was performed. The results are in Table 15 below.

Table 15: BZUC3003 Primary Efficacy Analysis: Original ITT Definition

BD Tablets (95% CI)	**Asacol** (95% CI)	% Difference (95% CI)	P-Value
(b) (4)=54.7%	(b) (4)=55.1%	-0.3% (b) (4)	(b) (4)

Using the original ITT population definition, the lower 95% CI is (b) (4) *compared to* (b) (4) *with the amended definition. As a further sensitivity assessment, the statistical reviewer treated all drop outs, regardless of reason, as treatment failures. That analysis is presented in below.*

Table 16: Sensitivity Assessment of the Primary Efficacy Endpoint: All Drop-outs Treated as Treatment Failures

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

**In this analysis, the Applicant 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

Although the Applicant conducted the primary efficacy on the PP population and a sensitivity analysis on the amended ITT population, one can argue that both the PP and the ITT population analyses have validity in NI studies. The results of the all-randomized patients were comparable to that of the amended PP and ITT population analysis However, if all drop-outs were treated as treatment failures, regardless of the reason for dropping out of the study, the lower limit of the 95% CI crossed the (b) (4) *NI margin.*

In summary, the choice of the (b) (4) *NI margin is inappropriate; referenced literature and studies in support of the Agency approval of Asacol yield a NI margin of less than 3%. Even with the Applicant's choice of a* (b) (4) *NI margin, the study would not succeeded if the analysis*

had been conducted on the ITT population as originally defined or if all drop-outs were treated as treatment failures regardless of reason.

6.1.4.4.3 Secondary Endpoint Analysis

In the hierarchical secondary endpoint analyses by the Applicant, none of the secondary endpoints met statistical significance. Therefore, as per protocol design, all secondary outcomes were considered exploratory. A summary of the secondary endpoint analyses are found in the follow table.

Table 17: Results of Secondary Endpoint Analysis

Key Secondary Efficacy Endpoints	BD Cohort N = 206	5-ASA Cohort N = 194	Difference in Proportions (95% CI)	p-value
Clinical Remission at Week 6/EOT[1]	77 (37.4%)	66 (34.0%)	3.3% (-6, 13)	0.42
Mucosal Healing[2]	106 (51.5)	92 (47.4)	4.0% (-6, 14)	0.39
Physician's Assessment[3]	125 (60.7)	108 (55.7)	5.0% (-5, 15)	0.27
Rectal Bleeding	145 (70.4)	139 (71.6)	-1.3% (-10, 8)	0.82
Bowel Frequency	110 (53.4)	104 (53.6)	-0.2% (-10, 10)	0.99
Total MMDAI Score	161 (78.2)	153 (78.9)	-0.7%	0.89

Modified from Applicant's Table 18, Module 5.3.5.1.2, p. 89
[1] Clinical remission was defined as a score of 0 for rectal bleeding and a combined score of ≤ 2 for bowel frequency and physician's assessment using the MMDAI subscales
[2] Mucosal healing was defined as an endoscopy score of 0 or 1
[3] Improvement in Physician's Assessment, Rectal Bleeding, Bowel Frequency, or Total MMDAI Score was defined six-week sub-score < baseline sub-score

Reviewer's Comment:

Since the primary efficacy endpoint did not succeed when a more appropriate NI margin was used (3%), the results of the secondary endpoints would have been exploratory regardless. Of note, since improvement in rectal bleeding was a component of the primary efficacy endpoint (in addition to clinical improvement), an analysis of rectal bleeding as an isolated secondary endpoint suggests that the study did not show statistical significance of non-inferiority to Asacol, even when the Applicant's NI margin of (b) (4) *is used.*

6.1.4.4.4 Findings in Special Populations/Sub-groups

BZUC3002

In her review of the original submission, Dr. Gibril made the following observations and conclusions. In BZUC3002, there was an observed gender disparity in treatment effect between male and female patients with UC. The findings of the previous review team are summarized first to enable comparisons with the BZUC3003 analysis. While the BD treatment-response rate was comparable between males and females (57% and 54%, respectively) in BZUC3002, the placebo-response was markedly different between male and female patients (20% vs 58%, respectively). As a result, a substantial treatment effect (BD treatment-response rate minus the placebo-response rate) was observed in men (37%), but none in women (-4%). The basis for the difference in placebo response rates was not clear. Additional information provided by the sponsor upon reviewer's request was non-contributory. Review of relevant published literature did not suggest gender as a factor for differences in placebo response rate in the population of interest. In a meta-analysis study recently published (Su et al., Gastroenterol 2007;132:516-526), the authors reported that placebo patients with higher mean disease activity scores at baseline were associated with lower placebo response rates. In the Applicant's study, the mean baseline disease activity scores were comparable across treatment groups as well as across gender: male patients had mean MMDAI scores of 8 in both BD- and placebo-treatment groups while female patients had mean MMDAI scores of 7.6 vs 8 for BD- and placebo-treatment groups respectively.

Table 18: BZUC3002 Results of Primary Endpoint Analysis by Sub-groups

	BD n/N (%)	Placebo n/N (%)	p-value
Total Population	(b) (4) (55)	(b) (4) (40)	**0.02**
Sex			
Male	(b) (4) (57)	(b) (4) 20)	<0.001
Female	(54)	(58)	(b) (4)

To further investigate the observed discrepancy in the primary endpoint analysis across gender, a post-hoc secondary endpoint analysis by gender was conducted. The findings were consistent with the primary endpoint findings; statistically significant differences in treatment responses were seen in men but not women. This observation was not surprising since the secondary endpoint variables were subsets of the primary composite endpoint.

In summary, based on the observed gender discrepancy in treatment effect for BZUC3002 and the inability to explain the high placebo-response rate in women, the reviewers concluded that this issue required resolution before BD tablets could be approved at a future date.

Table 19: BZUC3002 Results of Secondary Endpoints Analysis by Gender

Variables	BD n/N (%)	Placebo n/N (%)	p-value
Clinical Remission			
Males	28/81 (35)	5/40 (13)	0.01
Females			(b) (4)
Mucosal Healing			
Males	42/81 (52)	8/40 (20)	<0.001
Females			(b) (4)
Bowel Frequency			
Males	43/81 (53)	12/40 (30)	0.02
Females			(b) (4)
Rectal Bleeding			
Males	51/81 (63)	13/40 (33)	0.002
Females			(b) (4)
Complete Remission			
Males	12/81 (15)	0	0.01
Females			(b) (4)

BZUC3003

For the new study, the following table shows an analysis of efficacy for the primary endpoint for the special populations of gender, age, race, and disease severity.

Table 20: BZUC3003 Results of Primary Endpoint Analysis by Sub-groups

	BD n/N (%)	Asacol n/N (%)	Difference % (95% CI)
Sex			
Male	50/99 (51)	46/94 (49)	2% (-13, 16)
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)

Overall, the small number of patients in the over 65 years of age and non-white sub-populations limit the ability to make specific recommendations for BD use in these groups that would be generalizable to members of these sub-populations from the general UC patient population.

For the two antibiotics ciprofloxacin and metronidazole, that were permitted as part of the study design, the numbers of patients exposed to concomitant therapies with these agents were small. Of the 13 patients were treated with ciprofloxacin, seven patients were randomized to the BD treatment arm and six to the Asacol arm. Of note, the indication for ciprofloxacin treatment was urinary tract infection except for one patient with prostatitis and one patient with cholelithiasis. No patients were treated concomitantly with metronidazole.

Reviewer's Comment:

1. Given the concerns of gender from the BZUC3002 study, BZUC3003 fails to address the lack of evidence to support a treatment effect in women. The absence of a placebo arm for comparison as part of the BZUC3003 study design does not help to resolve the concerns. In an attempt to impute an appropriate placebo group, the statistical reviewer pooled the data from BZUC3002 and BZUC3003 and compared the results among the three different treatment arms. Of note, this reviewer acknowledges that the two clinical studies are not identical (different durations of treatment); however, the patient populations, inclusion/exclusion criteria, and primary efficacy endpoint were similar enough to justify pooling the data to allow for a surrogate placebo arm for the BZUC3003 study.

Table 21: Combined BZUC3002/BZUC3003 Results of Primary Endpoint Analysis by Gender: ITT Population

	BD n/N (%) (95% CI)	**Asacol** n/N (%) (95% CI)	**Placebo** n/N (%) (95% CI)	% Difference BD vs Placebo (95% CI)	% Difference Asacol vs Placebo (95% CI)	Difference BD vs Asacol (95% CI)
Male	(b) (4) (53%) (b) (4)	(b) (4) (49%) (b) (4)	(b) (4) (20%) (b) (4)	33% (b) (4)	29% (b) (4)	4% (b) (4)
Female	(b) (4)					

With the imputed placebo arm from BZUC3002, the proportion of female patients with a BD-treatment response compared to placebo-response was (b) (4) *with a 95% CI of* (b) (4) *leaving the gender treatment effect disparity still unresolved.*

To address this concern in greater depth, this reviewer looked at two additional sources of information to determine if they might assist in helping to explain the observed large placebo-treatment effect observed in women in BZUC3002. First, like Dr. Gibril, this reviewer completed a search of the medical literature for descriptions of differential placebo-response between male and female UC patients. Like her, this reviewer did not find specific references related to this topic. However, a meta-analysis was identified that assessed the efficacy of 5-ASA compounds for the treatment of active UC. In the publication by Kane, et. al. (Reviews in Gastroenterological Disorders. 2003; 3(4), 210-218), of 31 studies identified, 19 met the entry criteria:

1) *Randomized trials with a parallel group design*
2) *Study population of adults with mild or moderate active UC*
3) *Comparison of oral 5-ASA compounds to placebo, sulfasalazine, or non-oral 5-ASA agents*
4) *Evaluation of clinical improvement or remission*
5) *Studies on rectal preparations, combination therapies, maintenance of remission, or therapy for Crohn's disease were excluded.*

Although the referenced studies in this meta-analysis did not do sub-population analyses for gender, a survey of those studies that were placebo-controlled showed placebo-response rates (including both male and female patients) ranging from 9% to 50%. This reviewer acknowledges that the studies vary greatly in their design including duration of treatment; the data are therefore strictly intended to give a reference range only. Thus, although the placebo-response rate in women in the BZUC3002 study (58%) is greater than the highest identified placebo-response rates reported in the meta-analysis, the response rate is not out of the range of reasonable possibility. If there was not supporting evidence for a placebo-response rate as high as that seen in BZUC3002, then this reviewer would be more inclined to question the importance of the finding and perhaps consider the finding a statistical outlier of possibility. However, the study findings from published literature suggest otherwise.

Second, this reviewer looked at the studies submitted under NDA 20-610, the original NDA for the approval of Colazal, to determine if a gender disparity in treatment effect was found. The two main studies that lead to the approval of Colazal were of a non-inferiority study design without placebo-treatment arms. In addition, the Applicant submitted one placebo-controlled study. CP069101 was a Phase 3, randomized, placebo-controlled, double-blind, dose-response study designed to compare Colazal 4.5 g and 6.75 g with placebo in patients with mildly to moderately active UC. Unlike BZUC3002, the treatment period was for four-weeks instead of eight-weeks. Both studies used a composite primary efficacy endpoint. None of the primary or secondary endpoints showed statistical significant differences between Colazal 6.75- and placebo-treated patients. The reviewers agreed with the Applicant that the lack of response in CP069101 was likely secondary to too short of a treatment duration.

As part of the study's evaluation, a subgroup analysis by gender was completed. This analysis showed significantly higher improvement rates in stool bleeding in female patients compared with male patients treated with either Colazal or placebo. The results of the gender sub-population analysis are shown in the table below.

For many of the efficacy endpoints, there is an observed trend of improved responses in women versus men in both treatment groups. However, in the placebo-treatment arm, women have a greater efficacy response than men in six of the seven endpoints and the differences are more pronounced. Since not all of the data are available, calculated p-values would have to be inferred and would therefore not be reliable. That said, there does appear to be a trend towards a greater placebo-response in women than men. The Applicant for NDA 20-610 concluded that there was no evidence of statistically significant, gender-related differences for any of the efficacy endpoints, that determination was based on pooled data between the two Colazal treatment arms.

Although not conclusive, the gender sub-analysis for CP069101 provides additional concerns that there may, indeed, be a gender-specific response difference between men and women with UC treated with Colazal and also with placebo. The reasons for this potential gender disparity are unclear. However, until shown otherwise, this reviewer agrees with the concerns of Dr. Gibril and the original submission's review team and recommends that such discrepancies be adequately addressed before the future approval of BD tablets.

Table 22: CP069101 Clinical Efficacy Results: ITT-1 (missing values counted as failures)

Efficacy Endpoints	Colazal 6.75 g/day Men (n=46)	Colazal 6.75 g/day Women (n=26)	Placebo Men (n=19)	Placebo Women (n=16)
Stool Blood	33%	54%	21%	44%
Stool Frequency	42%	27%	26%	31%
Patient Functional Assessment	44%	35%	16%	38%
Abdominal Pain	22%	27%	16%	44%
Symptom Assessment	30%	39%	21%	38%
Sigmoidoscopy	48%	39%	47%	37%
Physician's Global Assessment	35%	39%	47%	50%

Modified from Applicant's NDA 20-610 submission, 1988, Vol 7.1, p. 164

Third, this reviewer evaluated the additional materials provided by the Applicant provided on 11 November, 2008, to address the gender imbalance in the placebo-response rates observed for

BZUC3002. The evidence submitted was previously shared with the Agency 11 March, 2008, in response to an Agency Information Request during the original NDA submission. The Applicant noted that one critical factor, based on a review of the literature, that has a profound effect on placebo-response in UC clinical trials is the number and frequency of study visits. In a published review (Ilnyckyj et al., Gastroenterology, 112(6):1854-8,1997) of 38 clinical trials in active UC patients, the variable that most significantly modified the placebo-response rate was the number of study visits. Notably, more frequent study visits (i.e., >3 vs <3) had a direct correlation with a greater placebo-treatment response. Ilnyckyj et al. concluded that a higher number of clinic visits resulting in patient interaction with a physician and subsequent physician assessments provide an added therapeutic benefit for patients and contribute to the placebo effect. Applying this observation to the BZUC3002 study, the Applicant noted that more placebo-treated female patients compared to placebo-treated male patients completed the study (70.0% vs 35.0%, respectively). This observation, together with a greater number of study visits by placebo-treated female patients, led the Applicant to conclude that these findings may have influenced an increased placebo-response in female patients, with repeated physician assessments at clinic visits having a positive therapeutic effect on the patients' health. This reviewer finds this line of reasoning questionable since BZUC3002 achieved success (p=0.02) secondary to a large drop-out rate among placebo-treated male patients by inference. Conversely, if one agrees with the Applicant's rationale for the observed gender discrepancy in placebo-treated patients, the study would likely have failed if more placebo-treated male patients had completed the study, thus likely increasing the overall placebo-response arm, thereby decreasing the overall BD-treatment effect.

2. Sub-analysis by prior UC treatment with BD therapy

As introduced in Section 6.1.3.1, Inclusion Criterion #5 allowed prior therapy with 5-ASA compounds as long as those drugs were not taken within the 14 days preceding initiation of study medication. However, Exclusion Criterion #1 disallowed patients whose UC symptoms had worsened or failed to improve during chronic therapy (greater than seven days) with ≥ 6.6 g/day of BD treatment within 30 days of screening. The concern is that excluding patients who were non-responsive to prior BD therapy may have potentially biased enrollment and "enriched" the chance of success. To evaluate this concern, Dr. Farr, at the request of this reviewer, conducted a sub-analysis of the primary efficacy endpoint, focusing on prior Colazal therapy.

Table 23: Sub-analysis of Primary Efficacy Endpoint by prior Colazal Therapy

Prior 5-ASA Use	BD Tablet	Asacol	Treatment Difference (95% CI)
Yes	92/160=57.5%	86/159=54%	3% (-8%, 14%)
No	24/46=52%	23/35=66%	-14% (-34%, 8%)

Those patients who had previously taken Colazal had a much improved response to BD tablet treatment than those who were naïve to BD therapy. In fact, for those patients without prior history of Colazal treatment, that subpopulation of patients would not have achieved success in the study, even using the Applicant's NI margin of (b) (4) *Although not conclusive, there remains concern that by excluding patients who were non-responsive to prior BD therapy, the Applicant may have biased the potential for study success.*

6.1.5 Clinical Microbiology

Not applicable for the proposed product.

6.1.6 Efficacy Conclusions

6.1.6.1 Study BZUC3002

In the sponsor's single placebo-controlled study (n=249, 166 in the BD-treatment arm), there was an unexplained difference in results between male and female patients. Identified during the original submission and prior review of BZUC3002, an sub-group analysis by gender showed that while both male and female patients responded similarly on BD therapy (57% of men and 54% of women were identified as responders in the primary endpoint efficacy analysis), there was a marked difference in placebo response (20% of men and 58% of women). When compared to placebo response, the treatment effect of BD therapy was superior to placebo in male patients ($p<0.001$) but the treatment difference was insignificant in females (b) (4) Consequently, a substantial therapeutic gain was demonstrated among men (37%), but none among women (-4%). The observed superior efficacy of BD tablets in the study was largely driven by a subpopulation's finding, namely, males. Conversely, the efficacy of BD tablets was not established in women with UC.

6.1.6.2 Study BZUC3003

In this non-inferiority, active-controlled study comparing BD tablets to Asacol, the Applicant's cited literature and rationale do not support the choice of a (b) (4) NI margin. Placebo-controlled studies of Asacol, the active comparator in BZUC3003, dosed comparably, in a similar patient population, for an analogous length of time, and with comparable efficacy endpoints, support a NI margin no greater than 3%. When this 3% NI is employed, the study fails to support that BD tablets are non-inferior to Asacol. In addition, since this study did not have a placebo-controlled cohort, the previously outstanding question regarding gender discrepancy in treatment response remains unanswered. And review of the literature and the studies that led to approval of Colazal are inconclusive to help address this observation, (b) (4)

7 INTEGRATED REVIEW OF SAFETY

Current Contraindications, Warnings, and Precautions for Colazal

In the context of background safety information for the active moiety balsalazide disodium, Colazal, the capsule formulation of BD approved in 2000, has a safety profile consistent with other members of the 5-ASA class of compounds. The current labeling for Colazal has the following information regarding safety concerns:

Contraindications

Patients with hypersensitivity to salicylates. Hypersensitivity reactions may include, but are not limited to, the following: anaphylaxis, bronchospasm, and skin reaction.

Warnings and Precautions

1. Exacerbations of Ulcerative Colitis. In adult clinical trials, 3 out of 259 patients reported exacerbation of UC symptoms. In pediatric clinical trials, 4 out of 68 patients reported symptoms of UC exacerbation.
2. Pyloric Stenosis: Patients with pyloric stenosis may have prolonged gastric retention of Colazal capsules.
3. Renal: Renal toxicity has been observed in animals and patients given other mesalamine products. Caution should be exercised with patients with known renal dysfunction or a history of renal disease.

Common Adverse Events in Adult UC Patients

In four controlled clincial studies, patients who received Colazal 6.75 g/day most frequently reported the following AEs: headache (8%), abdominal pain (6%), diarrhea (5%), nausea (5%), vomiting (4%), respiratory infection (4%), and arthralgia (4%). Some AEs (abdominal pain, fatigue, and nausea) were reported more frequently in women than in men. AEs reported by 1% or more of patients who participated in the four controlled clinical trials are presented in Table 24.

Table 24: AEs Occurring in ≥1% of Adult Colazal Patients in Phase 3 Clinical Trials

Adverse Reaction	Colazal 6.75 g/day N=259	Placebo N=35
Abdominal pain	16 (6%)	3 (1%)
Diarrhea	14 (5%)	3 (1%)
Arthralgia	9 (4%)	0 (0%)
Rhinitis	6 (2%)	0 (0%)
Insomnia	6 (2%)	0 (0%)
Fatigue	6 (2%)	0 (0%)
Flatulence	5 (2%)	0 (0%)
Fever	5 (2%)	0 (0%)
Dyspepsia	5 (2%)	0 (0%)
Pharyngitis	4 (2%)	0 (0%)
Coughing	4 (2%)	0 (0%)
Anorexia	4 (2%)	0 (0%)
Urinary tract infection	3 (1%)	0 (0%)
Myalgia	3 (1%)	0 (0%)
Flu-like disorder	3 (1%)	0 (0%)
Dry mouth	3 (1%)	0 (0%)
Cramps	3 (1%)	0 (0%)
Constipation	3 (1%)	0 (0%)

Modified from Colazal labeling Table 1.

Note: AEs occurring in at least 1% of Colazal patients which were less frequent than placebo for the same event were not included in the table.

Key safety findings from previous review cycle

For the original submission of NDA 22-205, Dr. Fathia Gibril noted the following findings in her clinical review:

Of a total of 250 patients randomized in BZUC3002, 247 were included in the safety population: 99.8% of patients in the BD-treatment group and 97.5% of the placebo-treatment group. No deaths were reported. A lower percentage of BD-treated patients experienced serious adverse events (2.4%), discontinued secondary to AEs (10%) and experienced treatment-related AEs (8%) than patients receiving placebo (5%, 13% and 9%, respectively). Worsening UC was the only SAE reported by >1% of subjects in either treatment group and occurred less frequently in subjects treated with BD tablets than with placebo (1.8% vs 3.8%). The most frequent AE leading to discontinuation from BD therapy was worsening UC. A total of 5.4% of BD-treated patients were withdrawn due to worsening UC, compared to 11.4% of placebo-treated patients.

A lower percentage of patients reported at least one adverse event (AE) in the BD group (55%) than in the placebo group (68%). Overall, events related to gastrointestinal (GI) disorder was the most frequently reported (30%) AE occurring in ≥2% of patients, but the event was less frequent in the BD group than in placebo group (26.2% vs 36.7%). While worsening of UC was the most common GI related event in either treatment group, it occurred less frequently in the BD group as compared to the placebo group (7% vs 14%). The only GI events that occurred in ≥2% of subjects in the BD tablets group and not in the placebo group were abdominal distension (4.2%) and flatulence (2.4%). Headache was the second most common AE with an incidence of 6% in the BD group and 14% in the placebo group. There were no clinically meaningful changes in laboratory parameters or vital signs in the study.

Very few AEs were considered to be related to either BD tablets or to placebo. The investigator considered the AEs to be related in a similar proportion of subjects treated with BD tablets and with placebo (8% and 9%, respectively). Drug-related events of nausea and rash (two patients each) were experienced by 1% of subjects in the BD-treatment group; no patients in the placebo group experienced drug-related nausea or rash.

The interim report from an ongoing long term, open label, safety extension study (BZUC3005) including patients showed a similar safety profile. The most frequent AEs were worsening UC (5%) and diarrhea (3%). SAEs were reported in two patients: worsening UC and bronchitis. Four patient s discontinued the study due to worsening UC. No deaths were reported in this study.

In summary, BD tablets were determined to safe and well-tolerated in patients with mildly to moderately active UC. The overall safety profile of the tablet dosage form was similar to the capsule dosage form, which was approved for marketing in the U.S. in July 2000.

7.1 Methods and Findings

The Applicant collected safety information from three clinical study sources as part of the BD tablet development program: the two Phase 3 clincial trials BZUC3002 and BZUC3003 as well as the long-term, open-label safety and tolerability study BZUC3005. Patients who completed either BZUC3002 or BZUC3003 were eligible for subsequent participation in BZUC3005. Patients enrolled in BZUC3005 received BD tablets 3.3 g BID as part of an open-label study design. At the discretion of the investigator, the dose could be increased to a maximum of 4.4 g BID. The date of the last patient enrolled in BZUC3005 was 13 August, 2007.

Table 25: Sources for Safety Data

	BZUC3002	BZUC3003	BZUC3005
Total Patients in Original NDA	250 from 55 centers	Not applicable	115 from 75 centers
Total Patients in Original 120-Day Safety Update	250 from 55 centers	410 from 79 centers	443 from 89 centers
Total Patients in CR Safety Update	250 from 55 centers	410 from 79 centers	443 from 89 centers
Total Patients in Resubmission 120-Day Safety Update	250 from 55 centers	410 from 79 centers	443 from 89 centers
Treatment Duration	8 Weeks	6 Weeks	24 Months minimum
Scheduled Visits	Weeks: 0, 1, 2, 4, 8	Weeks: 0, 1, 2, 6	Months: 0 then Q3
Countries	U.S.	U.S.	U.S.

For the purpose of the comprehensive safety data assessment, the Applicant pooled patient data from the three clincial trials for a total of 565 unique patients; for those patients randomized to a BD treatment arm in either BZUC3002 or BZUC3003, the data were grouped and termed "All Randomized Safety Subjects (ARSS)." Although no new patients were exposed to BD tablets at the time of this Complete Response submission (compared to the original 120-Day Safety Update), 342 patients had additional exposure data collected as part of enrollment in BZUC3005. For this resubmission, the median number of days of exposure to BD tablets for the ARSS BD patients was 256 days compared to 88 days in the previous 120-Day Safety Update. Mean (SD) exposure was 225 (156) days compared with 107 (74) days at the time of the original 120-Day Safety Update.

7.1.1 Deaths

One death was reported in the BD tablet development program. This event occurred after the data deadline for the prior 120-day Safety Update.

Patient B3003-0547-02 was a 63-year-old male who received BD tablets (3.3 g BID) for a total of 109 days during participation in the BZUC3003 and BZUC3005 studies. The patient was diagnosed with metastatic malignant melanoma during his participation in the BZUC3005. The immediate cause of death noted to be cerebral edema as a result of metastatic melanoma with multiple brain lesions. The patient was never withdrawn from the study drug or discontinued from the study due to AE.

Reviewer's Comment:

This reviewer agrees with the clinical investigator at the study site that the cause of death to be unlikely related to exposure to BD tablets.

7.1.2 Other Serious Adverse Events

The proportion of patients experiencing at least one serious adverse event (SAE) in the ARSS BD, Asacol, and placebo populations was 3%, <1%, and 6% respectively. Worsening UC symptoms was the only SAE reported for more than 1% of patients in all treatment groups, occurring at a frequency of 1% of ARSS BD patients, no Asacol patients, and 5% of placebo patients. None of the SAEs was considered by the investigators to be related to study drug.

Table 26: Treatment-Emergent SAEs during the Double-Blind Clinical Studies: BZUC3002 and BZUC3003

System Organ Class: Preferred Terms	ARSS BD N=378 n (%)	Asacol N=198 n (%)	Placebo N=79 n (%)
Number of patients with at least one SAE	10 (3)	1 (<1)	5 (6)
Colitis ulcerative	5 (1)	0	4 (5)
Dehydration	1 (<1)	0	1 (1)
Abdominal pain	2 (<1)	0	0
Anemia	1 (<1)	0	0
Ankle fracture	1 (<1)	0	0
Cholecystitis	1 (<1)	0	0
Colitis	0	0	1 (1)
Anal fistula	0	0	1 (1)
Cellulitis	1 (<1)	0	0
Pyrexia	1 (<1)	0	0
Arthritis	0	1 (<1)	0
Deep Vein Thrombosis	1 (<1)	0	0
Thrombophlebitis	1 (<1)	0	0

For the comprehensive safety population, of the 565 patients treated with BD tablets at the time of this Complete Response resubmission, no SAE preferred term was experienced by >2% of

patients treated with BD tablets, and only worsening UC (2%) occurred in 1% or more balsalazide-treated patients.

Table 27: Treatment-Emergent SAEs for the Comprehensive Safety Population (BZUC3002, BZUC3003, and BZUC3005)

Preferred Term	Comprehensive Safety Population N=565 n (%)
Patients with at least one SAE	28 (5)
Colitis ulcerative	10 (2)
Abdominal pain	4 (<1)
Cellulitis	3 (<1)
Anemia	2 (<1)
Intervertebral disc protrusion	2 (<1)
Abortion spontaneous	1 (<1)
Ankle fracture	1 (<1)
Bronchitis	1 (<1)
Cardiac failure congestive	1 (<1)
Chest pain	1 (<1)
Cholecystitis	1 (<1)
Clostridial infection	1 (<1)
Clostridial colitis	1 (<1)
Convulsion	1 (<1)
Dehydration	1 (<1)
Deep vein thrombosis	1 (<1)
Dyspnea	1 (<1)
Influenza	1 (<1)
Lower limb fracture	1 (<1)
Lymphedema	1 (<1)
Metastatic malignant melanoma	1 (<1)
Pancreatic enzymes increased	1 (<1)
Pneumonia	1 (<1)
Pyrexia	1 (<1)
Thrombophlebitis	1 (<1)
Weight decreased	1 (<1)

Note: All patients received BD treatment, either through randomization to the BD cohorts in BZUC3002 or BZUC3003 or as part of open-label treatment in BZUC3005

Overall, the incidence and type of recorded SAEs was comparable between the Complete Response Safety Update and the prior 120-Day Safety Update. New preferred terms not previously recorded in the BD-treated patients were: intervertebral disc protrusion (2), abortion spontaneous (1), cardiac failure congestive (1), clostridial infection (1), clostridial colitis (1),

convulsion (1), dyspnea (1), influenza (1), lymphedema (1), metastatic malignant melanoma (1), and weight decreased (1).

Reviewer's Comment:

Upon review of the SAE profile for BD tablets to date, this reviewer has not identified any new events of serious concern and for those events occurring in >2% of patients, the safety profiles are similar to those seen with Colazal and other 5-ASA compounds. Of note, there were no reported events related to either renal impairment, a warning included in the Colazal labeling.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 28 summarizes the disposition of patients for the comprehensive safety population, divided by source. Of the 565 patients enrolled in BZUC3002 and BZUC3003, 378 patients received BD therapy, 198 received Asacol, and 79 received placebo. The proportion of patients completing study enrollment was 76% of BD-treated patients, 82% of Asacol-treated patients, and 56% of placebo-treated patients. The most common reasons for discontinuation were lack of efficacy (13%) and withdrawal secondary to an AE (6%).

For BZUC3003, two patients (226-17 and 226-20) were assigned to the BD treatment arm, received study drug, had no post-baseline safety assessment, and were excluded from the safety analyses. For the patient who discontinued the study for "other" reasons, the patient stated the lack of commitment to completing the study. Of note, the ARSS combined safety data for BZUC3002 and BZUC3003 would reflect circumstances that affected each of the studies independently.

For BZUC3005, the Applicant listed three patients as "ongoing" in error secondary to a data discrepancy in each patient's CRF termination page. Each of these three patients was, in fact, discontinued early from the study: 0483-01 was lost to follow-up, 0483-03 had lack of efficacy, and 0483-05 requested to be withdrawn from the study. Table 28 reflects the appropriate disposition of those patients. Of note, no new patients enrolled in the BZC3005 study since the prior 120-Day Safety Update. Of the seven patients discontinued from the study for "other" reasons, four patients did not complete secondary to early study site closure, two patients became pregnant, and one patient took prohibited concomitant medications.

Table 28: Patient Disposition: All Randomized Safety Participants

	BD Tablets	Placebo	Asacol	Total
BZUC3003	**N=210**	**NA**	**N=198**	**N=408**
Randomized	100% (168)		100% (198)	100% (408)
Completed study	83% (175)		82% (163)	83% (338)
Discontinued study	17% (35)		18% (35)	17% (70)
Lack of efficacy	7% (15)		10% (20)	9% (35)
Adverse event	5% (10)		3% (6)	4% (16)
Patient request to withdraw	4% (8)		1% (2)	2% (10)
Patient lost to follow-up	<1% (2)		3% (5)	2% (7)
Patient non-compliance	0%		<1% (1)	<1% (1)
Other	0		<1% (1)	<1% (1)
ARSS Population: BZUC3002/BZUC3003	**N=378**	**N=79**	**N=198**	**N=655**
Randomized	100% (378)	100% (79)	100% (198)	100% (655)
Completed study	76% (286)	56% (44)	82% (163)	75% (493)
Discontinued study	24% (92)	44% (35)	18% (35)	25% (162)
Lack of efficacy	11% (43)	29% (23)	10% (20)	13% (86)
Adverse event	7% (25)	13% (10)	3% (6)	6% (41)
Patient request to withdraw	3% (12)	1% (1)	1% (2)	2% (15)
Patient lost to follow-up	<1% (3)	1% (1)	3% (5)	1% (9)
Patient non-compliance	<1% (2)	1% (1)	<1% (1)	<1% (4)
Other	2% (7)	1% (1)	<1% (1)	1% (9)
BZUC3005[a]	**N=253**	**N=48**	**N=142**	**N=443**
Rolled over from either BZUC3002/BZUC3003	100% (253)	100% (48)	100% (142)	100% (443)
Completed study	59% (149)	71% (34)	60% (85)	60% (268)
Discontinued study early	41% (104)	29% (14)	40% (57)	40% (175)
Lack of efficacy	13% (33)	13% (6)	14% (20)	13% (58)
Patient request to withdraw	11% (29)	8% (4)	8% (11)	10% (43)
Patient lost to follow-up	9% (23)	2% (1)	8% (11)	8% (34)
Adverse event	6% (15)	2% (1)	6% (8)	5% (24)
Other	1% (3)	4% (2)	1% (2)	2% (7)
Patient non-compliance	<1% (1)	0	4% (5)	1% (6)

Modified from Applicant's Vol 28, Table 4, pp. 33, 34.

[a] For patients enrolled in BZUC3005, all of the patients received open-label, BD therapy. The column information therefore reflects the randomization treatment assignment for the original study (BZUC3002 or BZUC3005) which qualified them for participation in BZUC3005.

7.1.3.2 Adverse events associated with dropouts in BZUC3003

Table 29 summarizes the treatment-emergent adverse events (TEAE) that led to discontinuation from participation in BZUC3003. A total of 16 patients (3.9%) were withdrawn from the study due to an AE. More patients withdrew secondary to an AE in the BD-treatment arm (4.8%) compared to the Asacol-treatment arm (3.0%). Worsening UC was the most common TEAE that led to study discontinuance (1.7% of all patients). A larger proportion of patients in the BD-treatment group (2.4%) discontinued the study due to worsening UC compared with the Asacol-treatment group (1.0%).

Table 29: BZUC3003 Treatment-Emergent AEs leading to Withdrawal

Preferred Term[1]	BD Tablets N=210	Asacol N=198	Total N=408
Proportion of patients reporting AE leading to withdrawal[2]	4.8% (10)	3.0% (6)	3.9% (16)
Colitis ulcerative	2.4% (5)	1.0% (2)	1.7% (7)
Nausea	1.0 (2)	0.5 (1)	0.7 (3)
Rectal haemorrhage	0 (0)	1.0 (2)	0.5 (2)
Frequent bowel movements	0.5 (1)	0 (0)	0.2 (1)
Vomiting	0.5 (1)	0 (0)	0.2 (1)
Erythema nodosum	0.5 (1)	0 (0)	0.2 (1)
Abdominal pain	0 (0)	0.5 (1)	0.2 (1)
Diarrhoea	0 (0)	0.5 (1)	0.2 (1)
Arthritis	0 (0)	0.5 (1)	0.2 (1)
Headache	0 (0)	0.5 (1)	0.2 (1)

[1] Preferred terms were coded using MedDRA Version 8.1
[2] Patients with more than one TEAE were only counted once
Modified from Applicant's submission, Module 5.3.5.1.2, Table 29, p. 111

For the comprehensive safety population, Table 30 summarizes the treatment-emergent adverse events (TEAE) that led to discontinuation from participation in all the studies as a whole. A total of 53 patients (9%) were withdrawn secondary to an AE. Worsening UC was the most common TEAE that led to study discontinuance (5% of all patients). All of the other AEs that led to study withdrawal occurred at a frequency of less than 1%.

Table 30: Discontinuation Secondary to AEs: Comprehensive Safety Population (BZUC3002, BZUC3003, and BZUC3005)

Preferred Term	Comprehensive Safety Population N=565 n (%)
Patients with at least one SAE leading to discontinuation	53 (9)
Colitis ulcerative	29 (5)
Pregnancy	4 (<1)
Vomiting	4 (<1)
Abdominal pain	3 (<1)
Erythema nodosum	2 (<1)
Nausea	2 (<1)
Rash	2 (<1)
Abdominal pain lower	2 (<1)
Biopsy mucosa abnormal	1 (<1)
Blood albumin	1 (<1)
Cardiac failure congestive	1 (<1)
Clostridial infection	1 (<1)
Constipation	1 (<1)
Diarrhea	1 (<1)
Dizziness	1 (<1)
Edema peripheral	1 (<1)
Frequent bowel movements	1 (<1)
Hematocrit	1 (<1)
Hemoglobin	1 (<1)
Muscle spasms	1 (<1)
Pharyngeal erythema	1 (<1)
Pyrexia	1 (<1)
Rectal Fissure	1 (<1)
Red blood cell count	1 (<1)
Sigmoidoscopy abnormal	1 (<1)
Weight decreased	1 (<1)

Modified from Applicant's Table 27, Module 5.3.5.3.2, Volume 28, p. 96\

7.1.3.3 Other significant adverse events

There were no other significant AEs.

7.1.4 Other Search Strategies

No other search strategies were evaluated.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The investigator was responsible for the detection and documentation of events meeting the definition of an AE or SAE. At each assessment, after the patients had an opportunity to spontaneously mention any problems, the investigator asked the patient about any medical problems experienced and if any new medications were taken since the last visit.

All AEs that occurred during the study, regardless of causality or seriousness, were assessed and recorded in the appropriate section of the case report form (CRF) as well as in the subject's medical records. All AEs and SAEs were followed until resolution, until the condition stabilized, until the event was otherwise explained, or until the subject was lost to follow-up. The investigator was responsible for ensuring that follow-up included any supplemental investigations as were necessary to elucidate as completely as practical the nature and/or causality of the AE or SAE.

For BZUC3003, AEs were assessed by the investigators at baseline, Week 1, Week 2, and Week 6/EOT. For BZUC3005, safety assessments were assessed at clinic study visits at Screening, Baseline, Month 1, Month 3, and every 3 months thereafter through the End-of-Treatment (EOT) visit.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded to standard preferred terms and body system using Medical Dictionary for Regulatory activities (MedDRA) Version 8.1 and are acceptable. Of note, the Applicant grouped the preferred terms colitis ulcerative, worsening of UC symptoms, and aggravation of UC as indicative of worsening UC symptoms/UC flare. Therefore, “worsening UC” will be used throughout this review in reference to this grouping of preferred terms to indicate the clinical presentation of a UC flare.

7.1.5.3 Incidence of common adverse events

<u>BZUC3003</u>

Of the 408 patients in the safety population in the BZUC3003, 58.1% experienced at least one treatment-emergent (TE) AE during the study (see the Table below). The proportion of patients who experienced any AEs was higher in the BD-treatment group (61.4%) compared with the Asacol-treatment group (54.5%). The most frequently reported System Organ Class (SOC) for treatment-emergent AEs was GI disorders with 27.9% of all patients experiencing at least one event. The proportion of patients experiencing a TE GI event was higher in the BD-treated patients (30.5%) compared to the Asacol-treated patients (25.3%). The proportion of patients

(7.1%) who experienced nausea (the most commonly reported TE GI disorder) was the same for both drug-treatment groups.

The most frequently reported AEs were headache (9.8%) and nausea (7.1%). The proportions of patients experiencing either headache or nausea were similar between the two drug-treatment groups. The incidence of worsening of UC symptoms was 7.1% in the BD-treated patients compared to 2.0% in patients treated with Asacol.

The majority of subjects experiencing treatment-emergent AEs had AEs that were mild (3.4%) or moderate (21.3%) in intensity compared to severe in intensity (5.9%).

The interim report from the ongoing long term open-label safety extension study (BZUC3005) showed a similar safety profile. The most frequent AEs were worsening UC (5%) and diarrhea (3%).

For a complete assessment of all common AEs reported by patients in the two double-blind Phase 3 studies, please refer to Table 31.

7.1.5.4 Common adverse event tables

Table 31: Summary of TEAEs Reported by ≥ 2% of Patients in Phase 3, Double-blind Studies (BZUC3002 and BZUC3003)

SOC/Preferred Term	ARSS BD[a] N=378 % (n)	Asacol N=198 % (n)	Placebo N=79 % (n)
Number of patients with at least one AE	59% (223)	55% (108)	70% (55)
Gastrointestinal Disorders	29 (109)	25 (50)	38 (30)
Colitis ulcerative	7 (26)	2 (4)	15 (12)
Nausea	6 (21)	7 (14)	5 (4)
Abdominal Pain	4 (15)	6 (12)	4 (3)
Vomiting	3 (12)	5 (10)	3 (2)
Diarrhea	3 (10)	3 (2)	3 (5)
Flatulence	2 (8)	3 (6)	0 (0)
Abdominal distension	2 (9)	2 (4)	0 (0)
Dyspepsia	2 (6)	3 (5)	3 (2)
Constipation	<1 (3)	1 (2)	5 (4)
Abdominal pain upper	1 (4)	0 (0)	3 (2)
Hemorrhoids	<1 (3)	2 (3)	0 (0)
Cardiac Disorders	2 (8)	2 (4)	3 (2)
Chest pain	2 (6)	2 (3)	1 (1)
General Disorders and Administration Site Conditions	9 (34)	6 (12)	14 (11)
Fatigue	3 (10)	3 (5)	5 (4)
Pyrexia	2 (8)	<1 (1)	1 (1)
Edema peripheral	1 (4)	<1 (1)	4 (3)

Pain	1 (4)	0 (0)	4 (3)
Asthenia	<1 (1)	<1 (1)	3 (2)
Infections and Infestations	19 (70)	15 (30)	18 (14)
Nasopharyngitis	4 (15)	4 (8)	5 (4)
Urinary tract infection	3 (12)	5 (9)	1 (1)
Influenza	3 (10)	2 (3)	4 (3)
Upper respiratory tract infection	3 (10)	2 (3)	3 (2)
Sinusitis	3 (10)	2 (3)	1 (1)
Herpes simplex	<1 (3)	0 (0)	3 (2)
Metabolism and nutrition disorders	2 (6)	1 (2)	6 (5)
Hypokalemia	<1 (2)	0 (0)	3 (2)
Hyperlipidemia	0 (0)	0 (0)	3 (2)
Musculoskeletal And Connective Tissue Disorders	10 (38)	12 (24)	8 (6)
Back pain	3 (12)	3 (6)	4 (3)
Arthralgia	2 (8)	2 (4)	1 (1)
Muscle spasms	2 (7)	2 (3)	0 (0)
Myalgia	1 (5)	2 (4)	1 (1)
Pain in extremity	2 (6)	1 (2)	1 (1)
Arthritis	0 (0)	2 (3)	0 (0)
Nervous System Disorders	11 (41)	14 (27)	15 (12)
Headache	8 (31)	10 (20)	14 (11)
Dizziness	1 (4)	2 (4)	0 (0)
Psychiatric Disorders	4 (14)	1 (2)	4 (3)
Insomnia	3 (10)	1 (2)	1 (1)
Renal and Urinary Disorders	8 (29)	4 (7)	3 (2)
Hematuria	<1 (1)	2 (3)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders	8 (29)	4 (7)	3 (2)
Pharyngolaryngeal pain	3 (12)	2 (3)	1 (1)
Cough	1 (5)	2 (3)	0 (0)
Skin and Subcutaneous Tissue Disorders	5 (20)	4 (8)	3 (2)
Rash	2 (7)	3 (5)	1 (1)

AEs were recorded in MedDRA version 8.1

[a] ARSS BD population are all patients who received BD-treatment in either BZUC3002 or BZUC3003

7.1.5.5 Identifying common and drug-related adverse events

For the double-blind studies, TEAEs were determined by the investigators to be drug-related or not. Overall, the proportion of patients who experienced drug-related TEAEs was comparable across the treatment groups (10% of BD-treated patients, 11% of Asacol-treated patients, and 9% of placebo-treated patients) as shown in Table 32. Drug-related AEs that occurred in >1% of BD-treated were worsening UC (1% BD-, 0% Asacol-, and 3% placebo-treated patients), diarrhea (1% BD-, 2% Asacol-, and 1% placebo-treated patients), nausea (3% BD-, 4% Asacol-, and 0% placebo-treated patients), and headache (1% BD-, 3% Asacol-, and 1% placebo-treated patients).

Table 32: Study Drug-Related TEAEs from Double-Blind Studies for Events Occurring >1% of BD-treated Patients

SOC/PT	ARSS BD N=378 % (n)	Asacol N=198 % (n)	Placebo N=79 % (n)
Patients with at least one AE	10% (37)	11% (21)	9% (7)
Gastrointestinal Disorders	6 (22)	7 (13)	5 (4)
Nausea	3 (10)	4 (7)	0 (0)
Diarrhea	1 (4)	2 (3)	1 (1)
Colitis ulcerative	1 (5)	0 (0)	3 (2)
Nervous System Disorders	2 (6)	3 (6)	1 (1)
Headache	1 (4)	3 (5)	1 (1)

Modified from Applicant's Table 19, Module 5.3.5.3.2, Volume 28, pp. 72-74

7.1.5.6 Additional analyses and explorations

Based on the mechanism of action of BD and other compounds which act through release or delivery of 5-ASA, an analysis of AEs by pancreatic, renal, and hepatic organ systems was conducted. For the cumulative analysis of the data from the two Phase 3 studies, BD-treated patients developed TEAEs that involved the renal system (nine patients) and hepatic system (six patients); no TEAEs for the pancreatic system were reported. The findings are shown in Table 33 below.

Reviewer's Comment:

1. Renal toxicity has been noted with other members of the 5-ASA drug class and is included in the warnings section of the Colazal labeling for BD capsules.

2. The Applicant has proposed adding the following to the "Warnings and Precautions" of the labeling for BD tablets: (b) (4)

For the six patients that developed elevated liver enzymes in the Phase 3 studies of BD tablets, none of them met the criteria for Hy's Law (transaminase elevations combined with increased bilirubin in the absence of increased alkaline phosphatase). In addition, these patients did not have evidence of irreversible liver damage; the transaminase elevations resolved to baseline levels. In the context of post-marketing safety reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine, the patients in the BD studies did not have pre-existing liver disease and did not develop liver failure.

Should BD tablets be approved in the future, attention should be paid to Applicant's proposal of a hepatic warning to the labeling. To address the issue in greater depth, a thorough post-marketing evaluation of safety reports for members of the 5-ASA class of compounds could be of

benefit. If the data indicate that a true hepatic signal exists, a class warning should be considered for Colazal and other members of the 5-ASA class.

Table 33: TEAEs Experienced by BD-Treated Patients Related to Renal and Hepatic Systems (BZUC3002 and BZUC3003 Studies)

SOC/PT	BD N=378 n (%)	Asacol N=378 n (%)	Placebo N=378 n (%)
Hepatic Function			
ALT increased	2 (<1)	0 (0)	0 (0)
AST increased	3 (<1)	0 (0)	0 (0)
Albumin	1 (<1)	0 (0)	0 (0)
Renal Function			
Bacteria urine	1 (<1)	0 (0)	1 (1)
Blood urine present	1 (<1)	0 (0)	1 (1)
Creatinine renal clearance decreased	1 (<1)	0 (0)	0 (0)
Hypokalemia	2 (<1)	0 (0)	2 (3)
Hematuria	1 (<1)	3 (2)	3 (2)
Renal failure	1 (<1)	0 (0)	0 (0)
White blood cells urine positive	2 (<1)	0 (0)	0 (0)

7.1.6 Less Common Adverse Events

A review of remaining AEs, not included in the above AE safety sections, did not identify any new safety concerns.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

All routine laboratory samples were analyzed by a central, licensed clinical laboratory. Hematology, blood chemistry, and urinalysis parameters were collected during the BZUC3002 (Screening, Day 14, and Day 56/EOT), BZUC3003 (Screening, Day 14, and Day 42/EOT), and

BZUC3005 (Month 1, Every 3 months/EOT) clinical studies. Laboratory values and changes from baseline in laboratory values were summarized descriptively by treatment group.

The normal range for each parameter was used to create categories of low, normal, or high. Any result higher than upper limit of normal (ULN) or lower than lower limit of normal (LLN) was categorized as high or low respectively, and any result within the lower and upper limits of normal was categorized as normal. The number and percentage of patients for each treatment group in each shift category from baseline to final evaluation was recorded for each parameter.

For the comprehensive safety population, mean values for all hematology, chemistry, and urinalysis parameters, both at baseline and end of treatment, were within normal range. Changes in laboratory values from baseline to end of treatment were reported, and although there were minor increases or decreases, the mean values were within the normal range. During study participation, a few chemistry abnormalities were noted and those findings are presented in Section 7.1.5.6.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

As determined by the protocol design, vital signs were recorded. Assessments included sitting systolic and diastolic blood pressure, temperature, and heart rate. Vital signs were measured throughout the studies at scheduled visits: BZUC3002 (Screening, Day 14, and Day 56/EOT), BZUC3003 (Screening, Day 14, and Day 42/EOT), and BZUC3005 (Month 1, Every 3 months/EOT).

Vital sign measurements were summarized at each time point. In addition, changes from baseline in vital sign measurements were summarized at each post-baseline time point. For each summary, the mean, median, minimum and maximum values were recorded by treatment group.

No clinically significant mean changes in systolic or diastolic blood pressure, pulse rate, body temperature was observed from screening to Week 6/EOT and the results obtained were comparable to the observations determined for BZUC3002.

7.1.9 Electrocardiograms (ECGs)

The applicant did not provide any clinical or adverse event data regarding ECGs in this application.

7.1.10 Immunogenicity

The applicant did not provide any clinical or adverse event data regarding Immunogenicity in this application.

7.1.11 Human Carcinogenicity

The Applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application.

7.1.12 Special Safety Studies

NDA 22-205 did not include special safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The majority of patients who participated in the Phase 3 studies were enrolled into the long-term safety extension study. All AEs following withdrawal of study drug underwent review by the Applicant and findings were not suggestive of an exaggerated or rebound pharmacological effect resulting in clinical consequences as a result of withdrawal of study drug. No case of drug abuse has been reported during the clinical trials with BD tablets.

7.1.14 Human Reproduction and Pregnancy Data

Pregnant women were excluded from participating in the study.

7.1.15 Assessment of Effect on Growth

There were no children involved in studies conducted under NDA 22-205.

7.1.16 Overdose Experience

No case of overdose has occurred with balsalazide disodium tablets.

7.1.17 Postmarketing Experience

Balsalazide disodium tablets are not currently approved for marketing in any country. However, the capsule formulation Colazal is approved in the U.S., has been marketed since 2000, and

results of post-marketing analyses conducted by Ann Corken Mackey (see OSE consult dated 14 January, 2008 including status update from 5 September, 2008) suggest that current safety concerns are adequately reflected in the product label.

The results of the OSE evaluation of post-marketing experience with BD are summarized below:

Based on adverse event reports submitted to the Adverse Event Reporting System (AERS) and the literature, BD is associated with serious adverse events that are labeled for the other 5-ASA compounds. DDRE recommends class labeling for all 5-ASA products to include the following warnings: myocarditis, pericarditis, vasculitis, pruritus, pleural effusion, pneumonia with and without eosinophilia, alveolitis, renal failure, interstitial nephritis, and pancreatitis.

Although evidence is limited (based on postmarketing reports), the following adverse events have been reported for other 5-ASA drugs and should be considered for inclusion in the BD label: interstitial lung disease, urticaria, pulmonary fibrosis, hemolytic uremic syndrome, angioedema, toxic epidermal necrolysis, pericardial effusion, leukopenia, and thrombocytopenia.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Populations Exposed and Extent of Exposure Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

For BZUC3003, a total of 408 patients were included in the safety population: 210 patients were treated with BD tablets and 198 patients were treated with Asacol. Two patients (226-17 and 226-20) were randomized, assigned to the BD treatment arm, received study drug, but had no post-baseline safety assessment and were excluded from the safety population.

For the comprehensive safety assessment, patients in the safety population included those who participated in BZUC3002, BZUC3003, and BZUC3005. As in the prior 120-Day Safety Update, 565 patients were exposed to BD tablets. While no new patients were exposed to BD tablets at the time of this Complete Response resubmission, 342 patients had additional exposure in the ongoing BZUC3005 study.

7.2.1.2 Demographics

In the comprehensive safety population, the demographics were similar between the treatment groups. By sex, males were represented as follows: 49% BD-, 51% Asacol-, and 40% placebo-treated patient. By race, whites were represented as follows: 84% BD-, 83% Asacol-, and 90% placebo-treated patient. By age, patients < 65 years of age were represented as follows: 93% BD-, 94% Asacol-, and 94% placebo-treated patient.

7.2.1.3 Extent of exposure (dose/duration)

The safety population included all randomized patients who received at least one dose of study drug and who provided at least one post-baseline safety assessment. For those patients who received study drug treatment in BZUC3003, the median number of days of exposure was 43.0 for both BD- and Asacol-treated patients. Mean exposure was also similar in both treatment groups (BD: 39.0 days; Asacol: 38.2 days). The details of the length of exposures in the safety population are outlined in the Table below.

Table 34: BZUC3003: Summary of Drug Exposure in the Safety Population

	BD Tablets N=210	Asacol N=198
Exposure Duration[1] (days)		
N	210	198
Mean (SD)	39.0 (13.1)	38.2 (11.4)
Median	43.0	43.0
Min, Max	6, 127	1, 58
% (N) of patients on study drug		
≥ 1 day	100 (210)	100 (198)
> 7 days	97.6 (205)	98.1 (194)
> 14 days	91.0 (191)	92.4 (183)
> 42 days	52.9 (111)	52.0 (103)

[1] Exposure Duration = date of last dose – date of first dose + 1
Modified from Applicant's Table 23, Module 5.3.5.1.2, p. 101

For the comprehensive safety assessment, patients in the safety population included those who participated in BZUC3002, BZUC3003, or BZUC3005. For this resubmission, the median number of days of exposure to BD tablets for the ARSS BD patients was 256 days compared to 88 days in the previous 120-Day Safety Update. Mean (SD) exposure was 225 (156) days compared with 107 (74) days at the time of the original 120-Day Safety Update. The details of the comprehensive safety population are provided in Table 35.

Table 35: Comprehensive BD Safety Population: Extent of Exposure to BD Tablets

	Comprehensive Safety Population N=565	Original 120-Day Safety Update Population N=565
Exposure Duration (days)		
N	565	565
Mean (SD)	225 (156)	107 (74)
Median	256	88
Min, Max	1, 553	1, 359
% (N) of patients on study drug		
≥ 1 day	100% (565)	100% (565)
> 56 days	76.1 (430)	70.0 (395)
> 182 days	58.6 (331)	15.9 (90)
> 365 days	25 (140)	0

Modified from Applicant's Table 5, Module 5.3.5.3.2, p. 35

Reviewer's Comment:

BZUC3005 is on ongoing, open-label study to collect additional, long-term data for patients exposed to BD tablets. With the intent to collect data for a minimum of two years, this reviewer finds that the Applicant's plan to collect safety data is adequate given that there have not been concerns of AEs related to chronic exposure to 5-ASA compounds to date. Although with some variation between treatment groups, the demographics are adequate for collecting safety data from the population as a whole. However, special population assessments for differences in drug effects may be difficult.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The interim report from the ongoing open-label safety extension study (BZUC3005) includes 443 patients in the safety population with UC who successfully participated in BZUC3002 or BZUC3003. For safety assessments, the enrolled patients are scheduled for clinic study visits at Screening, Baseline, Month 1, Month 3, and every 3 months thereafter through the End-of-Treatment (EOT) visit. The majority of patients (n=253) in this study received open-label BD tablets at 3.3g BID.

7.2.2.2 Postmarketing experience

Balsalazide disodium tablets are not currently approved for marketing in any country. However, the capsule formulation Colazal is approved and marketed since 2000. In addition, there are

other mesalamine-containing oral formulations that have been marketed for use in mildly to moderately active UC and the safety profile has been well established.

7.2.2.3 Literature

The Applicant provided several articles in paper format with this resubmission. This reviewer performed an additional review of the literature and incorporated those relevant articles as part of the discussion in sections of this clinical review. Although the literature referenced in support of the non-inferiority margin was adequate, the conclusions drawn by the Applicant were not appropriate. This information and the conclusions drawn from it can be found in Section 6.1.4.4.2 of this review.

7.2.3 Adequacy of Overall Clinical Experience

The study design and the protocol defined endpoints were acceptable. The trials were limited in their lack of sufficient geriatric population and racial subsets. Overall, data from the comprehensive safety population are adequate for assessment of baseline safety profiles. For rare events, the numbers of patients with an AE related to that signal may not be adequate to fully assess the safety concern. Although the maximal duration of treatment with BD tablets was eight weeks in controlled trials, 140 patients have been exposed to BD therapy for more than a year as part of participation in the long-term safety study BZUC3i005; there does not appear to be specific concerns regarding chronic exposure to BD tablets from the data collected thus far.

7.2.4 Adequacy of Routine Clinical Testing

The protocol defined clinical testing and safety assessments were adequate.

7.2.5 Adequacy of Evaluation for Potential Adverse Events for New Drug and Drug Class

BZUC3003 was appropriately designed to allow for adequate analysis of safety. Overall, the safety data demonstrated that the dose tested is safe and well tolerated. As the previous review team concluded for the original submission of this NDA, the comprehensive safety profile of BD tablet formulation is emerging to be similar to the BD capsule formulation, approved for marketing in the U.S. in July 2000 for the same indication and similar total daily dose.

Although the Applicant did not provide any clinical or adverse event data regarding ECGs in this application, mesalamine is believed to act locally in the colon, rather than systemic. Mesalamine products have been marketed for 16 years without identification of cardiac toxicities. In addition, no cardiac concerns have been identified for Colazal, the capsule formulation of BD.

7.2.6 Assessment of Quality and Completeness of Data

The data necessary to conduct a complete safety review were included in this NDA resubmission. Overall, the quality of the Applicant's assessment of the data was acceptable.

7.2.7 Additional Submissions, Including Safety Update

On 28 October, 2008, the Applicant submitted a 120-Day Safety Update for the Complete Response resubmission of NDA 22-205. This safety update contained additional data collected for BZUC3005 since the Complete Response submission 27 June, 2008. No new patients enrolled in any of the BD tablet studies and only a limited amount of new and up updated safety data had been generated since the Complete Response submission. Changes to the BD tablet safety data have been primarily collected from closing out the open-label BZUC3005 database. The BZUC3005 safety data presented represented available patient safety data as of 16 October, 2008.

A total of 21 patients had either a new or clarified TEAE since the Complete Response resubmission. Two patients enrolled in BZUC3003 (0547-03: ventricular dysfunction and 0853-03: appendicitis) experienced previously unreported serious AEs. Both serious AEs were resolved and judged by the assessing investigator as unrelated to BD treatment. No new deaths were reported.

Reviewer's Comment:

The limited amount of safety data for BZUC3005 does not substantially change the safety profile of BD tablets; no new safety signals were identified.

Upon review of the CRFs for the two new patients who experienced SAEs, this reviewer agrees that both were unlikely related to BD treatment. The ventricular dysfunction occurred in a 59 year old man with a prior history of coronary artery disease and appendicitis occurred in a 43 year old woman.

7.3 Summary of Selected Drug-Related AEs/Important Limitations of Data/Conclusions

Overall, the proportion of patients who experienced drug-related TEAEs was comparable across the treatment groups (10% of BD-treated patients, 11% of Asacol-treated patients, and 9% of placebo-treated patients). Drug-related AEs that occurred in >1% of BD-treated were worsening UC (1% BD-, 0% Asacol-, and 3% placebo-treated patients), diarrhea (1% BD-, 2% Asacol-, and 1% placebo-treated patients), nausea (3% BD-, 4% Asacol-, and 0% placebo-treated patients), and headache (1% BD-, 3% Asacol-, and 1% placebo-treated patients).

For the cumulative analysis of the data from the two Phase 3 studies, BD-treated patients developed TEAEs that involved the renal system (nine patients) and hepatic system (six

patients); no TEAEs for the pancreatic system were reported. Renal toxicity has been noted with other members of the 5-ASA drug class and is included in the warnings section of the Colazal labeling for BD capsules. Regarding the Applicant's proposed warning of use in patients with hepatic impairment, six patients were identified who had transient transaminase elevations without irreversible liver damage. To address this issue in greater depth, a thorough post-marketing evaluation of safety reports for members of the 5-ASA class of compounds could be of benefit. If the data indicate that a true hepatic signal exists, a class warning should be considered for Colazal and other members of the 5-ASA class.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

For the comprehensive safety assessment, data were pooled for patients who participated in either BZUC3002 or BZUC3003 and who were randomized to BD-treatment (the ARSS population). In addition, data collected from BZUC3005, the ongoing, open-label safety study, were also included to provide a more longitudinal safety assessment. Overall, the safety profiles for the ARSS BD-exposed population and the BZUC3005 BD-treated patients are similar without suggestion of previously unidentified safety concerns with longer treatment durations with BD tablets.

7.4.1.1 Pooled data vs. individual study data

The safety data for individual studies as well as pooled data for the comprehensive safety assessment are presented in this review. Although the duration of treatment was different between BZUC3002 (eight weeks) and BZUC3003 (six weeks), the patient populations and safety data assessments were similar.

7.4.1.2 Combining data

This review combined data from the Phase 3 and long-term safety study as indicated in the individual subsections. Beyond the number of patients exposed to a given treatment and the frequency of the events reported to those groups, no other pooling procedures were employed.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Dose ranging studies were not conducted under the clinical development program.

7.4.2.2 Explorations for drug-demographic interactions

BZUC3002

In her Clinical Review for the original submission, Dr. Gibril noted that, in the randomized safety population, smaller proportions of males and females treated with BD tablets reported any events compared to patients treated with placebo (28% vs 48% and 44% vs 50%, respectively). However, in the BD-treatment arm, women reported AEs more frequently than did men (44% vs 28%), while the frequency of AEs was comparable in the placebo arm (48% and 50%, respectively).

Overall, the most frequently reported AEs by men and women were GI-related disorders in both BD- and placebo- treatment arms (21% vs 39% and 31% vs 36%, respectively). A GI-related event was more frequent in women than men in the BD-treatment group (31% vs 21%), while frequency of a GI-related event was similar in the placebo group. In the BD-treatment group, more women than men reported GI events, including abdominal distention (7% vs 1.2%), abdominal pain (7% vs 2.4%) and vomiting (5.8% vs 1.2%). In the placebo group, vomiting was reported by 5.4% of men and none of the women. There was a higher incidence of worsening of UC symptoms in male patients than female patients in both treatment groups, but this trend was more pronounced in the placebo group (9% vs 24% and 4.7 vs 4.8%, respectively).

The clinical significance of the aforementioned GI events is unclear, given that most of the observed events are likely due to the underlying disease. The event of vomiting that was reported by women in the BD-treatment group and not in the placebo group may suggest a drug-related event, but the event also occurred with similar frequency (5.4%) in placebo men.

There were too few subjects over 65 years of age (7%) and non-white subjects (<10%) to evaluate whether there was a differential occurrence of AEs between treatment groups. Safety of BD tablets in pediatric subjects has not been evaluated in this study.

Comprehensive safety population for this Complete Response resubmission
Regarding gender, women reported TEAEs more frequently than did men (76% and 66%, respectively). TEAEs occurring in at least 5% of female patients and at least twice as frequent as in male patients were nausea (9% vs. 3%), back pain (5% vs. 2%), sinusitis (6% vs. 2%), and urinary tract infection (8% vs. 3%). Rectal hemorrhage was the only TEAE occurring in at least 5% of men and at least twice as often as women (6% vs. 2%). A similar number of men (13%) and women (12%) treated with BD tablets experienced a worsening of their UC symptoms.

Regarding other sub-populations, similar proportions of patients < 65 years of age (N=529) and ≥ 65 years of age (N=6) experienced TEAEs (71% and 69%, respectively). Additionally, similar proportions of both white and non-white patients treated with BD tablets experienced TEAEs. For each of these subgroup comparisons, no remarkable differences were observed in the incidence of specific AE preferred terms. However, the low numbers of patients for patients over 65 years of age and non-white patients limit any analysis of dose modifications in those groups.

The most common AE that led to study withdrawal was worsening of UC symptoms; no definitive trends were observed when a sub-population analysis was performed.

No clear effect was observed in subgroup differences in smoking history, renal function, NSAID/aspirin, or antibiotic usage on the incidence of AEs. Of note, there were limited numbers of patients who took concomitant medications because of the study design's concomitant medication use restrictions.

7.4.2.3 Explorations for drug-disease interactions

No explorations of drug-disease interactions were conducted.

7.4.2.4 Explorations for drug-drug interactions

There is no clear effect of AEs associated with concomitant medication use such as NSAIDS/Aspirin or antibiotics. As the Applicant indicated, there was limited numbers of patients who took these drugs because of entry criteria restrictions. Of note, as stated in the Colazal label, an *in vitro* study using human liver microsomes demonstrated that balsalazide and its metabolites (5-ASA, N-Ac-5-ASA, 4-ABA, and N-Ac-4-ABA) were not shown to inhibit the major CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) evaluated. Therefore, balsalazide and its metabolites are not expected to inhibit the metabolism of other drugs that are substrates for these CYP enzymes.

7.4.3 Causality Determination

Although BZUC3003 did not have a placebo-treatment arm, the safety database for the two Phase 3 studies does suggests that the use of BD tablets may be associated with transient elevations in transaminases without evidence of irreversible liver injury. Should BD tablets be approved in the future, attention should be paid to Applicant's proposal of a hepatic warning to the labeling. To address the issue in greater depth, a thorough post-marketing review of safety reports associated with members of the 5-ASA class could be of benefit. If the data indicate that a true hepatic signal exists, a class warning should be considered for Colazal and other members of the 5-ASA class.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended total daily dose is 6.6g to be taken twice daily (three 1.1g tablets BID) for up to eight weeks.

It should be noted that no separate dose-response trial was conducted with the BD tablets. The rationale was that the proposed total daily dose (6.6 g/day) for new tablet formulation is similar to that of the capsule formulation (6.75 g/day), Colazal, which was approved in 18 July, 2000, for the same indication. One goal of the clinical program was to provide a more convenient dosing regimen with the new tablet formulation as compared to capsule formulation (BID vs TID).

8.2 Drug-Drug Interactions

Drug-drug interaction studies have not been conducted with BD tablets. Of note, as stated in the Colazal label, an *in vitro* study using human liver microsomes demonstrated that balsalazide and its metabolites (5-ASA, N-Ac-5-ASA, 4-ABA, and N-Ac-4-ABA) were not shown to inhibit the major CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) evaluated. Therefore, balsalazide and its metabolites are not expects to inhibit the metabolism of other drugs which are substrates for these CYP enzymes.

8.3 Special Populations

As identified during the original submission and prior review of BZUC3002, a sub-group analysis by gender showed that while both male and female patients responded similarly on BD therapy (57% of men and 54% of women were identified as responders in the primary endpoint efficacy analysis), there was a marked difference in placebo response (20% of men and 58% of women). When compared to placebo response, the treatment effect of BD therapy was superior to placebo in male patients ($p<0.001$) but the treatment difference was insignificant in females (b) (4) Consequently, a substantial therapeutic gain was demonstrated among men (37%), but none among women (-4%). While a small sample size could be a potential factor for such a disparity, it is not likely in this case as women made up 51% of the evaluated patients. This gender disparity in treatment response was consistent in that evaluation of the secondary efficacy endpoints revealed a statistically significant response in male patients; the treatment differences were insignificant for all secondary endpoint variables in female patients. This finding is not surprising since secondary endpoint variables were subsets of the composite primary endpoint.

Although the gender disparity in treatment effect was one of the deficiencies identified in the original review cycle, the Applicant's submission of BZUC3003 in this Complete Response did not resolve this concern. In BZUC3003, a sub-group analysis by gender showed a consistent response rate between men and women for both BD- and Asacol-treatment (BD: 51% of men and (b) (4) of women; Asacol: 49% of men and (b) (4) of women). However, BZUC3003 failed to address the observed large placebo-response rate in women enrolled in BZUC3002; BZUC3003 was a NI study design without a placebo arm for comparison.

The Applicant postulated that a possible explanation for the gender disparity may be linked to a correlation between number of study visits completed and placebo response. In the reference cited by the Applicant, Ilnyckyj et al. concluded that a higher number of clinic visits, resulting in more frequent patient interaction with a physician and subsequent physician assessments, provide an added therapeutic benefit for patients and contribute to the placebo effect. Applying this observation to the BZUC3002 study, the Applicant noted that more placebo-treated female patients compared to placebo-treated male patients completed the study (70.0% vs 35.0%, respectively). This observation, together with a greater number of study visits by placebo-treated female patients, led the Applicant to conclude that the increased number of study visits by women may have influenced an increased placebo-response rate in female patients. The Applicant postulated that repeated physician assessments at clinic visits had a positive therapeutic effect on the patients' health. This reviewer finds this line of reasoning questionable since, by inference, BZUC3002 achieved success (p=0.02) secondary to a large drop-out rate among placebo-treated male patients. Conversely, if one agrees with the Applicant's rationale for the observed gender discrepancy in placebo-treated patients, the study would likely have failed if more placebo-treated male patients had completed the study, thus likely increasing the overall placebo-response arm, thereby decreasing the overall BD-treatment effect.

Since the reason for the observed discrepancy in the placebo response rates across gender was not clear, this reviewer looked at other sources for potential explanations. Review of relevant published literature did not suggest gender as a potential factor for differences in placebo response in the population of interest. A review of study CP-69101, a placebo-controlled study of Colazal (BD capsule formulation) submitted as part of NDA 20-610, showed a trend of improved responses in women versus men in both Colazal- and placebo-treated patients. In the placebo-treatment arm, women had a greater efficacy response than men in six of the seven endpoints. Although not conclusive, the gender sub-analysis for CP069101 provides additional concerns that there may, indeed, be a gender-specific response difference between men and women with UC. The reasons for this potential gender disparity are unclear.

Unless the issue of gender disparity can be resolved, this reviewer agrees with the concerns of Dr. Gibril that the observed superiority of BD tablets over placebo in BDUC3002 was driven by a sub-population's finding, namely, male patients. Conversely, the efficacy of BD tablets has not been established in women. This gender disparity in treatment effect needs to be adequately addressed before the future approval of BD tablets.

Regarding other special populations, safety and effectiveness of BD tables in pediatric patients have not been studied. There have been no studies with BD tablets in patients with renal or hepatic impairment. Pregnant women and nursing mothers were excluded from clinical trials

with BD tablets. The clinical program did not include sufficient number of patients aged 65 and older (<10%) to determine whether they respond differently than younger patients.

8.4 Pediatrics

The NDA did not include patients less than 18 years old. The Sponsor requested waiver for pediatric studies required under the Pediatric Research Equity Act (PREA), and provided the following justification: 1) Balsalazide Disodium has been granted orphan drug designation status for pediatric patients with UC indicating that the number of pediatric patients with UC is small, and 2) the new tablet formulation contains the same active ingredient as in the capsule formulation Colazal, which is already approved for use in pediatric patients with UC aged five years and above. Although only Colazal has been approved for this indication, both formulations would be intended for the treatment of mildly to moderately active UC at a similar total daily dose. Colazal capsules can be opened and sprinkled on applesauce as a pediatric administrative alternative; while the tablets may be more difficult to administer to pediatric population because of difficulty to swallow. Therefore, the implementation of the tablet formulation does not represent a meaningful benefit over the existing capsule formulation in terms of treatments (dosage and ability to administer) for pediatric patients.

The BD tablet (1100 mg), the subject of this NDA, contains the same active ingredient as the product Colazal capsule (750 mg), which is approved for a pediatric population (aged 5 years and older). Although only Colazal has been approved for this indication, both formulations would be intended for the treatment of mildly to moderately active ulcerative colitis. The tablet drug product is proposed to be administered for a total daily dose of 6.6 g/day (three 1100 mg tablets BID) whereas the capsule dose is a total of 6.75 g/day (three 750 mg capsules TID). An advantage of the Colazal capsules is that they can be opened and sprinkled on applesauce as a pediatric administrative alternative; the tablets may be more difficult to administer to the pediatric population because of the difficulty to swallow as well as the inability to more easily adjust for weight-based dosing of the product. A tablet formulation of balsalazide disodium would provide a slight clinical benefit (BID versus TID dosing) over the approved Colazal capsule formulation. But, that advantage would apply only to patients old enough to be able to swallow tablets and in whom weight-based dosing would be feasible given the tablet's dosage strength. Since an already approved pediatric product formulation of balsalazide disodium is currently marketed, the limited benefit of BID versus TID dosing in a small subset of the pediatric ulcerative colitis patient population is negligible. This reviewer therefore recommended full waiver, for consideration by the PERC committee, of pediatric studies for the balsalazide tablet formulation.

On 29 October, 2008, this recommendation for full waiver of pediatric studies with the BD tablet formulation was presented before the PERC committee. The outcome of the discussion was: 1) full waiver of studies for pediatric patients with UC under the age of 12, 2) should the product be approved, the label should include information for adolescent patients with UC aged 12 to 17, and 3) the Division has the discretion to determine if additional studies are required to adequately label for this adolescent UC patient population.

If the BD tablet formulation is approved in the future and such additional studies are required in the adolescent UC patient population, those studies need to be presented before the PERC committee for additional input and guidance. Should labeling for the tablet formation product more forward, this reviewer agrees with the PERC committee recommendations and concurs that instructions for use in adolescent UC patients should be included in the product label. Additional studies would not be required should the Clinical Pharmacology staff conclude that PK data from studies of both formulations of BD be sufficient.

8.5 Advisory Committee Meeting

There was no advisory committee meeting required for this NDA.

8.6 Literature Review

The published literature the Applicant submitted in paper format was reviewed. In addition, this reviewer conducted an independent review of the literature with respect to the observed gender disparity in BD treatment effect between men and women with UC. This information and the conclusions drawn from it can be found in Section 6.1.4.4.4 of this review.

For the non-inferiority (NI), the Applicant submitted the results of a literature search to justify the NI used for BZUC3003. Upon review of the studies included in this resubmission, the review team concluded that only one literature reference closely approximated the ICH E.10 guideline for appropriate NI trial design. This information and the conclusions drawn from it can be found in Section 6.1.4.4.2 of this review.

8.7 Postmarketing Risk Management Plan

Colazal, the capsule formulation of BD, does not have a risk map or REMs; there is no postmarketing risk management plan for the BD tablet formation.

8.8 Other Relevant Materials

The Agency's Division of Medication Error Prevention (DMEPA) was consulted for both the original and resubmission of this NDA. Although the current consult is still outstanding, the recommendation from the original review cycle (20 May, 2008) is summarized. The Applicant proposed the trade name Giazo for the tablet formulation of balsalazide disodium (BD); the approved capsule formulation of BD has the trade name Colazal. DMEPA concluded "that marketing this product with two different strengths, with differing frequencies and total daily dose, can be safely managed under one proprietary name [Colazal]."

9 OVERALL ASSESSMENT

9.1 Conclusions

For the original submission, the review team concluded that the Applicant's single placebo-controlled study, BZUC3002, was inadequate to support effectiveness of BD tablets. As stated in the approvable letter, BZUC3002 "did not demonstrate a statistically persuasive finding of treatment effect" and there was a "lack consistency of treatment effect between men and women, subsets that were equally represented in the study." While the response rate was comparable between men and women in the BD-treatment group (57% and 54%, respectively), it was markedly different in the placebo group (20% in men compared to 58% in women). Consequently, a substantial therapeutic gain was demonstrated among male patients (37%), but none among female patients (-4%). The observed superiority of BD tablets over placebo was driven by a subpopulation's finding, namely, male patients. Conversely, the efficacy of BD tablets was not established in female patients and the therapeutic effect in women was indeterminate secondary to the unexplained high placebo response rate in this subgroup. In the Executive Summary of her clinical review dated 4 April, 2008, Dr. Fathia Gibril recommended that the issuance of a future approval be dependent upon the review of additional efficacy data from an adequate and well-controlled study that would demonstrate substantial evidence of effectiveness and consistent finding across important subgroups, namely, male and female patients. In her Division Director review dated 17 May, 2008, Dr. Donna Griebel stated that although the primary efficacy endpoint analysis of BD tablets was found to be statistically significantly superior to placebo, the p-value was not persuasive, the finding was not consistent in an important subset analysis (gender) that represented half the study population, and the additional prospectively defined secondary endpoints that were found to significantly favor treatment with BD vs. placebo were not independent endpoints, but were linked to the primary endpoint and each other. She concluded that an additional study that supports the efficacy of BD tablets for mildly to moderately active UC should be submitted by the Applicant to support future approval.

After review of BZUC3003, a non-inferiority trial and the only study included for review in this resubmission application, this reviewer does not believe that the concerns of the previous review team have been adequately addressed. In summary, the following deficiencies were found: 1) the non-inferiority (NI) margin of success chosen by the Applicant was not appropriate and the study did not achieve success when a more representative NI margin was employed, 2) the lack of a placebo arm in the study did not address the gender response discrepancy found in BZUC3002, 3) additional evidence from the published literature and from the approval of Colazal, a capsule formulation of BD marketed by the Applicant, did not resolve the unexpected outcome of differential treatment response between men and women, and 4) the inability to provide adequate labeling guidance to the medical community regarding the observed differential efficacy between men and women with ulcerative colitis.

Although the safety profile for the two Phase 3 studies is similar to other members of the 5-ASA class including Colazal, the Applicant has proposed a hepatic warning to the labeling. Although six patients exposed to BD therapy developed transient transaminase elevations, all the laboratory abnormalities resolved and none went on to have irreversible liver damage. To address the issue in greater depth, a post-marketing analysis of safety data for all 5-ASA compounds could be of benefit, and if the data indicate that a true hepatic signal exists, a class warning should be considered for Colazal and other members of the 5-ASA class.

9.2 Recommendation on Regulatory Action

This reviewer recommends that a Complete Response regulatory action be taken on the Applicant's resubmission of marketing application (NDA 22-205) for balsalazide disodium (BD) tablets intended for use in mildly to moderately active ulcerative colitis (UC).

In the Approvable regulatory action letter in response to the original submission of NDA 22-205 the Agency concluded that the single placebo-controlled study, BZUC3002, was inadequate to support effectiveness of BD tablets. The review team determined that BZUC3002 did not demonstrate a statistically persuasive finding of treatment effect and lacked consistency of treatment effect between men and women, subpopulations that were equally represented in the study. Future approval of BD for the treatment of mildly to moderately active UC would be dependent upon the review of additional efficacy data from an adequate and well-controlled study that would demonstrate substantial evidence of effectiveness and consistent finding across important subgroups, namely, males and females.

In response to this approvable action, the Applicant resubmitted NDA 22-205 with the additional Phase 3, active-comparison study BZUC3003 as a Complete Response. Upon review of this study, this reviewer concludes that several deficiencies still remain and the data submitted are inadequate for final approval action at this time. The deficiencies are as follows:

1. Efficacy gender imbalance with regard to BD treatment effect

As an active-comparison, non-inferiority clinical trail, BZUC3003 did not have a placebo treatment arm. Therefore, the high placebo-response rate among women seen in BZUC3002 that resulted in the lack of a treatment effect in women has not been addressed. Upon review of the evidence in support of the approval of Colazal as well as published reports in the literature, these sources did not provide data to help explain the gender discrepancy outcome of the BZUC3002 clinical trial. The inability to provide adequate labeling guidance to the medical community regarding the observed differential efficacy between men and women with ulcerative colitis remains to be resolved.

2. The NI margin chosen for BZUC3003 is not appropriate

For the non-inferiority trial design, the NI margin chosen by the Applicant was not appropriate and did not achieve success when a more representative NI margin was employed. The Applicant's explanation for the choice of the (b) (4) NI margin was not convincing. In support of

the (b) (4) NI margin, the Applicant cited input from clinicians with experience in the treatment of active UC or made reference to several studies in the published literature. The conducted a meta-analysis only identified one study that evaluated Asacol, the active comparator in BZUC3003, in a placebo-controlled study with a similar study design. As outlined in the ICH E10 guidance, the choice of NI margin should be 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 from the Applicant's cited literature study as well as the original studies that led to the approval of Asacol, the review team concluded that the margin should not exceed 3%. When the 3% NI margin is employed for determination of success, BZUC3003 data do not support that BD is non-inferior to Asacol.

9.3 Recommendation on Postmarketing Actions

This reviewer does not recommend the need for post-marketing studies at this time.

9.3.1 Risk Management Activity

There is no applicable activity related to risk management for this NDA.

9.3.2 Required Phase 4 Commitments

This reviewer does not recommend any Phase 4 commitments. At present, Colazal, the capsule formation of BD, is approved for use in pediatric UC patients aged 5 to 17 years. Since Colazal has the same active ingredient as BD tablets, a pediatric formulation of the product is approved. In addition, this product has the added benefit of dosing the drug in younger patients using the broken capsule contents mixed with food. Discussion with the PERC committee led to the recommendation that since the BD tablet formulation had a slight dosing advantage over Colazal (BID vs TID), the product may be of benefit in those pediatric patients able to ingest the BD tablet formulation. If the product is to be approved in the future, additional pediatric studies may need to be conducted in order to label the product for pediatric patients aged 12 years to 17 years. The decision as to if such studies need to be conducted for labeling recommendations for adolescent UC patients will fall to the Division. If such pediatric studies are required, they should be presented to the PERC committee for further comment.

9.3.3 Other Phase 4 Requests

Should BD tablets be approved in the future, attention should be paid to Applicant's proposal of a hepatic warning to the labeling. To address the issue in greater depth, a post-marketing study could be of benefit, and if the data indicate that a true hepatic signal exists, a class warning should be considered for Colazal and other members of the 5-ASA class.

9.4 Labeling Review

Should BD tablets be approved at a future date, this reviewer recommends consideration of the following:

1) The BD tablet formulation should be labeled for use in adolescent UC patients aged 12 to 17 years
2) Consideration should be made to the recommendations put forth by Ann Corken Mackey in her OSE consult dated 14 January, 2008. Namely, DDRE recommends class labeling for all 5-ASA products to include the following warnings: myocarditis, pericarditis, vasculitis, pruritus, pleural effusion, pneumonia with and without eosinophilia, alveolitis, renal failure, interstitial nephritis, and pancreatitis. Although evidence is limited (based on postmarketing reports), the following adverse events have been reported for other 5-ASA drugs and should be considered for inclusion in the BD label: interstitial lung disease, urticaria, pulmonary fibrosis, hemolytic uremic syndrome, angioedema, toxic epidermal necrolysis, pericardial effusion, leukopenia, and thrombocytopenia.
3) The concomitant use of antibiotics with BD tablets should be addressed since such therapy may effect the composition of gut flora and thereby the effectiveness of BD given its pro-drug form. If necessary, a study addressing this topic may need to be conducted as part of a post-marketing commitment.
4) The Applicant's proposal of a warning for hepatic impairment should be considered.
5) Per the CMC recommendation from the original review cycle, the labeling for BD tablets requires a formatting change to bring the font size of the established name and the word "tablets" needs corrected, and the placement of the strength "1.1g" needs to be amended as well.

9.5 Comments to Applicant

In addition to the deficiencies outlined in Section 9.2, this reviewer recommends that the following suggestion be added to the CR letter to provide the Applicant with a potential path to help address the unresolved concerns.

"Future approval of BD tablets for the treatment of mildly to moderately active UC would be dependent upon the review of additional efficacy data from an adequate and well-controlled study that would demonstrate substantial evidence of effectiveness and consistent finding across important subgroups, namely, males and females. The design of this study could include three treatment arms for comparison: BD tablets, your marketed product Colazal, and placebo. We recommend an eight week course of treatment and a gender sub-analysis of treatment effect for each of the cohorts. The outcome of this study would address both the effectiveness of treatment of women with UC as well as provide efficacy comparison information to the capsule formation of the drug product. Before initiating such a study, we recommend that you obtain input from FDA regarding the study design including any use of non-inferiority comparisons."

10 APPENDICES

No appendices are attached.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christopher L Leptak
12/20/2008 06:25:00 AM
MEDICAL OFFICER

John, this is the final ClinRev with edits from
12/19 incorporated

John Hyde
12/20/2008 11:05:19 AM
MEDICAL OFFICER

Summary Review for Regulatory Action

Date	May 17, 2008
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 22-205
Applicant Name	Salix Pharmaceuticals, Inc.
Date of Submission	July 18, 2007
PDUFA Goal Date	May 17, 2008
Proprietary Name / **Established (USAN) Name**	Giazo/Balsalazide disodium tablets
Dosage Forms / Strength	1.1 g tablet
Proposed Indication(s)	Mild to moderately active ulcerative colitis
Action/Recommended Action	Approvable

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Fathia Gibril, MD/ Ruyi He, MD
Statistical Review	Shahla Farr, MS/Mike Welch, Ph.D.
Pharmacology Toxicology Review	Ke Zhang, Ph.D./Sushanta Chakder, Ph.D.
CMC Review/OBP Review	Maria Ysern, MSc/Moo-Jhong Rhee, Ph.D.
Microbiology Review	
Clinical Pharmacology Review	Insook Kim, Ph.D., Sue-Chih Lee, Ph.D.
DSI	Khairy Malek, MD/Constance Lewin, MD, MPH
OSE/DMETS	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Balsalazide, a prodrug, is cleaved by bacterial azoreductases in the colon cleave into the active moiety, 5-aminosalisylic acid (5-ASA) and an inactive carrier 4-amino benzoyl-β-alanine(4-ABA). The drug's activity is believed to result from a local anti-inflammatory effect on the colonic mucosa. Although, there is some systemic absorption of the prodrug and the metabolic products formed in the gut lumen, adverse events related to systemic exposure appear to be quite low. There have however been reports of renal toxicity in humans with 5-ASA products, and animal studies (rats and monkeys) have demonstrated that the kidney is a major organ of toxicity. In addition, there have been postmarketing reports of hepatoxicity for the applicant's capsule formulation of balsalazide, Colazal.

There are a number of 5-aminosalisylic acid containing products that have been approved by the FDA for the treatment of ulcerative colitis, including a balsalazide capsule marketed by the applicant of this NDA. The applicant submitted only one randomized, controlled trial in this application to support marketing approval of a new tablet formulation and dose, designed for a new dosing regimen, twice daily dosing. A second trial was submitted to the NDA at the time of the 120 safety update, but the Division informed the applicant that it would not review the second study during this review cycle.

Although prior evidence of the effectiveness of the same active moiety can be used as supportive evidence when evaluating the adequacy of a single trial to establish effectiveness, the 5-ASA historic data come from trials conducted with different formulations, different dosing schedules and different doses than that proposed in this application. Study designs, endpoints and statistical analysis plans varied across the prior approved products, including the applicant's own previously approved balsalazide capsule. The adequacy of the single study submitted in this NDA to establish the safety and effectiveness of balsalazide tablet 1.1g – three tablets BID – will be the major focus of this review. The *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* states that the characteristics of a single adequate and well controlled study that could support an effectiveness claim include:

1) Large, multicenter study
2) Consistency across study subsets.
3) Multiple studies within a single study
4) Multiple endpoints involving different events and the trial shows statistically persuasive evidence of effect on more than one of the endpoints
5) Statistically very persuasive finding – a very low p value.

The single trial submitted in this application to support approval of this new balsalazide tablet product was critically evaluated in light of the standards listed above.

2. Background

Salix Pharmaceuticals, Inc proposes to market a new formulation of balsalazide, a 1100 mg tablet, with a new dosing regimen, three tablets twice daily (a total daily dose of 6600mg) for the treatment of mild to moderately active ulcerative colitis. They have a previously approved balsalazide product for the same indication, a 750 mg capsule (Colazal), dosed three capsules three times a day (a total daily dose of 6750 mg). The product in the current application will provide a more convenient dose regimen at a slightly lower total daily dose, but higher dose at each administration. The applicant's capsule product was approved in July 2000 based on two randomized, controlled trials in which patients were randomized between two doses of balsalazide, 6750 mg/d and 2250 mg/d. The data from only one of the studies appears in the product label. The primary efficacy analysis in the labeled study was not the same as that utilized in the study submitted in the current application.

No dose response trial was conducted for the tablet formulation proposed for marketing in this application. At the End of Phase 2 meeting and the pre-NDA meeting for this application, the Division advised the Salix Pharmaceutical, Inc. to submit two studies in their application for this formulation. The applicant instead submitted a single randomized, controlled trial to support the indication of treatment of mild or moderate ulcerative colitis. The interim results of an open label, long term safety study were also provided. The sponsor subsequently submitted a second randomized, controlled trial with the NDA's 120 day safety update, without prior agreement with the Division that a second major trial could be submitted after filing and reviewed. The Division notified the applicant in December 2007 that the second study would not be reviewed during this review cycle.

3. CMC/Device

The CMC reviewer recommended approval of this NDA, pending agreement on recommended labeling revisions. I concur that the product is approvable, given the outstanding clinical/statistical review issues. The drug product review found that all excipients used are compendial, degradation products were absent, and the stability data support a 24-month expiration date when stored at 15-30° C. The tablets do not need to be protected from light. (b) (4)

The reviewer found that the font size of the established name and the word "tablets" is incorrect, and the placement of the strength "1.1g" is incorrect.

4. Nonclinical Pharmacology/Toxicology

No new studies were reviewed. Dr. Zhang's summary findings reflect information found in the currently approved balsalazide (Colazal) 750 mg capsule product label.

5. Clinical Pharmacology/Biopharmaceutics

The applicant submitted two new pharmacokinetic studies in this application: 1) a study that assessed the relative bioavailability of the new balsalazide tablet compared to the previously approved balsalazide capsule product and 2) a food effect study.

The relative bioavailability study included analysis of pharmacokinetics after a single dose of product and after multiple dosing. The doses evaluated were 3.3 g of the tablet and 2.25 g of the capsule. Table 7 of Dr. Insook Kim's review summarizes the single and multiple dose pharmacokinetic findings for each drug and for each of the parent molecule and the major metabolites. Although there was a higher amount of drug delivered, per dose, with the tablet formulation, the Cmax for systemic exposure of parent drug, balsalazide, is somewhat higher with the capsule than with the higher dose tablet. However, after a single dose, the Cmax of 5-ASA and N-Ac-5-ASA were somewhat higher for the tablet than the capsule. The tablet's multidosing AUC was higher than observed with the capsule for the balsalazide parent drug, 5-ASA and N-Ac-5-ASA. Table 6 of Dr. Kim's review compares the Cmax and AUC for balsalazide, 5-ASA, and N-Ac-5-ASA between males and females. The Cmax of 5-ASA in females was 123% of Cmax in males, and the AUC in females relative to males was 140%. Female exposure was also somewhat higher than males for balsalazide parent, Cmax=115%, and for N-Ac-5-ASA, AUC=110%.

In the food effects study, Dr. Kim noted that a high fat diet influenced the systemic exposure of 5-ASA and N-Ac-5-ASA. According to Table 9 in her review, the Cmax of 5-ASA was reduced by 66% and the AUC was reduced by 45%. The Cmax of the metabolite N-Ac-5-ASA decreased by 47%, and the AUC was reduced by 15%. The absorption of parent balsalazide was delayed by a high fat diet. The balsalazide Tmax was increased from 0.5 hour to 2.0 hours, the Cmax reduced by 43%, and the AUC decreased by 5%. These data suggest that gut uptake is slowed by a high fat diet. Conceivably the metabolism of the parent drug within the gut lumen could also have been impacted by the high fat diet if the intraluminal fat content impacted the colonic microflora.

6. Clinical Microbiology

NA.
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7. Clinical/Statistical-Efficacy

As discussed in the Introduction and Background Sections, only one randomized, controlled study had been submitted in the NDA at the time of filing to support the approval of this new balsalazide tablet formulation, dose and administration schedule. The interim results of an ongoing open label, long term safety study were also provided.

The randomized, placebo controlled study was a multi-center trial of 8 weeks duration. This multicenter study was conducted exclusively in the United States. Two hundred fifty patients

with mild to moderately active ulcerative colitis were randomized on a 2:1 basis between balsalazide tablet 3.3g (3-1.1g tablets) BID and placebo. The primary efficacy analysis was based on the Modified Mayo Disease Activity Index (MMDAI) score, a scoring system made up of 4 subscales, all with possible scores ranging from 0-3. Hence the total score for the entire MMDAI ranges 0-12, where low scores correspond with low disease activity. The 4 subscales are:

1, Stool frequency – assessed by patient diary in which the patient scores daily bowel frequency by comparing the number of stools in the day relative to what is normal for them. For example, a score of "1" is equal to "1-2 more stools than normal". A score of 3, the highest score, is equal to "5 or more stools than normal". The number of stools considered normal for the patient was recorded at baseline.
2. Bleeding – assessed by patient diary. A score of 0 = no blood, 1=streaks less than half the time, 2= obvious blood most of the time, 3= passing blood alone.
3. Sigmoidoscopy score - 0= normal or inactive disease, 1= mild disease (erythema, decreased vascular pattern), 2= moderate disease (marked erythema, absent vascular pattern, friability, erosions), and 3= severe disease (spontaneous bleeding, ulceration).
4. Physician's Global Assessment (PGA) – assessed by the physician at baseline and at the end of 8 weeks. The clinical reviewer, Dr. Fathia Gibril, reports that this assessment is made by the physician based on the above 3 parameters, and the patient's level of abdominal discomfort (from diary and rated 0-3) and overall well being (from diary and rated 0-3). A score of 0=normal, 1=mild disease, 2= moderate disease, and 3= severe disease.

PGA, a component of this composite score, is actually another "composite assessment" made by the physician of the other 3 component subscales the diary record of scores for abdominal discomfort and general well being.

Eligible patients were defined as having mild to moderate ulcerative colitis with acute flare if they had a total MMDAI score between 6 and 10, with rectal bleeding sub-score of at least 2 and an endoscopy sub-score of at least 2, i.e. to get into the study patients had to have at least "obvious blood most of the time" and moderate disease on endoscopy. Because the lowest total score to be eligible for the study also had to be at least 6, with a score of 2 for each of endoscopy and bleeding, the remaining 2/6 points in that MMDAI score could be distributed between stool frequency and PGA score. Presumably if the physician rated the endoscopy as moderate disease and they reviewed the bleeding score of "2", they would also assess the PGA score as moderate, i.e. 2 points. In fact, according to Tables 3-6 in Shahla Farr's statistical review, there was a strong correlation between PGA and endoscopy score at baseline. In fact, according to Tables 3-6 in the statistical review, there was a strong correlation between PGA and the endoscopy and bleeding scores at baseline.

	Balsalazide	Placebo
Endoscopy = Moderate (score of 2)	82%	85%
PGA = Moderate (score of 2)	84%	83%
Bleeding = 2	88%	88%
Stool Frequency = 2	33%	37%

Therefore, the baseline stool frequency in patients at the low end of the MMDAI score for entry was presumably near normal. Median MMDAI score at entry, however, was 8 in both arms. Thirty-six percent of the balsalazide patients and 26% of placebo patients had baseline stool frequencies that were normal or mild (score= 0 or1), but 32% and 37% respectively reported stool frequency of severe.

Dr. Gibril's review tables indicate that for the two subscales of the MMDAI that had to be at least a score of 2 for a patient to be eligible, endoscopy and bleeding, there were patients who entered the study with scores below the entry criteria. Six percent and approximately 4% of patients on the balsalazide and placebo arms, respectively, had endoscopy scores less than 2. Eight per cent and 10% had bleeding scores less than 2 (balsalazide and placebo, respectively).

The primary endpoint was a comparison of the proportion of patients who achieved both clinical improvement and improvement in the rectal bleeding subscale of the MMDAI, where clinical improvement was defined as at least a 3 point improvement from baseline in the MMDAI total score, and improvement in rectal bleeding was defined as at least 1 point improvement in the rectal bleeding score from baseline. The statistical analysis plan prespecified a hierarchical analysis of secondary endpoints if the primary efficacy endpoint was found to be statistically significant. Those secondary endpoints were variations of the evaluation of individual assessment components included in the primary endpoint.

Based on an intent to treat analysis, a higher proportion of the balsalazide (55%) met the criteria of clinical improvement plus improved rectal bleeding than on the placebo arm (40%), p=0.024. In a single trial, a p value of 0.02 is less than robust evidence of effectiveness and is not considered "statistically very persuasive" or "very low", as per the *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* .

Because the p value was <0.05, the applicant proceeded with the hierarchical analysis of the prespecified secondary endpoints. They found that the first two secondary endpoints, clinical remission and mucosal healing, were statistically significantly improved relative to placebo before they interrupted the planned progression through the secondary analyses due to a non-significant difference in the third comparison (stool frequency). Clinical remission, the first of the secondary endpoints, was defined as a rectal bleeding score of 0 plus a combined score of ≤2 for stool frequency and PGA. The second of the secondary endpoints, mucosal healing, was defined as an endoscopy score of 0 or 1. Given that mucosal healing is linked to the clinical remission endpoint, in that a component of the PGA assessment is the endoscopy score, it is perhaps not surprising that mucosal healing was also found to be statistically

significant. In fact, in the Results of Key Secondary Endpoint Analysis table from Dr. Gibril's review the proportion of patients with improvement in the PGA and proportion with improved mucosal healing was quite similar in each arm – 59.6% and 53% on the balsalazide arm AND 36% and 32.5% on the placebo arm. Although the two additional secondary endpoints were found to be significant in a prespecified hierarchical analysis, these endpoints related. Given their relatedness, they do not clearly meet the criterion from the *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, #4 in this review's Section 1 Introduction (multiple endpoints involving different events that show statistically persuasive evidence of effect in more than one of the endpoints).

To further evaluate the strength of evidence from this single trial, the clinical and statistical reviewers carefully evaluated subgroups for evidence of consistent findings within this study. Importantly, in the analysis by sex, the treatment effect observed for the overall study was not found in women, and women represented half of the study population. In fact the proportion of women considered responders as defined by the primary endpoint was higher in the placebo arm of the study than on the balsalazide arm – 58% vs. 54%. In men the placebo response was 20%. In men treated with balsalazide the proportion responding, 57%, was similar to the proportion of women who responded to placebo. Similarly, when Shahla Farr examined the first secondary endpoint, clinical remission, balsalazide was found to be associated with a statistically significant effect in men (34.6% vs. 12.5%, p=0.01), but not in women (43% vs. 34.9%, p (b) (4)). Again the placebo clinical remission rate in women, 34.9% mirrored the balsalazide clinical remission rate in men, 34.6%.

The review team evaluated the applicant's explanations for why there was a differential effect observed in this study's subset analysis by sex. The very high placebo effect in women seems to be responsible for the lack of demonstrated treatment effect in women – it was as high as the effect of balsalazide in men. The literature was reviewed to identify factors associated with high placebo responses in ulcerative colitis trials. Ultimately, no conclusive cause for the differential placebo effect observed in this study was identified by the reviewers. Based on the lack of consistent findings in a significant subgroup, half the study population, the review team concluded that this single trial did not provide robust evidence that the product was effective in the dose and administration schedule evaluated in this study. The review team believes that additional evidence must be submitted to demonstrate that the product is effective in its proposed usage.

The *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* states that the characteristics of a single adequate and well controlled study that could support an effectiveness claim include:

1) large, multicenter
2) Consistency across study subsets.
3) Multiple studies within a single study
4) Multiple endpoints involving different events and the trial shows statistically persuasive evidence of effect on more than one of the endpoints
5) Statistically very persuasive finding – a very low p value.

In the review team's evaluation of this single study, they found that it did not meet key characteristics that should be present for a single trial to be adequate to stand alone to establish effectiveness. The review team's major concerns included the dramatic lack of consistency of effect in men and women, groups that each represented 50% of the study population. The differential efficacy between men and women carried over into both of the two statistically significant secondary endpoints. The p-value of the primary efficacy analysis was not persuasively low, p=0.024, and the two secondary endpoints that were found statistically significant in hierarchical analysis were related, i.e. didn't involve different events.

8. Safety

Mesalamine (5-ASA) containing products are already marketed, including a balsalazide capsule formulation marketed by the applicant. There is substantial post-marketing safety experience with 5-ASA. The applicant's balsalazide capsule label carries a Warning that "renal toxicity has been observed in animals and patients given other mesalamine products. Therefore, caution should be exercised when administering Colazal to patients with known renal dysfunction or a history of renal disease." The label of the once daily dosage mesalamine product Lialda includes information about potential renal toxicity in the Precautions section, which states "Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with mesalamine medications (b) (4) For any patient with known renal dysfunction, caution should be exercised…" The postmarketing section of the Colazal label does not report any cases of nephrotoxicity, however it does report that there have been postmarketing adverse reactions of hepatotoxicity, including elevated liver function tests, jaundice, cirrhosis, hepatocellular damage including liver necrosis and liver failure.

There were 247 participants evaluable for safety in the major clinical trial reviewed in this NDA. Patients were treated for 8 weeks, and 168/247 received the active treatment, balsalazide tablet 3.3g BID, while the remaining 79 received placebo. The median number of days of exposure to balsalazide in the placebo controlled study was 56 days. In addition interim data from an open-label long term safety study that included 130 patients who successfully completed the randomized, controlled trial were available for review. Two doses were utilized in the safety study, 3.3g BID (N=111) and 4.4g BID (N=18). The total balsalazide exposed safety population in this application included 216 patients. The duration of exposure within those 216 patients ranged:

1-56 days:	29%
56-182 days:	63%
182-365 days:	8%

There was a low SAE rate in the randomized, placebo controlled trial submitted in this application, and a higher proportion occurred on the placebo arm. The only SAE that occurred in more than 1% of patients was worsening of ulcerative colitis, and that occurred more frequently on the placebo arm – 4% vs. 2% on balsalazide.

A relatively high proportion of patients withdrew from the study in both arms of the randomized controlled trial, although a higher proportion withdrew in the placebo arm (35/79, 44%) than on the balsalazide arm (57/168, 34%). Lack of efficacy was the reason for withdrawal in 28/57 (49%) patients who withdrew from the balsalazide arm and in 23/35 (68%) of those who withdrew from the placebo arm. In addition, of the 10% (n=17) of patients on the balsalazide arm who withdrew for adverse event, Dr. Gibril reports in her review that 9/17 (53%) of those who withdrew for an AE, the event was described as worsening of UC, as compared to 13% (N= 10, in a 2:1 randomization of B:P) of subjects who withdrew for adverse event on the placebo arm, of which 9/10 (90%) were described as worsening of UC. The summary table in Dr. Gibril's review comparing AEs leading to discontinuation from the study reveals a distribution of single patient events. Among the events listed in the table, those that occurred in more patients on the balsalazide arm than on the placebo arm were erythema nodosum (1 patient vs. 0 on placebo), hematocrit, hemoglobin, red blood cell abnormality, red blood cell count (one patient each vs. 0 on placebo), muscle spasms (1 patient vs. 0 on placebo), pharyngeal erythema, pyrexia, rash, abnormal sigmoidoscopy (each reported in a single patient vs. 0 on placebo), and vomiting (2/17 [12%] patients who withdrew for AE in the balsalazide arm vs. 1/10 who withdrew for AE on the placebo arm).

The most common treatment emergent adverse event in the randomized controlled trial was worsening ulcerative colitis, which was more common on the placebo arm (14%) than on balsalazide (7%), followed by headache (14% on placebo and 6% on balsalazide). In the long term open label study the most frequent adverse events were worsening of ulcerative colitis (5%) and diarrhea (3%).

Dr. Gibril further explored safety by examining drug-demographic interactions and found that more women than men treated with balsalazide reported adverse events – 44% vs. 28%. The most frequently reported adverse event in both men and women was GI disorder, and this occurred in a higher proportion of females relative to males on the balsalazide arm in contrast to the placebo arm, where the proportion who reported GI events was similar between sexes. More women than men on the balsalazide arm reported abdominal distention and pain (7% vs. approximately 2%), and more females than males on that arm reported vomiting (5.8% vs. 1.2%).

Overall, Dr. Gibril concluded that the safety profile in the database supporting this submission was consistent with what has been associated with this drug class. She found no unexpected adverse events and concluded that she had identified no safety concern that would preclude approval.

9. Advisory Committee Meeting

This product is not an NME. There was no Advisory Committee meeting for this NDA.

10. Pediatrics

There were no children under the age of 18 studied in this application. Dr. Gibril in her review supported the applicant's request for a waiver for pediatric studies required under the Pediatric Research Equity Act (PREA). The sponsor's other balsalazide formulation is a capsule formulation that can be opened and sprinkled on food for ease of administration in the pediatric population. It is approved for pediatric ulcerative colitis in children 5 years of age and older. Dr. Gibril further justified not pursuing a pediatric development plan for the twice daily administration formulation, given the possible advantage of BID dosing relative to TID dosing in a pediatric population, by pointing out that there is a mesalamine product that has been approved for once a day dosing that currently has a pediatric development plan under negotiation.

This issue was not taken the PERC this review cycle because the NDA is not going to be approved.

11. Other Relevant Regulatory Issues

DSI inspected 3 U.S. sites. Their overall recommendation was that the data could be used in support of the NDA.

Dr. Fathia Gibril reviewed the Financial Disclosures and identified two investigators who had reported significant financial relationships with the applicant in the form of payment of (b) (6) One of the investigators had only enrolled (b) (6) patients in the major study submitted to support approval, a number that is insignificant, and the other had enrolled (b) (6) of the participants in that study. The latter investigator's site was audited by DSI and was found to be acceptable. In addition, the biostatistics reviewer, Shahla Farr, reanalyzed the data from the study to evaluate that site's influence on the observed outcome and found that it did not influence the findings of efficacy.

12. Labeling

NA

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - I concur with the clinical and statistical reviewers' recommendation that this application should not be approved at this time, but instead should receive an approvable action. An additional study that supports the efficacy of balsalazide tablets 3.3g twice daily dose for mild to moderate ulcerative colitis should be submitted by the applicant for review. At that time, the postmarketing safety experience with balsalazide should be reassessed, with particular focus on hepatic and renal events.

- Risk Benefit Assessment
  The *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* states that the characteristics of a single adequate and well controlled study that could support an effectiveness claim include: large, multicenter study, statistically very persuasive finding (i.e. a very low p value), consistency across study subsets, multiple studies within a single study, multiple endpoints involving different events and the trial shows statistically persuasive evidence of effect on more than one of the endpoints. In the single study that was submitted in this NDA by the time of filing of the NDA, the balsalazide tablet administered 3 – 1.1g tablets BID was found to be statistically significantly superior to placebo in the pre-specified analysis of the primary endpoint, however the p-value was not persuasively low, p=0.02, the finding was not consistent in an important subset analysis (sex) that represented half the study population, and the additional prospectively defined secondary endpoints that were found to significantly favor treatment with balsalazide vs. placebo were not independent endpoints, but were linked to the primary endpoint and each other.

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/s/

Donna Griebel
5/16/2008 04:11:56 PM
DIRECTOR

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/9/2008

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

TO: Donna Griebel, MD
Director
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader Comments
NDA 22-205

APPLICANT: Salix Pharmaceuticals, Inc.

DRUG: Giazo (Balsalazide Disodium) Tablet (1.1g)

THERAPEUTIC CLASS: Mesalamine (Ant-inflammatory)

INDICATION: Treatment of mild to moderate ulcerative colitis

RECOMMENDATION:

I concur with Dr. Fathia Gibril's recommendations that NDA 22-205, Giazo (balsalazide disodium) tablets, be approvable for use in mild to moderate active ulcerative colitis (UC). The sponsor's single placebo controlled study demonstrated superiority of balsalazide disodium (BD) tablets over placebo in male subjects. The clinical benefit of BD tablets has not been established in female subjects that contributed 51% of the study population.

The issuance of an approval is dependent upon the review of additional efficacy data. The second phase III, active controlled study (BZUC3003) was recently completed and the study report has been provided by the sponsor. This study will be reviewed and should be adequate to support as additional efficacy data.

The Sponsor requested waiver for pediatric studies required under the Pediatric Research Equity Act (PREA). I recommend that the waiver request be granted. The proposed BD 1100 mg tablet contains the same active ingredient as in the approved product, BD 750mg capsules (Colazal), for pediatric population for the treatment of mild to moderate active UC. Both formulations are at a similar total daily dose. However, Colazal capsules can be opened and sprinkled on applesauce as a pediatric administrative alternative; while the tablets may be more difficult to administer to the pediatric population because of difficulty to swallow. Therefore, the implementation of the tablet formulation does not represent a meaningful benefit over the existing Colazal capsule formulation in terms of treatments (dosage and ability to administer) for pediatric patients.

BACKGROUND:

The sponsor, Salix, seeks approval for balsalazide disodium (BD) tablets for use in mild to moderate active UC. Each BD tablet contains 1.1g of BD, a prodrug that is enzymatically cleaved in the colon to release mesalamine, an anti-inflammatory drug. Although the exact mechanism of action of mesalamine is not fully understood, it appears to be local to the colonic mucosa rather than systemic. To date, five mesalamine containing oral agents have been approved for use in mild to moderate active UC: Asacol, Lialda (delayed release tablet), Sulfasalazine tablet, Colazal capsule (prodrug) and Pentasa (controlled release capsule).

In support of the proposed indication, the sponsor submitted the results from a single phase 3, double blind, randomized, multicenter, parallel group, placebo controlled study (BZUC3002) that was conducted in the US.

The proposed total daily dose (6.6g/day) for new tablet formulation is similar to that of the existing capsule formulation (6.75g/day), Colazal, which was approved in July 18, 2000 for the same indication. The goal of the clinical program was to provide a more convenient dosing regimen with the new tablet formulation as compared to capsule formulation (twice daily [BID] vs. three times daily [TID]).

A second larger phase III clinical trial (BZUC3003) is completed. The study is double-blind, double-dummy, randomized, active controlled study to evaluate the safety and efficacy of BD tablets versus Asacol delayed release tablets in approximately 400 subjects with mild to moderate active UC.

DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

DSI:

The Division of Scientific Investigation (DSI) has been consulted for this NDA. The single pivotal study submitted under this NDA was conducted at 55 centers in the US. Four cites (#216, 547, 675 and 834) were selected for auditing based on sample size. The report from

DSI audit including 3 sites (#216, #547 and #675) was finalized on April 3, 2008 and indicated that there were some violations at study sites 216 and 547, but concluded that the violations will not affect the validity of the data and thus can be used in support of NDA. There was no violation at site #675.

Chemistry and Manufacturing:

From the CMC perspective, this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP. From a CMC perspective, this NDA is recommended for "Approval" pending corrections to the label. For detail information, please see Dr. Maria Ysern's review.

Pre-Clinical Pharmacology/Toxicology:

From a preclinical standpoint, approval of Balsalazide disodium, 1.1 g tablets is recommended for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. Please see Dr. Ke Zhang's review in details.

Biopharmaceutics:

There is no new clinical pharmacology related information in this submission.
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 has reviewed the clinical pharmacology and biopharmaceutics information submitted to NDA 22-205 and found it acceptable from a clinical pharmacology standpoint. Please see Dr. Insook Kim's review in details.

Clinical/Statistical:

Efficacy

The efficacy of BD tablets was evaluated in a single phase 3, double blind, placebo controlled, multicenter trial in subjects with mild to moderate UC. Eligible subjects were randomized to receive BD tablets or placebo in a 2:1 ratio for 8 weeks.

Efficacy was assessed using the Modified Mayo Disease Activity Index (MMDAI) with a maximum total score of 12. The MMDAI evaluated 4 indices (stool frequency, rectal bleeding, physician's global assessment [PGA], and endoscopic findings) each on a scale from 0 to 3, with 3 being severe disease. A daily diary was kept by patients to record stool frequency, rectal bleeding and symptoms. A complete MMDAI score was calculated at screening/baseline and week 8 (end of study).

The prespecified primary efficacy endpoint was the proportion of subjects who achieved clinical improvement and improvement in rectal bleeding (RB) at the end of 8-week therapy. Clinical improvement was defined as a ≥ 3 point improvement from baseline to

week 8 in the total MMDAI score and improvement in RB was defined as a ≥ 1 point improvement from baseline to week 8 in RB score (a subscale of MMDAI).

Of the 250 subjects randomized, 249 were included in the ITT population. For the primary endpoint analysis compared to placebo, a significantly larger proportion of ITT subjects treated with BD tablets achieved clinical improvement and improvement in rectal bleeding: (b) (4) (55%) vs (40%) (b) (4); p=0.024. Similar results were observed in analysis of PP population: (b) (4) (57.6%) vs (40.6%) (b) (4); p=0.019.

For the secondary endpoint analysis, a significantly larger proportion of ITT subjects in the BD tablets group experienced clinical remission and mucosal healing compared with the placebo group: 64/166 (38.6%) vs. (22.9%) 19/83; p=0.0096 and 88/166 (53.0%) vs. (32.5%) 27/83; p=0.0035, respectively.

The primary and secondary efficacy results are summarized in the table below.

Table 1: Summary of Primary and Key Secondary Efficacy Results In ITT Population

Efficacy Endpoints	BD Tablets N = 166 n (%)	Placebo N = 83	Difference in Proportions %	p-value
Primary EP				
clinical improvement and improvement in RB	92 (55)	33 (40)	15	0.024
Key Secondary EP				
Clinical Remission	64 (38.6)	19 (22.9)	15.7	0.0096
Mucosal Healing	88 (53)	27 (32.5)	20.5	0.0035
Bowel Frequency	82 (49.4)	31 (37.3)	12.0	0.0750
Rectal Bleeding	98 (59)	35 (42.2)	16.9	0.0131
Physician's Assessment	99 (59.6)	30 (36.1)	23.5	0.0004
Complete Remission	34 (20.5)	11 (13.3)	17.2	0.0957

The third key secondary endpoint in the hierarchy (improvement in bowel frequency) failed to reach statistical significance, therefore, the analysis for this endpoint and the subsequent secondary endpoints were considered exploratory in nature as prespecified in the statistical analysis plan.

Primary Endpoint Analysis by Subgroups

In a subgroup primary endpoint analysis, including sex, age and race, BD tablet was superior over placebo in males (b) (4) 57% vs. 20% (b) (4) p<0.001), in subjects age <65

([86/154] 56% vs. 37% [29/78]; p=0.007) and in White population ([74/135] 55% vs. 40% [29/72]; p=0.05). By contrast, the treatment difference was insignificant in females (p= (b) (4) , in subjects age ≥65 (p=0.25) and in nonwhite population (p=0.22). While it is possible that the small sample size is a potential factor for lack of superiority in subjects age ≥65 and in nonwhite population subgroups (n=17 and n=42, respectively),

Table 2: Summary of Results of Primary Endpoint Analysis by Gender

	BD tablets n/N (%)	Placebo n/N (%)	p-value
Total Population	(b) (4) (55)	(b) (4) (40)	**0.02**
Sex			
Male	(b) (4) (57)	(b) (4) (20)	<0.001
Female	(b) (4) (54)	(b) (4) (58)	(b) (4)

The small sample size is a less likely factor in females (n=128) that contributed 51% of the ITT population.

In the study, the mean baseline disease activity scores were comparable across treatment groups as well as across gender: drug vs. placebo was 8 (each) in males and 7.6 vs. 8 in females.

To further investigate the observed discrepancy in the primary endpoint analysis across gender, a post hoc secondary endpoint analysis by gender was conducted by Dr. Shahla Farr as shown below.

Table 3: Summary of Key Secondary Endpoints Analysis by Gender

Variables	**BD tablets n/N (%)**	**Placebo n/N (%)**	**p-value**
Clinical Remission			
Males	28/81 (35)	5/40 (13)	0.01
Females	(b) (4)		
Mucosal Healing			
Males	42/81 (52)	8/40 (20)	<0.001
Females	(b) (4)		
Bowel Frequency			
Males	43/81 (53)	12/40 (30)	0.02
Females	(b) (4)		
Rectal Bleeding			
Males	51/81 (63)	13/40 (33)	0.002
Females	(b) (4)		
Complete Remission			
Males	12/81 (15)	0	0.01
Females	(b) (4)		

As summarized in the Table above, the findings were consistent with the primary endpoint findings, that is, statistically significant differences were observed in males but not in females.

In this single placebo controlled study (n=249, 166 on drug), there was unexplained difference in results between males and females. This was due to marked differences in placebo response rate between males and females (20% vs. 58%), while the response rate with BD treatment was similar. As a result, a substantial therapeutic effect was demonstrated in males, but not in females. The observed superior efficacy of BD tablet in the study was thus driven by a subpopulation's finding, namely, males. Conversely, due to the unexplained high placebo response rate in females, the efficacy of BD tablet has not been established in this subpopulation, which contributed 51% of the ITT population.

Safety

A total of 247 were included in the safety population: 168 subjects in the BD tablet group and 79 subjects in the placebo group.

In an 8 week placebo controlled clinical trial, a lower percentage of patients reported at least one adverse event (AE) in the BD group (55%) than in the placebo group (68%). Overall, events related to gastrointestinal (GI) disorder was the most frequently reported AE (26.2% in BD group and 36.7% in placebo group. While worsening of UC was the most common GI related event in either treatment group, it occurred less frequently in the BD group as compared to the placebo group (7% vs. 14%). Headache was the second common AE with an incidence of 6% in the BD group and 14% in the placebo group. There were no clinically meaningful changes in laboratory parameters or vital signs in the study.

A similar percentage of BD treated patients experienced serious adverse events (2.4%), discontinued due to AEs (10%) and experienced treatment related AEs (8%) as patients receiving placebo (5%, 13% and 9%, respectively). The most frequent AE leading to discontinuation from BD therapy was worsening UC. A total of 9/168 (5.4%) of BD tablets treated patients were withdrawn due to worsening UC, compared to 9/79 (11.4%) of placebo treated group. There were no deaths reported during this study.

Drug-related events of nausea and rash (2 subjects each) were experienced by 1% of subjects in the BD tablets group; no subjects in the placebo group experienced drug-related nausea or rash.

The interim report from an ongoing long term, open label, safety extension study (BZUC3005) including 130 subjects showed similar safety profile. The most frequent AEs were worsening UC (5%) and diarrhea (3%). SAEs were reported in 2 subjects: worsening UC (n=1) and bronchitis (n=1). Four subjects discontinued the study due to worsening UC. No deaths were reported in this study.

Based upon the data from the clinical program, BD tablets are safe and well tolerated in subjects with mild to moderate active UC. The overall safety profile of the tablet dosage

form is similar to the capsule dosage form, which was approved for marketing in the US since July 2000.

Pediatric Use:

The Sponsor requested waiver for pediatric studies required under the Pediatric Research Equity Act (PREA). I recommend that the waiver request be granted. The proposed BD 1100 mg tablet contains the same active ingredient as in the approved product, BD 750mg capsules (Colazal), for pediatric population for the treatment of mild to moderate active UC. Both formulations are at a similar total daily dose. However, Colazal capsules can be opened and sprinkled on applesauce as a pediatric administrative alternative; while the tablets may be more difficult to administer to the pediatric population because of difficulty to swallow. Therefore, the implementation of the tablet formulation does not represent a meaningful benefit over the existing Colazal capsule formulation in terms of treatments (dosage and ability to administer) for pediatric patients.

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/s/

Ruyi He
5/9/2008 06:00:22 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-205
Submission Code	N-000
Letter Date	July 16, 2007
Stamp Date	July 18, 2007
PDUFA Goal Date	May 17, 2008
Reviewer Name	Fathia Gibril, MD, MHSc, AGAF
Review Completion Date	April 4, 2008
Established Name	Balsalazide Disodium
(Proposed) Trade Name	Giazo
Therapeutic Class	Mesalamine (Ant-inflammatory)
Applicant	Salix Pharmaceuticals, Inc.
Priority Designation	S
Formulation	Tablet (1.1g)
Dosing Regimen	3.3g BID
Indication	Mild to moderate ulcerative colitis
Intended Population	18 years of age and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The reviewer recommends that an approvable action be taken on Salix marketing application (NDA 22-205) for balsalazide disodium (BD) tablets intended for use in mild to moderate active ulcerative colitis (UC). In the sponsor's single placebo controlled study, superiority of BD tablets was dependent on a subpopulation's finding, namely, male subjects. The lack of therapeutic effect in females was due to the unexplained high placebo response rate.

The issuance of an approval is dependent upon the review of additional efficacy data from adequate and well controlled study. The result from recently completed second phase 3 study (BZUC3003) is expected to demonstrate substantial evidence of effectiveness and consistent finding across important subgroups, namely, males and females.

Of note, review of the proposed Trade Name (Giazo) was not finalized by the Division of Medication Errors at the time this review was completed. Thus, the established name has been used throughout this review.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There is no applicable activity related to risk management for this NDA.

1.2.2 Required Phase 4 Commitments

The Sponsor requested waiver for pediatric studies required under the Pediatric Research Equity Act (PREA), and provided the following justification: the new tablet formulation contains the same active ingredient as in the approved capsule formulation (Colazal), for pediatric population. Both formulations are indicated for the treatment of mild to moderate active UC at a similar total daily dose. Colazal capsules can be opened and sprinkled on applesauce as a pediatric administrative alternative; while the tablets may be more difficult to administer to pediatric population because of difficulty to swallow. Therefore, the implementation of the tablet formulation does not represent a meaningful benefit over the existing capsule formulation in terms of treatments (dosage and ability to administer) for pediatric patients.

In the reviewer's opinion, the sponsor's justification appears adequate and recommends that a waiver be granted. But it should be noted that the new tablet formulation has a more convenient dosing regimen than the approved capsule formulation (BID vs TID), a potential benefit for improving adherence to therapy. As such, a request would have been made for developing age appropriate formulation for pediatric subjects unable to swallow the tablet. Nonetheless, the

reviewer opted to forgo the request since a Proposed Pediatric Study Request (PPSR) for another mesalamine preparation (Lialda) that offers once daily doing regimen for the same indication is submitted by Shire and is currently under review.

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests for this NDA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor seeks approval for balsalazide disodium (BD) tablets for use in mild to moderate active UC. Each tablet contains 1.1g of BD, a prodrug that is enzymatically cleaved in the colon to release mesalamine, an anti-inflammatory drug. Although the exact mechanism of action of mesalamine is not fully understood, it appears to be local to the colonic mucosa rather than systemic. To date, five mesalamine containing oral agents have been approved for use in mild to moderate active UC: Asacol, Lialda (delayed release tablet), Sulfasalazine tablet, Colazal capsule (prodrug) and Pentasa (controlled release capsule).

In support of the proposed indication, the sponsor submitted the results from a single phase 3, double blind, randomized, multicenter, parallel group, placebo controlled study (BZUC3002) that was conducted in the US. Eligible subjects (n=250) were randomized to receive either BD tablets or placebo in a 2:1 ratio for 8 weeks.

It should be noted that no separate dose response trial was conducted with the BD tablets. The rationale was that the proposed total daily dose (6.6g/day) for tablet formulation is similar to that of the capsule formulation (6.75g/day), Colazal, which was approved in July 18, 2000 for the same indication. The goal of the clinical program was to provide a more convenient dosing regimen with the tablet formulation as compared to capsule formulation (twice daily [BID] vs three times daily [TID]).

A second larger phase III clinical trial (BZUC3003) is currently ongoing. The study is double-blind, double-dummy, randomized, active controlled study to evaluate the safety and efficacy of BD tablets versus Asacol delayed release tablets in approximately 400 subjects with mild to moderate active UC.

The safety evaluation of BD tablets is based on data from a pivotal placebo controlled study and ongoing open-label, extension study (BZUC3005) designed to evaluate the long-term safety and tolerability of BD tablets. The interim report of the ongoing study includes 130 subjects in the safety population who successfully participated in BZUC3002 and received BD tablets at a dose of 3.3g or 4.4g BID.

Addendum
On November 16, 2007, without any prior agreement the sponsor submitted a full report from the second phase 3 study (BZUC3003) along with the required 120-day safety update. From the document submitted, it became apparent that the aforementioned study was completed shortly after the NDA was submitted. Nevertheless, on a teleconference held in December 2007, the sponsor was informed that the second study results will not be reviewed under the current review cycle.

It is of interest to note that at the End of Phase 2 meeting and Pre-NDA meeting (meeting minutes dated 08/08/05 and 08/27/07, respectively), the sponsor was advised to include two studies for marketing application and was informed that if a single study were submitted it would be expected to show substantial evidence of effectiveness and consistent finding across centers and subgroups. Despite the Division's repeated advice and the sponsor's knowledge that the second phase 3 study (BZUC3003) was near completion, it was decided to rely on a single study (BZUC3002) that failed to demonstrate consistent findings across important subgroups, namely, males and females as described below.

1.3.2 Efficacy

The efficacy of BD tablets was evaluated in a single phase 3, double blind, placebo controlled, multicenter trial in subjects with mild to moderate UC. Eligible subjects were randomized to receive BD tablets or placebo in a 2:1 ratio for 8 weeks.

Efficacy was assed using the Modified Mayo Disease Activity Index (MMDAI) with a maximum total score of 12. The MMDAI evaluated 4 indices (stool frequency, rectal bleeding, physician's global assessment [PGA], and endoscopic findings) each on a scale from 0 to 3, with 3 being severe disease. A daily diary was kept by patients to record stool frequency, rectal bleeding and symptoms. A complete MMDAI score was calculated at screening/baseline and week 8 (end of study).

The prespecified primary efficacy endpoint was the proportion of subjects who achieved clinical improvement and improvement in rectal bleeding (RB) at the end of 8-week therapy. Clinical improvement was defined as a ≥ 3 point improvement from baseline to week 8 in the total MMDAI score and improvement in RB was defined as a ≥ I point improvement from baseline to week 8 in RB score (a subscale of MMDAI).

Key Secondary Endpoints:

- The proportion of subjects with clinical remission at Week 8, where clinical remission was defined as a score of 0 for RB and a combined score of ≤ 2 for bowel frequency and PGA
- The proportion of subjects with mucosal healing at Week 8, where mucosal healing was defined as an endoscopy score of 0 or 1
- The proportion of subjects with improvement from baseline to Week (Wk) 8 in bowel frequency
- The proportion of subjects with improvement from baseline to Wk 8 in RB

- The proportion of subjects with improvement from baseline to Week 8 in PGA
- The proportion of subjects achieving complete remission at Week 8, where complete remission was defined as a MMDAI score of ≤ I

Reviewer's comments: Measurement of disease activity is critical in evaluating new therapies in UC clinical trials. Multiple instruments/indices have been developed for assessment of disease activity in UC trials, but none have been formally validated. However, the proposed MMDAI has been widely used in UC clinical trials including the clinical trials that led to approval of Lialda, the most recently approved oral mesalamine agent, for use in mild to moderate UC.

In addition, there has been no formal attempt to define efficacy endpoints such as clinical improvement or remission in UC clinical trials. However, remission defined as complete relief of inflammatory symptoms has been generally considered to represent a higher level of clinical response than clinical improvement where a given point reduction in disease activity score is selected at random. It is worth noting that while remission was the primary endpoint (PE) in clinical trials that led to approval of Lialda; clinical improvement is the proposed PE in the current application.

Efficacy Results

All efficacy analyses were performed using the intent-to-treat (ITT) population, which consisted of all randomized subjects who received at least 1 dose of study drug. In addition, the primary efficacy analysis was performed in the per protocol (PP) population, which consisted of ITT population without major protocol violations. Of the 250 subjects randomized, 249 were included in the ITT population. Subject 505-09 (BD tablet group) had no MMDAI scores recorded and was excluded from the ITT population. In the reviewer's opinion, exclusion of one subject will not influence the overall results.

<u>Primary Endpoint Analysis</u>
Compared to placebo, a significantly larger proportion of ITT subjects treated with BD tablets achieved clinical improvement and improvement in RB: (b) (4) (55%) vs (40%) (b) (4); p=0.024. Similar results were observed in analysis of PP population: (b) (4) (57.6%) vs (40.6%) (b) (4); p=0.019.

<u>Secondary Endpoint Analysis</u>
In the hierarchical secondary endpoint analysis, a significantly larger proportion of ITT subjects in the BD tablets group experienced clinical remission and mucosal healing compared with the placebo group: 64/166 (38.6%) vs (22.9%) 19/83; p=0.0096 and 88/166 (53.0%) vs (32.5%) 27/83; p=0.0035, respectively. The third key secondary endpoint in the hierarchy (improvement in bowel frequency) failed to reach statistical significance, therefore, the analysis for this endpoint and the subsequent secondary endpoints were considered exploratory in nature as prespecified in the statistical analysis plan.

Primary Endpoint Analysis by Subgroups

In a subgroup primary endpoint analysis, including sex, age and race, BD tablet was superior over placebo in males ([redacted] 57% vs 20% [redacted]; p<0.001), in subjects age <65 ([86/154] 56% vs 37% [29/78]; p=0.007) and in White population ([74/135] 55% vs 40% [29/72]; p=0.05). By contrast, the treatment difference was insignificant in females (p=[redacted]), in subjects age ≥65 (p=0.25) and in nonwhite population (p=0.22). While it is possible that the small sample size is a potential factor for lack of superiority in the latter two subgroups (n=17 and n=42, respectively), it is a less likely factor in females (n=128) that contributed 51% of the ITT population.

It is of interest to note that while the response rate was comparable between males and females in the BD tablet group ([redacted] 57% and 54% [redacted], respectively); it was markedly different in the placebo group ([redacted] 20% vs 58% [redacted]. Consequently, a substantial therapeutic gain was demonstrated among males (37%), but none among females (-4%).

The reason for the observed discrepancy in the placebo response rates across gender is not clear. Additional information provided by the sponsor upon reviewer's request was non-contributory. Review of relevant published literature does not suggest gender as a potential factor for differences in placebo response rate in the population of interest. In a meta-analysis study published recently, it has been reported that studies with higher mean disease activity scores at baseline in placebo patients were associated with lower placebo response rates. (Su et al. Gastroenterol 2007;132:516-526). In the sponsor's study, the mean baseline disease activity scores were comparable across treatment groups as well as across gender: drug vs placebo was 8 (each) in males and 7.6 vs 8 in females. In the most recent information provided, the sponsor claimed that females with more sever disease at baseline (MMDAI score ≥ 9) had a larger placebo response rates and no placebo males with sever disease at baseline responded. The sponsor's study result in females is in contrary to the published literature described above where placebo subjects with more sever disease at baseline would be expected to have a low response rate, rather than a high response rate as presented.

Secondary Endpoint Analysis by Gender

To further investigate the observed discrepancy in results across gender, a post hoc analysis of secondary endpoint by gender was conducted by the Division's statistician, Dr Shahla Farr, upon this reviewer's request. The results were consistent with the primary endpoint analysis. In males, a significantly larger proportion of subjects in the BD tablet group than in the placebo group experienced clinical remission (p=0.01), mucosal healing (p<0.001), improvement in bowel frequency (p=0.02), improvement in RB (p=0.002) and complete remission (p=0.01). By contrast, the treatment differences were insignificant for all secondary endpoint variables in females (p-values: [redacted], respectively). This is not surprising since secondary endpoint variables were subsets of the composite primary endpoint.

Based upon a comprehensive review of efficacy data generated from a single placebo controlled study, the reviewer concluded that the observed superiority of BD tablets over placebo was driven by a subpopulation's finding, namely, male subjects. Conversely, the efficacy of BD tablets has not been established in females that contributed 51% of the study population. The lack of therapeutic effect in females was due to the unexplained high placebo response rate.

1.3.3 Safety

Of a total of 250 subjects randomized in the pivotal study, 247 were included in the safety population: 168 (99.4%) subjects in the BD tablet group and 79 (97.5%) subjects in the placebo group. Two subjects in the placebo group and 1 subject in the BD tablet group did not have a post-baseline safety assessment and were excluded from the safety population.

In an 8 week placebo controlled clinical trial, a lower percentage of patients reported at least one adverse event (AE) in the BD group (55%) than in the placebo group (68%). Overall, events related to gastrointestinal (GI) disorder was the most frequently reported AE (30%) in ≥2% of subjects, but the event was less frequent in BD group than in placebo group (26.2% vs 36.7%). While worsening of UC was the most common GI related event in either treatment group, it occurred less frequently in the BD group as compared to the placebo group (7% vs 14%). The only GI events that occurred in ≥2% of subjects in the BD tablets group and not in the placebo group were abdominal distension (4.2%) and flatulence (2.4%). Headache was the second common AE with an incidence of 6% in the BD group and 14% in the placebo group. There were no clinically meaningful changes in laboratory parameters or vital signs in the study.

A lower percentage of BD treated patients experienced serious adverse events (2.4%), discontinued due to AEs (10%) and experienced treatment related AEs (8%) than patients receiving placebo (5%, 13% and 9%, respectively). Worsening UC was the only SAE reported by >1% of subjects in either treatment group and occurred less frequently in subjects treated with BD tablets than with placebo (1.8% vs 3.8%). The most frequent AE leading to discontinuation from BD therapy was worsening UC. A total of 9/168 (5.4%) of BD tablets treated patients were withdrawn due to worsening UC, compared to 9/79 (11.4%) of placebo treated group. There were no deaths reported during this study.

In the placebo controlled study, very few AEs were considered to be related to either BD tablets or to placebo. The investigator considered the AEs to be related in a similar proportion of subjects treated with BD tablets and with placebo (8% and 9%, respectively). Drug-related events of nausea and rash (2 subjects each) were experienced by 1% of subjects in the BD tablets group; no subjects in the placebo group experienced drug-related nausea or rash.

The interim report from an ongoing long term, open label, safety extension study (BZUC3005) including 130 subjects showed similar safety profile. The most frequent AEs were worsening UC (5%) and diarrhea (3%). SAEs were reported in 2 subjects: worsening UC (n=1) and bronchitis (n=1). Four subjects discontinued the study due to worsening UC. No deaths were reported in this study.

Based upon the data from the clinical program, BD tablets are safe and well tolerated in subjects with mild to moderate active UC. The overall safety profile of the tablet dosage form is similar to the capsule dosage form, which was approved for marketing in the US in July 2000.

1.3.4 Dosing Regimen and Administration

The recommended total daily dose is 6.6g to be taken in two divided doses (three 1.1g tablets BID) for up to 8 weeks.

It should be noted that no separate dose response trial was conducted with the new BD tablet formulation. The rationale was that the proposed total daily dose (6.6g/day) for new tablet formulation is similar to that of the capsule formulation (6.75g/day), Colazal, which was approved in July 18, 2000 for the same indication. The goal of the clinical program was to offer patients with a more convenient daily dosing regimen with the new tablet formulation (BID vs TID).

1.3.5 Drug-Drug Interactions

Drug interaction studies have not been conducted with BD tablets.

1.3.6 Special Populations

Safety and effectiveness of BD tables in pediatric population have not been studied. There have been no studies with BD tablets in subjects with renal or hepatic impairment. Pregnant women and nursing mothers were excluded from clinical trials with BD tablets. The clinical program did not include sufficient number of subjects aged 65 and older (<10%) to determine whether they respond differently than younger subjects.

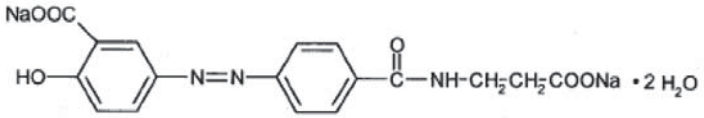
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

In the current NDA 22-205 submission, the sponsor seeks approval for BD tablet (1.1g) for use in mild to moderate active UC at a total daily dose of 6.6g to be administered BID (3 tablets BID) for up to 8 weeks.

Each tablet contains 1.1g of BD, a prodrug that is enzymatically cleaved in the colon to produce mesalamine (5-amnisalicylic acid, also referred to as 5-ASA), an anti-inflammatory drug. Each tablet of BD is equivalent to (b) (4) of mesalamine. Balsalazide disodium has the chemical name (E)-5-[[-4-[[(2-carboxyethyl) amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate.

Structural formula:



The exact mechanism of action of mesalamine is not fully understood, but appears to be local in the colon rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

Mesalamine is the active ingredient of many products marketed in the US for the treatment of mild to moderate UC.

2.2 Currently Available Treatment for the Indication

The following oral mesalamine preparations are currently marketed in the US for use in mild to moderate active UC:

- Lialda (1.2g tablet) at a total daily dose of 2.4g or 4.8g once daily
- Colazal (750mg capsule) at a total daily dose of 6.75g in 3 divided dose
- Asacol (400mg tablet) at a total daily dose of 2.4g in 3 divided dose
- Pentasa (250mg or 500mg capsule) at a total daily dose of 4g in 4 divided dose
- Sulfasalazine (500mg tablet) at a total daily dose of 3g TID

2.3 Availability of Proposed Active Ingredient in the United States

Mesalamine is the active ingredient of many products marketed in the US for the treatment of mild to moderate UC.

2.4 Important Issues With Pharmacologically Related Products

There are no important issues with pharmacologically related products.

2.5 Presubmission Regulatory Activity

Pertinent Regulatory Excerpt
It appears that there were limited presubmission regulatory activities for this clinical program. At the August 8, 2005, End of Phase 2 meeting and the August 27, 2007, pre-NDA meeting, the sponsor sought advice regarding submission of a single study for marketing application. The sponsor was informed that a standard recommendation for marketing application is two adequate and well-controlled studies and that if a single study were submitted, it would be expected to show substantial evidence of effectiveness and consistent finding across centers and subgroups.

2.6 Other Relevant Background Information

There is no other relevant background information. BD tablets are not marketed in any country in the world.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC review by Dr Maria Ysern was not finalized at the time this review was completed. However, she indicated that there are no outstanding issues with CMC.

3.2 Animal Pharmacology/Toxicology

No new animal studies were conducted under the NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical efficacy and safety data for this review was a single placebo controlled study (BZUC3002) conducted by the sponsor in the US and included in this submission as a paper version in the Common Technical Document format (CTD).

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4.2 Tables of Clinical Studies

Summary of all Clinical Studies

Type of Study	Study Number	Location of Study Report in CTD	Objective(s) of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	BZPK1002	Module 5.3.1.1.1, Study Report BZPK1002, p. 1	Relative bioavailability of single dose administered fasted versus fed	Open-label, randomized, single-dose, 2-period crossover	BSZ Tablets; 3.3 g (1.1 g x 3); oral	28 (26 in PK analysis)	Healthy Subjects	Single dose	Complete; Full
Relative BA	BZPK1003	Module 5.3.1.2.1, Study Report BZPK1003, p. 1	Relative bioavailability of BSZ tablet versus capsule (Colazal®)	Open-label, randomized, 2-period crossover	BSZ Tablets; 3.3 g (1.1 g x 3) BID (6.6 g/day) or BSZ Capsules; 2.25 g (750 mg x 3) TID (6.75 g/day); oral	24 (18 in PK analysis)	Healthy Subjects	Single dose and 7 days	Complete; Full
PK (meta-bolism)	XT055039	Module 5.3.2.3.1, Study Report XT055039, p. 1	Evaluate the ability of balsalazide to inhibit the major CYP enzymes in human liver microsomes	In vitro CYP inhibition	Balsalazide, 5-aminosalicylic acid, N-acetyl-5-aminosalicylic acid, 4-aminobenzoyl-ß-alanine, and N-acetyl-4-aminobenzoyl-ß-alanine at concentrations of 0.1 to 100 µM; in vitro	Samples pooled from 16 individuals	Human Liver Microsomes	Not applicable	Complete; Full
Efficacy	BZUC3002	Module 5.3.5.1.1, Study Report BZUC3002, p. 1	Efficacy and safety	Multicenter, randomized, double-blind, placebo-controlled, parallel group	BSZ Tablets; 3.3 g (1.1 g x 3) BID (6.6 g/day); oral	250 (167 BSZ Tablets, 83 Placebo)	Patients with Mildly to Moderately Active Ulcerative Colitis	8 weeks	Complete; Full
Safety	BZUC3005	Module 5.3.5.2.1, Interim Study Report BZUC3005, p. 1	Long-term safety and tolerability	Multicenter, open-label	BSZ Tablets; 3.3 g (1.1 g x 3) BID (6.6 g/day) or 4.4 g (1.1 g x 4) BID (8.8 g/day); oral	500 planned 179 enrolled (130 in Safety Population) [a]	Patients with Mildly to Moderately Active Ulcerative Colitis	24 months or until regulatory approval	Ongoing; Interim

BSZ = balsalazide disodium; BA = Bioavailability; BE = Bioequivalence; PK = Pharmacokinetics
[a] Date of Last Assessment for Interim Analysis, 26 April 2007.

4.3 Review Strategy

The applicant submitted the current NDA in the CTD format as a paper version. In this application, efficacy and safety data of the study drug were generated primarily from one pivotal phase III, placebo controlled clinical study (BZUC3002). The reviewer thoroughly reviewed the pivotal study with equal regard to safety and efficacy. In addition, the interim safety report from an open label, safety and tolerability extension study (BZUC3005) submitted in this application were reviewed to highlight the proposed indication.

The reviewer approached this submission first by focusing upon what the applicant has requested, and what evidence has been presented in support of the request. The protocol was examined first, and then the study report was assessed for safety and efficacy. The reviewer's final judgment on safety and efficacy for the proposed indication was based on safety profile of the drug and whether the stated primary objective of efficacy was achieved. Furthermore, additional information was sought from published clinical literature relevant to the proposed drug product and medical condition being treated. The reviewer also consulted Division's previous relevant marketing applications and electronic Physician Desk Reference.

4.4 Data Quality and Integrity

The Division of Scientific Investigation (DSI) has been consulted for this NDA. The single pivotal study submitted under this NDA was conducted at 55 centers in the US. Four cites (# 216, 547, 675 and 834) were selected for auditing based on sample size. In addition, the overall quality of data was discussed and reanalyzed for verification purpose by the Division's statistical reviewer, Dr Shahla Far, and was found to be acceptable.

The report from DSI audit including 3 sites (#216, #547 and #675) was finalized on April 3, 2008 and indicated that there were some violations at study sites 216 and 547, but concluded that the violations will not affect the validity of the data and thus can be used in support of NDA. There was no violation at site #675.

4.5 Compliance with Good Clinical Practices

The applicant documented that all studies were conducted in accordance with the current applicable regulations, International Conference on Harmonization (ICH), Good Clinical Practice (GCP) and local ethical and legal requirements. It was also documented that the study was conducted in accordance with the principles of the Declaration of Helsinki.

The applicant documented that patients were informed by the Investigator or an authorized staff member about the nature of the study prior to the start of the study. Each patient signed a study-specific consent form to serve as a participant in the study.

4.6 Financial Disclosures

The applicant documented that investigators submitted disclosure statements as required by the regulations 21 CRF Part 54. The applicant certified that they did not enter into financial agreement with the clinical investigators (with the exception of 2 investigators) whereby the value of their compensation could be affected the outcome of the study. Two investigators who participated in clinical studies BZUC3002 and BZUC3005 have financial arrangements required to be disclosed. (b) (6) has been paid approximately $165,000 for (b) (6) The aforementioned investigator enrolled (b) (6) subjects out of a total of 250 subjects in study BZUC3002 (double blind, placebo controlled pivotal study) and (b) (6) subject in study BZUC3005 (ongoing open label safety

study). In the reviewer's opinion, the potential impact to affect the study result is minimal given the small number of patients enrolled in each study.

The second investigator, (b) (6) holds equity approximately 25,000 shares of Salix stock. This investigator enrolled (b) (6) subjects (site (b) (6) out of a total of 250 in study BZUC3002. This site was audited by DSI and concluded that the data can be used in support of NDA as described above under section 4.4. In addition, to verify the integrity of the data, analysis of efficacy excluding site (b) (6) was conducted by the Division's statistician, Dr Shahla Farr, upon this reviewer's request. The result showed that the inclusion or exclusion of the aforementioned site did not have any impact on the overall study result; the p-vale remained the same (p=0.02).

5 CLINICAL PHARMACOLOGY

The exact mechanism of action of mesalamine is not fully understood, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

Mesalamine is the active ingredient of many products marketed in the US for the treatment of mild to moderate UC.

5.1 Pharmacokinetics

Biopharm review by Dr Insook Kim was not finalized at the time this review was completed. However, she indicated that there is no outstanding issue related to Biopharm data.

5.2 Pharmacodynamics

No pharmacodynamic study was conducted for this application, possibly because mesalamine is thought to have a local action in the colon rather than systemic action.

5.3 Exposure-Response Relationships

No dose response study was conducted for this application.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is for the treatment of adults with mild to moderate active UC.

6.1.1 Methods

In support of the proposed indication, the sponsor submitted the efficacy data from a single phase 3, double blind, randomized, multicenter, parallel group, placebo controlled study (BZUC3002) that was conducted in the US at 55 centers. A total of 250 eligible subjects were randomized to receive balsalazide disodium (BD) tablets or placebo in a 2:1 ratio for 8 weeks.

It should be noted that no separate dose response trial was conducted with the BD tablet formulation. The rationale was that the proposed total daily dose (6.6g/day) for new tablet formulation is similar to that of the existing capsule formulation (6.75g/day), Colazal, which was approved in July 18, 2000 for the same indication. The goal of the clinical program was to provide a more convenient dosing regimen with the new tablet formulation as compared to capsule formulation (BID vs TID).

Of note, in this review the term BD (balsalazide disodium) and BSZ (balsalazide) has been used interchangeably.

6.1.2 General Discussion of Endpoints

The prespecified primary efficacy endpoint was the proportion of subjects who achieved clinical improvement and improvement in rectal bleeding at week 8. Clinical improvement was defined as a ≥ 3 point improvement from baseline to week 8 in the total MMDAI score and improvement in the rectal bleeding, a subscale of MMDAI, was defined as a ≥ I point improvement from baseline to week 8 in rectal bleeding score.
Key secondary efficacy endpoints:

- The proportion of subjects with clinical remission at Week 8, where clinical remission was defined as a score of 0 for rectal bleeding and a combined score of ≤ 2 for bowel frequency and physician's assessment
- The proportion of subjects with mucosal healing at Week 8, where mucosal healing was defined as an endoscopy score of 0 or 1
- The proportion of subjects with improvement from baseline to Week 8 in bowel frequency
- The proportion of subjects with improvement from baseline to Week 8 in rectal bleeding
- The proportion of subjects with improvement from baseline to Week 8 in Physician’s assessment.
- The proportion of subjects achieving complete remission at Week 8, where complete remission was defined as a MMDAI score of ≤ I

As summarized in the Table below, the MMDAI evaluated 4 indices each on a scale of 0 to 3 (3 being severe disease) with a maximum total score of 12.

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Modified Mayo Disease Activity Index (MMDAI)

Index	Bowel Frequency	Bleeding	Physician's Global Assessment	Endoscopy/Sigmoidoscopy Findings
MMDAI or Ulcerative Colitis Symptom Score (UCSS)	0 = Normal number of stools per day for this subject 1 = 1 to 2 more stools than normal 2 = 3 to 4 more stools than normal 3 = 5 or more stools than normal	0 = no blood seen 1 = streaks of blood with stool less than half the time 2 = obvious blood with stool most of the time 3 = blood alone passed	0 = normal 1 = mild disease 2 = moderate disease 3 = severe disease	0 = normal or inactive disease 1 = mild disease (erythema, decreased vascular pattern*) 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = severe disease (spontaneous bleeding, ulceration)

- The modification that has been made to the Mayo Index is the deletion of "friability" from an endoscopy score equal to 1. With this modification, the presence of friability is indicative of an endoscopy score of 2 or 3.

Reviewer's comment: Measurement of disease activity is critical in evaluating new therapies in UC clinical trials. Multiple instruments/indices have been developed to measure disease activity in UC trials, but none have been formally validated. However, the proposed MMDAI has been widely used in UC clinical trials including the clinical trials that led to approval of Lialda, the most recently approved oral mesalamine agent, for use in mild to moderate UC.

In addition, there has been no formal attempt to define efficacy endpoints such as clinical improvement or remission in UC clinical trials. However, remission defined as complete relief of inflammatory symptoms has been generally considered to represent a higher level of clinical response than clinical improvement where a given point reduction in a total MMDAI score is usually selected at random. It is worth mentioning that while remission was the primary endpoint (PE) in clinical trials that led to approval of Lialda; clinical improvement is the proposed PE in the current application.

Efficacy Analysis

The Cochran-Mantel-Haenszel (CMH) test, stratified by analysis center was the prespecified test for analyzing the primary efficacy endpoint. The key secondary endpoints were defined a priori and were tested utilizing a hierarchical approach in order to control for the increased probability of Type 1 error due to multiple comparisons. Significance tests were to be reported until a non-significant p-value was found ($p>0.05$). Once a non-significant p-value occurred, all subsequent statistical testing was considered exploratory in nature.

All efficacy analyses were performed using the ITT population, which consisted of all randomized subjects who received at least 1 dose of study drug. The primary efficacy analysis was also evaluated in the PP population defined as ITT population without major protocol deviations such as violation of any inclusion/exclusion criteria and wrongful drug allocation. In analysis of proportion, subjects who terminated early/discontinued the study early were considered to be treatment failures.

REVIEWER'S COMMENTS: The statistic review by Dr Shahla Farr was not finalized at the time this review was completed, but indicated that the proposed statistical methods are acceptable.

6.1.3 Study Design

Title: Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial to Evaluate the Safety and Efficacy of a New Tablet Formulation and Dosing Regimen of Balsalazide Disodium 3.3g BID versus Placebo in Mildly to Moderately Active UC.

Study Started: 21 December 2005
Study completed: 05 April 2007

Study Design

This was randomized, double-blind, placebo-controlled, multicenter, 8-week study to evaluate the effectiveness and safety of BD tablets in subjects with mildly to moderately active UC. Eligible subjects were randomized to receive BD tablets or placebo in a 2: 1 ratio. The sponsor noted that subjects were randomly assigned to a treatment group using a centralized, automated IVRS system.

REVIEWER'S COMMENT: The study design appears appropriate for the study and provides a reasonable assessment of benefit.

Study Population

Key inclusion criteria:

- Male or non-pregnant and non-lactating female ≥18 years of age
- Subjects with mildly to moderately active UC experiencing an acute flare
- baseline MMDAI score between 6 and 10, and a score of ≥2 on rectal bleeding and a score of ≥ 2 on endoscopy
- Disease that extended at least 20 centimeters from the rectum on screening endoscopy

Key exclusion criteria:

- Subject's UC worsened or failed to improve during chronic therapy with ≥ 6.6 g/day of balsalazide disodium within 30 days of screening
- Treatment with intra-rectal aminosalicylates for ≥2 consecutive days within 7 days of screening
- Prior bowel surgery, with the exception of appendectomy or cholecystectomy
- Pregnant or lactating women
- The subject had infectious, ischemic, or immunologic diseases involving the GI tract
- Serum creatinine or blood urea nitrogen level that is 1.5 x ULN and creatinine clearance level of ≤ 60 ml/minute
- Positive stool culture for ovum and parasites or C. Difficile

- Treatment with anti TNF or methotrexate for UC within the last 30 days prior to screening
- Use of anti-diarrheal therapy during screening and at any time during the study
- Clinical or radiographic findings suggestive of serious UC complications

REVIEWER'S COMMENT: inclusion and exclusion criteria appear acceptable.

Study Procedure

The study consisted of a screening period, a treatment period (Visits 1 to 5), and a follow-up period completed 2 weeks post-treatment (see Table below). A daily diary was kept by the subject to record stool frequency, rectal bleeding and symptoms. During the 8-week treatment period, subjects returned to the study site at 5 scheduled visits for study assessments and allocation of study drug and diary cards. Subjects underwent a colonoscopy/sigmoidoscopy at or around the time of Screening and at Week 8. Subjects who discontinued prior to Week 8 underwent a colonoscopy/sigmoidoscopy, if possible, at their Early Termination visit. A complete MMDAI was calculated at Screening/Baseline visit, and at Week 8/visit 5 (or the Early Termination visit, if applicable). In addition, abbreviated MMDAI (excluding endoscopy) was calculated at visits 2 through 4.

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Study Schedule

STUDY ASSESSMENT	Visit 0 / SCREENING (3 to 7 days before randomization)	Visit 1 (Baseline/ Randomization) (Day 1)	Visit 2[f] (Day 7 ± 1 day)	Visit 3[f] (Day 14 ± 3 days)	Visit 4[f] (Day 28 ± 3 days)	Visit 5 EOT (Day 56 ± 3 days/ early termination)	Follow up Visit (2 week post-EOT ± 2 days)	UNSCHEDULED VISIT[e]
Informed consent	X							
Medical history/demographic information	X							
Physical examination	X	X[a]	X[a]	X[a]	X[a]	X	X[a]	X
Obtain vital sign measurements	X	X	X	X	X	X		X
Serum pregnancy test[b]	X					X		X
Record concomitant medications	X	X	X	X	X	X	X	X
Clinical laboratory tests[c]	X[d]			X		X		X
Colonoscopy or Flexible Sigmoidoscopy	X					X		X
IBD QoL questionnaire	X			X		X		X
Assign subject ID number	X							
Assign treatment ID number		X						
Dispense diary with complete instructions	X	X	X	X	X			
Dispense study drug		X	X	X	X			
Calculate complete/abbreviated MMDAI score (Modified Mayo Disease Activity Index)	X	X	X	X	X	X		X
Assess and record AEs		X	X	X	X	X	X	X
Retrieve AE and Subject diary		X	X	X	X	X		X
Collect study drug and determine compliance			X	X	X	X		X
Confirm subject meets all eligibility criteria	X	X						
Schedule/confirm next clinic visit	X	X	X	X	X	X		X

Abbreviations: IBD-QoL = Inflammatory Bowel Disease-Quality of Life., ID = identification number, MMDAI = Modified Mayo Disease Activity Index, AE = adverse event, EOT = end of treatment
a. This was a symptom-directed test performed only if necessary. b. For females of childbearing potential only. c. Included hematology, blood chemistry, and urinalysis.
d. Stool culture added for Ova & Parasites (O&P) and *C. Difficile* at Screening visit. e. To be done at investigator's discretion and/or symptom driven.
f. End of study procedures were initiated if required by protocol.

6.1.4 Efficacy Findings

- **Patient Disposition**

A total of 250 subjects were randomly assigned to treatment groups; 167 subjects in the BSZ tablets group and 83 subjects in the placebo group. A total of I55 (62.0%) subjects completed the study: 66.5% subjects in the BSZ tablets group and 53.0% subjects in the placebo group. Overall, the most common reason for discontinuation was lack of efficacy (20%). Study withdrawal was lower in the BSZ tablets group than placebo group (33.5% vs. 47.0%), and fewer subjects administered BSZ tablets versus placebo withdrew due to lack of efficacy (16.2% vs. 28.9%).

Patient Disposition

	BSZ Tablets (n=167)	Placebo (n=83)	Total (n=250)
	n (%)	n (%)	N (%)
Subjects randomized	167 (100.0)	83 (100.0)	250 (100.0)
Subjects completed the study	I1I (66.5)	44 (53.0)	155 (62.0)
Subjects withdrawn early	56 (33.5)	39 (47.0)	95 (38.0)
Reasons for withdrawal			
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)	I (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
Note: Other reasons included subject withdrawn in error; subject did not meet all inclusion/exclusion criteria; study drug not available at site; incorrect treatment kit dispensed; and subject unable to return to the study site due to transportation issue.

- **Patient Demographics**

The demographic characteristics of age, sex, race, and ethnicity were comparable across treatment groups. The mean age was 44.2 years (range, 19 - 80 years) and approximately 7% were ≥ 65 years. A little over half of all subjects (5I.4%) were female and most subjects were white (84%).

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Demographic Characteristics

Parameter/Statistic	BSZ Tablets 6.6 g/day (N=166)	Placebo (N=83)	Total (N=249)	P-value[a]
Age (years): n (%)[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	
Age group (years)				0.7967
<65: n (%)	154 (92.8)	78 (94.0)	232 (93.2)	
≥65: n (%)	12 (7.2)	5 (6.0)	17 (6.8)	
Sex: n (%)				1.0000
Male	81 (48.8)	40 (48.2)	121 (48.6)	
Female	85 (51.2)	43 (51.8)	128 (51.4)	
Race: n (%)[c]				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)	
Ethnicity: n (%)				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)	
BMI (kg/m^2)				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

- **Baseline Disease and other Characteristics**

The baseline characteristics were comparable across treatment groups as summarized in the Table below. The mean MMDAI total score at baseline was 7.9 and the mean abbreviated MMDAI score was 5.8. A larger proportion of subjects in the BSZ group (6.6%) reported a normal number of stools/day compared with the placebo group (1.2%), however, in the reviewer's opinion the clinical significance of this difference is questionable, as the sample size was too small (n=12). Most of the subjects in both treatment groups had obvious bleeding with stools most of the time (BSZ: 88.0%; placebo: 85.5%). Results of endoscopy examination indicated that the majority of subjects had moderate disease (BSZ: 81.9%; placebo: 83.1%). A lower proportion of subjects in the BSZ tablet group had moderate disease (MMDAI score ≥8) at baseline compared to the placebo group (59.0% vs 68.7%) and a higher proportion of BSZ tablet subjects had mild disease (MMDAI score <8) compared to placebo (41.0% vs 31.3%); however, the difference was not statistically significant (p = 0.1659).

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Baseline Disease Characteristics

Parameter/Statistic	BSZ Tablets 6.6 g/day (N=166)	Placebo (N=83)	Total (N=249)	P-value
MMDAI total score				0.3047[b]
N	166	83	249	
Mean (SD)	7.8 (1.4)	8.0 (1.4)	7.9 (1.4)	
Median	8.0	8.0	8.0	
Range (Min, Max)	1, 11	1, 10	1, 11	
Mild / moderate disease (n, %)				0.1659[c]
<8 (mild disease)	68 (41.0)	26 (31.3)	94 (37.8)	
≥8 (moderate disease)	98 (59.0)	57 (68.7)	155 (62.2)	
Abbreviated MMDAI Score[d] (n, %)				0.2907[b]
N	166	83	249	
Mean (SD)	5.7 (1.2)	5.9 (1.2)	5.8 (1.2)	
Median	6.0	6.0	6.0	
Range (Min, Max)	0, 8	1, 8	0, 8	
Endoscopy/Sigmoidoscopy				0.5392[a]
Mean (SD)	2.1 (0.4)	2.1 (0.4)	2.1 (0.4)	
0 = normal or inactive disease	0 (0)	1 (1.2)	1 (0.4)	
1 = mild disease	10 (6.0)	2 (2.4)	12 (4.8)	
2 = moderate disease	136 (81.9)	69 (83.1)	205 (82.3)	
3 = severe disease	20 (12.0)	11 (13.3)	31 (12.4)	
Bowel Frequency (n, %)				0.1689[a]
Mean (SD)	1.9 (0.9)	2.1 (0.8)	2.0 (0.9)	
0 = normal number of stools/day	11 (6.6)	1 (1.2)	12 (4.8)	
1 = 1 to 2 more stools than normal	48 (28.9)	21 (25.3)	69 (27.7)	
2 = 3 to 4 more stools than normal	54 (32.5)	31 (37.3)	85 (34.1)	
3 = 5 or more stools than normal	53 (31.9)	30 (36.1)	83 (33.3)	
Rectal Bleeding (n, %)				0.9885[a]
Mean (SD)	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)	
0 = none seen	5 (3.0)	3 (3.6)	8 (3.2)	
1 = streaks of blood with stool less than half the time	9 (5.4)	5 (6.0)	14 (5.6)	
2 = obvious blood with stool most of the time	146 (88.0)	71 (85.5)	217 (87.1)	
3 = blood alone passed	6 (3.6)	4 (4.8)	10 (4.0)	

Ref. Sponsor's Table 9, Mod 5, vol. 16

a P-value calculated using Wilcoxon rank sum test.
b P-value calculated using t-test.
c P-value calculated using Fisher's exact test.
d The sum of rectal bleeding, physician's global assessment, and bowel frequency subscales of the MMDAI.

As summarized in the Table below, there were no significant differences between treatment groups in other baseline characteristics, including mean time since initial diagnosis of UC, mean number of daily stools, time since most recent flare of UC, the number of newly diagnosed subjects, prior 5-ASA treatment, or smoking history.

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Other Baseline Characteristics

Parameter/Statistic	BSZ Tablets 6.6 g/day (N=166)	Placebo (N=83)	Total (N=249)	P-value
Time since initial diagnosis of UC (days) [d]				
N	166	83	249	0.4219[a]
Mean (SD)	2642 (3166)	2321 (2518)	2535 (2964)	
Median	1836	1179	1597	
Range (Min, Max)	1, 20696	1, 10954	1, 20696	
Normal number of daily stools				
N	166	82	248	0.0671[b]
Mean (SD)	1.8 (1.1)	2.1 (1.2)	1.9 (1.1)	
Median	2.0	2.0	2.0	
Range (min, max)	1, 9	1, 5	1, 9	
Time since onset of most recent flare (days) [e]				
N	166	83	249	0.5666[a]
Mean (SD)	55.4 (136)	46.3 (64.9)	52.4 (117)	
Median	22.0	22.0	22.0	
Range (Min, Max)	-346, 1093	-6, 332	-346, 1093	
Newly diagnosed UC (n, %)				0.8488[c]
Yes	25 (15.1)	11 (13.3)	36 (14.5)	
No	141 (84.9)	72 (86.7)	213 (85.5)	
Prior 5-ASA treatment (n, %)				0.8753[c]
Yes	125 (75.3)	64 (77.1)	189 (75.9)	
No	41 (24.7)	19 (22.9)	60 (24.1)	
Smoking history (n, %)				0.4183[c]
Never smoked	93 (56.0)	40 (48.2)	133 (53.4)	
Ex-smoker	51 (30.7)	32 (38.6)	83 (33.3)	
Smoker	22 (13.3)	11 (13.3)	33 (13.3)	
Ex-smokers: Time since quitting (years)				
N	51	32	83	0.4513[a]
Mean (SD)	10.2 (12.0)	12.0 (9.1)	10.9 (11.0)	
Median	5.0	10.0	6.0	
Range (Min, Max)	0, 57	0, 35	0, 57	
Smokers: Packs/day				
N	70	42	112	0.4149[a]
Mean (SD)	1.7 (2.9)	2.6 (9.2)	2.0 (6.1)	
Median	1.0	1.0	1.0	
Range (min, max)	0, 20	0, 60	0, 60	

Ref. Sponsor's Table 10 Module 5 vol.16

- **Analysis of Efficacy**

Of the total of 250 subjects randomized, 249 were included in the ITT population. Subject 505-09 (BSZ tablet group) had no MMDAI scores recorded and was excluded from the ITT population. In the reviewer's opinion, the exclusion of one subject will not influence the overall results.

Primary Endpoint Analysis

Compared to placebo, a significantly larger proportion of ITT subjects treated with BSZ tablets achieved clinical improvement and improvement in rectal bleeding (55% vs 40%; p=0.024). Similar results were observed in the PP population (p (b) (4) as summarized in the Table below.

Results of Primary Endpoint Analysis - ITT and PP Populations

Analysis of Primary Endpoint				
Population	BSZ Tablets n/N (%)	Placebo n/N (%)	Difference in proportion	p-value
ITT	(b) (4) (55)	(b) (4) (40)	15%	0.024
PP	(b) (4) (58)	(b) (4) (41)	17%	0.019

Ref. Reviewer's modified table from Sponsor's Table 14, Module 5 vol. 16.

Secondary Endpoint Analysis

In the hieratical secondary endpoint analyses, a larger proportion of subjects in the BSZ tablets group experienced clinical remission and mucosal healing compared with the placebo group: 38.6% vs 22.9% (p=0.0096) and 53.0% vs 32.5% (p=0.0035), respectively. The third key secondary endpoint in the hierarchy (i.e. improvement in bowel frequency) failed to reach statistical significance, therefore, the analysis for this endpoint and the subsequent key secondary endpoints were considered exploratory in nature as prespecified in the protocol and statistical analysis plan.

Results of Key Secondary Endpoint Analysis

Key Secondary Efficacy Endpoints	BSZ Tablets N = 166	Placebo N = 83	Difference in Proportions	95% CI	p-value
Clinical Remission	64 (38.6%)	19 (22.9%)	15.7%	3.1, 28.3	0.0096
Mucosal Healing	88 (53.0%)	27 (32.5%)	20.5%	7.0, 34.0	0.0035
Bowel Frequency	82 (49.4%)	31 (37.3%)	12.0%	-1., 25.8	0.0750
Rectal Bleeding	98 (590%)	35 (42.2%)	16.9%	3.0, 30.8	0.0131
Physician's Assessment	99 (59.6%)	30 (36. i1%)	23.5%	9.8, 37.1	0.0004
Complete Remission	34 (20.5%)	11 (13.3%)	17.2%	3.2, 17.7	0.0957

Ref: reviewer's Table with a slight modification from sponsor's Table 2.7.3-13, Module 2

Primary Endpoint Analysis by Subgroups

In the primary efficacy analyses by subgroups, the groups that did not show statistically significant differences between treatment arms are likely due to their small sample sizes as summarized in the Table below. By contrast, despite the similarly in sample size between males and females (n=121 and n=128, respectively) BSZ was superior over placebo among males (p<0.001), but not among females (p (b) (4). In fact, the placebo response rate was numerically higher than the BD response rate in females (58% vs 54%).

It is of interest to note that while the response rate was comparable between males and females in the BSZ group (57% and 54%, respectively); it was markedly different in the placebo group (20% vs 58%). As a result, a substantial therapeutic gain was observed in males (37%), but none in females (-4%). The basis for the difference in placebo response rates is not clear. Additional information provided by the sponsor upon reviewer's request was non-contributory. Review of relevant published literature does not suggest gender as a factor for differences in placebo response rate in the population of interest. In a meta-analysis study published recently, it has been reported that studies with higher mean disease activity scores at baseline in placebo patients were associated with lower placebo response rates. (Su et al. Gastroenterol 2007;132:516-526). In the sponsor's study, the mean baseline disease activity scores were comparable across treatment groups as well as across gender: drug vs placebo was 8 (each) in males and 7.6 vs 8 in females. In the most recent information provided, the sponsor claimed that females with more sever disease at baseline (MMDAI score ≥ 9) had a larger placebo response rates and no placebo males with sever disease at baseline responded. The sponsor's study result in females is in contrary to the published literature described above where placebo subjects with more sever disease at baseline would be expected to have a low response rate rather than a high response rate.

Results of Primary Endpoint Analysis by Subgroups

	BSZ tablets n/N (%)	Placebo n/N (%)	p-value
Total Population	(b) (4) (55)	(b) (4) (40)	**0.02**
Sex			
Male	(b) (4) (57)	(b) (4) (20)	<0.001
Female	(54)	(58)	(b) (4)
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)	29/72 (40)	0.05
Non-White	18/31 (58)	4/11 (36)	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 (55)	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

Ref: Generated by the Division's statistical reviewer as per this reviewer's request

Secondary Endpoints Analyses by Gender

To further investigate the observed discrepancy in the primary endpoint analysis across gender, a post hoc secondary endpoint analysis by gender was conducted by the Division's statistician (Dr Shahla Farr) upon this reviewer's request. As summarized in the Table below, the findings were consistent with the primary endpoint findings, that is, statistically significant differences were observed in males but not in females. This is not surprising since the secondary endpoint variables were subsets of the primary composite endpoint.

Results of Key Secondary Endpoints Analysis by Gender

Variables	**BSZ tablets n/N (%)**	**Placebo n/N (%)**	**p-value**
Clinical Remission			
Males	28/81 (35)	5/40 (13)	0.01
Females	(b) (4)		
Mucosal Healing			
Males	42/81 (52)	8/40 (20)	<0.001
Females	(b) (4)		
Bowel Frequency			
Males	43/81 (53)	12/40 (30)	0.02
Females	(b) (4)		
Rectal Bleeding			
Males	51/81 (63)	13/40 (33)	0.002
Females	(b) (4)		
Complete Remission			
Males	12/81 (15)	0	0.01
Females	(b) (4)		

Ref. Division's Statistician's Table as per this reviewer's request

6.1.5 Clinical Microbiology

Not applicable for the proposed product.

6.1.6 Efficacy Conclusions

In the sponsor's single placebo controlled study (n=249, 166 on drug), there was unexplained difference in results between males and females. This was due to marked differences in placebo response rate between males and females (20% vs 40%), while the response rate with BSZ treatment was similar. As a result, a substantial therapeutic effect was demonstrated in males, but none in females. The observed superior efficacy of BSZ tablet in the study was thus driven by a subpopulation's finding, namely, males. Conversely, due to the unexplained high placebo response rate in females, the efficacy of BSZ tablet has not been established in this subpopulation, which contributed 51% of the ITT population.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths reported during this study.

7.1.2 Other Serious Adverse Events

During treatment period of the pivotal study, the proportion of subjects experiencing at least 1 serious adverse event (SAE) was less in subjects treated with BSZ tablets compared with subjects treated with placebo (2.4% vs 5.1%) as shown in the Table below. Worsening UC was the only SAE reported for more than 1 % of subjects in either treatment group and occurred with less frequency in subjects treated with BSZ tablets than with placebo (2% vs. 4%). Other SAEs in subjects treated with BSZ tablets were anemia, abdominal pain, ankle fracture (1 subject each), and dehydration in 1 subject treated with placebo. None of the SAEs was considered by the investigators to be related to study drug.

During the follow-up period, a total of 5 subjects (2%) experienced a SAE. Four of these events (UC, anemia, colitis, and dehydration) were SAEs that occurred during the treatment period, but remained unresolved into the follow-up period. A SAE of anal fistula, was reported for the placebo group and occurred in 1 subject (1 .3%).

In an ongoing open-label study (BZUC3005), 2 subjects reported SAEs. One subject reported mild bronchitis and another subject reported severe worsening ulcerative colitis. No death was reported in this study.

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Summary of Serious Adverse Events

Preferred Term[b]	Number of Distinct Subjects (%)[a] BSZ Tablets 6.6g/Day (N=168)	Placebo (N = 79)	Total (N=247)
	n (%)	n (%)	n (%)
Subjects with one or more treatment-emergent SAE	4 (2.4)	4 (5.1)	8 (3.2)
Colitis ulcerative	3 (1.8)	3 (3.8)	6 (2.4)
Abdominal pain	1 (0.6)	0 (0)	1 (0.4)
Anemia	1 (0.6)	0 (0)	1 (0.4)
Ankle fracture	1 (0.6)	0 (0)	1 (0.4)
Colitis	0 (0)	1 (1.3)	1 (0.4)
Dehydration	0 (0)	1 (1.3)	1 (0.4)
Subjects with one or more SAEs following withdrawal of study drug	1 (0.6)	4 (5.1)	5 (2.0)
Colitis ulcerative	1 (0.6)	2 (2.5)	3 (1.2)
Anemia	1 (0.6)	0 (0)	1 (0.4)
Anal fistula[c]	0 (0)	1 (1.3)	1 (0.4)
Colitis[c]	0 (0)	1 (1.3)	1 (0.4)
Dehydration	0 (0)	1 (1.3)	1 (0.4)

a= At each level of summarization, subjects reporting more than one AE were only counted once.
b =AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) Version 8.l.
c =Subject 591-06 experienced SAEs greater than 14 days following withdrawal of study drug.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the pivotal placebo controlled study, a smaller proportion of subjects treated with BZS tablets withdrew early from the study compared with subjects treated with placebo: 34% (57/168) vs. 44% (35/79). The most common reasons for early withdrawal from the study were lack of efficacy and AEs. Lack of efficacy was the reason for withdrawal in 17% (28/168) of subjects treated with BSZ tablets compared with 29% (23/79) of subjects treated with placebo. AE was the reason for withdrawal in 10% (16/168) of subjects treated with BSZ disodium tablets compared with 13% (10/79) of subjects treated with placebo.

7.1.3.2 Adverse events associated with dropouts

Adverse events that led to discontinuation were experienced by l0% (17/168) of subjects in the BSZ tablets group and 13% (10/79) of subjects in the placebo group (see Table below). The most common AE leading to withdrawal from the study was worsening UC, with a greater proportion of subjects in the placebo group (11%) discontinuing due to this event compared with BSZ tablet group (5%). The investigator considered the worsening UC to be serious in 2 subjects treated with BSZ tablets and in 4 subjects treated with placebo.

Three subjects were discontinued due to vomiting; 2 subjects (1%) in the BSZ group and 1 subject (1%) in the placebo group. All other AEs leading to discontinuation from the study

occurred in 1 subject each. Subject 453-07/R-1 had a decrease in albumin, hematocrit, red blood cells and hemoglobin that were considered moderate and not related to BSZ therapy. This subject had worsening of UC and it is likely that the observed laboratory abnormalities were due to the underlying disease.

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Summary of Adverse Events Resulting in Discontinuation from Study

	Lead-in Study Treatment	
MedDRA Preferred Term	BSZ Tablets N = 168	Placebo N = 79
	Number (%) of Subjects	
Number of Subjects Reporting ≥1 AE Leading to Withdrawal	17 (10%)	10 (13%)
Abdominal pain	0	1 (1%)
Aspartate aminotransferase	0	1 (1%)
Biopsy mucosa abnormal	1 (<1%)	0
Blood albumin	1 (<1%)	0
Blood bilirubin increased	0	1 (1%)
Blood potassium	0	1 (1%)
Blood triglycerides	0	1 (1%)
Chromaturia	0	1 (1%)
Colitis ulcerative	9 (5%)	9 (11%)
Creatinine renal clearance	0	1 (1%)
Dehydration	0	1 (1%)
Erythema nodosum	1 (<1%)	0
Haematocrit	1 (<1%)	0
Haemoglobin	1 (<1%)	0
Laboratory test abnormal	0	1 (1%)
Muscle spasms	1 (<1%)	0
Nausea	0	1 (1%)
Nitrite urine present	0	1 (1%)
Pharyngeal erythema	1 (<1%)	0
Pyrexia	1 (<1%)	0
Rash	1 (<1%)	0
Rectal fissure	1 (<1%)	0
Red blood cell abnormality	0	1 (1%)
Red blood cell count	1 (<1%)	0
Sigmoidoscopy abnormal	1 (<1%)	0
Urine abnormality	0	1 (1%)
Vomiting	2 (1%)	1 (1%)
White blood cell count	0	1 (1%)

Ref: Sponsor's Table 2.7.4-15 (Module 2)

7.1.3.3 Other significant adverse events

There were no other significant AEs.

7.1.4 Other Review Strategies

Oral Mesalamine preparations have been marketed for use in mild to moderate UC for many years and have a well established safety profile.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The investigator was responsible for the detection and documentation of events meeting the definition of an AE or SAE. At each assessment, after the subjects had an opportunity to spontaneously mention any problems, the investigator asked the subject about any medical problems they experienced and if they had taken any new medicines since their last visit.

All AEs that occurred during the study, regardless of causality or seriousness, were assessed and recorded in the appropriate section of the case report form (CRF) as well as in the subject's medical records. All AEs and SAEs were followed until resolution, until the condition stabilized, until the event was otherwise explained, or until the subject was lost to follow-up. The investigator was responsible for ensuring that follow-up included any supplemental investigations as were necessary to elucidate as completely as practical the nature and/or causality of the AE or SAE.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded to standard preferred terms and body system using Medical Dictionary for Regulatory activities (MedDRA) Version 8.1 and are acceptable.

7.1.5.3 Incidence of common adverse events

Of the 247 subjects in the safety population in the pivotal study, 59.5% experienced at least one AE during the study (see the Table below). The proportion of subjects who experienced any AEs was higher in the placebo group (68.4%) compared with the BSZ tablets group (55.4%). The most frequently reported system organ class for treatment-emergent AEs was gastrointestinal (Gl) disorders with 29.6% of all subjects experiencing at least one event. However, the event was higher in the placebo group (36.7%) than in the BSZ tablets group (26.2%). The only GI events that occurred in ≥2% of subjects in the BSZ tablets group and not in the placebo group were abdominal distension (4.2%) and flatulence (2.4%).

The most commonly reported treatment emergent AE related to GI was worsening UC, and occurred less frequently in subjects treated with BSZ tablets compared with subjects treated with placebo (7% vs. 14%). Headache was the next most common AE reported during the trial, experienced by 8.5% of subjects. The proportion of subjects reporting headache was larger in the placebo group (14%) compared with the BSZ tablet group (6%).

The interim report from the ongoing long term open-label safety extension study (BZUC3005) including 130 subjects in the safety population showed similar safety profile. The most frequent AEs were worsening UC (5%) and diarrhea (3%).

7.1.5.4 Common adverse event tables

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Treatment-Emergent Adverse Events Reported by ≥2 % of Subjects

System Organ Class/ Preferred Term[b]	Number of Distinct Subjects (%)[a] BSZ Tablets 6.6g/Day (N=168)	Placebo (N = 79)	Total (N=247)
	n (%)	n (%)	n (%)
Number of subjects reporting any AEs	93 (55.4)	54 (68.4)	147 (59.5)
Gastrointestinal disorders	44 (26.2)	29 (36.7)	73 (29.6)
Colitis ulcerative	11 (6.5)	11 (13.9)	22 (8.9)
Abdominal pain	8 (4.8)	3 (3.8)	11 (4.5)
Nausea	6 (3.6)	4 (5.1)	10 (4.0)
Diarrhea	6 (3.6)	2 (2.5)	8 (3.2)
Vomiting	6 (3.6)	2 (2.5)	8 (3.2)
Abdominal distension	7 (4.2)	0 (0)	7 (2.8)
Constipation	2 (1.2)	4 (5.1)	6 (2.4)
Flatulence	4 (2.4)	0 (0)	4 (1.6)
Abdominal pain upper	2 (1.2)	2 (2.5)	4 (1.6)
Dyspepsia	1 (0.6)	2 (2.5)	3 (1.2)
Infections and infestations	30 (17.9)	14 (17.7)	44 (17.8)
Nasopharyngitis	6 (3.6)	4 (5.1)	10 (4.0)
Upper respiratory tract infection	7 (4.2)	2 (2.5)	9 (3.6)
Influenza	5 (3.0)	3 (3.8)	8 (3.2)
Sinusitis	4 (2.4)	1 (1.3)	5 (2.0)
Urinary tract infection	4 (2.4)	1 (1.3)	5 (2.0)
Herpes simplex	1 (0.6)	2 (2.5)	3 (1.2)
Nervous system disorders	16 (9.5)	11 (13.9)	27 (10.9)
Headache	10 (6.0)	11 (13.9)	21 (8.5)
General disorders and administration site conditions	15 (8.9)	11 (13.9)	26 (10.5)
Fatigue	5 (3.0)	4 (5.1)	9 (3.6)
Pain	2 (1.2)	3 (3.8)	5 (2.0)
Edema peripheral	1 (0.6)	3 (3.8)	4 (1.6)
Asthenia	1 (0.6)	2 (2.5)	3 (1.2)
Musculoskeletal and connective tissue disorders	15 (8.9)	6 (7.6)	21 (8.5)
Back pain	4 (2.4)	3 (3.8)	7 (2.8)
Arthralgia	4 (2.4)	1 (1.3)	5 (2.0)
Respiratory, thoracic, and mediastinal disorders	14 (8.3)	2 (2.5)	16 (6.5)
Pharyngolaryngeal pain	6 (3.6)	1 (1.3)	7 (2.8)
Skin and subcutaneous tissue disorders	12 (7.1)	2 (2.5)	14 (5.7)
Rash	5 (3.0)	1 (1.3)	6 (2.4)
Blood and lymphatic system disorders	8 (4.8)	5 (6.3)	13 (5.3)
Anemia	6 (3.6)	2 (2.5)	8 (3.2)
Lymphadenopathy	2 (1.2)	2 (2.5)	4 (1.6)

Ref. Sponsor's Text Table 26, Module 5, vol. 16
[a] At each level of summarization, subjects reporting more than one AE were counted only once.
[b] AE were coded using MedDRA)Version 8. 1

7.1.5.5 Identifying common and drug-related adverse events

In a placebo controlled study very few AEs were considered to be related to either BSZ tablets or to placebo (8% and 9%, respectively) as summarized in the Table below. Drug-related events of nausea and rash (2 subjects each) were experienced by 1% of subjects in the BSZ tablets group; no subjects in the placebo group experienced drug-related nausea or rash.

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Treatment-related Adverse Events in ≥ 1% of subjects- Pivotal Study

MedDRA System Organ Class Preferred Term	Lead-in Study Treatment BSZ Tablets N = 168	Lead-in Study Treatment Placebo N = 79
	Number (%) of Subjects	
Number of Subjects Reporting ≥1 Treatment-Related AE	14 (8%)	7 (9%)
Gastrointestinal Disorders	8 (5%)	4 (5%)
Colitis ulcerative	3 (2%)	2 (3%)
Constipation	0	1 (1%)
Diarrhoea	2 (1%)	1 (1%)
Nausea	2 (1%)	0
General Disorders and Administrative Site Conditions	3 (2%)	1 (1%)
Pyrexia	0	1 (1%)
Nervous System Disorders	2 (1%)	1 (1%)
Headache	0	1 (1%)
Investigations	1 (<1%)	1 (1%)
Bacteria urine	0	1 (1%)
Skin and Subcutaneous Tissue Disorders	2 (1%)	0
Rash	2 (1%)	0

Ref. Sponsor's Table 2.7.4-8, Module 2, vol 2

7.1.5.6 Additional analyses and explorations

See section 7.4.2 of this review

7.1.6 Less Common Adverse Events

A review of less common AEs did not identify any safety concern.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Hematology, blood chemistry, and urinalysis parameters were summarized at baseline, Week 2 and Week 8, as well as changes from baseline to Week 2, and Week 8. Laboratory values and changes from baseline in laboratory values were summarized descriptively by treatment group.

The normal range for each parameter was used to create categories of low, normal, or high. Any result higher than upper limit of normal (ULN) or lower than lower limit of normal (LLN) was categorized as high or low respectively, and any result within the lower and upper limits of normal was categorized as normal. The number and percentage of subjects for each treatment group in each shift category from baseline to final evaluation was recorded for each parameter.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Mean changes from baseline to Week 8 or end of treatment (EOT) in hematology laboratory values were minimal and no notable differences among BSZ tablets and placebo subjects were apparent. Mean values for all hematology parameters were within the normal range at each visit.

Mean changes from baseline to Week 8/EOT for most chemistry laboratory values were comparable for BSZ tablet and placebo subjects. Mean values for all chemistry parameters were within the normal range at each study visit. Urinalysis test results were comparable between the 2 treatment groups and were within the normal reference range for most subjects.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured and included sitting systolic and diastolic blood pressure, temperature, and heart rate. Vital signs were measured throughout the study at scheduled visits.

Vital sign measurements were summarized at each time point. In addition, changes from baseline in vital sign measurements were summarized at each post-baseline time point. For each summary, the mean, median, minimum and maximum values were recorded by treatment group.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

No clinically significant mean changes in systolic or diastolic blood pressure, pulse rate, body Temperature were observed from screening to Week 8/EOT and results obtained were comparable for the BSZ tablet and placebo treatment groups.

7.1.9 Electrocardiograms (ECGs)

The applicant did not provide any clinical or adverse event data regarding ECGs in this application. Mesalamine is believed to act locally in the colon, rather than systemic. Mesalamine products have been marketed for many years and have a well established safety profile.

7.1.10 Immunogenicity

The applicant did not provide any clinical or adverse event data regarding Immunogenicity in this application. It should be noted the proposed product is a chemical product.

7.1.11 Human Carcinogenicity

The applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application.

7.1.12 Special Safety Studies

The NDA did not include special safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No case of drug abuse has been reported during the clinical trials with BD tablets. No potential rebound effects were observed following withdrawal of study drug.

7.1.14 Human Reproduction and Pregnancy Data

Pregnant women were excluded from participating in the study.

7.1.15 Assessment of Effect on Growth

There were no children involved in this NDA

7.1.16 Overdose Experience

No case of overdose has occurred with balsalazide disodium tablets.

7.1.17 Postmarketing Experience

Balsalazide disodium tablets are not currently approved for marketing in any country in the world. However, the capsule formulation (Colazal) is available in the market for many years and postmarketing experience is reflected in the current product labeling.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The safety population included all randomized subjects who received at least 1 dose of study drug and who provided at least 1 post-baseline safety assessment. A total of 247 subjects were included in the safety population in the pivotal study: 168 subjects in the balsalazide disodium tablets group and 79 subjects in the placebo group.

Overall, the median number of days of exposure in the balsalazide disodium tablets treatment group and placebo treatment group was 56.0 days and 55.0 days, respectively (see the Table below). A total of 56 subjects (33.3%) in the balsalazide disodium group and 21 subjects (26.6%) in the placebo group received study drug for 29 to 56 days. Sixty-four subjects (38.1 %) in the balsalazide disodium tablet group and 24 subjects (30.4%) in the placebo group received balsalazide disodium tablets or placebo for greater than 56 days.

Reviewer's comments: The active ingredient, mesalamine, has been marketed for many years for the treatment of mild to moderate active UC and has a well established safety profile.

Summary of Drug Exposure

Parameter	BSZ Tablets 6.6g/Day (N=168)	Placebo (N = 79)
Exposure Duration (days)[a]		
N	168	79
Mean (SD)	43.3 (20.8)	38.5 (22.4)
Median	56.0	55.0
Min, max	2, 75	1, 72
N (%) of subjects on study drug		
Day 1	0 (0)	1 (1.3)
> 1 Day to ≤ 7 Days	11 (6.5)	2 (2.5)
> 7 Days to ≤ 14 Days	21 (12.5)	15 (19.0)
> 14 Days to ≤ 28 Days	16 (9.5)	16 (20.3)
> 28 Days to ≤ 56 Days	56 (33.3)	21 (26.6)
> 56 Days	64 (38.1)	24 (30.4)

Ref: Sponsor's Text Table 24 Mod 5, vol. 16.

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7.2.1.1 Study type and design/patient enumeration

The safety population included all randomized subjects who received at least 1 dose of study drug and who provided at least 1 post-baseline safety assessment. A total of 247 subjects were included in the safety population: 168 subjects in the balsalazide disodium tablets group and 79 subjects in the placebo group.

The interim report from the ongoing open-label, safety extension study (BZUC3005) includes 130 subjects who successfully participated in the pivotal study. Scheduled study visits to the clinic occur at Screening, Baseline, Month 1, Month 3, and every 3 months thereafter through the End-of-Treatment (EOT) visit. Two weeks following Data from BZUC3005 up to an interim cut-off date of 26 April 2007 are included in this submission.

Overview of Studies in Safety Database

	Placebo-Controlled Study	Open-Label Study
Protocol Number	**BZUC3002**	**BZUC3005**
Study Objective	Efficacy and safety	Long-term safety and tolerability
Study Design	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Multicenter, open-label
Test Drug	Balsalazide disodium tablets	Balsalazide disodium tablets
Doses of BSZ Tablets	3.3 g (3 x 1.1 g tablets) BID	3.3 g (3 x 1.1 g tablets) BID 4.4 g (4 x 1.1 g tablets) BID
Treatment Duration	8 weeks	24 months or regulatory approval or Sponsor termination
Scheduled Visits	Day 1, Weeks 1, 2, 4, 8	Day 1, Months 1, 3, 6, 9, 12, and every 3 months through the end of treatment (EOT)
Post-Treatment Follow-up	~2 weeks after the last dose	~2 weeks after the last dose
Subject Population	Subjects with mildly to moderately active UC, ≥18 years of age	Subjects with UC in remission or mildly to moderately active UC who successfully participated in BZUC3002 (and BZUC3003)[a]
Subjects Planned/Completed	Total planned: 225 (2:1 ratio, balsalazide:placebo) Total completed: 250 (167 balsalazide, 83 placebo)	Total planned: 500[b]
Subjects Exposed to Balsalazide Tablets	168 (6.6 g/day)	111 (6.6 g/day)[b] 18 (8.8 g/day)[b]

[a] Subjects are currently being recruited into the BZUC3003 trial from 75 US clinical sites. It is anticipated that safety data from the ongoing BZUC3003 study will be submitted in the 120-day Safety Update.

[b] Based on data from 216 subjects who successfully participated in study BZUC3002 and enrolled in the long-term safety extension study BZUC3005. See also footnote [a]. Data from BZUC3005 up to an interim cut-off date of 26 April 2007 are included in this ISS for the original NDA submission.

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7.2.1.2 Demographics

In randomized safety population, the demographics were similar between BSZ tablets and placebo treatment groups. In subjects treated with balsalazide disodium tablets, 51 % were female, 82% were white, 11 % were Hispanic or Latino, 93% were under 65 years of age, and the mean age was 43.6 years. In subjects treated with placebo, 52% were female, 88% were white, 11 % were Hispanic or Latino, 94% were under 65 years of age, and the mean age was 45.6 years.

7.2.1.3 Extent of exposure (dose/duration)

In a placebo controlled study and open label extension safety study, the median number of days of exposure to BSZ tablets was 85.5 days (range: 2 days to 253 days). A total of 29% of subjects received 6.6 g/day of balsalazide disodium for a period of 1 to 56 days, 63% from 56 to 182 days, and 8% from 182 days to 365 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The interim report from the ongoing open-label safety extension study (BZUC3005) includes 130 subjects in the safety population with UC who successfully participated in BZUC3002. Scheduled study visits to the clinic occur at Screening, Baseline, Month 1, Month 3, and every 3 months thereafter through the End-of-Treatment (EOT) visit. The majority of subjects (n=111) in this study received open label BSZ tablets at 3.3g BID. Two weeks following Data from BZUC3005 up to an interim cut-off date of 26 April 2007 are included in this submission.

7.2.2.2 Postmarketing experience

Balsalazide disodium tablets are not currently approved for marketing in any country in the world. However, the capsule formulation (Colazal) is available in the market for many years and postmarketing experience is reflected in the current product labeling. In addition, there are other various mesalamine containing oral formulations that have been marketed for use in mild to moderate active UC and the safety profile has been well established.

7.2.2.3 Literature

The applicant provided a few articles in paper format with this application. The reviewer performed additional literature review utilizing the Agency's on line database as well as resources and used them in describing various sections of this review.

7.2.3 Adequacy of Overall Clinical Experience

The study design and the protocol defined endpoints were acceptable. The trials were limited in their lack of sufficient geriatric population and racial subsets.

7.2.4 Adequacy of Routine Clinical Testing

The protocol defined clinical testing and safety assessments were adequate.

7.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The pivotal study was appropriately designed to allow for adequate analysis of safety. Overall, the safety data demonstrated that the dose tested is safe and well tolerated. The overall safety profile of BSZ tablet formulation is similar to the BSZ capsule formulation, which was approved for marketing in the US in July 2000 for the same indication and similar total daily dose.

7.2.6 Assessment of Quality and Completeness of Data

The data necessary to conduct safety review were included in the NDA. Overall, the applicant's quality of assessment was acceptable.

7.2.7 Additional Submissions, Including Safety Update

The safety update submitted in November 16, 2007 includes mainly data from the second randomized, double blind, phase 3 active controlled study. The full report from this study will be reviewed in the second review cycle.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the placebo controlled trial, events assessed as possibly or probably related to study drug administration in 1% of patients were rash and nausea.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The safety database includes results from one placebo controlled study and the interim safety report from an ongoing long term, open label, extension study including 130 subjects who successfully participated in the pivotal study. However, emphasis has been placed on analysis of

the placebo controlled study since only here that unbiased assessment of the safety of the study drug could be made. Nonetheless, the interim report from an ongoing open label study showed similar safety profile.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Dose ranging studies were not conducted under the clinical development program.

7.4.2.2 Explorations for drug-demographic interactions

In the randomized safety population, smaller proportions of males and females treated with BSZ tablets reported any events compared to subjects treated with placebo (28% vs 48% and 44% vs 50%, respectively). However, in the BSZ arm, females reported AEs more frequently than did males (44% vs 28%), while the frequency of AEs was comparable in the placebo arm (48% and 50%, respectively).

Overall, the most frequently reported AEs by males and females were GI related disorders in both BSZ vs placebo arms (21% vs 39% and 31% vs 36%, respectively). The GI event was more frequent in females than males in BSZ group (31% vs 21%), while it was similar in the placebo group. In BSZ group more females than males reported GI events, including abdominal distention (7% vs 1.2%), abdominal pain (7% vs 2.4%) and vomiting (5.8% vs 1.2%). In the placebo group vomiting was reported by 5.4% of males and none of females (0%). There was a higher incidence of worsening of UC in male subjects than females in both treatment groups, but this trend was more pronounced in the placebo group (9% vs 24% and 4.7 vs 4.8%, respectively).

The clinical significance of the aforementioned GI events is unclear, given that most of the observed events are likely due to the underlying disease. The event of vomiting that was reported by females in BSZ group and not in placebo group may suggest drug related event, but the event also occurred with similar frequency (5.4%) in placebo males.

There were too few subjects over 65 years of age (7%) and non-white subjects (<10%) to evaluate whether there was a differential occurrence of AEs between treatment groups. Safety of BD tablets in pediatric subjects has not been evaluated in this study.

7.4.2.3 Explorations for drug-disease interactions

In both treatment arms, subjects who were not newly diagnosed (> 4 weeks) with UC reported AEs more frequently than newly diagnosed subjects (≤ 4 weeks): for BSZ and placebo respectively, 46% and 58% vs 10% and 10%. Overall, a higher proportion of subjects with moderate disease severity at baseline reported any AEs (33%) compared to subjects with mild disease severity (22%). Approximately twice as many subjects with moderate disease than mild disease reported AEs related to GI disorders (18% versus 9%).

7.4.2.4 Explorations for drug-drug interactions

In the pivotal study, no clear effect was seen in subjects using concomitant medications such as NSAIDs/aspirin or antibiotics. However, the sponsor indicated that there was limited number of subjects who took the aforementioned drugs often due to entry criteria during the study.

7.4.3 Causality Determination

The safety database including data from a placebo controlled study does not suggest that the use of BD tablets is associated with any new safety signal. The overall safety profile was as expected according to the drug class.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended total daily dose is 6.6g to be taken twice daily (three 1.1g tablets BID) for up to 8 weeks.

It should be noted that no separate dose response trial was conducted with the BD tablets. The rationale was that the proposed total daily dose (6.6g/day) for new tablet formulation is similar to that of the capsule formulation (6.75g/day), Colazal, which was approved in July 18, 2000 for the same indication. The goal of the clinical program was to provide a more convenient dosing regimen with the new tablet formulation as compared to capsule formulation (BID vs TID).

8.2 Drug-Drug Interactions

Drug-drug interaction studies have not been conducted with BD tablets.

8.3 Special Populations

Safety and effectiveness of BD tables in pediatric patients have not been studied. There have been no studies with BD tablets in subjects with renal or hepatic impairment. Pregnant women and nursing mothers were excluded from clinical trials with BD tablets. The clinical program did not include sufficient number of subjects aged 65 and older (<10%) to determine whether they respond differently than younger subjects.

8.4 Pediatrics

The NDA did not include subjects < 18 years old.

8.5 Advisory Committee Meeting

There was no advisory committee meeting required for this NDA.

8.6 Literature Review

The applicant provided a few articles in paper format with the application. The reviewer performed additional literature search utilizing the Agency's on line database as well as resources and used them in various sections of this review as deemed appropriate.

8.7 Postmarketing Risk Management Plan

There are no applicable issues related to postmarketing risk management plan in this NDA.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

NDA 22-205 sought approval for BD 1100mg tablet for use in adults with mild to moderate active UC at a dose of 6.6g/day BID. BD 750mg capsule (Colazal) was approved in July 2000 for the same indication at a dose of 6.75g/day TID. While the total daily dose is similar between the two formulations, the new tablet formulation offers a more convenient daily dosing regimen (BID vs TID), a rationale for the clinical development. In support of the application, data from a single pivotal study (BCZUC3002) and interim safety report from an ongoing open label, long term safety study (BZUC3005) were submitted.

<u>Clinical Efficacy</u>
The sponsor's single randomized, double blind, placebo controlled study (n=249, 166 on drug) demonstrated superiority of BD tablets (p=0.02), but this result was dependent on a subpopulation's finding, namely, male subjects (n=121, 81 on drug). In female subjects (n=128, 85 on drug) that contributed 51% of the ITT population, the finding on drug could not be differentiated from the finding on placebo. In fact, the placebo response rate was numerically higher than the drug response rate among female subjects (58% vs 54%).

It is of interest to note that while the response rate was comparable between males and females in the BD tablet group (57% vs 54%); it was markedly different in the placebo group (20% vs 58%). Consequently, a substantial therapeutic gain was demonstrated in males (37%), but none in females (-4%). The basis for the observed discrepancy in the placebo response rate across gender in not clear. Review of relevant published literature does not suggest gender as a potential factor for differences in placebo response rate in the population of interest. In a meta-analysis study published recently, it has been reported that studies with higher mean disease activity scores at baseline in placebo patients were associated with lower placebo response rates. (Su et al. Gastroenterol 2007;132:516-526). In the sponsor's study, the mean baseline disease activity scores were comparable across treatment groups as well as across gender: drug vs placebo was 8

(each) in males and 7.6 vs 8 in females. In the most recent information provided as an explanation for the observed discrepancy, the sponsor claimed that females with more sever disease at baseline (MMDAI score ≥ 9) had a larger placebo response rates and no placebo males with sever disease at baseline responded. The sponsor's result in females is in contrary to the published literature described above where placebo subjects with more sever disease at baseline would be expected to have a low response rate, rather than a high response rate as presented.

Clinical Safety
The overall safety profile was as expected according to the drug class. No unexpected AEs were reported in the data submitted.

Based upon comprehensive review of the data presented and additional information obtained upon request, it is concluded that the superiority of BD tablets was dependent on a subpopulation's finding, namely, male subjects. Due to the unexplained high placebo response rate, efficacy of BD tablets has not been established in females that contributed 51% of the ITT population. The reviewer has no safety concern in this NDA for the proposed indication.

Addendum
On November 16, 2007, without any prior agreement the sponsor submitted the full report from the second phase 3, active controlled study (BZUC3003) along with the required 120-day safety update. From the document submitted, it became apparent that the aforementioned study was completed shortly after the NDA was submitted. Nevertheless, on a teleconference held in December 2007, the sponsor was informed that the new study results will not be reviewed under the current review cycle.

It is of interest to note that at the End of Phase 2 meeting and Pre-NDA meeting (meeting minutes dated 08/08/05 and 08/27/07, respectively) the sponsor was advised to include two studies for NDA submission and was informed that if a single study were submitted it would be expected to show robust evidence of effectiveness and consistent findings across centers and subgroups. Despite the Division's repeated advice and the sponsor's knowledge that the second larger phase 3 study (BZUC3003) was near completion, it was decided to rely on a single study (BZUC3002) that failed to demonstrate consistent findings across important subpopulation, namely, males and females.

9.2 Recommendation on Regulatory Action

The reviewer recommends that an approvable action be taken on Salix marketing application (NDA 22-205) for BD tablets intended for use in mild to moderate active UC. In the sponsor's single placebo controlled study, the superiority of BD tablets was dependent on a subpopulation's finding, namely, male subjects. Due to the unexplained high placebo response rate, the efficacy of BD tablets has not been established in females, which contributed 51% of the study population.

The issuance of an approval is dependent upon the review of additional efficacy data from adequate and well controlled study. In the second phase III study (BZUC3003) that has been

recently completed, it is expected that the results demonstrate substantial evidence of effectiveness as well as consistent finding across centers, and more importantly, across subgroups, namely, males and females.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There is no applicable activity related to risk management for this NDA.

9.3.2 Required Phase 4 Commitments

The Sponsor requested waiver for pediatric studies required under PREA, and provided the following justification: the new tablet formulation contains the same active ingredient as in the approved capsule formulation (Colazal), for pediatric population. Both formulations are indicated for the treatment of mild to moderate active UC at a similar total daily dose. Colazal capsules can be opened and sprinkled on applesauce as a pediatric administrative alternative; while the tablets may be more difficult to administer to the pediatric population because of difficulty to swallow. Therefore, the implementation of the tablet formulation does not represent a meaningful benefit over the existing capsule formulation in terms of treatments (dosage and ability to administer) for pediatric patients.

In the reviewer's opinion, the sponsor's justification appears adequate and recommends that a waiver be granted. But it should be noted that the new tablet formulation has a more convenient dosing regimen than the capsule formulation (BID vs TID), a potential benefit for improving adherence to therapy. As such, a request for developing age appropriate formulation for pediatric subjects unable to swallow the tablet would have been appropriate. Nonetheless, the reviewer opted to forgo the request since a Proposed Pediatric Study Request for another mesalamine preparation (Lialda) that offers once daily doing regimen is submitted by Shire and is currently under review.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests for this NDA.

9.4 Labeling Review

The proposed labeling will need to be changed as dictated by the results of the required additional study.

9.5 Comments to Applicant

There are no additional comments to applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

The NDA includes one pivotal study that has been summarized under Sections 6 and 7 of this review.

10.2 Line-by-Line Labeling Review

The proposed labeling will need to be changed as dictated by the results of the required additional study.

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/s/

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