CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022205Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	22-205
Submission Date	08/02/2011; 10/13/2011
Trade Name	Giazo®
Active Ingredient	Balsalazide disodium
Dosage Forms/ Strength	Tablet for oral administration Each tablet contains 1.1 g balsalazide disodium
Indication	Treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older
Sponsor	Salix Pharmaceuticals, Inc.
Type of Submission	Class 2 Resubmission
Reviewer	Insook Kim, Ph.D.
Secondary Reviewer	Sue-Chih Lee, Ph.D.

Executive Summary

Submitted is a class 2 resubmission in response to the complete response letter issued by the Agency in October 2009. There was no clinical pharmacology deficiency identified during review of the original submission dated July 16, 2007. No new clinical pharmacology information was submitted in this application.

The sponsor also submitted a response to the Agency Information Request (SDN 42) dated October 13, 2011 regarding bioanalytical studies conducted by Cetero Research in Houston, Texas for the proposed product. The sponsor stated that no studies conducted Cetero during April 1, 2005 to June 15, 2010. This reviewer confirmed that Cetero Research in Houston was not involved in conduct of studies BZPK1002 (food effect study) and BZPK1003 (multiple dose study) by reviewing the study reports. As such there is no remaining issue regarding bioanalytical assay

Recommendation
The Division of Clinical Pharmacology 3 has reviewed the labeling and following labeling comments should be conveyed to the sponsor.

Proposed Labeling and Recommended Revisions

2 DOSAGE AND ADMINISTRATION

For treatment of active ulcerative colitis in adult male patients, the usual dose is three 1.1 g GIAZO tablets to be taken 2 times a day with or without food (6.6 g per day) for up to 8 weeks (see 12.3.Pharmacokinetics).

Reviewer's comment: In phase 3 trial, the proposed product was administered without

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regard of food intake. (b) (4)

According to the previous clinical pharmacology review, the reviewer thoughts that it might be acceptable from a safety standpoint; however, the review of labeling language was deferred until NDA approval.

We recommend that the dosage administration be without regard of food. This is because the product was taken without regard of food in phase 3 trials. In addition, because the systemic exposure to mesalamine is likely reflective of the availability of mesalamine in the colon based on its release mechanism mediated by colonic microflora but the impact of reduced systemic exposure to mesalamine due to concomitant food intake on the efficacy is unknown.

7 DRUG INTERACTIONS

Based on in vitro studies, balsalazide and its metabolites (5 aminosalicylic acid, N-acetyl-5-aminosalyicylic acid, 4 aminobenzoyl-ß-alanine, and N-acetyl-4-aminobenzoyl-ß-alanine) are not expected to inhibit the metabolism of other drugs that are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

(b) (4)

(**Reviewer's comment:** We recommend that this paragraph be revised to avoid redundancy)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Balsalazide is a prodrug of mesalamine (5-aminosalicylic acid, 5-ASA). The mechanism of action of 5-ASA is unknown, but appears to be local to the colonic mucosa rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with ulcerative colitis, and it is possible that 5-ASA diminishes inflammation by blocking production of arachidonic acid metabolites in the colon.

Reference ID: 3073598

12.3 Pharmacokinetics

(b) (4)

(**Reviewer's comment**: We recommend that this sentence be deleted since it is not relevant to the subsection 12.3.)

Following oral administration, balsalazide is cleaved by azoreductases produced by anaerobic bacteria, found in the gut, to release equimolar quantities of 5-ASA, the active moiety, and 4-aminobenzoyl-ß-alanine (4-ABA), a carrier moiety. Both of these moieties are N-acetylated to form N-Ac-5-ASA and N-Ac-4-ABA, respectively.

Absorption

After single-dose administration of 3.3 g GIAZO in 18 healthy subjects, the median time of peak plasma concentration (T_{max}) was 0.5 hr for balsalazide and~~, while the median Tmax was~~ 12 hr for both 5-ASA and N-Ac-5-ASA (Table 2). Pharmacokinetic parameters exhibited high variability, with %CV ranging from 31% to 67% for AUC and from 27% to 68% for C_{max}.

Pharmacokinetic (b) (4) were (b) (4) after (b) (4) repeated doses of 3.3 g GIAZO tablets every 12 hours for 7 days. Upon (b) (4) doses, steady-state was achieved after about 3 days for balsalazide and all metabolites. The AUC and C_{max} were the highest for N-Ac-5-ASA, followed by 5-ASA and balsalazide. There was minimal accumulation of balsalazide, as suggested by a 1.2 -fold increase in AUC. On the other hand, a larger increase in the systemic exposure to metabolites was observed at steady-state. The accumulation ratios based on AUC for the metabolites were 6.1 for 5-ASA, 3.6 for N-Ac-5-ASA, 4.8 for 4-ABA, and 3.6 for N-Ac-4-ABA.

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Table 2: Pharmacokinetic Parameters for Balsalazide and Metabolites (5-ASA and N-Ac-5-ASA) Following Single- and Repeated-Doses (Q12) of 3.3 g Balsalazide Disodium as GIAZO (N=18)

	Single Dose		Repeated Dose (7 days)	
Parameter	**Mean**	**SD**	**Mean**	**SD**
C_{max} (mcg/mL)				
Balsalazide	0.3	0.2	0.3	0.2
5-ASA	0.5	0.3	1.5	0.6
N-Ac-5-ASA	1.2	0.4	2.2	0.6
T_{max}[a] (hours)				
Balsalazide	0.5	(0.5-2)	0.5	(0.5-2)
5-ASA	12	(8-16)	12	(1.5-16)
N-Ac-5-ASA	12	(8-16)	10	(1-16)
AUC_{tau} (mcg•h/mL)				
Balsalazide	1.3	0.7	1.6	0.9
5-ASA	2.2	1.6	13.4	6.3
N-Ac-5-ASA	5.9	2.9	21	6.4
$AUC_{0-\infty}$ (mcg•h/mL)				
Balsalazide	1.4	0.8	NA	NA
5-ASA	8.5	3.9	NA	NA
N-Ac-5-ASA	33.5	14.1	NA	NA
$T_{½}$[b] (hour)				
Balsalazide	1.9	0.7	8.4	12.4
5-ASA	9.5[b]	10.1	9.0	8.6
N-Ac-5-ASA	10.4[b]	17.6	7.2	6.8

a Expressed as median and range.
b N=17.

Food effect

After administration of single dose of 3.3 g (3 × 1.1 g tablets) of GIAZO with a high-fat meal, the AUC of balsalazide was unaffected compared to fasted administration, but the presence of food reduced both peak concentrations and AUC of the metabolites 5-ASA and N-Ac-5-ASA. Under fed conditions, the mean C_{max} was reduced by 44% for balsalazide, 65% for 5-ASA, and 48% for N-Ac-5-ASA. No significant changes were observed for $AUC_{0-\infty}$ for balsalazide; however, $AUC_{0-\infty}$ was reduced for 5-ASA by 46% and for N-Ac-5-ASA by 17%. A high fat meal increased the median T_{max} for balsalazide from 0.5 to 2 hours; for 5-ASA from 12 to 24 hours; and for N-Ac-5-ASA from 12 to 24 hours.

Reviewer's comments: Editorial changes

Distribution

The binding of balsalazide to human plasma proteins was ≥ 99%; 5-ASA and N-Ac-5-ASA were 43% and 78% bound, respectively, to plasma proteins.

Reference ID: 3073598

Metabolism and Excretion

Following oral administration, balsalazide is cleaved by bacterial azoreduction to release equimolar quantities of 5-ASA, the active moiety, and 4-ABA, a carrier moiety. Mesalamine (5-ASA) and 4-ABA are further acetylated to N-Ac-5-ASA and N-Ac-4-ABA, respectively in the intestinal mucosa and liver. The terminal half-life was 1.9 h for balsalazide, 9.5 h for 5-ASA, and 10.5 h for N-Ac-5-ASA.

At steady-state following administration of repeated doses of 3.3 g GIAZO every 12 hours in healthy volunteers, the combined % of dose excreted in urine for balsalazide and its metabolites over 12 hours was 23%. The mean % of dose excreted in urine over 12 hours was 0.16% for balsalazide, 4.6% for 5-ASA, 15.6% for N-Ac-5-ASA, 0.40% for 4-ABA, and 1.8% for N-Ac-4-ABA.

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/s/

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01/18/2012

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01/20/2012

REVIEW OF CLINICAL PHARMACOLOGY

NDA	22-205	Submission Date(s)	10/26/2009
Brand Name		Giazo	
Generic Name		Balsalazide disodium	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
OCP Division		Division of Clinical Pharmacology III	
OND Division		Division of Gastroenterology Products	
Sponsor		Salix Pharmaceuticals, Inc.	
Relevant IND(s)		IND 38,492	
Submission Type; Code		Class 2 Resubmission of a Complete Response to the Agency's Complete Response	
Formulation; Strengths; Regimen		Tablet, 1.1 g Three tablets twice daily per oral	
Proposed Indication		The treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older	

Background

During the original NDA review, the Agency identified following deficiency and conveyed to the sponsor in the Complete Response dated May 16, 2008. The sponsor submitted a Complete Response on August 16, 2008 to which the Agency issued a Complete Response on December 22, 2008. Submitted is a resubmission of a Complete Response to the Agency's Complete Response dated December 22, 2008.

The deficiency identified by the Agency in a Complete Response dated May 16, 2008 is as below:

> "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."

There were no clinical pharmacology specific deficiencies identified by the Agency.

In this submission, the sponsor used available pharmacokinetic data as a supporting evidence to address the deficiency.
The sponsor's arguments are as below:

- The potential difference in treatment effect in females has been carefully examined. Analyses of the BZUC3002 and BZUC3003 studies show a consistent response to BD tablet treatment in males and females, and address differences in placebo response rates by gender observed in study BZUC3002. Results of these analyses confirm that treatment is equally beneficial in both males and females, providing sufficient evidence that the observed placebo response in

females who participated in study BZUC3002 is a spurious finding and likely due to specific aspects regarding the design of the trial.

In addition, analysis of existing pharmacokinetic data by gender demonstrates that there is not an appreciative difference between males and females in the rate and extent of bioconversion of balsalazide disodium to mesalamine.

- Available pharmacokinetic and dissolution data for the comparison of the new BD (balsalazide disodium) tablet formulation to the currently marketed BD capsule formulation (Colazal®) support equivalent 24-h exposure for the two formulations; demonstrate very similar pharmacokinetics between males and females with no gender differences in the rate and extent of prodrug to active drug conversion; and show equivalence in the in vitro dissolution profile, confirming that no relevant differences exist between the immediate release formulations.

Recommendations to the Division Of Gastroenterology Products

The sponsor's argument using comparable systemic exposure to balsalazide and its metabolites between men and women is not acceptable to address a lack of consistency of treatment effect between men and women. Therefore, the decision should be made based on the available clinical efficacy data.

For the immediate release products of balsalazide disodium, the bioequivalence for balsalazide and its active metabolite mesalamine has been accepted for the approval of generic products. Based on this practice, the sponsor argues that the similar systemic exposure to balsalazide and its metabolites including mesalamine between healthy men and women should support the similar therapeutic efficacy between these two important subpopulations.

This argument can not be used to address the current deficiency of inconsistent treatment effect between men and women. 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.

Post-Marketing Study Recommendation

1) Post-Marketing Requirement

If this product was to be approved, we recommend that the pharmacokinetics of balsalazide, mesalamine and N-acetyl aminosalicylic acid after administration of Giazo be characterized in applicable pediatric patients and pharmacokinetic parameters be compared to those in adults. The pediatric dose should be adequately justified.

As a similar product Colazal has been already approved for use in pediatric patients, the sponsor may leverage available knowledge to design a clinical trial if required by the clinical division without a separate pharmacokinetic study to guide a dose selection in this patient group. In such case, the PK study can be a sub-study of pediatric efficacy and safety trial.

2) Post-Marketing Commitment

We recommend that the effect of concomitant antibiotics on the conversion of balsalazide to mesalamine by gut-flora be evaluated in patients.

The release of active moiety, mesalamine is dependent on the metabolism of balsalazide by gut-flora. Theoretically, the alteration of gut-flora by concomitantly administered antibiotics may lead to less conversion of balsalazide to mesalamine and consequently low efficacy. The systemic exposure to balsalazide, mesalamine and N-acetyl mesalamine should be assessed with and without concomitant course of antibiotic treatment.

Summary of Clinical Pharmacology Findings

Sponsor's Response: Section 4.6. in the sponsor's resubmission of complete response

The sponsor provided AUCtau and Cmax for balsalazide and its metabolites including mesalamine in healthy subjects by gender based on a previously submitted study BZPK1003. The AUCtau and Cmax were normalized by a body-weight adjusted dose (g/kg). Based on p-value > 0.5 (except for Cmax for 4-ABA for which p=0.0402), the sponsor concluded that the pharmacokinetics of balsalazide and its metabolites are not significantly different between females and males and this finding is consistent with the similar efficacy based on their new analysis.

Reviewer's Comments:

The reanalysis by the sponsor was based on 12 male and 12 female subjects while the original study report for BZPK1003 stated that 18 out of 24 enrolled patients completed the study and reported PK parameters for 10 male and 8 female subjects.

In healthy subjects, previous analysis by this reviewer showed that systemic exposure after multiple doses tended to be higher in female subjects than in male subjects (Table 1). Similarly the urinary excretion of all analytes was higher in female subjects than in male subjects. This suggests combined with the mode of activation i.e. cleavage of balsalazide by gut-flora to mesalamine (5-aminosalicylic acid: 5-ASA) and 4-aminobenzoyl-β-alanine (4-ABA), the systemic/local availability of mesalamine, the active metabolite in female subjects is likely no less than that in male subjects. However, it should be noted that this is a qualitative not quantitative evaluation as the number of subjects is not sufficient to draw a firm conclusion.

Table 1. The mean pharmacokinetic parameters at steady-state by gender following multiple doses of 3.3 g Giazo twice a day[1].

	Multiple doses			
Balsalazide	Cmax	S.D.	AUCtau	S.D.
Female (n=8)	307	114	1576	812
Male (n=10)	267	197	1499	943
Female/Male (%)	**115**		**105**	
5-ASA	Cmax	S.D.	AUCtau	S.D.
Female	1535	675	14592[2]	7217[2]
Male	1248	626	10395	5112

Female/Male (%)	**123**		**140**	
N-Ac-5-ASA	Cmax	S.D.	AUCtau	S.D.
Female	2096	656	21138[2]	7450[2]
Male	2120	587	19291	5614
Female/Male (%)	**99**		**110**	

[1]From original clinical pharmacology review.
[2]In the original Clinical Pharmacology review, data for AUC∞ of 5-ASA and N-Ac-5-ASA in female subjects was presented instead of AUCtau.

Sponsor's response: Section 5. for the sponsor's resubmission of complete response

The sponsor provided a relative BA data after multiple dosing of Giazo (tablets given 3.3 g two times a day (6.6 g/day)) and Colazal (capsules given 2.25 g three times a day (6.75g/day)) based on total daily AUC (Table 2). Based on the point estimate and the associated 90% confidence interval, the sponsor claims that two products have equivalent in vivo pharmacokinetic exposure. The sponsor also pointed out that the FDA has accepted a bioequivalence for balsalazide drug products based on dissolution and PK.

Table 2. The 90% Confidence Interval and Geometric Mean Ratio for 5-ASA Total Daily AUC After Multiple Dosing in Study BZPK1003

Compound	Treatment	Geometric LS Mean	p-value[a]	GMR (Tablet/ Capsule)[b]	90% CI for GMR		Power[b]
					Lower	Upper	
5-ASA	Capsule	23500	0.8013	102.88	84.73	124.92	60.2
	Tablet	24200					

Abbreviations: Total Daily AUC (in units of ng•h/mL) = AUC_{tau} multiplied by the dosing frequency in a day, where AUC_{tau} = area under the plasma concentration versus time curve from time 0 to the end of the dosing interval; CI = confidence interval; LS = least squares; GMR = geometric mean ratio
a P-value for testing difference in natural log-transformed Total Daily AUC between capsule and tablet treatments.
b Expressed as a percent.

Reviewer's comments:

The total daily AUC (AUCtau multiplied by dosing frequency) may be used for a qualitative comparison of the systemic exposure after administration of each product under different dosage regimens.

However, in this case it is not acceptable as an evidence of in vivo pharmacokinetic equivalency because the study was not adequately designed to determine the bioequivalence (e.g. multiple dose PK with different dosage regimens). In particular, because of the different dosage regimens, even the bioequivalent systemic exposure between two products were demonstrated, it can not independently support equivalent efficacy and safety in a similar way to the generic approval.

Detailed Labeling Recommendations

12.1 Mechanism of Action

(b) (4)

Balsalazide is a prodrug of mesalamine (b) (4)

The mechanism of action of 5-ASA is unknown, but appears to be local to the colonic mucosa rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with (b) (4), and it is possible that 5-ASA diminishes inflammation by blocking production of arachidonic acid metabolites in the colon.

12.3 Pharmacokinetics

(b) (4)

Reviewer's comments: Chemical properties. Recommend to move to 11. Description.

(b) (4)

Reviewer's comment: Move to metabolism.

Following oral administration, balsalazide is cleaved by (b) (4) to release equimolar quantities of (b) (4) 5-ASA, the active moiety, and the 4-aminobenzoyl-ß-alanine (4-ABA) carrier moiety.

Absorption

After single-dose administration of 3.3 g Balsalazide (BSZ) disodium (b) (4) in 18 healthy subjects, (b) (4) the median time to peak plasma concentration (T_{max}) of 0.5 hr while (b) (4) the median T_{max} of 12 hr for 5-ASA and N-Ac-5-ASA (Table 2). Pharmacokinetic parameters (b) (4) variability (CV%) ranged from 31 to 67% for AUC and from 27 to 68% for C_{max}.

(b) (4)

(b) (4)

Table 2 Pharmacokinetic Parameters for Balsalazide and Metabolites (5-ASA, N-Ac-5-ASA, 4-ABA, N-Ac-4-ABA) Following Single- and (b) (4) (Q12) of Balsalazide Disodium as GIAZO (N=18)

	Single Dose		Multiple Dose	
Parameter	**Mean**	**SD**	**Mean**	**SD**
C_{max} (μg/mL)				
Balsalazide	0.3	0.2	0.3	0.2
5-ASA	0.5	0.3	1.5	0.6
N-Ac-5-ASA	1.2	0.4	2.2	0.6
T_{max}[a] (hour)				
Balsalazide	0.5	(0.5-2)	0.5	(0.5-2)
5-ASA	12	(8-16)	12	(1.5-16)
N-Ac-5-ASA	12	(8-16)	10	(1-16)
AUC_{tau} (μg•h/mL)				
Balsalazide	1.3	0.7	1.6	0.9
5-ASA	2.2	1.6	13.4	6.3
N-Ac-5-ASA	5.9	2.9	21	6.4
$AUC_{0-\infty}$ (μg•h/mL)				
Balsalazide	1.4	0.8	NA	NA
5-ASA	8.5	3.9	NA	NA
N-Ac-5-ASA	33.5	14.1	NA	NA
$T_{½}$ (hour)				
Balsalazide	1.9	0.7	8.4	12.4
5-ASA	9.5[b]	10.1	9.0	8.6
N-Ac-5-ASA	10.4[b]	17.6	7.2	6.8

a Expressed as median and range.
b N=17.

(b) (4)

Reviewer's comments: Provide details in the table only for key metabolites

Food effect:

After administration of single dose 3.3 g (3 × 1.1 g tablets) of GIAZO with a high-fat meal, [redacted] (b) (4) AUC) of balsalazide was unaffected, but the presence of food significantly reduced both peak concentrations and AUC of the key metabolites, 5-ASA and N-Ac-5-ASA. A high fat meal increased the median T_{max} for balsalazide from 0.5 to 2.0 hours; for 5-ASA from 12 to 24 hours; and for N-Ac-5-ASA from 12 to 24 hours. Under fed condition, the mean C_{max} was [redacted] (b) (4) reduced [redacted] (b) (4) [redacted] (b) (4) No significant changes were observed for $AUC_{0-\infty}$ for balsalazide; however, $AUC_{0-\infty}$ were reduced for 5-ASA by 46% and for N-Ac-5-ASA by 17%.

[redacted] (b) (4)

Distribution

The binding of balsalazide to human plasma proteins was ≥ 99%.

Reviewer's comment: Sponsor to add protein binding of mesalamine and N-Ac-5-ASA. Appropriate literature articles will be acceptable.

Metabolism and Excretion

[redacted] (b) (4)

(b) (4)

[redacted]

At steady-state following administration of (b) (4) doses of 3.3 g GIAZO every 12 hours in, the combined % of dose excreted in urine for balsalazide and its metabolites over 12 hours was 22.6% .

The mean% of dose excreted in urine over 12 hours for balsalazide, 5-ASA, N-Ac-5-ASA, 4-ABA, and N-Ac-4-ABA was 0.155 %, 4.64 %; 15.6%; 0.403%; and 1.78 %, respectively.

(b) (4)

[redacted]

Reviewer's comments: Data with different dosage forms or dosage regimens.

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/

INSOOK KIM
04/07/2010

SUE CHIH H LEE
04/07/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**22-205**	*Submission Date(s)*	**7/16/2007** **11/21/2007** **3/28/2008**
Brand Name		**To be determined**	
Generic Name		**Balsalazide disodium**	
Reviewer		**Insook Kim, Ph.D.**	
Team Leader		**Sue-Chih Lee, Ph.D.**	
OCP Division		**Division of Clinical Pharmacology III**	
OND Division		**Division of Gastroenterology and In-born error of metabolism products**	
Sponsor		**Salix Pharmaceuticals, Inc.**	
Relevant IND(s)		**IND 38,492**	
Submission Type; Code		**Original**	
Formulation; Strengths; Regimen		**Tablet, 1.1 g, three tablets twice daily per oral**	
Indication		**The treatment of mild to moderate ulcerative colitis in patients 18 years and older**	

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1 Executive Summary

NDA 22-205 for Balsalazide disodium tablet 1.1 g (Tradename®) was submitted seeking the marketing approval for the treatment of mildly and moderately active ulcerative colitis by a 505(b)(1) regulatory pathway. The marketing of Balsalazide disodium has been approved in capsule formulation (Colazal®; NDA 20-610) since July 18, 2000 for the same indication for three times daily dose of 2.75 g and use of Colazal® in pediatric patients was approved in December, 2006. The subject of current NDA 22-205 is a new tablet formulation of Balsalazide disodium for twice daily dose of 3.3 g. To support approval of Tradename®, included in this

submission are the final study reports for an in vitro drug interaction study, a food effect study and a relative bioavailability study between a single and multiple doses of tablet and capsule administration and a single phase 3 efficacy and safety study. Subsequent to the original submission, the sponsor submitted an additional phase 3 study report along with the 180 day-safety update. There is no new clinical pharmacology related information in this submission.

1.1 Recommendations

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. Since the "approvable" action will be taken, the recommendation on the labeling was not made at this time.

1.2 Phase IV Commitments

None

1. 3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Balsalazide (BSZ) is a prodrug which is designed to release an active moiety 5-aminolsalicylic acid (5-ASA) and an inactive carrier moiety 4-amino benzoyl-β-alanine (4-ABA) in the colon by gut microflora. The 5-ASA and 4-ABA is further metabolized to N-acetyl-5-ASA (5-Ac-5-ASA) and N-acetyl-4-ABA (N-Ac-5-ABA), respectively. For this NDA the pharmacokinetic characteristics for BSZ and all four metabolites were evaluated, nonetheless, the discussion was focused on BSZ and key metabolites 5-ASA and N-Ac-5-ASA since the carrier moiety 4-ABA appears to be mostly inert. The clinical pharmacology and biopharmaceutics program in support of BSZ Tablet consists of the study BZPK1002 to evaluate food effect on the pharmacokinetics of BSZ and metabolites and the study BZPK 1003 to assess the relative bioavailability of BSZ tablet to Colazal® after administration of a single dose and multiple doses. In addition, an in vitro drug interactions study report was submitted. The same study report was previously submitted as a Prior Approval Supplement dated May 3, 2007 for Colazal® and reviewed by Dr. Abimbola Adelowale of the Division of Clinical Pharmacology 3. There was no significant metabolism-based drug interaction observed in *in vitro* study and the current Colazal® label reflects the study findings.

Study BZPK1003: Single-dose PK and multiple-dose PK (fasting condition)-The absorption of mesalamine and N-Ac-5-ASA appears to be delayed than BSZ and metabolites accumulate after multiple doses

After a single-dose and multiple-dose administration of BSZ tablet in 18 healthy male and female subjects, the mean time to peak plasma concentration (T_{max}) for BSZ was 0.5 hr and it was 10-12 hr for 5-ASA and N-Ac-5-ASA, respectively (table 1). The AUC and Cmax were the highest for N-Ac-5-ASA followed by 5-ASA and BSZ after a single and multiple dose administration. The terminal half-life determined after a single-dose administration was 1.9 h, 9.5 h, and 10.5 h for BSZ, 5-ASA and N-Ac-5-ASA, respectively. After about 3 days of dosing, the steady-state was achieved for BSZ and all metabolites. In comparison with after a single-dose admisnitration, the $\mathbf{AUC_{tau}}$ of the parent drug BSZ was increased by 1.2 folds while Cmax was not significantly altered after multiples doses however, a significant increase in AUCtau and Cmax of all metabolites was observed.

Table 1. Summary of PK parameters after administration of a single-dose and multiple doses of BSZ tablets

Parameter	Single Dose Mean	SD	Multiple Dose Mean	SD
C_{max} (ng/mL)				
Balsalazide	310	155	316	161
5-ASA	474	266	1490	642
N-Ac-5-ASA	1150	422	2190	600
4-ABA	29.6	13.4	72.4	49.0
N-Ac-4-ABA	81.2	33.0	140	84.8
T_{max}[a] (hour)				
Balsalazide	0.50	(0.5-2)	0.50	(0.5-2)
5-ASA	12.0	(8-16)	12.0	(1.5-16)
N-Ac-5-ASA	12.0	(8-16)	10.0	(1-16)
4-ABA	12.0	(12-48)	8.0	(0.5-24)
N-Ac-4-ABA	16.0	(8-48)	8.0	(0.5-16)
AUC_{tau} (ng•h/mL)				
Balsalazide	1330	720	1610	870
5-ASA	2210	1570	13400	6310
N-Ac-5-ASA	5860	2870	21000	6380
4-ABA	140	77.5	665	494
N-Ac-4-ABA	330	162	1180	737
AUC_T (ng•h/mL)				
Balsalazide	1370	745	1770	911
5-ASA	8130	3930	33300	15200
N-Ac-5-ASA	29000	8910	60800	25500
4-ABA	726	358	1650	1110
N-Ac-4-ABA	2330	1190	3320	2040
$AUC_{0-\infty}$ (ng•h/mL)				
Balsalazide	1380	746	NA	NA
5-ASA	8460	3880	NA	NA
N-Ac-5-ASA	33500	14100	NA	NA
4-ABA	837	412	NA	NA
N-Ac-4-ABA	2730	1310	NA	NA
$T_{½}$[b] (hour)				
Balsalazide	1.9	0.7	8.4	12.4
5-ASA	9.5[c]	10.1	9.0	8.6
N-Ac-5-ASA	10.4[c]	17.6	7.2	6.8
4-ABA	8.3	8.1	5.5	2.6
N-Ac-4-ABA	9.1	9.6	7.0	4.5

a Expressed as median and range.
b Expressed as harmonic mean and pseudo standard deviation based on jackknife variance.
c N=17.

Study BZPK1003: Relative bioavailability between BSZ tablet and BSZ capsule (Colazal®)-At steady state, AUC over 24 hours of mesalamine and N-Ac-5-ASA was comparable between dosage regimen with tablets and capsules.

The PK parameters after a single and multiple doses of BSZ tablet and BSZ capsule (Colazal®) were compared. The dosage regimen was 3.3 g twice daily for tablet and 2.25 g three times daily for capsule, respectively. After a single-dose administration the exposure of 5-ASA and N-Ac-5-ASA were higher with tablets at 3.3 g than capsules at 2.25g which is in consistent with the higher dose for the tablet. The Cmax ratio after administration of tablet to capsule after a single-dose was 80%, 174.3% and 132.4% for BSZ, 5-ASA and N-Ac-5-ASA, respectively. Unexpectedly, the mean Cmax for BSZ was lower with tablet than with capsule despite the higher dose for tablet. At steady-state the Cmax ratio (%) of tablet to capsule was 73.8%, 110.3%, and

107.7% for BSZ, 5-ASA and N-Ac-5-ASA, respectively. The shorter dosing interval for Colazal capsule attributes to the smaller difference in Cmax at steady state between tablet and capsule for 5-ASA and N-Ac-5-ASA. On the other hand, the Cmax of BSZ at steady-state was about 26% lower than after capsule administration. The relative bioavailability of BSZ, 5-ASA and N-Ac-5-ASA as a ratio of AUC_{24} after multiple doses of tablet to capsule was 83%, 102%, and 104% for BSZ, 5-ASA and N-Ac-5-ASA, respectively.

Table 2, The 90% Confidence Interval and Geometric Mean Ratio for Balsalazide, 5-ASA, N-Ac-5-ASA, 4-ABA and N-Ac-4-ABA Total Daily AUC After Multiple Dosing in Study BZPKI003

Compound	Treatment	Geometric LS Mean	p-value[a]	GMR (Tablet/ Capsule)[b]	90% CI for GMR		Power[b]
					Lower	Upper	
Balsalazide	Capsule	3410	0.0269	82.87	72.43	94.82	86.6
	Tablet	2820					
5-ASA	Capsule	23500	0.8013	102.88	84.73	124.92	60.2
	Tablet	24200					
N-Ac-5-ASA	Capsule	38400	0.5637	104.67	91.43	119.84	86.3
	Tablet	40200					
4-ABA	Capsule	926	0.1526	118.19	97.32	143.54	60.2
	Tablet	1090					
N-Ac-4-ABA	Capsule	1550	0.0351	124.28	105.38	146.56	72.7
	Tablet	1930					

Abbreviations: Total Daily AUC (in units of ng•h/mL) = AUC_{tau} multiplied by the dosing frequency in a day, where AUC_{tau} = area under the plasma concentration versus time curve from time 0 to the end of the dosing interval; CI = confidence interval; LS = least squares; GMR = geometric mean ratio
a P-value for testing difference in natural log-transformed Total Daily AUC between capsule and tablet treatments.
b Expressed as a percent.

Urinary excretion of Balsalazide and its metabolites was assessed by collecting urine during a dosing interval i.e. 12 or 8 hrs over 24 hours for tablets and capsules, respectively during dosing. The percentage of dose excreted each analyte was calculated based on doses normalized for each component in total dose. The mean percentage of dose excreted in urine during a dosing interval was about 20.4% after tablet and 20.3% after capsule administration. The renal clearance of BSZ and four metabolites (ml/min and ml/min/kg) and the individual components total excretion were comparable between tablet regimen and capsule regimen.

Study BZPK1002: Effect of a high fat meal on PK-Under fed status, the AUC and Cmax of 5-ASA and N-Ac-5-ASA was decreased while T_{max} was delayed

The high fat diet significantly attenuated the absorption BSZ and metabolites such that the median Tmax was increased from 12 hr to 24 hr for 5-ASA and N-Ac-5-ASA and from 0.5 hr to 2 hr for BSZ. The rate and extent of absorption of 5-ASA was significantly decreased by high fat diet such that Cmax and AUC∞ was decreased by 65% and 46%, respectively. The exposure to N-Ac-5-ASA was affected by high fat diet as was 5-ASA such that the Cmax and AUC∞ were decreased by 48% and 17%, respectively. The mean $t_{1/2}$ of 5-ASA and N-Ac-5-ASA was increased by 3.3 hr 0.8 hr respectively under fed condition compared to fasting condition. On the other hand, the median Tmax of BSZ increased from 0.5 hr to 2.0 hr while $t_{1/2}$ and AUC∞ of BSZ was not significantly altered by high fat diet. Clinical pharmacology information request was sent to the sponsor for the clarification of drug administration procedure in regard of concomitant food intake in phase 3 trials. In the response dated March 24, 2008 the sponsor clarified that no specific instructions were provided in the study protocol regarding drug administration with or without food. Presumably, BSZ tablets have been taken without regard of food, therefore, BSZ

tablet can be labeled to be taken without regard of food. Nonetheless, the sponsor indicated that they do not oppose to label the product given with food to reduce systemic exposure as a precautionary measure given the BSZ is locally acting drug and the recent reports of certain adverse events with the related product Colazal®.

Table 3. The geometric mean ratios (GMRs) and their 90% CIs for the PK parameters of balsalazide and its key metabolites following a single dose administration:

Compound/ Parameter	Treatment	Geometric LS Mean	GMR (Fed/Fasted)	90% CI for GMR	
				Lower	Upper
Balsalazide					
C_{max} (ng/mL)	Fed	188	56.42	49.70	64.05
	Fasted	334			
AUC_T (ng·h/mL)	Fed	1200	91.27	81.89	101.72
	Fasted	1320			
$AUC_{0-\infty}$ (ng·h/mL)	Fed	1210	91.28	81.88	101.75
	Fasted	1330			
5-ASA					
C_{max} (ng/mL)	Fed	157	34.33	29.16	40.42
	Fasted	456			
AUC_T (ng·h/mL)	Fed	4110	52.37	46.51	58.96
	Fasted	7850			
$AUC_{0-\infty}$ (ng·h/mL)	Fed	4340	54.45	48.48	61.16
	Fasted	7980			
N-Ac-5-ASA					
C_{max} (ng/mL)	Fed	665	52.46	47.29	58.19
	Fasted	1270			
AUC_T (ng·h/mL)	Fed	23600	80.55	74.96	86.56
	Fasted	29200			
$AUC_{0-\infty}$ (ng·h/mL)	Fed	25100	83.41	76.27	91.22
	Fasted	30100			

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The current NDA 22-205 was submitted to a 505(b)(1) regulatory pathway in support of new twice daily dosage regimen with new tablet formulation of Balsalazide disodium (BSZ) for the treatment of adult patients with mildly and moderately active ulcerative colitis in patients 18 years of age and older. The BSZ in was approved in capsule formulation(Colazal®, NDA 20-610) for the treatment of adult patients with mildly and moderately active ulcerative colitis for a three times daily dose of three 750 mg capsules (6.75 g/day) for 8 weeks in July 2000. In December 2006, the use of Colazal® in children ages 5 through 17 was approved for the doses of

250 mg and 750 mg three times daily (2.25 g/day and 6.75 g/day, respectively). The new tablet formulation of BSZ is proposed to be used for a similar total daily dose (6.6 g/day for tablets and 6.75 g/day for Colazal capsules, respectively) and the identical duration of treatment (8 weeks). In support of the current NDZ, the sponsor submitted the final report of three clinical trials including one phase 3 trial and two phase 1 studies including a food effect study and a relative bioavailability between the tablets and the capsules.

2.1.2 What are the highlights of the chemistry of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Balsalazide is a prodrug composed of 5-amino salicylic acid (5-ASA,mesalamine) and a carrier, 4-amino benzoyl-β-alanine (4-ABA), linked by an azo bond. When administered orally, colonic bacterial azoreductases cleaves the azo bond to release 5-ASA, the active moiety, and 4-ABA in the colon. BSZ is an intestinal anti-inflammatory agent and the mechanism of action of its active metabolite mesalamine is unknown but is considered locally acting to the gastrointestinal mucosa rather than systemic.

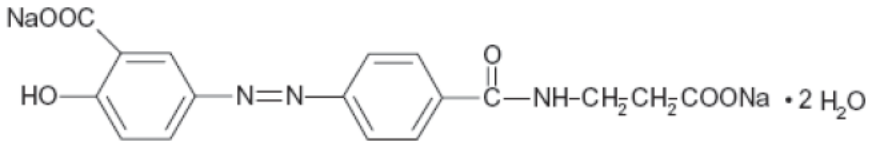


Table 4. Composition of Balsalazide disodium tablets

Component	Reference to Quality Standard	Function	mg/tablet
	(b) (4) tablet		
Balsalzide disodium	In-house standard	Active ingredient	1100
Hypromellose	USP	(b) (4)	
Magnesium stearate	USP		
(b) (4)	USP		
	USP		
	USP		
	USP		
Opadry II Yellow (b) (4)			
(b) (4)	USP		
(b) (4)	**Tablet Weight**		**1192.32**

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies and pharmacokinetic characteristics?

The study BZPK1002 was an open-label, randomized, single-dose, 2-period crossover study in healthy male and female subjects to characterize a single-dose and multiple dose pharmacokinetics of BSZ and its metabolites to compare PK parameters after tablets with capsules administration. The study BZPK1003 was an open-label, randomized, 2-period crossover study in healthy male and female subjects to evaluate food effect on the PK of BSZ and its metabolites.

After a single-dose administration, the Tmax was longer for metabolites than for balsalazide and the systemic exposure was the highest for N-Ac-5-ASA.
In the studies the concentrations of BSZ and its four major metabolites, 5-ASA, N-Ac-5-ASA, 4-ABA and N-Ac-4-ABA were evaluated in plasma and in urine. The summary of PK parameters is presented in table 1. After a single-dose administration, the mean t_{max} was 0.5 hr for BSZ and 12 hr for 5-ASA and N-Ac-5-ASA. The t_{max} for 5-ASA and N-Ac-5-ASA varied with a range of 8-16 h and the longer t_{max} for 5-ASA and N-Ac-5-ASA suggest that the absorption of two metabolites is significantly attenuated compared to the parent drug BSZ. After a single-dose of 3.3 g BSZ tablets, the exposure was the highest for N-Ac-5-ASA among analytes. The mean terminal half-life after a single-dose was 1.9 h, 9.5 h and 10.4 h for BSZ, 5-ASA and N-Ac-5-ASA, respectively.

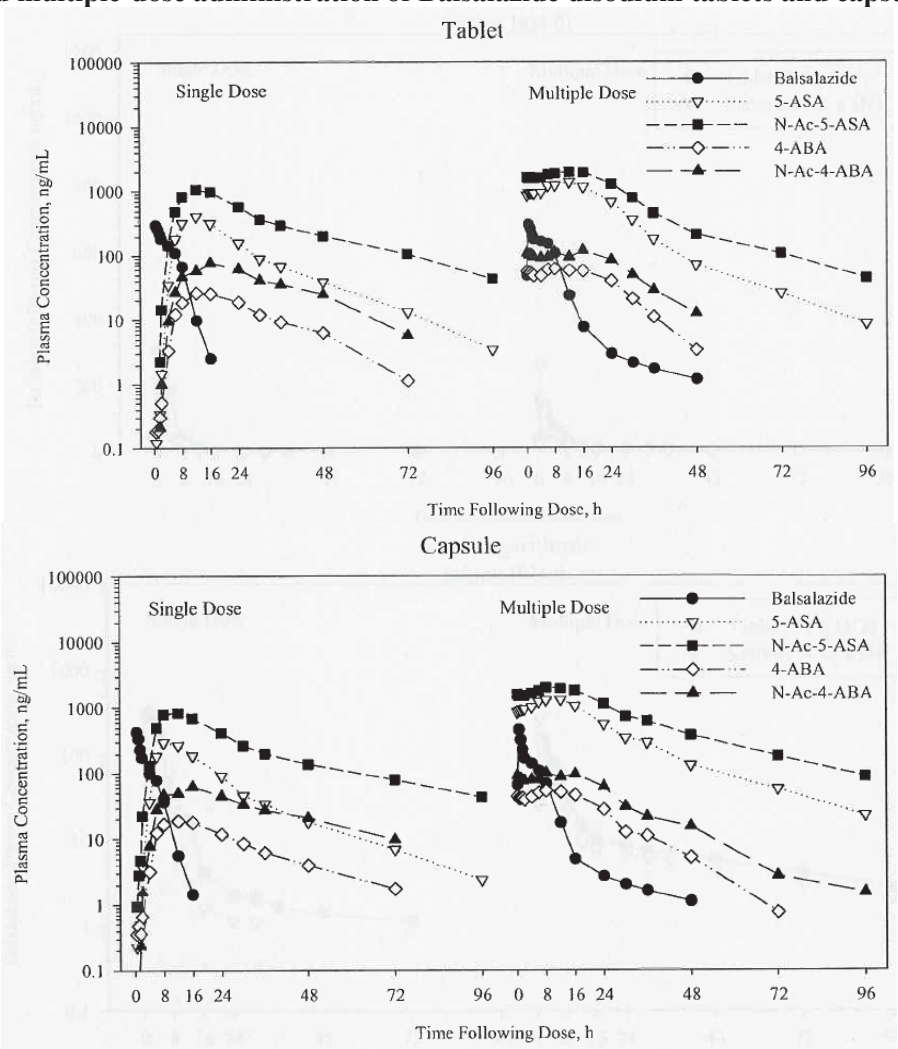
At steady-state metabolites significantly accumulate in plasma.
The attainment of steady-state was assessed by trough concentrations measured twice a day during the first six days of multiple dosing period. The steady-state was achieved on days 1 or 2 for BSZ and on day 3 for all other metabolites. At steady-state the mean C_{max} of N-Ac-5-ASA was 21.9 μg/ml which was 6.9- and 1.5 folds higher than that of BSZ and 5-ASA, respectively and the mean AUC_{tau} of N-Ac-5-ASA was 21 μg h/ml which was 13- and 1.6 folds higher than that of BSZ and 5-ASA, respectively. A significant increase in AUC by 4-9 folds was observed for all metabolites after multiple doses such that the C_{max} was higher by 3 and 1.9 folds for 5-ASA and N-Ac-5-ASA, respectively and by 2.4 and 1.7 folds for 4-ABA and N-Ac-4-ABA, respectively compared with after a single-dose. The AUC of the parent drug BSZ was increased by 1.3 folds while C_{max} was not significantly altered after multiple doses. The mean half-life after multiple doses was 8.4 h, 9.0 h and 7.2 h for BSZ, 5-ASA and N-Ac-5-ASA, respectively.

Reviewer's comment: *Following the multiple doses the mean plasma BSZ concentration decreased poly-exponentially while it decreased single-exponentially after a single-dose administration. This may be due to incomplete sampling duration after a single-dose administration limited by the bioanalytical assay sensitivity. As such the half-life of BSZ after a single-dose administration obtained after a single-dose administration is not the terminal elimination half-life. Nonetheless, the terminal half-life about 2 hours estimated after a single-dose administration is short compared to the dosing interval 12 hours for tablets so the majority of BSZ is eliminated prior to the next dose.*

There were 3 occurrences of carryover plasma concentrations from study period 1 to study period 2 after 7 days of washout period during cross-over single-dose and multiple dose PK study. The plasma concentration was greater than 5 % of C_{max} of 5-ASA and N-Ac-5-ASA for the first day of study period 2 dosing in one subject and less than 5% of C_{max} in two subjects. The plasma concentrations for these subjects were corrected for carry-over concentration by subtracting the contributing 5-ASA or N-Ac-5-ASA plasma concentration using the equation: $C=C_0\ e^{-\lambda t}$ where C0 is the study period 2 predose concentration, t is the study period 2 plasma concentration time-point, and λ is the terminal rate constant from study period 1.

Reviewer's comment: *The sponsor included a subject with pre-dose plasma concentration higher than 5% of the C_{max} for analysis. Generally it is recommended to exclude a subject from BE analysis if the pre-dose plasma concentration is higher than 5% of the C_{max} and to include a subject if the pre-dose plasma concentration is lower than 5% of the C_{max} (Guidance for Industry; Bioavailability and Bioequivalence studies for orally administered drug products-general considerations). Inclusion of one subject after plasma concentration correction for carry-over concentration greater than 5% is not expected to have a significant impact on the interpretation of relative BA results.*
In some subjects, the time-BSZ concentration profile showed double peaks suggesting that BSZ may undergo enterohepatic circulation. While the clinical significance is unknown, it may in part contribute to a high variability in the time to peak (Tmax) and longer half-life of metabolites.

Figure 2. Mean Balsalazide and metabolite plasma concentration-time profiles following single- and multiple-dose administration of Balsalazide disodium tablets and capsules



2.3 Intrinsic Factors

2.3.1 Does the gender influence urinary excretion and plasma concentrations of BSZ and its key metabolites?

The sponsor noted that the mean amount of all analytes excreted in urine was higher in females (n=9) than in males (n=9) over two (tablet) or three (capsule) consecutive dosing intervals regardless of formulation. The mean total urinary excretion of percentage of dose based on the combination of BSZ, 5-ASA and N-Ac-5-ASA was 15% for males and 25% in females and the % dose excreted for 5-ASA and N-Ac-5-ASA was 2.16% and 12.8%, respectively in males and 7.11% and 18.5%, respectively in females. The weight corrected renal clearance (ml/min/kg) was also higher for BSZ, 5-ASA, N-Ac-5-ASA and 4-ABA in females than in males. The renal clearance (ml/min and ml/min/kg) for N-Ac-4-ABA on the other hand, was higher in males than in females while the the % dose excretion was higher in females.

Reviewer's comments: *The sponsor also eluded that the plasma pharmacokinetics did not significantly differ by gender. According to this reviewer's calculation, the geometric mean AUC was higher in females compared to males for BSZ, 5-ASA and N-Ac-5-ASA by 5-40% after multiple doses of BSZ tablets. After BSZ capsule administration, AUC for 5-ASA was higher in females by 27% than in males and AUC for BSZ was 10% and N-Ac-5-ASA was 4% higher in females compared to males. Although the large inter-subject variability makes the interpretation tenuous, it was noted that the incidence of adverse effects considered drug-related was higher in females than in males regardless of formulations. In study BZPK1003, 7 drug-related AEs including diarrhea, nausea, dizziness, lethargy, headache, general body ache and chill were reported in females while one incidence of nausea was reported in males. Similarly in food effect study BZPK1002, there was no AEs reported for males but five drug-related AEs including dizziness, headache, diarrhea, and dry-mouth were reported for females. All reported AEs were considered mild. However, according to the clinical reviewer's safety review, no definitive trend in terms of the gender effect on the incidence of adverse events was observed. It is unknown the clinical significance of the noted difference in urinary excretion and plasma concentration by gender to this extent nonetheless it does not seem sufficient to support any dosage adjustment based on gender.*

Table 5: Summary ofurinary excretion of Balsalazide and metabolites by gender

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Table 10 Summary of Urinary Excretion for Balsalazide and Metabolites (5-ASA, N-Ac-5-ASA, 4-ABA, N-AC-4-ABA) Following Multiple-Dose Administration of Balsalazide Disodium Tablets (Male vs Female)

Parameter/ Compound	Male Subjects: Tablet Q12 (N=9)					Female Subjects: Tablet Q12 (N=9)				
				95% CI					95% CI	
	Mean	SD	CV%	Lower	Upper	Mean	SD	CV%	Lower	Upper
Amount Excreted[a] (mg)										
Balsalazide	3.59	2.52	70.1	1.66	5.53	4.77	2.43	50.9	2.90	6.63
5-ASA	24.9	29.1	116.6	2.58	47.3	82.2	55.4	67.4	39.6	125
N-Ac-5-ASA	182	53.7	29.6	140	223	273	124	45.4	177	368
4-ABA	1.09	0.892	81.5	0.409	1.78	11.6	10.7	92.3	3.36	19.8
N-Ac-4-ABA	26.2	13.5	51.7	15.8	36.6	41.0	24.6	60.0	22.1	59.9
% of Dose Excreted[a] (%)										
Balsalazide	0.133	0.0935	70.1	0.0614	0.205	0.177	0.0900	50.9	0.108	0.246
5-ASA	2.16	2.52	116.6	0.223	4.09	7.11	4.80	67.4	3.43	10.8
N-Ac-5-ASA	12.8	4.10	32.1	9.62	15.9	18.5	8.40	45.4	12.0	25.0
4-ABA	0.0696	0.0568	81.5	0.0260	0.113	0.737	0.681	92.3	0.214	1.26
N-Ac-4-ABA	1.39	0.717	51.7	0.837	1.94	2.17	1.30	60.0	1.17	3.17
Renal Clearance (mL/min)										
Balsalazide	43.3	17.8	41.1	29.6	56.9	52.0	24.2	46.5	33.4	70.6
5-ASA	36.0	31.2	86.5	12.1	60.0	86.9	32.4	37.3	62.0	112
N-Ac-5-ASA	164	75.5	46.1	106	222	208	58.3	28.0	163	253
4-ABA	45.5	36.9	81.2	17.1	73.9	206	74.1	35.9	149	263
N-Ac-4-ABA	716	730	102.0	155	1280	472	201	42.5	318	626
Renal Clearance (mL/min/kg)										
Balsalazide	0.550	0.231	41.9	0.373	0.727	0.697	0.334	47.9	0.440	0.954
5-ASA	0.441	0.356	80.7	0.168	0.715	1.17	0.435	37.1	0.840	1.51
N-Ac-5-ASA	2.05	0.844	41.2	1.40	2.70	2.78	0.611	22.0	2.30	3.25
4-ABA	0.572	0.453	79.3	0.224	0.921	2.79	0.968	34.7	2.04	3.53
N-Ac-4-ABA	9.33	10.1	108.1	1.58	17.1	6.21	2.10	33.9	4.59	7.83

[a] Mean amount excreted or mean % of dose excreted in urine during two Q12 consecutive dosing intervals.
Source: Summary Tables A-1 through A-10 and B-1 through B-10, Section 14.2.2

Table 6: The mean PK parameters for BSZ, 5-ASA and N-Ac-5-ASA following multiple doses of BSZ tablets in male and female subjects

	Multiple doses			
Balsalazide	Cmax	S.D.	AUCtau	S.D.
Female	307	114	1576	812
Male	267	197	1499	943
F/M (%)	**115**		**105**	
5-ASA	Cmax	S.D.	AUC∞	S.D.
Female	1535	675	38491	12568
Male	1248	626	10395	5112
F/M (%)	**123**		**140**	
N-Ac-5-ASA	Cmax	S.D.	AUC∞	S.D.
Female	2096	626	60515	14600
Male	2120	587	19291	5614
F/M (%)	**99**		**110**	

2.3.2 Does circadian rhythm influence urinary excretion and plasma concentrations of BSZ and its key metabolites?

The sponsor noted that there was a diurnal or circadian variation regardless of formulations at the steady-state. The trough concentrations were lower for BSZ in the evening while higher for 5-ASA and N-Ac-5-ASA in the evening compared to in the morning. The significance of the observed diurnal variation is unknown.

Reviewer's comment: *The clinical significance of the apparent diurnal variation observed in the trough concentration is unknown. Nevertheless, it suggests that the assessment of systemic exposure for BSZ and its metabolites regardless of formulations needs to be done using actual blood sample data rather than AUCtau multiplied by a dosing frequency due to intra-day fluctuation in plasma concentrations. Nonetheless, for this submission, AUC24 based on AUCtau multiplied by a dosing frequency seems reasonable to be compared because the diurnal variation appears to be formulation independent.*

2.4 Extrinsic Factors

2.4.1 Does Balsalazide have in vivo drug interaction potential?

The in-vitro enzyme inhibition study (Study XT005039) was conducted to evaluate inhibitory effects of BSZ, 5-ASA, N-Ac-5-ASA, 4-ABA, and N-Ac-4-ABA, on human cytochrome P450 enzymes. The study report was previously submitted to fulfill phase 4 commitment for balsalazide disodium capsule approval (Colazal® NDA 20-610, SLR 017 dated May 03, 2007) and previously reviewed by office of clinical pharmacology (reviewer Dr. Abi Adebowale). The study result is reflected in the current approved Colazal® label. As such the detailed review is referred to the previous review. Below is excerpt from the section 7 drug interactions in the Colazal® label.

> ***"7 DRUG INTERACTIONS***
> *In an in vitro study using human liver microsomes, balsalazide and its metabolites [5-aminosalicylic acid (5-ASA), N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), 4-aminobenzoyl-ß-alanine (4-ABA) and N-acetyl-4-aminobenzoyl- ß –alanine (N-Ac-4-ABA)] were not shown to inhibit the major CYP enzymes evaluated (CYP1A2, CYP2C9,CYP2C19, CYP2D6, and CYP3A4/5). Therefore, balsalazide and its metabolites are notexpected to inhibit the metabolism of other drugs with are substrates of CYP1A2,CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. "*

2.5 General Biopharmaceutics

Study BZPK1003: Relative bioavailability between Balsalazide tablets and Balsalazide capsules (Colazal®)-Total AUC_{24} at steady-state after BSZ tablet and BSZ capsule administration was comparable.

The PK parameters after a single 3.3 g dose of BSZ tablet and 2.25 g dose of capsule were compared. The exposure of 5-ASA, N-Ac-5-ASA and BSZ were higher after a single-dose administration of BSZ tablets at 3.3 g than capsule at 2.25g in consistent with the higher dose for tablet. Without dose-normalization the Cmax ratio of tablet to capsule after a single-dose was 80%, 174.3% and 132.4% for BSZ, 5-ASA and N-Ac-5-ASA, respectively. Unexpectedly the mean Cmax for BSZ was lower after tablet than after capsule despite the higher BSZ dose for unexplained reason. On the other hand, the relative BA as a ratio of dose-normalized AUC_{inf}

after tablet to capsule administration was 87%, 123%, and 93% for BSZ, 5-ASA and N-Ac-5-ASA, respectively.

The plasma concentration of BSZ and its metabolites was analyzed after the last dose of multiple doses for 7 days. After multiple doses the exposure of key metabolites was increased by a greater extent after capsule regimen such as 21.8- and 8.2 folds for 5-ASA and N-Ac-5-ASA respectively than tablet regimen such as 9.2 and 4.5 folds 5-ASA and N-Ac-5-ASA respectively compared to a single-dose. The accumulation degree of BSZ after multiple doses was comparable between tablets and capsules.

Reviewer's comment: *The greater increase in exposure for capsules is not unexpected because of more frequent dosing for capsule than for tablet. On the other hand, the comparable accumulation for BSZ despite of the different dosing frequency seems consistent with the relatively short terminal half-life of BSZ determined after a single-dose. The half-life of BSZ was estimated about 1.9h after a single-dose administration regardless of formulations. As such, the majority of BSZ was eliminated from the system during the dosing interval 8 hr for capsules and 12 hr for tablets resulting in minimal after multiple doses regardless of formulations.*

The C_{max} ratio (%) of tablet to capsule after multiple doses was 73.8%, 110.3%, and 107.7% for BSZ, 5-ASA and N-Ac-5-ASA, respectively. Due to a greater accumulation for capsule than for tablet, the difference in Cmax was decreased for 5-ASA and N-Ac-5-ASA after multiple doses than after a single-dose however the difference slightly increased for BSZ from 20% to 26%.

The relative bioavailability as a ratio of dose-normalized AUCtau at steady state after administration of tablets to capsules was 89% for BSZ, 115% for 5-ASA, and 112% for N-Ac-5-ASA.

Reviewer's comment: *Because BSZ is considered locally acting, the systemic exposure information is useful from a safety standpoint. Since the objective of the study is to assess the relative bioavailability and given the high variability with attenuated release of 5-ASA from BSZ, this reviewer believes that the AUC over 24 h without dose-normalization is a better measure for comparison of b.i.d. tablet dosage regimen and t.i.d. capsule dosage regimen in the steady state. The AUC24 obtained during the dosing period for each dosage regimen with tablets and capsules would have provided most accurate measure of daily exposure to BSZ and metabolites since this way the intraday variability between dosing period could be taken into account given there appears to be a diurnal variation in plasma concentration of BSZ and metabolites. However, it was also noted that such diurnal variation in Cmin was observed regardless of formulations; therefore, the AUC_{24} calculated by AUCtau multiplied by the dosing frequency serve as a reasonable parameter for the relative bioavailability between two dosage regimens. The non-dose normalized AUC24 was provided by the sponsor per this reviewer's request in Table 2. Generally, exposure of metabolites was higher with tablets than with capsules and BSZ exposure was lower with tablet than with capsule. .*

The mean urinary excretion of BSZ, 5-ASA and N-Ac-5-ASA during a dosing interval appears consistent between each dosing interval. The mean percentage of dose excreted in urine during a dosing interval was 20.3 % after tablet and 20.4% after capsule administration. The percent (%) dose excretion of each analyte was comparable between tablet and capsule regimen such that it was 0.155% vs 0.157% for BSZ, 4.64% and 5.10% for 5-ASA, 15.6% and 15.2% for N-Ac-5-ASA, 0.403% vs 0.385% for 4-ABA and 1.78% vs. 1.56% for N-Ac-4-ABA. Consistently, the renal clearance of BSZ, 5-ASA and N-Ac-5-ASA after tablet and capsule administration was

comparable. Similarly, the ratio of dose-normalized AUCtau of tablet and capsule for BSZ, 5-ASA, and N-Ac-5-ASA was 89%, 115%, and 112%, respectively.

Reviewer's comment: *In the sponsor's calculation, the mean percentage of dose excreted in urine during a dosing interval was about 22.6% after tablet and 22.4% after capsule administration. These results appear to be slightly overestimated because the percent exrecretion of all metabolites and BSZ was combined. Because the formation of 5-ASA and 4-ABA is theoretically 1:1 split from BSZ, the total percent dose excretion should be estimated based on one metabolic pathway with a higher excretion. As such, the mean total percent urinary excretion as an combination of BSZ, 5-ASA and N-Ac-5-ASA is 20.3% for tablets and 20.4% capsules, respectively.*

Table 7. Summary of PK parameters following single- and multiple-dose administration of Balsalazide disodium tablets and capsules

Compound/ Parameter	Treatment	Single Dose Mean	95% CI Single Dose	Multiple Dose Mean	95% CI Multiple Dose
Balsalazide					
C_{max} (ng/mL)	Tablet	310	232, 387	316	236, 396
	Capsule	431	304, 558	452	350, 555
AUC_{tau} (ng•h/mL)	Tablet	1330	977, 1690	1610	1170, 2040
	Capsule	1100	741, 1460	1280	930, 1620
$AUC_{0-\infty}$ (ng•h/mL)	Tablet	1380	1010, 1750	-	--
	Capsule	1210	823, 1590	-	--
5-ASA					
C_{max} (ng/mL)	Tablet	474	342, 606	1490	1170, 1810
	Capsule	337	246, 428	1430	1210, 1650
AUC_{tau} (ng•h/mL)	Tablet	2210	1430, 2990	13400	10200, 16500
	Capsule	734	445, 1020	8390	6850, 9930
$AUC_{0-\infty}$ (ng•h/mL)	Tablet	8460	6530, 10400	--	--
	Capsule	5360	4380, 6350	--	--
N-Ac-5-ASA					
C_{max} (ng/mL)	Tablet	1150	940, 1360	2190	1890, 2490
	Capsule	918	772, 1060	2140	1830, 2450
AUC_{tau} (ng•h/mL)	Tablet	5860	4430, 7290	21000	17800, 24200
	Capsule	2070	1540, 2610	13200	11500, 14900
$AUC_{0-\infty}$ (ng•h/mL)	Tablet	33500	26500, 40500	--	--
	Capsule	25300	22000, 28600	--	--

Table 8. Mean Urinary excretion during a dosing interval of BSZ tablets or Colazal.

Parameter/ Compound	Tablet Q12 (N=18)					Capsule Q8 (N=18)				
				95% CI					95% CI	
	Mean	SD	CV%	Lower	Upper	Mean	SD	CV%	Lower	Upper
Amount Excreted[a] (mg)										
Balsalazide	4.18	2.48	59.2	2.95	5.41	2.89	1.59	55.1	2.10	3.68
5-ASA	53.6	52.1	97.2	27.7	79.5	40.2	36.4	90.6	22.1	58.3
N-Ac-5-ASA	227	104	45.7	176	279	153	81.4	53.2	113	194
4-ABA	6.34	9.13	144.0	1.80	10.9	4.12	4.48	108.8	1.89	6.35
N-Ac-4-ABA	33.6	20.7	61.6	23.3	43.9	20.1	12.3	61.2	14.0	26.2
% of Dose Excreted[a] (%)										
Balsalazide	0.155	0.0918	59.2	0.109	0.201	0.157	0.0865	55.1	0.114	0.200
5-ASA	4.64	4.51	97.2	2.39	6.88	5.10	4.62	90.6	2.80	7.40
N-Ac-5-ASA	15.6	7.06	45.2	12.1	19.1	15.2	8.11	53.2	11.2	19.3
4-ABA	0.403	0.581	144.0	0.115	0.692	0.385	0.418	108.5	0.177	0.593
N-Ac-4-ABA	1.78	1.10	61.6	1.23	2.32	1.56	0.955	61.2	1.09	2.04
Renal Clearance (mL/min)										
Balsalazide	47.6	21.1	44.3	37.1	58.1	42.2	20.0	47.3	32.3	52.2
5-ASA	61.5	40.5	65.8	41.4	81.6	68.1	48.7	71.6	43.8	92.3
N-Ac-5-ASA	186	69.3	37.3	151	220	190	80.8	42.5	150	230
4-ABA	126	100	79.7	76.0	176	177	157	88.7	99.2	256
N-Ac-4-ABA	594	534	89.9	328	860	652	588	90.3	359	944
Renal Clearance (mL/min/kg)										
Balsalazide	0.624	0.288	46.3	0.480	0.767	0.545	0.244	44.8	0.423	0.666
5-ASA	0.808	0.539	66.8	0.540	1.08	0.896	0.637	71.0	0.580	1.21
N-Ac-5-ASA	2.41	0.806	33.4	2.01	2.81	2.47	1.01	40.9	1.97	2.97
4-ABA	1.68	1.36	80.7	1.01	2.35	2.35	2.07	88.1	1.32	3.38
N-Ac-4-ABA	7.77	7.25	93.3	4.17	11.4	8.41	7.31	86.9	4.78	12.0

[a] Mean amount excreted or mean % of dose excreted in urine during two (Tablet Q12) or three (Capsule Q8) consecutive dosing intervals.
Source: Summary Tables A-1 through A-10 and B-1 through B-10, Section 14.2.2

In general, both dosage regimen using b.i.d tablets at 6.6 g daily and i.i.d. capsules at 6.75 g was considered well-tolerated. Nevertheless, it was noted that the frequency of the treatment-emergent drug-related adverse events including nausea, diarrhea, headache, dizziness and, lethargy was higher during tablet regimen than capsule regimen. It was also noted that larger mean decrease in triglycerides during the tablet regimen (overall -21 mg/dL) compared to the capsule regimen (-14.5 mg/dL) as well as decrease in mean glucose values only during the tablet regimen (overall -5.2 mg/dL) not during the capsule regime (overall 0.8 mg/dL). The noted difference in blood chemistry was not considered clinically relevant.

2.5.3 What is the effect of food on the bioavailability (BA) of the balsalazide disodium tablet?

A single dose food effect study was conducted after the administration of BSZ tablets with a standardized high-fat meal and under fasting conditions and the exposure parameters of BSZ and key metabolites 5-ASA and N-Ac-5-ASA were evaluated. High fat diet significantly attenuated the rate of absorption of 5-ASA and N-Ac-5-ASA indicated by the increased median t_{max} from 12 hours to 24 hours compared to under fasting. The C_{max} and AUC∞ of 5-ASA was decreased by 65% and 46%, respectively with food. The exposure to N-Ac-5-ASA was affected by high fat diet as was its precursor, 5-ASA such that the C_{max} and AUC∞ were decreased by 48% and 17%, respectively compared to fasting condition. The mean half-life of 5-ASA was 5.3 and 8.6 hours under fasting and fed condition, respectively and it was 9.1 and 10.9 h for N-Ac-5-ASA under fasting and fed condition, respectively. The absorption of BSZ was also significantly delayed by high fat diet such that the median t_{max} increased from 0.5 hour to 2.0 hours with food while the terminal half-life and AUC∞ of BSZ was not significantly altered by the high fat diet.

Therefore, the administration of BSZ tablet should take meal intake into consideration. Because the exposure is higher under fasting condition, it should be ascertained that the safety under the higher exposure situation was also evaluated. Per this reviewer's request, the sponsor clarified

that the BSZ tablets were given without regard of food in the phase 3 trial. In addition, the sponsor also indicated that since the systemic exposure decreased by concomitant food intake, from a safety standpoint, the sponsor would not oppose to the administration instruction indicating that BSZ tablets should be taken with food.

Reviewer's comment: Because balsalzide is recommended for a chronic use and the efficacy of the drug is not believed to be relevant to attainment of Cmax, this reviewer agrees that the decreased systemic exposure to BSZ and metabolites under fed condition is favorable from a safety standpoint. Therefore while BSZ taken can be labeled to be taken without regard of food, it is reasonable to label to take BSZ tablet with food.

Table 9. Summary of Pharmacokinetic Parameters for Balsalazide and Metabolites under fasting and fed condition

	Fasted (N=26)		Fed (N=26)	
	Mean	S.D.	Mean	S.D.
Cmax				
BSZ	370	188	208	104
5-ASA	551	416	190	109
N-Ac-5-ASA	1400	742	737	322
Tmax	Mean	(min, max)	Mean	(min, max)
BSZ	0.5	0.5-2.0	2	0.5-6.0
5-ASA	12	8.0-30.0	24	8.0-36.2
N-Ac-5-ASA	12	6.0-30.0	24	8.0-36.2
AUCinf	Mean	S.D.	Mean	S.D.
BSZ	1470	716	1390	836
5-ASA	9480	5550	5190	2730
N-Ac-5-ASA	33900	15300	28700	15200

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma/urine in the clinical pharmacology and biopharmaceutics studies?

Balsalazide and its four metabolites, the active metabolite 5-ASA and its major metabolite N-Ac-5-ASA and the carrier moiety 4-ABA and its N-acetyl metabolite N-Ac-4-ABA in plasma were quantified following selective derivatization and liquid-liquid-extraction.

BSZ and metabolites in human plasma and urine were assayed using HPLC-MS/MS method. BSZ in plasma samples were acidified and extracted by a mixture of methylene chloride and methyl tertiary-butyl ether (MTBE) and the extracts were separated by HPLC using a BetaMax Acid column maintained at 35 ºC and further analyzed by ESI-quadrupole MS/MS.

Metabolites, N-Ac-4-ABA, 4-ABA, N-acetyl-5-ASA and 5-ASA were derivatized with propionic anhydride prior to a liquid-liquid extraction and separated by HPLC using an XTerra RP18 column maintained at 35 ºC. The extract was further analyzed by ESI-quadrupole MS/MS.

The bioanalytical assay method was adequately validated with acceptable accuracy, precision and selectivity for analysis of BSZ and metabolites, N-Ac-4-ABA, 4-ABA, N-Ac-5-ASA and 5-ASA in human plasma and urine.

The range of the standard curve, and LLOQ for each analyte is presented in below table

Table 10. Bioanalytical Assay validation for BSZ and metabolites analysis in plasma and urine

Balsalazide	Plasma (ng/ml)	Urine (μg/ml)
Standard conc.	1-200	0.0625 – 25
LLOQ	1	0.0625
Intra-assay precision (CV%) at LLOQ	3.4	7.3
Inter-assay precision (CV%) at LLOQ	3.4	3.5
Intra-assay accuracy (%deviation) at LLOQ	-4.8	-7.8
Inter-assay accuracy (%deviation) at LLOQ	3.0	1.6
5-ASA	Plasma (ng/ml)	Urine (μg/ml)
Standard conc.	1 - 400	0.625 - 250
LLOQ	1	0.625
Intra-assay precision (CV%) at LLOQ	7.9	5.5
Inter-assay precision (CV%) at LLOQ	5.5	2.4
Intra-assay accuracy (%deviation) at LLOQ	10	4.5
Inter-assay accuracy (%deviation) at LLOQ	-1	0
N-Ac-5-ASA	Plasma (ng/ml)	Urine (μg/ml)
Standard conc.	5 - 2000	2 - 800
LLOQ	5	2
Intra-assay precision (CV%) at LLOQ	5.1	3.5
Inter-assay precision (CV%) at LLOQ	2.9	2.4
Intra-assay accuracy (%deviation) at LLOQ	4.6	2.5
Inter-assay accuracy (%deviation) at LLOQ	1.2	0.5
4-ABA	Plasma (ng/ml)	Urine (μg/ml)
Standard conc.	0.5 - 200	0.05- 20
LLOQ	0.5	0.05
Intra-assay precision (CV%) at LLOQ	7.8	6.0
Inter-assay precision (CV%) at LLOQ	11	3.1
Intra-assay accuracy (%deviation) at LLOQ	5.2	7.0
Inter-assay accuracy (%deviation) at LLOQ	1.4	-2.0
N-Ac-4-ABA	Plasma (ng/ml)	Urine (μg/ml)
Standard conc.	1 – 400	0.5 -200
LLOQ	1	0.5
Intra-assay precision (CV%) at LLOQ	8.8	2.1
Inter-assay precision (CV%) at LLOQ	11.3	4.6
Intra-assay accuracy (%deviation) at LLOQ	8.0	5.8
Inter-assay accuracy (%deviation) at LLOQ	1.0	-1.6

3 Appendices

3.1 Proposed Package Insert

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3.2 Study synopsis

6.1. Study Report BZPK1002 Synopsis

BZPK1002 Synopsis	
Name of Sponsor Company: Salix Pharmaceuticals, Inc.	
Name of Active Ingredient: Balsalazide disodium	
Formulation: Tablet	
Title of Study:	An Open-Label, Randomized, Single-Dose, Two-Period Crossover Study to Evaluate the Bioavailability of a Single-Oral Dose of Balsalazide Disodium Tablets with a High-Fat Meal or After Fasting in Healthy Volunteers
Investigator and Study Center:	Patricia A. Chandler, MD Covance Clinical Research Unit Inc., Dallas, Texas
Publication (reference):	None at the time of this clinical study report.
Phase of Development:	Phase 1
Study Period (months/years):	12 December 2006 (first subject, first visit) through 23 December 2006 (last subject, last visit)
Objectives:	The primary objective of the study was to determine the relative bioavailability of balsalazide disodium 3.3 g (3 × 1.1 g) administered as a single oral tablet dose with a standardized high-fat breakfast relative to after fasting in healthy volunteers.
Methodology:	This was an open-label, randomized, single-dose, 2-period crossover study of 2 treatments: balsalazide disodium tablets administered with a high-fat meal (tablet fed) versus balsalazide disodium tablets administered after fasting (tablet fasted). Each treatment administration was separated by a minimum of 7 days. Healthy volunteers received a single oral 3.3 g (3 × 1.1 g tablets) dose of balsalazide disodium in each study period in either a fasting state or following a high-fat breakfast. Blood samples for pharmacokinetic (PK) analyses of balsalazide and its metabolites were collected predose and up to 96 hours postdose following each administration of study drug.
Number of subjects:	**Planned:** 28; **Analyzed:** Safety: 28, PK: 26
Diagnosis and main criteria for inclusion	A subject was eligible for inclusion in this study only if all of the following criteria applied: 1. The subject signed and dated a written informed consent form (ICF) prior to any study related activities, including discontinuation of any prohibited medications. 2. Subject was a male, or if the subject was female, she was eligible to enter if she met applicable protocol-defined criteria regarding childbearing potential. 3. The subject was between the ages of 18 and 45 years. 4. The subject had a body mass index (BMI) between 18 and 32 kg/m^2. 5. The subject was medically normal with no significant abnormal findings at the screening physical examination as evaluated by the clinical investigator. 6. The subject had normal (or abnormal and clinically insignificant) laboratory values at screening.

BZPK1002 Synopsis	
Name of Sponsor Company: Salix Pharmaceuticals, Inc.	
Name of Active Ingredient: Balsalazide disodium	
Formulation: Tablet	
	7. The subject had the ability to understand the requirements of the study and willingness to comply with all study procedures. Subjects were excluded from the study if they had any clinically significant medical (including allergies), social, or emotional problem, or an abnormal nutritional status. A complete list of exclusion criteria is provided in Section 9.3.2.
Test treatment, dose and mode of administration, batch/lot number:	Balsalazide disodium 3.3 g (3 × 1.1-g tablets) orally administered Lot number: 320369
Reference treatment, dose and mode of administration, batch number:	None.
Duration of treatment:	Following a screening period of up to 14 days, subjects were planned to participate in two 6-day study periods, each associated with the administration of a single dose of balsalazide disodium tablets, for a total study duration of up to 26 days. Each treatment dose administration was separated by a minimum of 7 days.
Criteria for evaluation:	
Pharmacokinetic:	Plasma concentrations of balsalazide disodium, 5-aminosalicylic acid (5-ASA), N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), 4-aminobenzoyl-β-alanine (4-ABA), and N-acetyl-4-ABA (N-Ac-4-ABA) were determined for each treatment regimen (tablet fasted and tablet fed). The following PK parameters were calculated using individual subject plasma concentration time data by standard model-independent methods using WinNonlin Version 4.1 or Microsoft Excel: maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), area under the plasma concentration-time curve from time 0 (predose) through the last quantifiable concentration-time point (AUC_T), area under the plasma concentration versus time curve from time 0 (predose) to time infinity ($AUC_{0-\infty}$), terminal half life ($T_{1/2}$), the terminal phase rate constant (λ_z), the coefficient of determination (Rsq), relative bioavailability (Fr), and the ratio of fed C_{max} to fasted C_{max} (C_{max} Ratio).
Safety:	Safety assessments performed during this study included physical examinations, monitoring of vital signs, clinical laboratory measurements (hematology, serum chemistry, and urinalysis), and adverse event (AE) monitoring.
Statistical methods:	All subjects who received any study medication were included in the overall safety evaluation. Safety summary tabulations are presented for the number of subjects evaluated (N), mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical variables. All subjects who received study medication and completed both treatment periods were considered evaluable for the analysis population for PK parameters. Pharmacokinetic analyses were performed for each treatment regimen on plasma concentration-time data and computed parameters were calculated from these

BZPK1002 Synopsis	
Name of Sponsor Company: Salix Pharmaceuticals, Inc.	
Name of Active Ingredient: Balsalazide disodium	
Formulation: Tablet	
	data. Statistical analyses were conducted using WinNonlin Version 4.1 or SigmaStat, Version 2.03. Balsalazide, metabolite plasma concentrations, and PK parameters were summarized by number of subjects evaluated (N), mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum. Testing for bioequivalence was conducted in accordance with the Food and Drug Administration (FDA) guidances entitled: 'Statistical Approaches to Establishing Bioequivalence (January 2001)' and 'Food-Effect Bioavailability and Fed Bioequivalence Studies (December 2002).[3,6] Following log-transformation (natural log), C_{max}, AUC_T, and $AUC_{0-\infty}$ results for balsalazide, 5-ASA, and N-Ac-5-ASA were compared between the two treatment regimens using the 2 one-sided t-test procedure. The analysis procedure utilized the following analysis of variance (ANOVA) model: response = treatment regimen + period + sequence+ subject (sequence). The 90% confidence interval (CI) approach was implemented to examine the difference between the tablet fasted versus tablet fed treatment regimens. Comparisons were judged bioequivalent if the 90% CI about the ratio of geometric means fell within 80 to 125% for C_{max}, AUC_T, and $AUC_{0-\infty}$. In addition, 95% confidence intervals were also calculated for the mean of each treatment regimen. The Wilcoxon Signed Rank test was used to evaluate T_{max}. A paired t-test or the Wilcoxon Signed Rank test was used to statistically evaluate λ_z.
Results:	
Disposition, Demographics, and Baseline Characteristics:	A total of 28 subjects were enrolled and 26 (92.9%) of these subjects completed the study. Two subjects entered Study Period 1, but did not enter Study Period 2. The mean age for the subjects in this study was 35.5 years with a range of 20 to 45 years. The safety population was equally split with regard to sex and race, with 14 (50%) male and female subjects and 14 (50%) black and white subjects. Nine subjects (32.1%) were of Hispanic or Latino ethnicity.

6.2. Study Report BZPK1003 Synopsis

BZPK1003 Synopsis	
Name of Sponsor Company: Salix Pharmaceuticals, Inc.	
Name of Finished Product: Balsalazide disodium	
Formulation: Tablet	
Title of Study:	A Phase I, Randomized, Single- and Multiple-Dose, Two-Period, Relative Bioavailability and Pharmacokinetic Crossover Study of Balsalazide Disodium Tablets and Capsules Administered Orally to Healthy Volunteers
Investigator and Study Center:	Patricia A. Chandler, MD Covance Clinical Research Unit Inc., Dallas, TX
Publication (reference):	None at the time of this clinical study report.
Phase of Development:	Phase 1
Study Period (months/years):	09 January 2007 (first subject, first visit) through 15 February 2007 (last subject, last visit)
Objectives:	The objectives of this study were to evaluate the relative bioavailability of a new tablet formulation relative to the currently marketed balsalazide disodium capsule formulation, Colazal®, and to characterize the single- and multiple-dose pharmacokinetics (PK) of the tablet formulation in healthy volunteers.
Methodology:	This was an open-label, randomized, 2-period crossover study of the relative bioavailability and PK of 2 different formulations of balsalazide disodium (tablet versus capsule) after both single and multiple oral doses. For Study Period 1, healthy volunteers received a single dose of the balsalazide disodium tablet formulation or the currently marketed balsalazide disodium capsule formulation. Following a 1-week washout period, each subject received multiple oral doses of the assigned single dose formulation for 7 days. The capsule treatment was administered every 8 hours (Q8) as a 2.25-g (3 × 750 mg) dose. The tablet treatment was administered every 12 hours (Q12) as a 3.3-g (3 × 1.1 g) dose. For Study Period 2, following a second 1-week washout period, each subject was crossed over to the alternate formulation for treatment and received single and multiple doses of balsalazide disodium tablets or capsules as detailed for Study Period 1. Blood samples for PK analyses of balsalazide and its metabolites were collected predose and up to 96 hours postdose following single-dose administration and following the final multiple-dose administration for both study periods. Blood samples for PK analyses of balsalazide and its metabolites were also collected during the first through sixth days of multiple-dose administrations for both study periods at protocol-specified intervals. Urine samples for PK analyses of balsalazide and its metabolites were collected at screening (1 sample) and over two 24-hour intervals during the study. The first 24-hour interval began on Day 13 (Study Period 1) before the first daily dose and the second 24-hour interval began on Day 33 (Study Period 2) before the first daily dose. Urine was collected Q8 during the 24-hour interval for capsule treatment and Q12 during the 24-hour interval for tablet treatment.
Number of subjects:	**Planned:** 24; **Analyzed:** Safety: 24, PK: 18

BZPK1003 Synopsis	
Name of Sponsor Company: Salix Pharmaceuticals, Inc.	
Name of Finished Product: Balsalazide disodium	
Formulation: Tablet	
Diagnosis and main criteria for inclusion	A subject was eligible for inclusion in this study only if all of the following criteria applied: 8. The subject signed and dated a written informed consent form (ICF) prior to any study related activities, including discontinuation of any prohibited medications. 9. Subject was a male, or if the subject was female, she was eligible to enter if she met applicable protocol-defined criteria regarding childbearing potential. 10. The subject was between the ages of 18 and 45 years. 11. The subject had a body mass index (BMI) between 18 and 32 kg/m^2 (weight/[height]^2). 12. The subject was medically normal with no significant abnormal findings at the screening physical examination as evaluated by the clinical investigator. 13. The subject had normal (or abnormal and clinically insignificant) laboratory values at screening. 14. The subject had the ability to understand the requirements of the study and willingness to comply with all study procedures. Subjects were excluded from the study if they had any clinically significant medical (including allergies), social, or emotional problem, or an abnormal nutritional status. A complete list of exclusion criteria is provided in Section 9.3.2.
Test treatment, dose and mode of administration, batch/lot number:	Balsalazide disodium tablets, 3.3 g (3 × 1.1 g) orally administered Lot number: 320369
Reference treatment, dose and mode of administration, batch/lot number:	Balsalazide disodium capsules (Colazal), 2.25 g (3 × 750 mg) orally administered Lot number: 318430
Duration of treatment:	Following a screening period of up to 21 days, subjects were housed in the evaluation unit during both study periods (including a 2-day separation between study periods) for 39 days, for a total study duration of up to 60 days.
Criteria for evaluation:	
Pharmacokinetic:	Plasma concentrations of balsalazide disodium, 5-aminosalicylic acid (5-ASA), N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), 4-aminobenzoyl-β-alanine (4-ABA), and N-acetyl-4-ABA (N-Ac-4-ABA) were determined for each treatment regimen (tablet and capsule) after single and multiple dosing. Urine concentrations for balsalazide disodium and its metabolites were determined for each treatment after multiple dosing. The following PK parameters were calculated using individual subject plasma concentration-time data by standard

BZPK1003 Synopsis	
Name of Sponsor Company: Salix Pharmaceuticals, Inc.	
Name of Finished Product: Balsalazide disodium	
Formulation: Tablet	
	model-independent methods using WinNonlin Version 4.1 or Microsoft Excel: maximum observed plasma concentration after dosing (C_{max}), plasma concentration observed at the end of the dosing interval (C_{min}), time to maximum observed plasma concentration (T_{max}), area under the plasma concentration versus time curve from time 0 (predose) to the end of the dosing interval (AUC_{tau}), area under the plasma concentration versus time curve from time 0 (predose) to the last quantifiable time point (AUC_T), area under the plasma concentration versus time curve from time 0 (predose) to time infinity ($AUC_{0-\infty}$), terminal half-life ($T_{1/2}$), the terminal phase rate constant (λ_z), the coefficient of determination (Rsq), relative bioavailability (Fr), the ratio of tablet C_{max} to capsule C_{max} (C_{max} Ratio) (not dose normalized), and the accumulation ratio (Rc). In addition, the percent excreted in urine and renal clearance (CLr) were determined from urine data.
Safety:	Safety assessments performed during this study included physical examinations with medical history, monitoring of vital signs, monitoring of concomitant medications, clinical laboratory measurements (hematology, serum chemistry, and urinalysis), and adverse event (AE) monitoring.
Statistical methods:	All subjects who received any study drug were included in the overall safety evaluation. Safety summary tabulations are presented for the number of subjects evaluated (N), mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and the number and percent per category for categorical variables. All subjects who received study drug and completed both treatment periods were considered evaluable for the analysis population for PK parameters. Pharmacokinetic analyses were performed for each treatment regimen on plasma and urine concentration-time data and computed parameters were calculated from these data. Statistical analyses were conducted using WinNonlin Version 4.1 and Microsoft Excel (2002). Balsalazide and metabolite plasma concentrations, urine amounts, and PK parameters were summarized by N, mean, SD, coefficient of variation (CV), median, minimum, and maximum. The 95% confidence intervals (CIs) for the mean of each treatment were calculated to provide a detailed descriptive summary of the effect of dosage form on the PK of balsalazide and its metabolites in plasma.
Results:	
Disposition, Demographics, and Baseline Characteristics:	A total of 24 subjects were enrolled into the study and 18 (75.0%) subjects completed the study. One subject failed to complete Study Period 1; 5 subjects withdrew prior to completing Study Period 2. The mean age for subjects in this study was 32.1 years, with an age range of 22 to 45 years. There were 12 (50%) subjects of each sex enrolled into the study. Fifteen (62.5%) subjects were white, and 9 (37.5%) subjects were black. Thirteen subjects (54.2%) were of Hispanic or Latino ethnicity.

3.3 OCP Filing Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-205**	**Brand Name**	
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**Balsalazide disodium**
Medical Division	**GI**	**Drug Class**	
OCP Reviewer	**Insook Kim, Ph.D.**	**Indication(s)**	**Ulcerative colitis**
OCP Team Leader	**Sue-Chih Lee, Ph.D.**	**Dosage Form**	**Tablet**
		Dosing Regimen	**1100 mg tid**
Date of Submission	**July 16, 2007**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**March, 2008**	**Sponsor**	**Salix**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**5/17/2008**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			

Healthy Volunteers-				
single dose:	**Fasting & fed**			
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	**Effects on human liver microsomal enzymes**			
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	**X**			
solution as reference:				
alternate formulation as reference:	**capsule**			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**			

Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies	**3**			

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Insook Kim
5/6/2008 03:58:16 PM
BIOPHARMACEUTICS

Sue Chih Lee
5/6/2008 04:03:31 PM
BIOPHARMACEUTICS